Dose-response effects of aerobic exercise on quality of life in postmenopausal women: Results from the Breast Cancer and Exercise Trial in Alberta (BETA)

By: Kerry S. Courneya, Jessica McNeil, Rachel O'Reilly, Andria R. Morielli, and Christine M. Friedenreich

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Abstract:

Background: Exercise generally improves quality of life (QoL) and psychosocial functioning in adult populations but few randomized trials have examined dose-response effects. **Purpose:** The purpose of the present study was to report the QoL and psychosocial outcomes from the Breast Cancer and Exercise Trial in Alberta (BETA). **Methods:** Healthy but inactive postmenopausal women at risk for breast cancer were randomized to a year-long aerobic exercise intervention consisting of either 150 min/week (moderate volume group, $n = 200$) or 300 min/week (high volume group, $n = 200$). QoL was assessed at baseline and 1 year using the short form-36 health survey. Sleep quality, depression, anxiety, stress, self-esteem, and happiness were also assessed. Participant preference for group assignment (i.e., exercise volume) was assessed at baseline and tested as a moderator. **Results:** There were no statistically significant dose-response effects of aerobic exercise on any QoL, sleep quality, or psychosocial outcome. Participant preference for group assignment did not moderate any QoL, sleep quality, or psychosocial responses. Marital status was a significant moderator (p for interaction = 0.01) and obesity showed a trend towards being a moderator (p for interaction = 0.08) of the dose-response effects of aerobic exercise on global sleep quality such that unmarried and obese women improved sleep quality with the higher volume of aerobic exercise. **Conclusions:** A higher volume of aerobic exercise, approximately double the minimum public health guideline, did not provide additional QoL or psychosocial benefits compared to the minimum public health guideline in inactive postmenopausal women, even for women who preferred the higher volume of exercise at baseline. **Trial Registration:** Trial Registration clinicaltrials.gov identifier: NCT1435005.

Keywords: Anxiety | Depression | Happiness | Physical activity | Sleep quality | Stress

Article:

Exercise generally improves quality of life (QoL) and psychosocial outcomes in adult populations including postmenopausal women. Specifically, systematic reviews with meta-analyses have concluded that exercise has small-to-moderate positive effects on QoL [1, 2], sleep quality [3], depression [2, 4], anxiety [4–6], and self-esteem [2]. In the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial, we reported that a year-long exercise intervention comparing 225 min/week of moderate-to-vigorous intensity aerobic exercise to no exercise improved several components of QoL in 320 postmenopausal women [7]. In an exploratory analysis, we also found that higher exercise adherence was associated with larger QoL improvements including some additional gains from exercising >225 min/week compared to 150–225 min/week. In the ALPHA Trial, however, the dose-response analysis was a non-randomized comparison that did not address the causal dose-response effects of aerobic exercise on QoL. Although numerous dose-response exercise trials have been conducted in adult populations, few have reported QoL or psychosocial outcomes [8–11].

One notable exception is the Dose-Response to Exercise in postmenopausal Women (DREW) Trial [8, 9]. The DREW Trial randomized over 400 sedentary overweight postmenopausal women to either a no exercise control group or three levels of the public health aerobic exercise guidelines consisting of 75 min/week (50%), 150 min/week (100%), or 225 min/week (150%). The DREW trial demonstrated a dose-response effect of aerobic exercise on QoL [8] and sleep quality [9] with the 225 min/week group having the largest and broadest effects on QoL components [8] and sleep quality indicators [9]. The purpose of the present study was to extend the results of the DREW Trial by reporting the secondary QoL and psychosocial outcomes from the Breast Cancer and Exercise Trial in Alberta (BETA) [12].

The BETA Trial was a primary prevention trial focused on adiposity and biomarkers related to breast cancer risk. In comparison to the DREW Trial, the BETA Trial compared the effects of 300 min/week (200%) versus 150 min/week (100%) of aerobic exercise over a 1-year period in 400 postmenopausal women [12]. We also collected a more comprehensive battery of patient-reported outcomes including QoL, sleep quality, depression, anxiety, stress, self-esteem, and happiness. Finally, we incorporated a measure of participant preference for group assignment (i.e., exercise volume) which may be an important determinant of QoL and psychosocial responses when comparing more than one exercise intervention [13].

The primary outcome of the BETA Trial was adiposity [12] for which we observed that 300 min/week of exercise was more effective in reducing total fat and other adiposity measures compared to 150 min/week. Based on the DREW Trial [8, 9], we hypothesized that 1 year of 300 min/week of aerobic exercise would be superior to 150 min/week of aerobic exercise for all QoL, sleep quality, and psychosocial outcomes [15]. Moreover, we hypothesized that participants randomized to their preferred exercise volume would report more positive QoL and psychosocial responses compared to participants randomized to their non-preferred exercise volume. Finally, we explored other potential moderators of the dose-response effects of aerobic exercise based on plausible demographic and health factors including age, marital status, baseline recreational physical activity, baseline aerobic fitness, body mass index, and number of comorbidities.

Methods

Setting and Participants

The BETA Trial methods have been reported elsewhere [14]. Briefly, the trial was a two-center, two-armed, year-long randomized controlled exercise intervention trial in healthy, postmenopausal women. The study protocol was approved by the Alberta Cancer Research Ethics Committee, the Conjoint Health Research Ethics Board of the University of Calgary and the Health Research Ethics Board of the University of Alberta and all participants provided written informed consent. The trial was conducted between June 2010 and June 2014. Eligibility criteria included being a resident of Calgary or Edmonton, between the ages of 50 and 74 years, a body mass index (BMI) between 22 and 40 kg/m^2, a non-smoker, able to do unrestricted physical activity as assessed by physician screening, and inactive (defined as <90 min/week of exercise or if between 90 and 120 min/week, having a VO_{2max} <34 ml/kg/min as assessed by a submaximal fitness test).

Randomization

Participants were stratified by center (Calgary, Edmonton) and BMI (<27.5, ≥27.5 m/kg^2) before being randomized in a 1:1 ratio to the two intervention groups. The randomization sequence was created by the study biostatistician using a random number program with blocks randomly sized between four and six within strata. The study coordinator in Calgary, who was blinded to the randomization sequence, revealed the randomization from sealed opaque envelopes after all baseline assessments were completed.

Exercise Interventions

Participants were randomized to either a moderate volume of aerobic exercise based on 100% of the minimum public health guideline of 150 min/week (n = 200) or a high volume of aerobic exercise based on double (200%) the minimum public health guideline of 300 min/week (n = 200) [15]. Participants were asked to exercise 5 days per week at 65–75% of their heart rate reserve for either 30 min each day (moderate volume group) or 60 min each day (high volume group) and could choose any aerobic activity to perform. The exercise intervention was supervised 3 days/week by certified exercise trainers at fitness facilities in Calgary and Edmonton; the two additional days/week of exercise were unsupervised at a location determined by the participant. There were very few group exercise sessions although participants typically exercised when other trial participants were present and informal interaction did occur. Exercise adherence was monitored using weekly exercise logs. Heart rate monitors were worn to ensure that at least 50% of exercise sessions were completed within the target heart rate zone.

Outcome Measures

Patient-reported outcomes were assessed at baseline (pre-intervention) and postintervention (1 year). The primary outcome of interest in the present paper was QoL assessed by the Medical Outcomes Study Short Form-36 Survey (SF-36) [16]. The SF-36 covers eight health domains including general health, physical functioning, role-physical limitations, bodily pain, vitality, social functioning, role-emotional limitations, and mental health. The standardized, norm-based

domain scores were then used to create a physical component and mental component score (summary scales). Scores for each health domain ranged from 0 to 100 with higher scores indicating higher function or well-being. A single item assessed the perceived change in health (how much better or worse your health is now compared to 1 year ago). The SF-36 has demonstrated validity and reliability in clinical and nonclinical populations [16]. Secondary outcomes of interest included global sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI) [17] and various psychosocial outcomes assessed by the Center for Epidemiological Studies Depression Scale (CES-D) [18], the Spielberger State Anxiety Inventory [19], the Perceived Stress Scale (PSS) [20], the Happiness scale [21], and the Rosenberg Self-Esteem Scale [22].

Proposed Moderators

We explored seven common moderators based on their scientific plausibility, clinical utility, distribution in our data set, and support in previous research [13, 23–25]. The primary moderator of interest was participant preference for group assignment (moderate versus high versus no preference). Participant preference was assessed prior to randomization by asking participants "Which exercise program would you prefer if you had the choice?" The three options were: (a) the moderate amount of aerobic exercise, (b) the higher amount of aerobic exercise, and (c) no preference. Secondary moderators of interest were age (<60 years versus ≥60 years), marital status (married or common law versus unmarried), baseline recreational physical activity (equivalent of <10 versus ≥10 metabolic equivalent task hours/week), baseline aerobic fitness (<25 versus ≥25 ml/kg/min), body mass index (<30.0 versus ≥30 kg/m^2), and number of comorbidities (none versus ≥1). Physical activity was assessed using the validated Past Year Total Physical Activity Questionnaire (PYTPAQ) [26]. VO_{2max} was estimated using a sub-maximal, multistage, modified Balke treadmill protocol [27] and validated prediction formula [28]. BMI was assessed from measured standing height and weight by research staff using a balance beam scale and stadiometer.

Statistical Analyses

Sample size for the trial was based on the primary endpoint of adiposity. For the present analyses, we estimate that our planned sample size of 400 (200 per group) would allow us to detect between group differences on the patient-reported outcomes of about 0.25 standard deviations with a power of 0.80 and two-tailed alpha of 0.05. We used intention-to-treat analyses that included all participants with 12-month follow-up data (complete case analysis) regardless of their protocol adherence. The main effect of the intervention group was assessed using linear models, where change in the outcome was predicted, adjusted for baseline value of outcome, and study site (Calgary, Edmonton). Least squares mean difference between intervention groups was estimated as well as least squares mean change from baseline to end of study. An exploratory analysis was undertaken to assess changes from baseline to end of study, combining randomization groups, assessing the null hypothesis of no change in outcome. Effect modification was assessed by linear models predicting change in outcome, adjusted for baseline outcome and study site, and *p* values for interaction between potential effect modifier and intervention group were estimated. To understand possible subgroup variations, the same models were run within each subgroup of potential effect modifier. Interaction effects were tested only

for the SF-36 physical and mental component scores, global sleep quality, and the five psychosocial outcomes (anxiety, depression, stress, self-esteem, and happiness). All analyses were conducted using SAS (SAS 9.2 for Linux, SAS Institute Inc).

Results

A flow chart for the BETA Trial has been reported elsewhere [12]. In brief, there were 863 women who met the inclusion criteria and 400 of these women (46%) were randomized to either the high (n = 200) or the moderate (n = 200) volume exercise groups. QoL data were obtained at postintervention (1 year) from 185 participants (93%) in the moderate volume group and 188 participants (94%) in the high volume group. Baseline characteristics of the two groups were similar [12] including for the proposed moderators in the present report (Table 1). Overall, 88 (22%) participants preferred the moderate volume intervention, 147 (37%) preferred the high volume intervention, and 163 (41%) had no preference.

Table 1. Baseline proposed moderators overall and by group assignment in the BETA Trial

Baseline characteristics	**Overall (n = 400)**	**Moderate group (n = 200)**	**High group (n = 200)**
Participant preference, *n* (%)			
Moderate volume	88 (22)	39 (20)	49 (25)
High volume	147 (37)	67 (34)	80 (40)
No preference	163 (41)	94 (47)	69 (35)
Age (years), *n* (%)			
≥60	160 (40)	84 (42)	76 (38)
<60	240 (60)	116 (58)	124 (62)
Marital status, *n* (%)			
Married/common law	275 (69)	139 (70)	136 (68)
Unmarried	125 (31)	61 (31)	64 (32)
Body mass index (kg/m^2), *n* (%)			
≥30	155 (39)	78 (39)	77 (39)
<30	245 (61)	122 (61)	123 (62)
Estimated VO_2 max (ml/kg/min), n (%)			
≥25	270 (68)	135 (68)	135 (68)
<25	130 (33)	65 (33)	65 (33)
Baseline recreational physical activity (MET hours/week), *n* (%)			
≥10	134 (34)	71 (36)	63 (32)
<10	266 (67)	129 (65)	137 (69)
Presence of comorbidities[a], *n* (%)			
Yes	271 (68)	138 (69)	133 (67)
No	129 (32)	62 (31)	67 (34)

[a] Medical conditions as reported by participants, including heart attack, angina, stroke, arthritis, osteoporosis, blood clots, thyroid problems, high cholesterol, and other
MET metabolic equivalent of task

Adherence to the intervention has been reported elsewhere [12]. Briefly, excluding the 3-month ramp-up period, the median (interquartile range) exercise level for the moderate volume group was 137 (111–150) min/week (91% adherence) and for the high volume group was 254 (166–290) min/week (85% adherence). In terms of the time in the target heart rate zone based on heart

rate monitors (excluding the ramp-up period), the median (interquartile range) was 88 (53–115) and 128 (66–185) min/week for the moderate and high volume groups, respectively, representing 64 and 50% of exercise time in the targeted heart rate zones. During the 12-month period, total recreational physical activity increased more in the high volume group than in the moderate volume group (26.5 vs. 14.2 MET-h/week). VO_{2max} increased significantly in both groups with a significantly larger increase in the high volume group (5.1 ml/kg/min) compared to the moderate volume group (4.0 ml/kg/min).

Dose-Response Effects on Quality of Life and Psychosocial Outcomes

There were no statistically significant dose-response effects of aerobic exercise on any QoL (Table 2), sleep quality (Table 3), or psychosocial outcomes (Table 4). Combining intervention groups, there were statistically significant main effects for time showing an overall improvement from baseline to 1 year in physical functioning (0.9; 95% CI 0.3 to 1.6; $p<0.01$), vitality (1.6; 95% CI 0.7 to 2.5; $p<0.01$), general health (0.9; 95% CI 0.2 to 1.6; $p<0.05$), subjective sleep quality (−0.1; 95% CI 0.0 to −0.1; $p<0.05$), and self-esteem (0.6; 95% CI 0.2 to 1.0; $p<0.01$). There was also a main effect for time ($p<0.01$) showing a more positive health transition at postintervention compared to baseline (Fig. 1). Specifically, 14.4% of participants reported better general health at baseline compared to 1 year ago (i.e., before the intervention) whereas 74.3% reported better general health at 1 year compared to 1 year ago (i.e., after the intervention). Conversely, there were statistically significant main effects for time showing an overall decline in role-physical (−3.3; 95% CI −1.8 to −4.7; $p<0.01$), bodily pain (−3.0; 95% CI −2.1 to −3.9; $p<0.01$), social functioning (−1.4; 95% CI −0.5 to −2.3; $p<0.01$), and the physical component score (−1.2; 95% CI −0.4 to −2.1; $p<0.01$).

Table 2. Dose-response effects of aerobic exercise on quality of life outcomes in the BETA Trial

Variable	Baseline *M* (SD)	1 year *M* (SD)	Least squares mean change[a] *M* (95% CI)	Least squares group difference[a] *M* (95% CI)	*p* value
Physical functioning					
Moderate group (*n* = 185)	51.6 (5.4)	52.1 (6.7)	+0.2 (−0.6 to 1.1)	+0.8 (−0.3 to 2.0)	0.14
High group (*n* = 189)	51.4 (6.0)	52.8 (5.5)	+1.1 (0.2 to 1.9)		
Role-physical					
Moderate group (*n* = 185)	54.2 (7.3)	50.3 (12.8)	−3.4 (−5.4 to −1.5)	−0.2 (−2.5 to 2.8)	0.91
High group (*n* = 189)	52.8 (8.9)	50.1 (13.0)	−3.3 (−5.3 to −1.3)		
Bodily pain					
Moderate group (*n* = 185)	56.1 (6.1)	53.0 (9.4)	−3.2 (−4.5 to −1.9)	−0.0 (−1.8 to 1.7)	0.97
High group (*n* = 189)	55.4 (6.3)	52.6 (8.8)	−3.2 (−4.5 to −1.9)		
General health					
Moderate group (*n* = 185)	53.8 (6.7)	54.5 (7.2)	+0.7 (−0.4 to 1.7)	+0.1 (−1.2 to 1.5)	0.85
High group (*n* = 189)	53.1 (7.1)	54.2 (8.2)	+0.8 (−0.2 to 1.8)		
Vitality					
Moderate group (*n* = 185)	52.7 (8.9)	53.7 (9.1)	+0.7 (−0.5 to 2.0)	+0.9 (−0.7 to 2.5)	0.28
High group (*n* = 188)	52.1 (8.7)	54.3 (9.6)	+1.6 (0.4 to 2.8)		
Social functioning					
Moderate group (*n* = 185)	53.3 (6.7)	51.8 (8.5)	−1.7 (−3.0 to −0.5)	+0.1 (−1.5 to 1.8)	0.87
High group (*n* = 189)	53.3 (6.7)	51.9 (8.6)	−1.6 (−2.8 to −0.3)		
Role-emotional					
Moderate group (*n* = 185)	50.2 (12.1)	48.3 (14.8)	−1.9 (−3.9 to 0.1)	+1.3 (−1.4 to 3.9)	0.34

Variable	Baseline *M* (SD)	1 year *M* (SD)	Least squares mean change[a] *M* (95% CI)	Least squares group difference[a] *M* (95% CI)	*p* value
High group (*n* = 189)	50.8 (11.2)	49.9 (13.2)	−0.6 (−2.6 to 1.4)		
Mental health					
Moderate group (*n* = 185)	53.9 (7.2)	53.8 (7.1)	−0.1 (−1.1 to 0.9)	+1.2 (−0.1 to 2.5)	0.07
High group (*n* = 188)	53.6 (7.3)	54.9 (7.4)	+1.1 (0.2 to 2.1)		
Physical health component					
Moderate group (*n* = 185)	50.3 (5.8)	48.8 (9.0)	−1.5 (−2.7 to −0.3)	0.0 (−1.6 to 1.6)	0.99
High group (*n* = 188)	49.4 (6.2)	48.4 (8.1)	−1.5 (−2.7 to −0.3)		
Mental health component					
Moderate group (*n* = 185)	52.2 (9.8)	51.8 (10.7)	−0.4 (−1.8 to 0.9)	+1.2 (−0.6 to 3.1)	0.19
High group (*n* = 188)	52.5 (9.4)	53.3 (10.4)	+0.8 (−0.6 to 2.2)		

M mean, *SD* standard deviation, *n* sample size, *CI* confidence interval

[a] Least squares mean change and least squares group difference in mean change are calculated based on a model adjusted for baseline value and location (Calgary/Edmonton)

Table 3. Dose-response effects of aerobic exercise on sleep quality outcomes in the BETA Trial

Variable	Baseline *M* (SD)	1 year *M* (SD)	Least squares mean change[a] *M* (95% CI)	Least squares group difference[a] *M* (95% CI)	*p* value
Subjective sleep quality					
Moderate group (*n* = 183)	1.0 (0.7)	1.0 (0.7)	−0.0 (−0.1 to 0.1)	−0.1 (−0.2 to 0.1)	0.34
High group (*n* = 188)	1.0 (0.7)	0.9 (0.7)	−0.1 (−0.2 to 0.0)		
Sleep latency					
Moderate group (*n* = 183)	1.0 (0.8)	1.0 (1.0)	+0.1 (0.0 to 0.2)	−0.1 (−0.3, 0.1)	0.23
High group (*n* = 189)	1.0 (1.0)	0.9 (0.9)	0.0 (−0.1 to 0.1)		
Sleep duration					
Moderate group (*n* = 183)	1.1 (1.0)	1.1 (0.9)	−0.1 (−0.2 to 0.1)	−0.1 (−0.2 to 0.1)	0.37
High group (*n*=189)	1.1 (1.0)	1.0 (1.0)	−0.1 (−0.2 to −0.0)		
Habitual sleep efficiency					
Moderate group (*n* = 183)	0.6 (0.9)	0.6 (0.8)	0.0 (−0.2, 0.1)	0.0 (−0.2, 0.1)	0.76
High group (*n* = 188)	0.6 (0.9)	0.6 (0.9)	−0.1 (−0.2, 0.1)		
Sleep disturbances					
Moderate group (*n* = 183)	1.2 (0.5)	1.2 (0.5)	0.0 (−0.1, 0.1)	0.0 (−0.1, 0.1)	0.44
High group (*n* = 188)	1.3 (0.5)	1.2 (0.5)	0.0 (−0.1, 0.1)		
Use of sleep medication					
Moderate group (*n* = 183)	0.4 (0.9)	0.5 (0.9)	0.0 (−0.1, 0.1)	0.0 (−0.1, 0.2)	0.73
High group (*n* = 188)	0.4 (0.9)	0.5 (0.9)	0.0 (−0.1, 0.1)		
Daytime dysfunction					
Moderate group (*n* = 183)	0.7 (0.6)	0.8 (0.6)	0.1 (0.0, 0.2)	0.0 (−0.1, 0.1)	0.67
High group (*n* = 188)	0.7 (0.6)	0.8 (0.7)	0.1 (−0.0, 0.2)		
Global score					
Moderate group (*n* = 183)	6.0 (3.4)	6.1 (3.3)	+0.1 (−0.3 to 0.5)	−0.3 (−0.8 to 0.2)	0.28
High group (*n* = 188)	6.0 (3.6)	5.8 (3.7)	−0.2 (−0.6 to 0.2)		

M mean, *SD* standard deviation, *n* sample size, *CI* confidence interval

[a] Least squares mean change and least squares group difference in mean change are calculated based on a model adjusted for baseline value and location (Calgary/Edmonton)

Table 4. Dose-response effects of aerobic exercise on psychosocial outcomes in the BETA Trial

Variable	Baseline *M* (SD)	1 year *M* (SD)	Least squares mean change[a] *M* (95% CI)	Least Squares group difference[a] *M* (95% CI)	*p* value
Anxiety					
Moderate group (*n* = 185)	16.3 (4.7)	16.4 (5.0)	+0.1 (−0.7 to 0.8)	+0.3 (−0.7 to 1.2) 0.60	0.61
High group (*n* = 189)	16.7 (4.9)	16.8 (5.8)	+0.3 (−0.4 to 1.0)		
Depression					
Moderate group (*n* = 186)	4.3 (4.0)	4.1 (4.1)	−0.2 (−0.7 to 0.4)	+0.1 (−0.7 to 0.8)	0.87
High group (*n* = 189)	3.8 (3.8)	3.9 (4.3)	−0.1 (−0.7 to 0.5)		
Stress					
Moderate group (*n* = 185)	17.1 (7.3)	17.1 (7.7)	+0.2 (−0.9 to 1.2)	+0.3 (−1.1 to 1.7)	0.69
High group (*n* = 190)	17.1 (7.1)	17.4 (8.1)	+0.4 (−0.6 to 1.5)		
Self-esteem					
Moderate group (*n* = 186)	33.7 (4.2)	34.5 (4.4)	+0.9 (0.3 to 1.4)	−0.4 (−1.1 to 0.3)	0.26
High group (*n* = 190)	33.3 (4.7)	33.8 (4.6)	+0.5 (−0.1 to 1.0)		
Percent happiness					
Moderate group (*n* = 185)	63.2 (23.8)	62.1 (24.3)	−0.8 (−4.2 to 2.6)	+4.1 (−0.4 to 8.6)	0.07
High group (*n* = 188)	62.7 (25.6)	65.9 (25.2)	+3.3 (−0.1 to 6.7)		

M mean, *SD* standard deviation, *n* sample size, *CI* confidence interval

[a] Least squares mean change and least squares group difference in mean change are calculated based on a model adjusted for baseline value and location (Calgary/Edmonton)

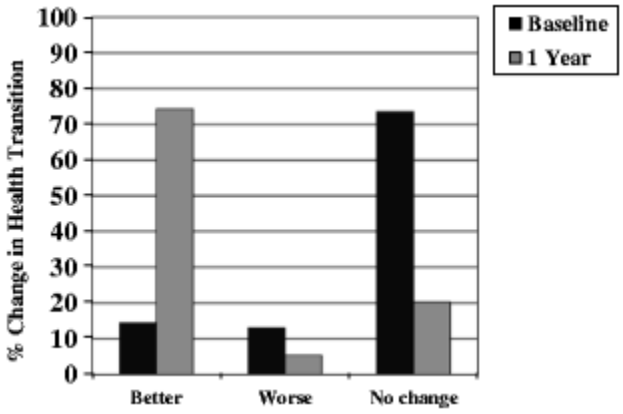

Fig. 1. Change in health transition from baseline to 1 year in the combined sample in the BETA Trial

Moderators of Dose-Response Effects on Quality of Life and Psychosocial Outcomes

Participant preference for group assignment did not moderate the dose-response effects of aerobic exercise on any QoL, sleep quality, or psychosocial outcome (data not shown). The only significant or trend towards interactions between randomized group assignment and the proposed moderators were for global sleep quality. Specifically, marital status moderated the dose-response effects of aerobic exercise on global sleep quality (*p* for interaction=0.01) such that unmarried women improved sleep quality with the high volume exercise program whereas married/common law women showed no dose-response effect (Fig. 2a). BMI showed a trend towards moderating the dose-response effects of aerobic exercise on global sleep quality (*p* for

interaction=0.08) such that obese women improved sleep quality with the high volume exercise program whereas nonobese women showed no dose-response effect (Fig. 2b).

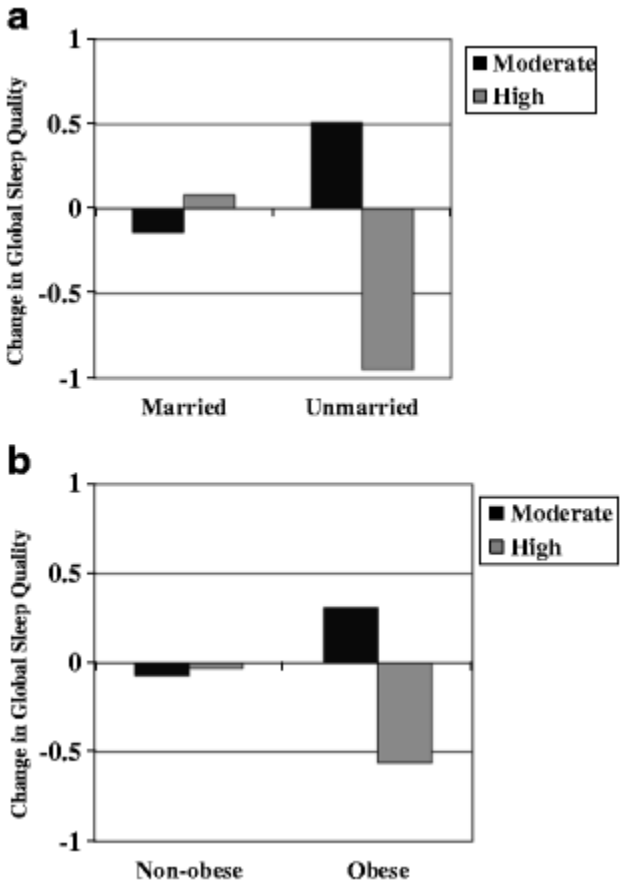

Fig. 2. Dose-response effects of aerobic exercise on global sleep quality by marital status (a) and obesity (b) in the BETA Trial. Negative change scores indicate improved sleep quality

Discussion

In this year-long randomized dose comparison trial of 300 versus 150 min/week of aerobic exercise in postmenopausal women, we found no evidence of dose-response effects on QoL, sleep quality, or psychosocial outcomes. In the Dose-Response to Exercise in Women (DREW) trial, Martin et al. [8] examined the effects of a 6-month, moderate intensity exercise program performed at three different exercise volumes (75, 150, and 225 min weekly) compared to a no intervention group in 430 postmenopausal women at high risk for cardiovascular disease. Results showed a general dose-response effect on all QoL subscales except bodily pain with the 225 min/week group demonstrating the largest and broadest effects on the various QoL components. The Trial of Exercise on Aging and Memory (TEAM) used the same four-arm design as the DREW Trial but was focused on cognitive outcomes in 101 older adults [11]. In terms of the QoL outcomes, there were no statistically significant or meaningful dose-response effects of aerobic exercise among the control group and the three levels of exercise volume. In Project Four-IN-onE (FINE), 64 overweight and sedentary young men were randomized to a sedentary control group, 2000 kcal/week, or 3800 kcal/week of exercise energy expenditure for

11 weeks [10]. Again, there were no differences in QoL between the exercise groups and the control group or between the two exercise volumes. Overall, these data suggest limited support for a dose-response effect of aerobic exercise on QoL and psychosocial outcomes in nonclinical adult populations.

There are several possible explanations for the limited support for dose-response effects of aerobic exercise on QoL and psychosocial outcomes in nonclinical adult populations. First, higher doses of aerobic exercise may only produce modest additional improvements in the proposed biological and physiological mechanisms of improved psychosocial outcomes such as endorphins, monoamine neurotransmitters, cerebral blood flow, cardiovascular fitness, muscular strength, or body composition. For example, in the BETA Trial, the high volume group only improved VO_{2max} by 1.1 ml/kg/min more than the moderate volume group and only lost an additional 1.0 kg of body fat [12]. Second, the lower volume exercise interventions are likely sufficient to address many of the psychosocial explanations for improved QoL and psychosocial outcomes such as increased social interaction, behavioral activation, expected benefits, distraction from daily worries, sense of achievement, and positive feedback from others [29]. Third, most dose-response aerobic exercise trials have increased the exercise dose by increasing session duration, rather than intensity or frequency, which may be less likely to improve the biological or physiological mechanisms [30–33] and, paradoxically, may actually increase boredom. Dose-response exercise trials based on increasing intensity (continuous or interval) or frequency are needed to address this question. Interestingly, Norris et al. [34] recently reported a pilot study suggesting that 3 days/week compared to 2 days/week of resistance training may actually blunt psychosocial outcomes in prostate cancer survivors (i.e., a negative dose-response effect for frequency). Finally, BETA participants were not selected based on any QoL or psychosocial impairments; therefore, there may be limited room for improvements in many of the outcomes (i.e., ceiling or floor effects).

Most trials showing that exercise improves QoL and psychosocial outcomes in adults have compared an exercise intervention to no intervention [1–6]. Comparing exercise to nothing maximizes differences in all of the proposed mechanisms of psychosocial benefit. It is also possible that most or all of the QoL and psychosocial benefits of exercise are based on doing some exercise rather than none at all. Nevertheless, most exercise trials have compared at least the recommended volume of exercise (i.e., ≥150 min/week of moderate intensity exercise) to no exercise raising the possibility that a fairly large volume of exercise is needed for improved QoL and psychosocial functioning [1–6]. Interestingly, in the BETA Trial, the overall effects of both exercise volumes compared to baseline were mixed. There were overall improvements in physical functioning, vitality, general health, subjective sleep quality, self-esteem, and health transition; however, there were overall declines in role-physical, bodily pain, social functioning, and the physical component score. It is possible that the demanding nature of the exercise interventions (i.e., 5 days/week, moderate-to-vigorous intensity, 30 or 60 min) over a 1-year period induced some bodily pain which may have influenced overall changes in QoL, sleep quality, and psychosocial functioning.

Our primary prespecified moderator in the BETA Trial was patient preference for group assignment. Patient preference for group assignment is a potentially important but often ignored factor in unblinded trials [35]. Participants assigned to their non-preferred intervention may

suffer “resentful demoralization” or have a negative placebo response (i.e., expectation of less benefit), resulting in lower adherence and/or a negative psychosocial response to the intervention [35]. Participants assigned to their preferred intervention may have higher expectations of benefit (i.e., a placebo effect) or they may be better matched to the intervention [35]. Few exercise RCTs have examined patient preference effects in any population [36, 37]. In the Supervised Trial of Aerobic versus Resistance Training (START), we found that breast cancer patients who preferred resistance training improved quality of life when assigned to RET whereas patients with no preference improved quality of life when assigned to aerobic exercise [13]. In the BETA Trial, we found no evidence that participant preference for a given exercise volume moderated any of the dose-response effects of exercise on patient-reported outcomes. These data suggest that allowing postmenopausal women to choose their preferred exercise volume will not necessarily result in greater QoL or psychosocial improvements.

The only evidence for possible moderation in the BETA Trial was for marital status and obesity with respect to sleep quality. Specifically, unmarried women benefited from the high volume program compared to the moderate volume program by about 1.5 points (a standardized effect size *d* of about 0.43) whereas married/common law women did not experience any benefit. It is possible that unmarried women may benefit more from the high volume intervention because they are less likely to have a bed partner who may interfere with the beneficial effects of exercise. It is also possible that unmarried women benefited more from the social aspects of the exercise intervention (i.e., social interactions with the trainers and other participants) because of less social support at home. Some of our previous exercise trials in breast cancer patients undergoing chemotherapy [13] and lymphoma patients [25] have shown that unmarried patients experience greater improvements in quality of life in response to the exercise intervention. Finally, it is possible that unmarried women benefit more from an intervention because they report more sleep problems [38, 39]; however, that was not the case in our study with no baseline differences in sleep quality between married and unmarried women ($p = 0.58$).

We also found a trend that obese women improved sleep quality with the high volume exercise program but nonobese women did not. Specifically, obese women improved their sleep quality by about 0.9 points, equivalent to a standardized effect size *d* of about 0.25. It is possible that obese women benefitted more from the high volume program because they have worse sleep quality to begin with and more room for improvement [40–44]; however, there was only a trend towards worse sleep quality for obese women at baseline in our study ($p = 0.12$). It is also possible that they benefited more because they experienced greater weight loss that may be tied to improved sleep quality [40–44]. In the BETA Trial, we found a significant interaction between obesity and weight loss such that obese women lost 2 kg of weight more with the high volume program whereas nonobese women showed no dose-response effect for weight loss. Nevertheless, given the large number of analyses, it is possible that both of these interactions are chance findings.

The strengths of the BETA trial are that it is one of the few dose-response exercise trials in postmenopausal women, the exercise intervention was 1 year long and mostly supervised, adherence in both groups was excellent, loss-to-follow-up was minimal, the sample size was large, and we had comprehensive and validated measures of QoL, sleep quality, and psychosocial outcomes. The limitations of BETA include the highly select population based on

education, ethnicity, and health status that restricts the generalizability of the findings; the fact that the women were not selected based on poor QoL or psychosocial functioning; and the large number of analyses which increases the chances of false positive findings.

In summary, the BETA Trial showed that a higher volume of aerobic exercise, approximately double the minimum public health guideline, did not provide any additional QoL or psychosocial benefits in inactive postmenopausal women compared to the minimum public health guideline, even for women who preferred the higher volume program. Nevertheless, higher doses of aerobic exercise derived by increasing session duration may produce other health benefits for postmenopausal women including fat loss, improved cardiorespiratory fitness, and lower risk of breast cancer and other chronic diseases [12]. Future trials may examine the dose-response effects of aerobic exercise on patient-reported outcomes by manipulating intensity or frequency.

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Author notes

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with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.