Dose-response effects of aerobic exercise on adiposity markers in postmenopausal women: pooled analyses from two randomized controlled trials

By: Paola Gonzalo-Encabo, Jessica McNeil, Alberto Pérez-López, David Valadés, Kerry S. Courneya, and Christine M. Friedenreich

Gonzalo-Encabo P, McNeil J, Pérez-Lopez A, Valadés Cerrato D, Courneya KS, Friedenreich CM. Dose-response effects of aerobic exercise on adiposity markers in postmenopausal women: pooled analyses from two randomized controlled trials. International Journal of Obesity, https://doi.org/10.1038/s41366-021-00799-1

Abstract:

Background/objective: Exercise may reduce the risk of breast cancer through adiposity changes, but the dose-response effects of exercise volume on adiposity markers are unknown in postmenopausal women. We aimed to compare the dose-response effects of prescribed aerobic exercise volume on adiposity outcomes. **Participants/methods:** Data from the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) and Breast Cancer and Exercise Trial in Alberta (BETA) were pooled for this analysis ($N = 720$). These were 12-month randomized controlled trials, where participants were randomized to 225 min/week (mid-volume) of aerobic exercise versus usual inactive lifestyle (ALPHA), or 150 min/week (low-volume) versus 300 min/week (high-volume) (BETA). Fat mass and fat-free mass were measured using DXA and intra-abdominal and subcutaneous fat area were assessed with computed tomography. **Results:** After 12 months of aerobic exercise, increasing exercise volumes from no exercise/control to 300 min/week resulted in statistically significant reductions in BMI, weight, fat mass, fat percentage, intra-abdominal and subcutaneous fat area ($P < 0.001$). Compared with controls, fat mass loss was −1.13, −1.98 and −2.09 kg in the low-, mid- and high-volume groups, respectively. Similarly, weight loss was −1.47, −1.83, −2.21 kg in the low-, mid- and high-volume groups, respectively, compared to controls, and intra-abdominal fat area loss was −7.44, −15.56 and −8.76 cm^2 in the low-, mid- and high-volume groups, respectively, compared to controls. No evidence for a dose-response effect on fat-free mass was noted. **Conclusion:** A dose-response effect of exercise volume on adiposity markers was noted, however, the differences in adiposity markers were smaller when comparing 225 min/week to 300 min/week of exercise. Given the strong positive associations between obesity and postmenopausal breast cancer risk, this study provides evidence on the importance of exercise volume as part of the exercise prescription to reduce adiposity and, ultimately, postmenopausal breast cancer risk.

Keywords: postmenopausal | breast cancer risk | exercise | adiposity

Article:

Introduction

Obesity prevalence is higher among women compared to men, especially in postmenopausal women [1]. Specifically, menopause can contribute to increase total and intra-abdominal fat mass, coupled with decreases in muscle mass, as a result of metabolic changes (e.g., reductions in resting metabolic rate and the production of sex-steroid hormones by the ovaries) [2,3,4]. Excess fat mass accumulation during menopause is related to several chronic diseases, including cardiovascular disease, diabetes, hypertension and several types of cancers [5, 6]. A particularly strong association was found between obesity and invasive breast cancer risk in postmenopausal women [7], a relationship mediated by an increase in estrogen production by adipocytes, inflammation and insulin resistance in peripheral tissues [8, 9]. Therefore, the development of weight management strategies is a major public health priority in postmenopausal women with overweight or obesity to prevent postmenopausal breast cancer risk [10, 11].

Several weight management strategies (e.g., lifestyle, pharmacologic and surgery interventions) have been assessed in clinical settings with the aim of preventing postmenopausal breast cancer [12, 13]. Exercise is a widely used non-invasive strategy to prevent breast cancer risk through fat mass reductions in middle-aged women [10]. Moreover, in postmenopausal women, exercise training can produce multiple additional benefits, such as improved cardiorespiratory fitness [14], insulin sensitivity [15], preserved bone mineral density [16], and increased muscle mass [17]. The American College of Sport Medicine (ACSM) published a position stand in 2009 focused on recommendations for weight loss and weight maintenance, and recommended a minimum of 150 min/week of moderate-intensity physical activity for individuals with overweight and obesity to improve overall health, however, 200–300 min/week were recommended for long-term weight loss [18]. Recently published guidelines from the World Health Organization on physical activity and sedentary behavior also concluded that there is insufficient evidence on the effects of prescribing different volumes of exercise on health outcomes in various populations, including individuals living with chronic diseases [19, 20]. There is currently little evidence of exercise dose recommendations to reduce adiposity outcomes in a population of postmenopausal women with a primary focus on breast cancer prevention through adiposity reductions [21, 22].

The Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial and the Breast Cancer and Exercise Trial in Alberta (BETA) were designed to determine the effects of 12-month aerobic exercise interventions on hypothesized mechanisms of postmenopausal breast cancer risk [23, 24]. In the ALPHA Trial, 320 women were randomized to either 225 min/week of exercise or to a control group without an exercise prescription, finding greater reductions in fat measurements within the exercise group [24]. In BETA, 400 women were randomized to either 300 or 150 min/week of aerobic exercise to provide some evidence of a dose-response effect of exercise volume on biologic markers of breast cancer risk. This study reported that 300 min/week lead to greater reductions in adiposity outcomes, and consequently in reducing breast cancer risk [24, 25].

For the present analyses, we combined data from the ALPHA trial and BETA to assess the effects of an incremental dose of exercise (+75 min/week) on adiposity markers in postmenopausal women. Given the similarities in study populations, inclusion criteria and

methods used in the ALPHA trial and BETA, we were able to pool these two large trials to maximize statistical power and assess the effects of three incremental doses of exercise on adiposity markers, and estimate breast cancer risk reductions via adiposity changes. To our knowledge, no other study has compared the effects of three incremental volumes of aerobic exercise on detailed and objective measures of adiposity (e.g., total fat mass and intra-abdominal and subcutaneous fat area) in postmenopausal women. We hypothesized that in postmenopausal women there would be a dose-response relationship between exercise volume and adiposity markers, with greater fat mass reductions occurring with higher exercise volumes.

Materials and methods

Study design and participants

The study design and methods for the ALPHA Trial and BETA are described in more detail elsewhere [23, 26]. Both studies were approved by the Alberta Cancer Research Ethics Committee and the Conjoint Health Research Ethics Board of the University of Calgary and the Health Research Ethics Board of the University of Alberta. Briefly, these studies were both two-center, two-arm, 12-month randomized controlled trials conducted in Calgary and Edmonton, Alberta, Canada. A total of 320 postmenopausal women were recruited in the ALPHA Trial and randomized to either 225 min/week (mid-volume) of aerobic exercise or to a control group (received no exercise prescription). In BETA, a total of 400 postmenopausal women were recruited and randomized to either 150 min/week (low-volume) or 300 min/week (high-volume) of aerobic exercise (Fig. 1). Eligibility criteria for both trials were the same. Women were postmenopausal, aged 50–74 years, had no previous cancer diagnosis, had a BMI between 22 and 40 kg/m^2, were able to speak English, non-smokers, not currently taking hormone replacement therapy, inactive (<90 min/week of physical activity), did not have diabetes, received medical approval for participation in an exercise program and were not planning to participate in a dietary intervention or any kind of weight loss program. Written consent was obtained from each participant after a full explanation of the purpose and nature of all procedures used. Numbered envelopes with participant's allocation were prepared by staff unrelated with the study. The research staff who took body composition measurements was blinded to the randomization group.

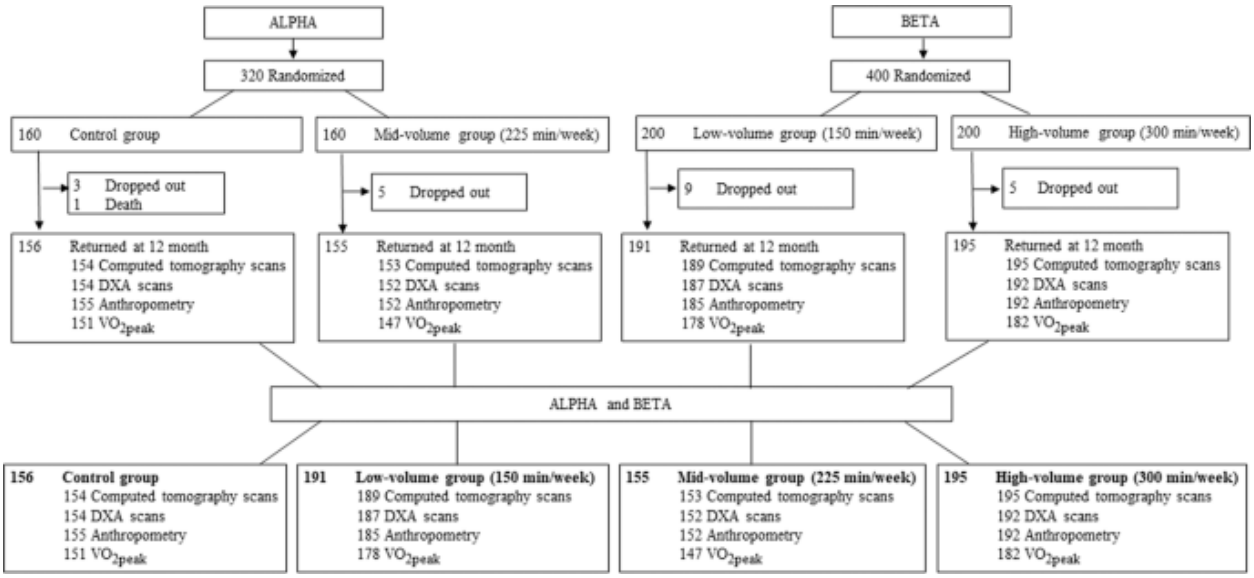

Fig. 1. Participant flow diafram for the ALPHA Trial and BETA, Alberta, Canada, 2008–2012. ALPHA, the Alberta Physical Activity and Breast Cancer Prevention trial; BETA, the Breast Cancer and Exercise Trial in Alberta; DXA, whole-body Dual X-ray Absorptiometry; Min/week, minutes per week; VO_{2peak}, Peak Oxygen Consumption.

Exercise interventions

The exercise prescription in the ALPHA Trial was moderate-to-vigorous intensity aerobic exercise (70–80% of heart rate reserve) for at least 45 min on 5 days/week (225 min/week) for 12 months. Women in BETA completed aerobic exercise at moderate-to-vigorous intensity (65–75% heart rate reserve) on 5 days/week during 30 min/session (150 min/week group) or 60 min/session (300 min/week group). For both trials, the exercise sessions were supervised on at least 3 days/week by certified exercise trainers at fitness facilities in Calgary and Edmonton. The exercise prescription (intensity, volume, and frequency) was gradually increased in both trials over 3 months and then maintained for an additional 9 months [23, 24]. The exercise trainers re-assessed their cardiorespiratory fitness every 3 months to adjust exercise prescription. Adherence to the intervention was monitored with a Polar® heart rate monitor and weekly exercise logs completed by participants and the trainers. Study participants in both trials were asked to maintain their usual diet [23, 24], which was assessed with the Canadian Diet History Questionnaire-II at each time point. Total physical activity time was also assessed at each time point with the validated Past Year Total Physical Activity Questionnaire [27]. These results have been published elsewhere [25, 26]. Briefly, in the ALPHA Trial, there were no statistically significant differences in non-recreational physical activity levels, however, decreases in energy intake were significantly greater in the control versus the exercise groups (−161 kcal/day versus −45 kcal/day) [26]. For BETA, there were no statistically significant group differences in energy intake, dietary fat intake, and non-recreational physical activity time at 12 months between groups [25].

Body composition measurements

Anthropometric measurements were collected using the same protocol for the ALPHA Trial and BETA. At baseline and 12 months, height and body weight were measured using standardized

methods with a conventional stadiometer and balance beam scale. Measurements were taken by research staff in duplicate, if differences between the two measurements were noted, a third measure was taken, and the average was used in the analyses.

In both trials, fat-free mass (kg), fat mass (kg) and body fat percentage (%) were measured using whole-body dual X-ray absorptiometry (DXA). Full-body scans were taken with a Hologic DXA system in Calgary (Hologic Inc, Bedford, MA, USA) for both studies, and a General Electric Lunar iDXA in Edmonton using the enCORE Software 6.70.01 before November 2004 and version 8.60 after November 2004 (Lunar General Electric Medical Systems, Madison, WI, USA), to analyze the data. Research staff calibrated the DXA scanner every day before use. All scans were done following a standardized procedure in Calgary and Edmonton.

In the ALPHA Trial, intra-abdominal and subcutaneous fat area were measured by computed tomography with a single slice at the umbilicus. In Calgary, a PQ5000 VisionMaster CT scanner (Marconi, Cleveland, OH, USA) was used, and in Edmonton a MX8000 multi-slice CT Scanner (Phillips Medical Systems, Cleveland, OH, USA) was used. Images were sent to the study radiologist who used an image software (Silicone Graphics Inc., Sunnyvale, CA, USA) to identify the subcutaneous and the intra-abdominal fat areas. For BETA, these measurements were also made using computed tomographic scans using four single slices centered at the umbilicus. A Phillips Brillance Big Bore and a Toshiba Aquilion were used. In BETA, images were sent to the study radiologist who used an image software (Aquarius Intuition byTeraRecon, Inc) to quantify and identify subcutaneous and intra-abdominal fat areas (cm^2). Scans had very high reliability with an intraclass correlation >0.99.

Cardiorespiratory fitness

Cardiorespiratory fitness (VO_{2peak}) was assessed in both trials using a modified Balke treadmill test protocol and estimated using the ACSM metabolic equations and the multistage model [28]. The submaximal test was completed when participants reached 85% of their age-predicted maximum heart rate or after exhaustion. VO_{2peak} was normalized by fat-free mass [29] to assess changes in cardiorespiratory fitness regardless of body weight changes. Therefore, our results show VO_{2peak} in ml/kg of fat-free mass/min.

Covariate measures

Demographic baseline characteristics were measured with a Baseline Health Questionnaire, which included information on age, medical history (first-degree family history), marital status (married/common law versus unmarried), education (high school or less versus beyond high school), employment (full-time versus not employed full-time), ethnicity (White versus other) and study site (Calgary versus Edmonton).

Statistical analyses

Sample sizes for both trials were based on adiposity [24, 25]. For the present analyses, the power calculation revealed that a sample size of ≥675 women provides a power of 95% to detect differences of 3–4% between the low-volume group and the control group in fat mass (effect

size = 0.16; α = 0.05) (v3.1, G*power, Dusseldorf University, Germany). The percentage of change in the mid-volume and high-volume groups is expected to be higher compared to the control and low-volume groups; therefore, our sample provides enough power to detect differences between these groups as well. Quantile-Quantile plots and histograms were used to assess data distribution. Assumptions of homogeneity were assessed by examining the plots of the residuals versus the fitted values. Given the normal distribution of our data, no transformations were needed. One-way analysis of variance (ANOVA) and Chi-squared tests were used with continuous and categorical variables, respectively, to compare groups at baseline.

An analysis of covariance (ANCOVA) was used to analyze the effect of different exercise volumes (control, low-volume, mid-volume and high-volume) on body composition parameters and cardiorespiratory fitness at 12 months after adjusting for baseline outcome values and by study center (Calgary/Edmonton). In a *post hoc* analysis, linear regression models were used to analyze pairwise comparisons among treatment arms after adjusting for baseline outcome values and study center. In accordance with an intent-to-treat analysis, all women randomized in the ALPHA Trial and BETA with baseline and post-intervention body composition measurements were included in the present analyses.

Effect modification was investigated by determining the statistical significance of the interaction term among each exercise intervention (low-volume, mid-volume, high-volume) with the control group, by each hypothesized moderator (BMI and VO_{2peak} at baseline) on our outcomes of interest after adjusting for baseline outcome values. Intervention effects within all subgroups tested were reported regardless of the statistical significance of the interaction term in the general linear models. Each hypothesized moderator was dichotomized using the mean for VO_{2peak} at baseline normalized by fat-free mass ($VO_{2peak} < 47.81$ ml/kg fat-free mass/min and $VO_{2peak} \geq 47.81$ ml/kg fat-free mass/min), and BMI categories (BMI < 30 versus ≥30 kg/m^2).

Analyses were conducted using STATA (version 15.1, College Station, TX: StataCorp LLC). Values are reported as means and 95% of confidence intervals (95% CI), unless otherwise stated. Statistical significance was set at $P < 0.05$.

Results

Of the 320 women randomized in the ALPHA Trial and the 400 women randomized in BETA, 311 and 386 returned at 12-months for at least 1 outcome measurement, respectively (Fig. 1). Within each study, there were no differences in baseline characteristics except for ethnicity in BETA, whereas statistically significant differences were found between studies for baseline age, employment, education, past year total physical activity participation, fat-free mass, fat (%) and intra-abdominal fat area (Table 1). Body weight change was −0.47 kg, −1.91 kg, −2.26 kg, −2.65 kg in the control, low-, mid- and high-volume groups, respectively. This body weight change resulted mostly from fat mass loss in all groups. Specifically, 76, 77, 98 and 95% of body weight change was fat mass in the control, low-, mid- and high-volume groups, respectively.

Table 1. Participant characteristics at baseline in ALPHA and BETA, Alberta, Canada, 2008–2012, *N* = 720.

	Control group (*n* = 160)	**Low-volume (150 min/week) group (*n* = 200)**	**Mid-volume (225 min/week) group (*n* = 160)**	**High-volume (300 min/week) group (*n* = 200)**	***P* Value among the 4 groups**	***P* Value within ALPHA**	***P* Value within BETA**
Age (years)	59.9 [56.1, 64.3]	58.2 [56, 62.4]	60.71 [56.9, 64.7]	58.5 [55.6, 62.3]	0.001	0.33	0.82
Ethnicity							
White, *N* (%)	145 (90.6)	186 (93)	144 (90.6)	172 (86)	0.13	0.99	0.02
Other, *N* (%)	15 (9.3)	14 (7)	15 (9.4)	28 (14)			
Employment							
Employed full time, *N* (%)	79 (51.30)	59 (29.5)	82 (54.7)	71 (35.5)	<0.001	0.56	0.20
Not employed full time, *N* (%)	75 (48.7)	141 (70.5)	68 (45.3)	129 (64.5)			
Education							
High school or less, *N* (%)	57 (35.8)	45 (22.5)	47 (29.6)	45 (22.5)	0.01	0.23	1.00
Beyond high school, *N* (%)	102 (64.2)	155 (77.5)	112 (70.4)	155 (77.5)			
Married or common law							
No, *N* (%)	35 (21.9)	61 (30.5)	46 (28.9)	64 (32)	0.17	0.15	0.75
Yes, *N* (%)	125 (78.1)	139 (69.5)	113 (71.1)	136 (68)			
First-degree family history of breast cancer							
No, *N* (%)	125 (78.1)	161 (80.5)	128 (80.5)	166 (83.4)	0.65	0.60	0.45
Yes, *N* (%)	35 (21.9)	39 (19.5)	31 (19.5)	33 (16.6)			
Past year total physical activity participation (MET-hours/week)	110.4 [76.4, 164.4]	87.1 [58.6, 121.9]	101.9 [75.7, 140.2]	89.5 [62.0, 115.8]	<0.001	0.05	0.68
Peak oxygen consumption (VO_{2peak}, mL/kg of fat-free mass/min)	49.6 [42.4, 55.5]	46.7 [40.8, 52.6]	49.7 [42.4, 51.7]	46.7 [41.4, 51.1]	0.06	0.86	0.76
Anthropometrics and body composition							
BMI (kg/m^2)	28.72 [25.89, 32.45]	28.64 [25.93, 32.98]	28.41 [25.66, 31.48]	28.39 [25.29, 31.71]	0.84	0.93	0.41
Body weight (kg)	75.0 [67.2, 84.3]	75.8 [66.1, 86.9]	73.4 [66.2, 81.6]	74.8 [66.9, 86.3]	0.52	0.62	0.97
Fat mass (kg)	30.59 [25.26, 36.06]	29.82 [24.28, 37.71]	29.59 [25.19, 35.46]	29.73 [23.80, 36.85]	0.96	0.69	0.79
Fat-free mass (kg)	40.73 [37.76, 44.79]	43.48 [39.5, 47.62]	40.92 [37.75, 43.81]	43.67 [39.80, 47.94]	<0.001	0.67	0.89
Body fat (%)	42.81 [38.41, 45.66]	40.30 [32.89, 44.9]	42.00 [38.68, 45.34]	40.41 [44.27, 36.16]	0.001	0.75	0.72
Intra-abdominal fat area (cm^2)	101.25 [55.44, 134.6]	126.0 [99.41, 165.9]	90.97 [140.5, 56.51]	118.8 [84.99, 161.3]	<0.001	0.77	0.12
Subcutaneous fat area (cm^2)	320.9 [253.3, 399.9]	313.2 [244.3, 384.7]	308.9 [230.6, 404.4]	300.1 [237.6, 383.5]	0.18	0.39	0.98

Values are reported as median [IQR] and *N* (%) for continuous and categorical variables, respectively.

N number of women randomized to each intervention group, *BMI* body mass index, *MET* metabolic equivalent of task.

Table 2. Mean differences in adiposity markers and VO_{2peak} among exercise interventions at 12 months in ALPHA and BETA, Alberta, Canada, 2008–2012, $N = 720$.

	N	12-month adjusted[a] means (95% CI)	Mean adjusted[b] difference among groups at 12 months						ANCOVA[c]
BMI (kg/m^2)									
Control	155	28.97 (28.72, 29.22)	Referent						F (3, 678) = 11.5, $P < 0.001$
Low-volume (150 min/wk)	185	28.34 (28.11, 28.57)	−0.63 (−0.97, −0.29)	$P < 0.001$	Referent				
Mid-volume (225 min/wk)	152	28.25 (28.00, 28.50)	−0.72 (−1.07, −0.37)	$P < 0.001$	−0.09 (−0.43, 0.26)	$P = 0.62$	Referent		
High-volume (300 min/wk)	192	27.98 (27.75, 28.20)	−0.99 (−1.33, −0.65)	$P < 0.001$	−0.36 (−0.68, −0.04)	$P = 0.03$	−0.28 (−0.62,0.07)	$P = 0.11$	
Body weight (kg)									
Control	155	76.04(75.41, 76.68)	Referent						F (3, 678) = 9.2, $P < 0.001$
Low-volume (150 min/wk)	185	74.58 (74.01, 75.16)	−1.47 (−2.34, −0.59)	$P = 0.001$	Referent				
Mid-volume (225 min/wk)	152	74.22 (73.57, 74.86)	−1.83 (−2.73, −0.93)	$P < 0.001$	−0.36 (−1.24, 0.51)	$P = 0.42$	Referent		
High-volume (300 min/wk)	192	73.84 (73.27, 74.41)	−2.21 (−3.07, −1.34)	$P < 0.001$	−0.74 (−1.55, 0.07)	$P = 0.07$	−0.38 (−1.25, 0.49)	$P = 0.39$	
Fat mass (kg)									
Control	153	30.54 (30.01, 31.07)	Referent						F (3, 678) = 13.54, $P < 0.001$
Low-volume (150 min/wk)	187	29.41 (28.93, 29.89)	−1.13 (−1.85, −0.40)	$P = 0.002$	Referent				
Mid-volume (225 min/wk)	152	28.55 (28.01, 29.09)	−1.98 (−2.73, −1.23)	$P < 0.001$	−0.86 (−1.58, −0.13)	$P = 0.02$	Referent		
High-volume (300 min/wk)	192	28.44 (27.96, 28.92)	−2.09 (−2.82, −1.37)	$P < 0.001$	−0.97 (−1.64, −0.29)	$P = 0.01$	−0.11 (−0.83, 0.61)	$P = 0.76$	
Fat-free mass (kg)									
Control	153	42.55 (42.29, 42.81)	Referent						F (3, 678) = 3.470, $P = 0.261$
Low-volume (150 min/wk)	187	42.51 (42.28, 42.75)	−0.04 (−0.39, 0.32)	$P = 0.84$	Referent				
Mid-volume (225 min/wk)	152	42.62 (42.36, 42.88)	0.07 (−0.29, 0.43)	$P = 0.71$	0.11 (−0.25, 0.46)	$P = 0.56$	Referent		
High-volume (300 min/wk)	192	42.82 (42.59, 43.05)	0.27 (−0.08, 0.62)	$P = 0.13$	0.31 (−0.02, 0.63)	$P = 0.06$	0.20 (−0.15,0.55)	$P = 0.26$	
Body fat (%)									
Control	155	41.23 (40.78, 41.68)	Referent						F (3, 681) = 16.94,

	N	12-month adjusted[a] means (95% CI)	Mean adjusted[b] difference among groups at 12 months						ANCOVA[c]
Low-volume (150 min/wk)	187	40.16 (39.75, 40.57)	−1.07 (−1.68, −0.46)	$P = 0.001$	Referent				$P < 0.001$
Mid-volume (225 min/wk)	153	39.47 (39.01, 39.92)	−1.77 (−2.40, −1.13)	$P < 0.001$	−0.69 (−1.31, −0.08)	$P = 0.03$	Referent		
High-volume (300 min/wk)	192	39.18 (38.78, 39.59)	−2.05 (−2.66, −1.44)	$P < 0.001$	−0.98 (−1.55, −0.41)	$P = 0.001$	−0.28 (−0.89, 0.33)	$P = 0.37$	
Intra-abdominal fat area (cm^2)									
Control	154	112.95 (109.53, 116.36)	Referent						F (3, 685) = 13.87, $P < 0.001$
Low-volume (150 min/wk)	189	105.51 (102.41, 108.60)	−7.44 (−12.13, −2.75)	$P = 0.002$	Referent				
Mid-volume (225 min/wk)	153	97.38 (93.93, 100.83)	−15.56 (−20.33, −10.80)	$P < 0.001$	−8.13 (−12.86, −3.39)	$P = 0.001$	Referent		
High-volume (300 min/wk)	195	104.19 (101.16, 107.21)	−8.76 (−13.38, −4.14)	$P < 0.001$	−1.32 (−5.59, 2.94)	$P = 0.54$	6.81 (2.15, 11.46)	$P = 0.004$	
Subcutaneous fat area (cm^2)									
Control	154	314.37 (307.58, 321.17)	Referent						F (3, 685) = 15.37, $P < 0.001$
Low-volume (150 min/wk)	189	295.49 (289.39, 301.60)	−18.88 (−28.09, −9.68)	$P < 0.001$	Referent				
Mid-volume (225 min/wk)	153	288.50 (281.70, 295.30)	−25.87 (−35.41, −16.34)	$P < 0.001$	−6.99 (−16.19, −2.21)	$P = 0.14$	Referent		
High-volume (300 min/wk)	195	284.70 (278.67, 290.72)	−29.68 (−38.84, −20.52)	$P < 0.001$	−10.79 (−19.31, −2.28)	$P = 0.01$	−3.81 (−12.96, 5.35)	$P = 0.41$	
VO_{2peak} (mL/kg of fat-free mass/min)									
Control	148	48.76 (47.23, 50.29)	Referent						F (3, 652) = 11.01, $P < 0.001$
Low-volume (150 min/wk)	177	53.48 (52.08, 54.87)	4.72 (2.63, 6.80)	$P < 0.001$	Referent				
Mid-volume (225 min/wk)	146	53.07 (51.53, 54.61)	4.31 (2.16, 6.46)	$P < 0.001$	−0.41 (−2.50, 1.68)	$P = 0.70$	Referent		
High-volume (300 min/wk)	182	54.50 (53.12, 55.88)	5.74 (3.66, 7.81)	$P < 0.001$	1.02 (−0.93, 2.96)	$P = 0.30$	1.43 (−0.65, 3.51)	$P = 0.18$	

P value derived from the model correspond to the differences between each group with the reference group

N number of women with measures at baseline and 12 months, *CI* Confidence interval, *Min/wk* minutes/week, *VO_{2peak}* Peak oxygen Consumption, *BMI* body mass index.

[a]12-month means with 95% confidence intervals (95% CI) adjusted for baseline value and study location (Calgary/Edmonton).

[b]Mean differences among groups at 12 months adjusted for baseline value and study location (Calgary/Edmonton).

[c]Analysis of covariance (ANCOVA) for 12-month differences among the four groups adjusted for baseline value and study location (Calgary/Edmonton).

In the intent-to-treat analysis (Table 2), we noted statistically significant differences among the four groups at 12-months for BMI, body weight, fat mass, fat percentage, intra-abdominal and subcutaneous fat area, whereas no statistically significant differences between groups were noted for fat-free mass. Results were similar when the model was adjusted for covariates such as age, education, employment, ethnicity and marital status (results not shown).

Mean body weight among women randomized to the high-volume group was estimated to be −2.21 kg (95% CI: −3.07, −1.34; $P < 0.001$) lower than women in the control group at 12-months (Table 2). In the mid-volume group, body weight was estimated to be −1.83 kg (95% CI: −2.73, −0.93; $P < 0.001$) lower than the control group. For the low-volume group, body weight was estimated to be −1.47 kg (95% CI: −2.34, −0.59; $P = 0.001$) lower compared to the control group. However, no statistically significant differences were found among the three exercise groups for body weight change. Compared with the control group, BMI significantly decreased in the three exercise groups ($P < 0.001$, Table 2). Thus, a greater reduction in BMI was noted in the high-volume group compared with the low-volume group at 12-months (−0.36 kg/m^2; 95% CI: −0.68, −0.04; $P = 0.03$).

Greater decreases in total fat mass were achieved with a greater amount of exercise. Compared to the control group, all exercise groups showed a significant decrease in fat mass ($P < 0.01$; Table 2). Furthermore, compared with the low-volume group, we found a statistically significant decrease in fat mass at 12-months in the mid-volume group (−0.86 kg, 95% CI: −1.58, −0.13; $P = 0.02$) and in the high-volume group (−0.97 kg, 95% CI: −1.64, −0.29; $P = 0.01$). No differences were found between the high-volume and mid-volume exercise groups for fat mass. Body fat percentage showed similar results than those presented for fat mass (Table 2).

Intra-abdominal fat area (cm^2) and subcutaneous fat area (cm^2) showed a statistically significant decrease for all exercise groups compared with controls ($P < 0.01$; Table 2). Significantly lower intra-abdominal fat area was noted in the mid-volume group compared to the low-volume group (−8.13 cm^2, 95% CI: −12.86, −3.39; $P = 0.001$). A statistically significant increase in intra-abdominal fat area was found in the high-volume group compared to the mid-volume group (6.81 cm^2, 95% CI: 2.15, 11.46; $P = 0.004$). For subcutaneous fat mass area, a statistically significant decrease was found in the high-volume versus mid-volume groups (−10.79 cm^2, 95% CI: −19.31, −2.28; $P = 0.01$).

Mean increases in VO_{2peak} (ml/kg of fat-free mass/min) at 12-months were estimated to be 5.74 ml/kg/min (95% CI: 3.66, 7.81; $P < 0.001$; Table 2) higher in the high-volume group compared with the control group after adjusting for baseline differences. In comparison with controls, the mid-volume group also had higher VO_{2peak} at 12 months (4.31 ml/kg/min, 95% CI: 2.16, 6.46; $P < 0.001$), as did the low-volume group (4.72 ml/kg/min (95% CI: 2.63, 6.80; $P < 0.001$). No differences for VO_{2peak} were found between exercise groups.

When testing for effect modification, significant interactions were found between the exercise groups and BMI at baseline for changes in body fat percentage and fat-free mass (Supplementary Table 1). The stratified analyses indicated that the effects of exercise dose on body fat percentage was greater among women randomized to the low-volume group who had a BMI < 30 kg/m^2 at baseline when compared to the control group (Supplementary Table 1). For fat-free mass,

women in the high-volume group with a BMI < 30 kg/m^2 at baseline had a statistically significant increase in fat-free mass at 12-months compared with the control group, whereas an inverse pattern of response was noted in women with a BMI > 30 kg/m^2. Although the interaction term was not statistically significant, a greater reduction in fat mass and body weight with increasing exercise volumes for women with obesity (BMI ≥ 30 kg/m^2) was observed in the stratified analysis (Supplementary Table 1). Lastly, there was no evidence of effect modification in the association between VO_{2peak} at baseline and exercise volume on any body composition parameters (Supplementary Table 2).

Discussion

In this pooled analysis of data from two previously conducted exercise intervention trials in inactive postmenopausal women without comorbidities, we found a dose-response effect of prescribed exercise volume on adiposity outcomes. Specifically, after 12 months of aerobic exercise, we found that increasing aerobic exercise volumes from no exercise up to 300 min/week resulted in statistically significant reductions in BMI, body weight, fat mass (kg and %), intra-abdominal fat area and subcutaneous fat area. In addition, participants randomized to the mid- and high-volume groups had greater reductions in these outcomes compared to the low-volume exercise group, and small non-statistically significant differences in these outcomes were seen between the mid- and high-volume exercise groups, except for intra-abdominal fat mass that showed a statistically significant increase in the high-volume exercise group compared to the mid-volume group. No changes were found for fat-free mass. In addition, there were statistically significant differences for all adiposity markers and for cardiorespiratory fitness between the three exercise volumes prescribed and the control group.

The ACSM recommends at least 150 min of moderate intensity physical activity to prevent chronic diseases [30], and 200–300 min/week of moderate intensity physical activity for weight loss and weight loss maintenance. During the intervention, a greater percentage of body weight loss was attributed to total fat mass loss in all groups. Furthermore, the percentage of fat mass loss was greater at higher volumes of exercise, specifically at 225 and 300 min/week of aerobic exercise (98% and 95%, respectively). Our results are supported by previous studies that found that aerobic exercise was able to preserve fat-free mass in overweight and obese older adults [31]. In addition, these results support the evidence put forth by the ACSM's recommendations for weight loss and weight loss maintenance [18], suggesting that greater volumes of exercise are recommended for greater reductions in fat mass, but also suggest that greater volumes of exercise are recommended for maintaining fat-free mass coupled with reductions in fat mass. One previous clinical trial called The Dose-Response to Exercise in Postmenopausal Women (DREW Trial) [14] also tested the dose-response effects of exercise on cardiorespiratory fitness and risk factors for cardiovascular disease in postmenopausal women with high blood pressure at baseline over 6 months. No evidence of a dose-response effect of exercise on body weight and body fat percentage was observed in this trial, which may be partially attributable to the intervention duration (6 months), the differences in exercise prescription and the methods used for body composition measurements in the DREW Trial compared to ALPHA Trial and BETA. The Physical Activity for Total Health Study [32] also reported a dose-response effect of exercise volume on adiposity measures following a per protocol analysis based on exercise adherence during the intervention, where greater decreases in fat mass and intra-abdominal fat

area were noted among postmenopausal women who participated in ≥195 min of exercise/week. Two final studies [33, 34] explored the dose-response relationships between walking and health outcomes in postmenopausal women, with one of these studies reporting a dose-response effect of walking volume (150 versus 225 min/week) on fat mass loss over 12 weeks [34]. Therefore, greater volumes of aerobic exercise can produce greater body weight loss, specifically fat mass loss.

Visceral fat mass, independently of total fat mass, may also increase breast cancer risk [35, 36]. Few trials [37] have investigated the effects of exercise on intra-abdominal and subcutaneous fat area using computed tomography scans in postmenopausal women and reported decreases in intra-abdominal fat and subcutaneous fat area in response to exercise only [32], or with exercise plus diet [38, 39]. No trial to date has previously reported the effects of three incremental exercise volumes on intra-abdominal and subcutaneous fat area. Therefore, our results showing a greater reduction in intra-abdominal and subcutaneous abdominal fat area with greater exercise volumes contribute to current exercise prescription recommendations for postmenopausal breast cancer prevention.

To our knowledge, no previous study has investigated the dose-response effects of aerobic exercise on fat-free mass exclusively in postmenopausal women. In this study, no differences between groups were found for fat-free mass. These results are consistent with previous studies where fat-free mass maintenance in response to aerobic exercise was observed in inactive postmenopausal women [17, 40]. It is known that resistance training is a good strategy to prevent fat-free mass loss and/or contribute to gains in fat-free mass in this population [17, 41]. However, the percentage of body weight loss attributable to fat-free mass loss was very low in both the mid-volume (2%) and high-volume (5%) groups, compared to the control (24%) and low volume groups (23%). A narrative review showed that high volumes (>120–225 min per week) of aerobic exercise could have anti-catabolic effects in physically inactive individuals [42]. Furthermore, in severe energy deficit conditions, exercise facilitates muscle mass preservation by promoting the partial inhibition of the autophagy-lysosomal system [43]. Therefore, it may be hypothesized that an aerobic exercise volumes of 225–300 min/week would be a sufficient stimulus to promote the partial inhibition of autophagy, hence mitigating muscle mass loss despite the weight loss experienced by postmenopausal women in this study. Future trials are needed to corroborate this hypothesis and the role of the autophagy-lysosomal system in muscle mass preservation in postmenopausal women. Furthermore, trials that combine different volumes and different types of exercises (e.g., resistance training and aerobic training) during weight loss are needed.

Adipose tissue is an endocrine organ with several functions [44]. In an inflammatory state, adipose tissue releases inflammatory proteins and hormones, which may then increase breast cancer risk in postmenopausal women [45]. The degree of fat mass loss seen in women randomized to the high-volume group is estimated to correspond with a 4.4% reduction in postmenopausal breast cancer risk [46]. It is important to note that adipose tissue itself is not the only mechanism by which exercise can reduce breast cancer risk [9]. Skeletal muscle is also an endocrine organ that releases myokines into the bloodstream in response to exercise [47]; these molecules having anti-inflammatory effects can also contribute to reducing cancer risk [48, 49].

We noted that the effects of the intervention on fat-free mass were moderated by BMI at baseline. Fat-free mass was significantly greater in the high-volume group in comparison with the control group in women with a BMI < 30 kg/m^2 at baseline, whereas the opposite effect was noted in women with obesity (BMI ≥ 30 kg/m^2). These results are not consistent with previous studies that suggest smaller decreases in fat-free mass in individuals with obesity compared to their normal-weight counterparts [50]. It is possible that an infiltration of inflammatory cells (mainly macrophages and monocytes) in skeletal muscles [51, 52] leading to metabolic dysfunction in myocytes [53], may partially explain why participants with obesity may have greater difficulties in maintaining muscle mass compared to lean participants in response to exercise. Given the detrimental consequences of muscle mass and strength loss with age [50], future interventions in postmenopausal women with obesity should focus on exercise prescriptions that could be used to optimize muscle quality by increasing muscle strength and preserving muscle [54]. In addition, we noted that 150 min/week of aerobic exercise may not be sufficient to achieve a significant decrease in body fat percentage for women with obesity, whereas 225–300 min/week of aerobic exercise lead to greater reductions in adiposity in these women compared to those with a BMI < 30 kg/m^2. These results suggest that greater volumes of exercise may be needed to induce greater reductions in adiposity in women with obesity, which are consistent with results from previous weight loss trials in women with overweight and obesity and the ACSM position stand on weight loss and weight loss maintenance [18, 55].

Strengths of the ALPHA Trial and BETA include the use of a randomized controlled trial design with a 12-month supervised exercise intervention, a large sample size, very low drop-out rates (97% completion rates for both trials), comprehensive measures of covariates and objective measurements of body composition using DXA and CT scans. Our limitations include: varying adherence rates to the exercise prescriptions throughout the 12-month interventions and between groups, suggesting that the prescribed exercise may not entirely reflect the actual amount of exercise completed [24, 25]. Furthermore, the intensity of the exercise prescription was slightly lower in BETA compared to the ALPHA Trial. In addition, we noted some differences in baseline outcomes between the two trials. We attempted to mitigate this issue by adjusting our analyses for baseline outcome values as covariates, however, the differences seen in intra-abdominal fat mass between the mid-volume and the high-volume groups may be partially attributable to a difference in baseline values. Lastly, our trials included postmenopausal women who were mostly white, married or common law, and had high education levels at baseline, therefore results may not be generalizable to other subpopulations of postmenopausal women.

In conclusion, there was a dose-response effect of prescribed exercise volume on BMI, body weight, fat mass, body fat percentage, intra-abdominal fat area and subcutaneous fat area, whereas no dose-response effects were noted for fat-free mass. These reductions in adiposity markers and improvements in VO_{2peak} with increasing exercise volumes may be beneficial for breast cancer prevention [5]. Results from the present study contribute evidence on the importance of higher exercise volumes not only to promote weight loss, but also to reduce postmenopausal breast cancer risk through reductions in adiposity markers. One observational study found that 5 kg of body weight loss may reduce postmenopausal breast cancer risk by 10% [46]. We also estimate that the mean reductions in body weight noted in the present study may lead to an estimated 4.4, 3.7 and 2.9% breast cancer risk reduction for the high, mid- and low-volume exercise prescriptions. To experience higher risk reductions, an intervention including

other lifestyle changes may be needed [56, 57]. While study participants were able to achieve the exercise prescriptions during these trials, the long-term maintenance of exercise may be more challenging. Given the difficulties in long-term exercise adherence in this population, it is important that future research focus on assessing facilitators and barriers to long-term exercise maintenance. Future dose-response trials should also focus on other parameters of exercise prescription, such as exercise type (aerobic versus resistance exercise), to provide more comprehensive and specific information on exercise prescriptions for postmenopausal breast cancer prevention.

Acknowledgements

The ALPHA Trial was funded by a research grant (no. 017468) from the Canadian Breast Cancer Research Alliance. BETA was funded by a research grant from the Alberta Cancer Foundation (#24404). Paola Gonzalo-Encabo is supported by a Predoctoral Fellowship by the Spanish Ministry of Education, Culture and Sports. Dr JM is supported by a Postdoctoral Fellowship Awards from the Canadian Institutes of Health Research and Alberta Innovates-Health Solutions. Dr Kerry Courneya holds a Tier I Canada Research Chair. Dr Christine Friedenreich holds a Health Senior Scholar Award from Alberta Innovates-Health Solutions and the Alberta Cancer Foundation Weekend to End Women's Cancers Breast Cancer Chair.

Funding

Research Grant No. 017468 from the Canadian Breast Cancer Research Alliance (ALPHA Trial); Research Grant No. 24404 from the Alberta Cancer Foundation (BETA Trial).

References

1. Lambrinoudaki I, Brincat M, Erel CT, Gambacciani M, Moen MH, Schenck-Gustafsson K, et al. EMAS position statement: managing obese postmenopausal women. Maturitas. 2010;66:323–6.
2. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, et al. Changes in body composition and weight during the menopause transition. JCI Insight. 2019;4:e124865.
3. El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause. 2019;26:1213–27.
4. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond). 2008;32:949–58.
5. Dennis KE. Postmenopausal women and the health consequences of obesity. J Obstet Gynecol Neonatal Nurs. 2007;36:511–7. quiz 518–9.
6. Arnold M, Pandeya N, Byrnes G, Renehan PAG, Stevens GA, Ezzati PM, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 2015;16:36–46.

7. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, et al. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. JAMA Oncol. 2015;1:611–21.

8. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. CA Cancer J Clin. 2017;67:378–97.

9. Neilson HK, Conroy SM, Friedenreich CM. The Influence of Energetic Factors on Biomarkers of Postmenopausal Breast Cancer Risk. Curr Nutr Rep. 2014;3:22–34.

10. Ligibel JA, Basen-Engquist K, Bea JW. Weight Management and Physical Activity for Breast Cancer Prevention and Control. Am Soc Clin Oncol Educ Book. 2019;39:e22–33.

11. Teede HJ, Lombard C, Deeks AA. Obesity, metabolic complications and the menopause: an opportunity for prevention. Climacteric. 2010;13:203–9.

12. Campbell KL, Foster-Schubert KE, Alfano CM, Wang CC, Wang CY, Duggan CR, et al. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. J Clin Oncol. 2012;30:2314–26.

13. Chlebowski RT, Luo J, Anderson GL, Barrington W, Reding K, Simon MS, et al. Weight loss and breast cancer incidence in postmenopausal women. Cancer. 2019;125:205–12.

14. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA. 2007;297:2081–91.

15. Bueno-Notivol J, Calvo-Latorre J, Alonso-Ventura V, Pasupuleti V, Hernandez AV, Perez-Lopez FR, et al. Effect of programmed exercise on insulin sensitivity in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Menopause. 2017;24:1404–13.

16. Gonzalo-Encabo P, McNeil J, Boyne DJ, Courneya KS, Friedenreich CM. Dose-response effects of exercise on bone mineral density and content in post-menopausal women. Scand J Med Sci Sports. 2019;29:1121–9.

17. Gonzalo-Encabo P, Valades D, Garcia-Honduvilla N, de Cos Blanco A, Friedenreich CM, Perez-Lopez A. Exercise type and fat mass loss regulate breast cancer-related sex hormones in obese and overweight postmenopausal women. Eur J Appl Physiol. 2020;120:1277–87.

18. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK, et al. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc. 2009;41:459–71.

19. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54:1451–62.

20. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. JAMA. 2018;320:2020–8.

21. Chen X, Wang Q, Zhang Y, Xie Q, Tan X. Physical Activity and Risk of Breast Cancer: a Meta-Analysis of 38 Cohort Studies in 45 Study Reports. Value Health. 2019;22:104–28.

22. Chan DSM, Abar L, Cariolou M, Nanu N, Greenwood DC, Bandera EV, et al. World Cancer Research Fund International: continuous Update Project-systematic literature review and meta-analysis of observational cohort studies on physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk. Cancer Causes Control. 2019;30:1183–200.

23. Friedenreich CM, MacLaughlin S, Neilson HK, Stanczyk FZ, Yasui Y, Duha A, et al. Study design and methods for the Breast Cancer and Exercise Trial in Alberta (BETA). BMC Cancer. 2014;14:919.

24. Friedenreich CM, Woolcott CG, McTiernan A, Terry T, Brant R, Ballard-Barbash R, et al. Adiposity changes after a 1-year aerobic exercise intervention among postmenopausal women: a randomized controlled trial. Int J Obes (Lond). 2011;35:427–35.

25. Friedenreich CM, Neilson HK, O'Reilly R, Duha A, Yasui Y, Morielli AR, et al. Effects of a High vs Moderate Volume of Aerobic Exercise on Adiposity Outcomes in Postmenopausal Women: a Randomized Clinical Trial. JAMA Oncol. 2015;1:766–76.

26. Friedenreich CM, Woolcott CG, McTiernan A, Ballard-Barbash R, Brant RF, Stanczyk FZ, et al. Alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among postmenopausal women. J Clin Oncol. 2010;28:1458–66.

27. Friedenreich CM, Courneya KS, Neilson HK, Matthews CE, Willis G, Irwin M, et al. Reliability and validity of the Past Year Total Physical Activity Questionnaire. Am J Epidemiol. 2006;163:959–70.

28. Medicine ACoS. ACSM's Guidelines for Exercise Testing and Prescription. 6th edn. Philadelphia: Lippincott Williams and Wilkins; 2000.

29. Kohler A, King R, Bahls M, Gross S, Steveling A, Gartner S, et al. Cardiopulmonary fitness is strongly associated with body cell mass and fat-free mass: the Study of Health in Pomerania (SHIP). Scand J Med Sci Sports. 2018;28:1628–35.

30. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43:1334–59.

31. Weinheimer EM, Sands LP, Campbell WW. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. Nutr Rev. 2010;68:375–88.

32. Irwin ML, Yasui Y, Ulrich CM, Bowen D, Rudolph RE, Schwartz RS, et al. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA. 2003;289:323–30.

33. Asikainen TM, Miilunpalo S, Kukkonen-Harjula K, Nenonen A, Pasanen M, Rinne M, et al. Walking trials in postmenopausal women: effect of low doses of exercise and exercise fractionization on coronary risk factors. Scand J Med Sci Sports. 2003;13:284–92.

34. Dalleck LC, Allen BA, Hanson BA, Borresen EC, Erickson ME, De Lap SL. Dose-response relationship between moderate-intensity exercise duration and coronary heart disease risk factors in postmenopausal women. J Womens Health (Larchmt). 2009;18:105–13.

35. Pahk K, Joung C, Kim S. Visceral fat metabolic activity evaluated by preoperative (18)F-FDG PET/CT significantly affects axillary lymph node metastasis in postmenopausal luminal breast cancer. Sci Rep. 2020;10:1348.

36. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. Diabetol Metab Syndr. 2011;3:12.

37. Merlotti C, Ceriani V, Morabito A, Pontiroli AE. Subcutaneous fat loss is greater than visceral fat loss with diet and exercise, weight-loss promoting drugs and bariatric surgery: a critical review and meta-analysis. Int J Obes (Lond). 2017;41:672–82.

38. van Gemert WA, Peeters PH, May AM, Doornbos AJH, Elias SG, van der Palen J, et al. Effect of diet with or without exercise on abdominal fat in postmenopausal women - a randomised trial. BMC Public Health. 2019;19:174.

39. Nicklas BJ, Wang X, You T, Lyles MF, Demons J, Easter L, et al. Effect of exercise intensity on abdominal fat loss during calorie restriction in overweight and obese postmenopausal women: a randomized, controlled trial. Am J Clin Nutr. 2009;89:1043–52.

40. Chubak J, Ulrich CM, Tworoger SS, Sorensen B, Yasui Y, Irwin ML, et al. Effect of exercise on bone mineral density and lean mass in postmenopausal women. Med Sci Sports Exerc. 2006;38:1236–44.

41. Marin-Cascales E, Alcaraz PE, Ramos-Campo DJ, Rubio-Arias JA. Effects of multicomponent training on lean and bone mass in postmenopausal and older women: a systematic review. Menopause. 2018;25:346–56.

42. Konopka AR, Harber MP. Skeletal muscle hypertrophy after aerobic exercise training. Exerc Sport Sci Rev. 2014;42:53–61.

43. Martin-Rincon M, Perez-Lopez A, Morales-Alamo D, Perez-Suarez I, de Pablos-Velasco P, Perez-Valera M, et al. Exercise Mitigates the Loss of Muscle Mass by Attenuating the Activation of Autophagy during Severe Energy Deficit. Nutrients. 2019;11:2824.

44. Kusminski CM, Bickel PE, Scherer PE. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nat Rev Drug Discov. 2016;15:639–60.

45. Crespi E, Bottai G, Santarpia L. Role of inflammation in obesity-related breast cancer. Curr Opin Pharmacol. 2016;31:114–22.

46. Trentham-Dietz A, Newcomb PA, Egan KM, Titus-Ernstoff L, Baron JA, Storer BE, et al. Weight change and risk of postmenopausal breast cancer (United States). Cancer Causes Control. 2000;11:533–42.

47. Pérez-López A, Gonzalo-Encabo P. Myokines relevance in exercise adaptations. A world still to be discovered. Arch Med Deporte. 2018;35:214–6.

48. Dethlefsen C, Pedersen KS, Hojman P. Every exercise bout matters: linking systemic exercise responses to breast cancer control. Breast Cancer Res Treat. 2017;162:399–408.

49. Dethlefsen C, Lillelund C, Midtgaard J, Andersen C, Pedersen BK, Christensen JF, et al. Exercise regulates breast cancer cell viability: systemic training adaptations versus acute exercise responses. Breast Cancer Res Treat. 2016;159:469–79.

50. Cava E, Yeat NC, Mittendorfer B. Preserving Healthy Muscle during Weight Loss. Adv Nutr. 2017;8:511–9.

51. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A Biol Sci Med Sci. 2002;57:M326–32.

52. Goodpaster BH, Chomentowski P, Ward BK, Rossi A, Glynn NW, Delmonico MJ, et al. Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. J Appl Physiol (1985). 2008;105:1498–503.

53. Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. J Clin Investig. 2017;127:43–54.

54. Maltais ML, Desroches J, Dionne IJ. Changes in muscle mass and strength after menopause. J Musculoskelet Neuronal Interact. 2009;9:186–97.

55. McTiernan A, Sorensen B, Irwin ML, Morgan A, Yasui Y, Rudolph RE, et al. Exercise effect on weight and body fat in men and women. Obesity (Silver Spring). 2007;15:1496–512.

56. van Gemert WA, Schuit AJ, van der Palen J, May AM, Iestra JA, Wittink H, et al. Effect of weight loss, with or without exercise, on body composition and sex hormones in postmenopausal women: the SHAPE-2 trial. Breast Cancer Res. 2015;17:120.

57. McTiernan A. Behavioral risk factors in breast cancer: can risk be modified? Oncologist. 2003;8:326–34.