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

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Context Low levels of cardiorespiratory fitness are associated with high risk of mortality, and improvements in fitness are associated with reduced mortality risk. However, a poor understanding of the physical activity–fitness dose response relation remains.

Objective To examine the effect of 50%, 100%, and 150% of the NIH Consensus Development Panel recommended physical activity dose on fitness in women.

Design, Setting, and Participants Randomized controlled trial of 464 sedentary, postmenopausal overweight or obese women whose body mass index ranged from 25.0 to 43.0 and whose systolic blood pressure ranged from 120.0 to 159.9 mm Hg. Enrollment took place between April 2001 and June 2005 in the Dallas, Tex, area.

Intervention Participants were randomly assigned to 1 of 4 groups: 102 to the nonexercise control group and 155 to the 4-kcal/kg, 104 to the 8-kcal/kg, and 103 to the 12-kcal/kg per week energy-expenditure groups for the 6-month intervention period. Target training intensity was the heart rate associated with 50% of each woman's peak $\dot{V}O_2$.

Main Outcome Measure The primary outcome was aerobic fitness assessed on a cycle ergometer and quantified as peak absolute oxygen consumption ($\dot{V}O_2$abs, L/min).

Results The mean (SD) baseline $\dot{V}O_2$abs values were 1.30 (0.25) L/min. The mean (SD) minutes of exercising per week were 72.2 (12.3) for the 4-kcal/kg, 135.8 (19.5) for the 8-kcal/kg, and 191.7 (33.7) for the 12-kcal/kg per week exercise groups. After adjustment for age, race/ethnicity, weight, and peak heart rate, the exercise groups increased their $\dot{V}O_2$abs compared with the control group by 4.2% in the 4-kcal/kg, 6.0% in the 8-kcal/kg, and 8.2% in the 12-kcal/kg per week groups ($P<.001$ for each vs control; P for trend $<.001$). There was no treatment × subgroup interaction for age, body mass index, weight, baseline $\dot{V}O_2$abs, race/ethnicity, or baseline hormone therapy use. There were no significant changes in systolic or diastolic blood pressure values from baseline to 6 months in any of the exercise groups vs the control group.

Conclusion In this study, previously sedentary, overweight or obese postmenopausal women experienced a graded dose-response change in fitness across levels of exercise training.

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Low levels of cardiorespiratory fitness are associated with high risk of cardiovascular disease (CVD) and all-cause mortality, and improvements in fitness are associated with reduced mortality risk.[1-6] Although higher levels of fitness are associated with better CVD risk factor profiles, the fitness-CVD and all-cause mortality relation is only moderately attenuated when traditional CVD risk factors are taken into account.[1,4-6] Taken in sum, low fitness is a powerful, independent risk factor for premature mortality. Continuing to identify and refine efficient, safe, and acceptable exercise prescriptions to improve fitness is of substantial public health importance.

Even though fitness has a genetic contribution, physical activity habits are the primary determinant of fitness in adults and changes in physical activity result in changes in fitness and subsequent mortality.[2,7,8] Previous reports have combined the findings of different studies to create dose response curves for changes in physical activity and changes in fitness.[9] However, relatively few reports have evaluated different doses of physical activ-

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ity on fitness within a single large, well-controlled study, particularly analyzing effects of the National Institutes of Health (NIH) Consensus Development Panel recommendation of engaging in at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week.[10] This recommendation is commonly used to prescribe physical activity for promoting general health and is similar to those put forth in the US Surgeon General's report on physical activity and health,[11] the Centers for Disease Control and Prevention and the American College of Sports Medicine[12] and the American Heart Association.[13]

Unanswered questions with important practical and clinical implications include: "Will sedentary individuals obtain improvements in fitness if they perform less than 30 minutes of physical activity on most days of the week?" and "If individuals perform more physical activity than this recommendation, will they obtain greater (or proportionally greater) improvements in fitness?" Given the strong inverse relation between fitness and mortality, having a better understanding of the physical activity–fitness dose-response relation is important, particularly for populations with CVD or type 2 diabetes and for those at high risk for these and other chronic diseases.

More than 1 in 3 US women are postmenopausal, and CVD is the primary cause of death among women of postmenopausal age.[14,15] Among women in the postmenopausal age range, 30% report no physical activity at all, and the prevalence of inactivity progressively increases with age.[16] This may in part explain the observation that fitness levels decline 1% to 2% per year during the postmenopausal years.[17] However, physiological changes associated with aging may decrease the body's ability to maintain or improve fitness.[17] Although working to increase physical activity and improve fitness levels in this age group should be a national public health priority, there is a need to better understand the expected gains in fitness for specific doses of physical activity. The primary aim of the Dose-Response to Exercise in postmenopausal Women (DREW) trial was to examine the effect of 50%, 100%, and 150% of the NIH Consensus Panel physical activity recommendation on cardiorespiratory fitness in sedentary, overweight or obese postmenopausal women with elevated blood pressure.

METHODS

Study Design

A complete description of DREW design and methods has been published.[18] In brief, the study was a randomized, dose-response exercise trial with a no-exercise control group and 3 exercise groups with incrementally higher doses of energy expenditure. The research protocol was reviewed and approved annually by The Cooper Institute's institutional review board, and written informed consent was obtained from all participants prior to their joining the study.

Study Participants

We conducted a total of 4545 telephone screening interviews between April 2001 and June 2005 (FIGURE 1). After providing written informed consent, 464 postmenopausal women aged 45 to 75 years who were sedentary (not exercising $>$20 minutes on $\geq$3 d/wk, and taking $<$8000 steps/d assessed over the course of 1 week), overweight or obese (body mass index of 25.0-43.0; body mass index is calculated as weight in kilograms divided by height in meters squared), and had a systolic blood pressure that ranged from 120.0 to 159.9 mm Hg were randomly assigned to 1 of the 4 groups. Exclusion criteria included history of stroke, heart attack, or any serious medical condition that prevented participants from adhering to the protocol or exercising safely. Participants were recruited using a wide variety of techniques, including newspaper, radio, television, mailers, community events, and e-mail distributions.

Nonexercise Control

Women in the nonexercise control group were asked to maintain their level of activity during the 6-month study period. All participants were asked to record their daily steps (see below) and complete monthly medical symptoms questionnaire forms.

Exercise Training

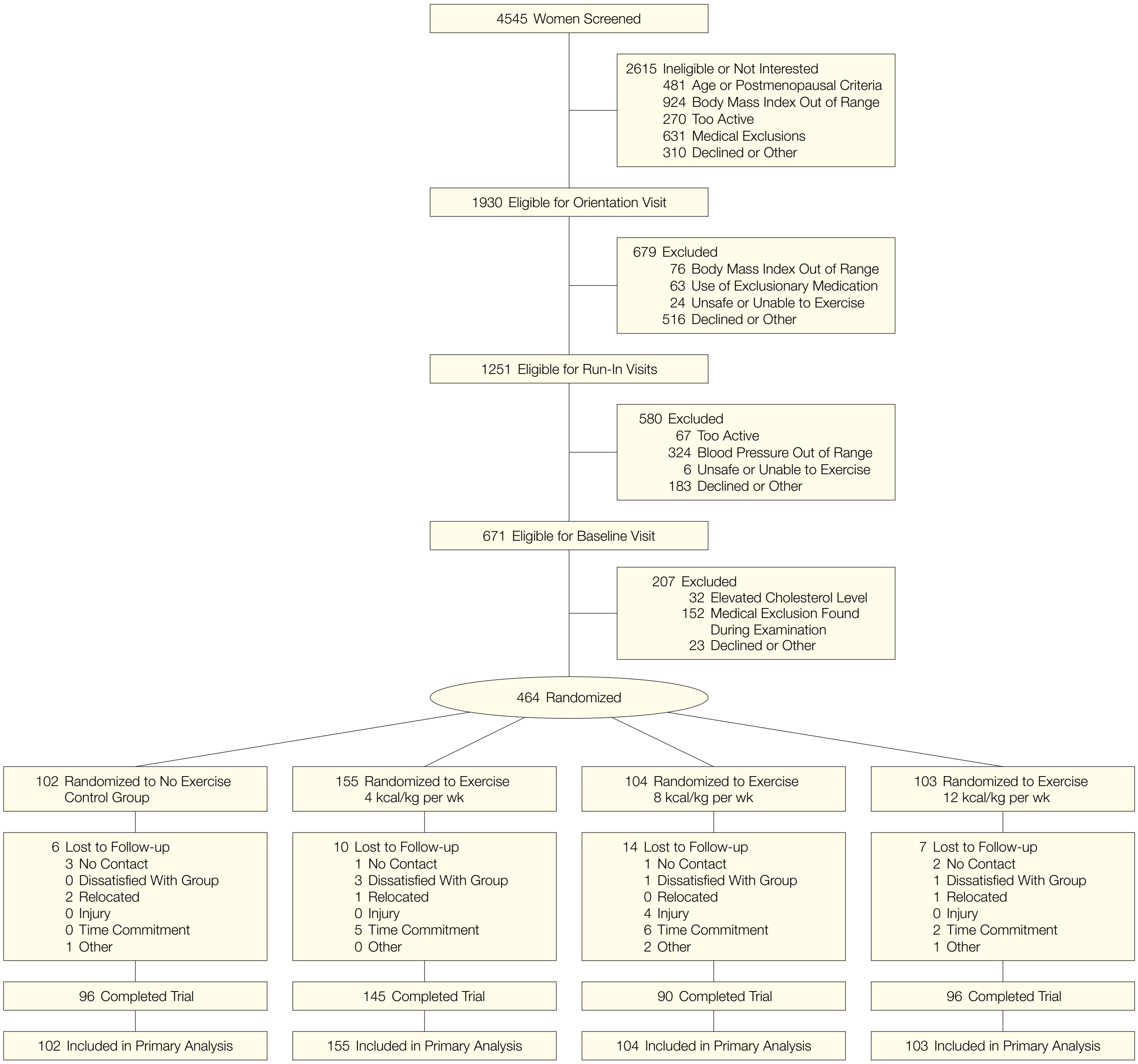
We calculated the exercise energy expenditure for women in the DREW age range associated with meeting the consensus public health recommendation from the NIH and other organizations.[10,11] We used data from sedentary women recruited for previous exercise trials conducted by our group, and also from our large cohort study.[1,2,19,20] We estimated that the typical sedentary postmenopausal woman who started an activity program and followed the consensus public health recommendation would expend 8 kcal/kg per week in the exercise program. Details of these calculations are presented in the DREW design and methods report.[18] A major objective of DREW was to evaluate exercise levels 50% below and 50% above the current public health recommendations to test whether the lower dose provides any benefit and whether the higher dose provides proportionally more benefit than the standard exercise levels of 8 kcal/kg per week. Thus, women were assigned to either a nonexercise control group or to groups that expended 4, 8, or 12 kcal/kg per week.

Exercising women participated in 3 or 4 training sessions each week for 6 months with training intensity at the heart rate associated with 50% of each woman's peak $\dot{V}O_2$. During the first week, each group expended 4 kcal/kg. Those assigned to that level continued to expend 4 kcal/kg per week for 6 months. All the other groups increased their energy expenditure by 1 kcal/kg a week until they reached level required for their group. All exercise sessions were performed under observation and supervision in an exercise laboratory with complete and strict monitoring of the amount of exercise completed in each session. Two exercise training facilities were used in this study: one in North Dallas and the other in Oak Cliff (South Dallas), Tex. Participants were weighed each week and their weight was multiplied by their exercise dosage to determine the number of calories to be expended for the week. Women in the exercise groups alternated training sessions on semirecumbent cycle ergometers and treadmills. Adherence to exercise training during the entire 6-month period was calculated for each individual by dividing the kilocalories expended during the exercise training by the kilocalories prescribed for the training period × 100%.

Outcomes

The primary outcome for assessing change in fitness was peak absolute oxygen consumption ($\dot{V}O_2$abs, L/min). Secondary fitness outcomes included peak relative oxygen consumption (mL/kg per minute; $\dot{V}O_2$rel) and peak power output quantified in watts (Wpeak). Maximal metabolic equivalent tasks (METs) achieved during testing were derived by dividing peak relative oxygen consumption by 3.5 (1 MET is defined as the energy expended at rest, which is equivalent to body oxygen consumption of 3.5 mL/kg per minute).

Figure 1. Participant Flow Diagram



Fitness Testing

Fitness testing was conducted using a Lode Excalibur Sport cycle ergometer (Groningen, the Netherlands), an electronic, rate-independent ergometer. Participants cycled at 30 W for 2 minutes, 50 W for 4 minutes, followed by increases of 20 W every 2 minutes until they could no longer maintain a pedal cadence of 50 rpm. Respiratory gases were measured using a Parvomedics True Max 2400 Metabolic Measurement Cart. Volume and gas calibrations were conducted before each test. Gas-exchange variables ($\dot{V}O_2$, CO_2 production, ventilation, and respiratory exchange ratio [RER]) were recorded every 15 seconds. Heart rate was measured directly from the electrocardiographic monitoring system. Ratings of perceived exertion were obtained using the 20-point Borg scale. Two fitness tests were performed on separate days at baseline and follow-up.

Daily Physical Activity and Other Measures

To assess potential changes in nonsupervised physical activity, all participants wore a step counter (Accusplit Eagle, Japan) to record their daily steps. Exercisers removed the step counter during supervised exercise sessions. Weight was measured on an electronic scale (Siemens Medical Solutions, Malvern, Pa), and height was measured using a standard stadiometer. Smoking history and medication use were assessed by a detailed questionnaire. Diet was assessed by the Food Intake and Analysis System semiquantitative food frequency questionnaire.[21] Blood pressure was measured after a 30-minute rest period using a Colin STBP-780 automated blood pressure unit with participants in the recumbent position. A minimum of 4 blood pressure measurements were taken 2 minutes apart.

Participant Retention and Adherence

To reduce participant dropout and maintain adherence, several strategies were used including a 2-week prerandomization run-in period, behavioral contracts, and consistent support from staff members. Participants were reimbursed \$150 (\$75 each) for completion of baseline and follow-up assessments. Participants could earn another \$350 in incentives based on adherence. For the control group, adherence was based on returning monthly step-count forms and medical symptoms questionnaires. For each month missed, \$50 was deducted from the \$350 incentive. For the exercise groups, the \$350 was reduced by \$50 for each week of missed sessions beyond the 90% adherence target.

Although this incentive is a substantial amount, it was considered appropriate because the study objective was to evaluate the dose-response effects of exercise. For this reason, excellent adherence to both intervention and measurement is necessary. If DREW were testing the effectiveness of an exercise intervention as a public health strategy, such a payment would not be appropriate. However, DREW was not testing whether financial incentives encourage individuals to exercise; rather, it was evaluating specific responses to various doses of exercise.

Blinding

There were distinct and separate intervention and assessment teams and all assessment staff were blinded to participant randomization assignment. The exercise testing and exercise training laboratories were on separate floors of the building. We regularly reminded participants not to discuss their randomization assignments with assessment team members.

Randomization

Eligible participants were randomly assigned after completing run-in and baseline assessments. The randomization sequence was computer generated. The sequence was determined from randomly permuted blocks of equal length with fixed numbers of treatment allotments each, to balance treatment enrollments over time. Randomization was implemented with treatment assignment letters placed into sequentially numbered, opaque envelopes sealed by the statistician.[18]

Statistical Analysis

Statistical power considerations were reported previously.[18] The calculations assumed 10% of participants would drop out over 6 months and 15% of partial adherers who would gain half the benefit of fully adherent exercisers. Extra participants were allotted to the 4-kcal/kg per week condition to increase power for smaller anticipated fitness gains in this group. Statistical power was estimated to range from 85% to 99% for detecting fitness increases ranging from 7% to 15% tested at 5% significance and 97% for testing a linear dose-response trend across exercise levels.

We anticipated reductions of 5, 7, and 9 mm Hg in systolic blood pressure at 6 months across the 3 increasing dose levels and a change score SD of 9 mm Hg. We computed the statistical power to be 0.84 for the 4-kcal/kg, 0.98 for the 8-kcal/kg, and 0.99 for the 12-kcal/kg per week groups for significant reductions in systolic blood pressure compared with those in the control group. The test for a significant dose response trend across the 3 exercise groups has power of 85%.

Fitness was defined as the mean of 2 exercise test assessments at both baseline and 6 months. The reproducibility of the 2 fitness tests ($\dot{V}O_2$abs) was examined and characterized by an intraclass correlation of 0.88 at both baseline and follow-up testing. Mean systolic and diastolic blood pressures were calculated from all available measures ($\geq$3) with the first measured value discarded. Descriptive baseline characteristics of groups were tabulated as mean (SDs) or as percentages but were not tested for differences. Mean step data were calculated per month for each group. Between-group differences were tested using analysis of covariance without adjustment and within-group differences were tested using *t* tests.

Differences in primary and secondary outcomes among the randomization groups were tested by analysis of variance with adjustment for select prespecified covariates. For statistically significant analyses of variance ($P<.05$), all pairwise comparisons among the groups were tested using Tukey studentized range adjustment. Results are presented as adjusted least-squares means with confidence intervals (CIs). We defined elevated systolic blood pressure as 140 mm Hg or higher and calculated the prevalence of elevated systolic blood pressure in each randomization group at baseline and follow-up. Between-group differences at baseline and follow-up in prevalence were examined using χ^2 tests and within-group differences in prevalence of elevated systolic blood pressure between baseline and follow-up were examined using the McNemar test.

Subgroup analyses compared dose-response effects across predefined baseline groups with significance of interactions assessed by the multiple regression. We conducted all analyses using the intent-to-treat principle; if the outcome value was missing for the participant, we inserted the baseline value for that outcome (ie, last observation carried forward). For exploratory purposes, all fitness outcomes were tested using only available data, without using baseline values carried forward for missing follow-up data. There were no substantive differences in any of the fitness outcomes findings compared with the analyses with baseline values carried forward; therefore, only the primary analyses are presented. All reported P values are 2-sided. All analyses were performed using SAS version 9.0 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 464 randomized participants, 427 returned for follow-up testing (92.0%). The return for follow-up across groups ranged from 86.5% to 94.1% (Figure 1). The 4 individuals who dropped out of the study because of injury were in the 8-kcal/kg per week group. Of those 4 injuries, one was an acute job-related injury that prevented exercise; the other 3 had preexisting conditions (chronic back pain, torn knee ligament, and arthritis of knee) exacerbated by exercising.

As summarized in **TABLE 1**, the mean (SD) age of the study population was 57.3 (6.4) years; the mean (SD) educational achievement was 14.0 (2.1) years; and the mean (SD) body mass index was 31.8 (3.8). About 35% were nonwhite. Although the mean (SD) baseline systolic blood pressure was high (139.8 [12.9]) in our sample, baseline low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and fasting glucose levels were within acceptable clinical ranges. Despite a mean (SD) respiratory exchange ratio of 1.13 (0.07) suggesting that maximal effort was obtained during exercise testing, the mean $\dot{V}O_2$abs and $\dot{V}O_2$rel values were very low at 1.30 (0.25) L/min and 15.5 (2.8) mL/kg per min, respectively, documenting a very low-fit group at baseline.

TABLE 2 presents the exercise training data excluding the initial ramping period for all individuals with fol-

Table 1. Baseline Participant Characteristics*

			Exercise Groups		
Characteristics	All (N = 464)	Control (n = 102)	4 kcal/kg (n = 155)	8 kcal/kg (n = 104)	12 kcal/kg (n = 103)
Age, mean (SD), y	57.3 (6.4)	57.2 (5.8)	57.7 (6.6)	57.3 (6.6)	56.6 (6.6)
Education, mean (SD), y	14.0 (2.1)	14.0 (2.0)	13.8 (2.0)	14.4 (2.0)	14.0 (2.3)
Ethnicity/race, No (%)					
White	299 (64.5)	67 (65.7)	94 (60.6)	63 (60.6)	75 (72.8)
African American	137 (29.5)	25 (24.5)	52 (33.6)	34 (32.7)	26 (25.3)
Hispanic or other	28 (6.0)	10 (9.8)	9 (5.8)	7 (6.7)	2 (1.9)
Current cigarette smoking, No (%)	25 (5.3)	5 (4.9)	9 (5.8)	4 (3.9)	7 (6.8)
Medication use, No. (%)					
Blood pressure	132 (28.6)	25 (24.8)	42 (27.1)	33 (32.0)	32 (31.1)
Cholesterol	76 (16.5)	16 (15.8)	31 (20.0)	17 (16.5)	12 (11.7)
Thyroid	71 (15.4)	16 (15.8)	19 (12.2)	16 (15.5)	20 (19.4)
Antidepressant	84 (18.2)	18 (17.8)	29 (28.7)	18 (17.5)	19 (18.4)
Current hormone therapy	209 (45.0)	52 (51.0)	67 (43.2)	44 (42.3)	46 (44.6)
Energy intake, mean (SD), kcal/d	2238 (973)	2238 (961)	2184 (962)	2251 (966)	2306 (1019)
Cardiovascular disease factors, mean (SD), mg/dL					
Cholesterol					
Low-density lipoprotein	118.3 (26.3)	118.5 (26.5)	117.1 (26.9)	117.9 (25.2)	120.5 (26.3)
High-density lipoprotein	57.4 (14.6)	57.3 (15.3)	57.9 (14.6)	56.7 (15.0)	57.6 (13.7)
Triglycerides	129.5 (63.4)	133.3 (67.8)	130.0 (59.1)	129.9 (58.5)	124.6 (70.0)
Fasting glucose	95.0 (9.1)	96.3 (10.3)	94.4 (8.6)	94.5 (9.2)	95.1 (8.4)
Blood pressure, mean (SD), mm Hg					
Systolic	139.8 (12.9)	141.8 (12.0)	139.1 (13.1)	140.0 (13.3)	138.3 (12.8)
Diastolic	81.0 (8.4)	81.1 (7.8)	81.0 (9.0)	81.1 (8.2)	80.8 (8.6)
Anthropometrics, mean (SD)					
Weight, kg	84.5 (11.9)	85.9 (12.4)	83.7 (11.3)	85.1 (12.8)	83.9 (11.2)
Body mass index*	31.8 (3.8)	32.3 (3.9)	31.6 (3.8)	32.1 (4.1)	31.3 (3.6)
Body fat, %	28.8 (4.8)	30.7 (5.4)	27.5 (4.0)	29.0 (4.8)	28.6 (4.8)
Waist circumference, cm	100.9 (11.7)	102.6 (11.9)	100.0 (11.1)	101.5 (12.4)	99.6 (11.7)
Exercise test variables, mean (SD)					
Maximal heart rate, beats/min	151.2 (16.4)	150.2 (16.4)	150.6 (17.1)	151.2 (15.3)	153.1 (16.6)
Respiratory exchange ratio	1.13 (0.07)	1.12 (0.06)	1.13 (0.08)	1.13 (0.07)	1.14 (0.07)
Peak absolute $\dot{V}O_2$, L/min	1.30 (0.25)	1.33 (0.27)	1.29 (0.24)	1.26 (0.24)	1.33 (0.24)
Peak relative $\dot{V}O_2$, mL/kg per minute	15.5 (2.8)	15.6 (2.9)	15.5 (2.9)	14.9 (2.4)	16.0 (2.9)
Maximal power output, W	94.7 (20.9)	96.1 (22.0)	93.8 (20.3)	91.4 (20.7)	98.0 (20.8)

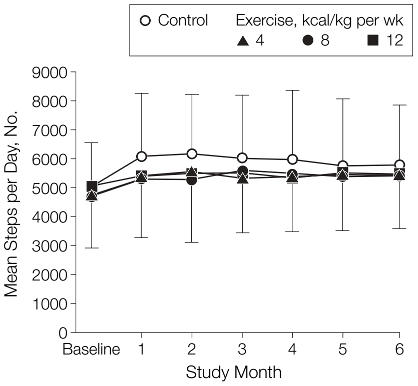
Abbreviation: $\dot{V}O_2$, volume of oxygen consumed.
SI conversions: To convert low-density lipoprotein and high-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; and fasting glucose to mmol/L, multiply by 0.0555.
*Calculated as weight in kilograms divided by height in meters squared.

Table 2. Descriptive Training Data for Individuals Who Completed the Exercise Intervention*

	Exercise Groups		
	4 kcal/kg	**8 kcal/kg**	**12 kcal/kg**
Prescribed energy expenditure, kcal/wk†	335 (45)	681 (102)	1006 (132)
Time exercise, min/wk‡	72.2 (12.3)	135.8 (19.5)	191.7 (33.7)
Average METs per session‡			
Cycle ergometer	3.8 (0.4)	3.8 (0.3)	3.9 (0.4)
Treadmill	3.1 (0.6)	3.3 (0.6)	3.5 (0.8)
Sessions/wk‡	2.6 (0.3)	2.8 (0.4)	3.1 (0.5)
6-mo adherence, %			
All	94.6 (16.6)	89.0 (25.6)	93.3 (20.3)
Completers	98.0 (8.4)	97.8 (7.7)	97.4 (11.0)

Abbreviation: METs, metabolic equivalents (1 MET = 3.5 mL O_2 uptake/kg per minute).
*All data are presented as mean (SD).
†Data for all participants and based on baseline weight.
‡Data for all individuals who completed the intervention. Data are for exercise training period excluding the initial ramping period which represents 6 months of data for the 4-kcal/kg, 5 months for the 8-kcal/kg, group, and 4 months for the 12-kcal/kg week groups. Adherence was calculated for each individual by dividing the kilocalories expended during the 6-month exercise training by the kilocalories prescribed for the training period × 100%.

Figure 2. Mean Steps per Day During Study Months



Participants With Complete Step Data

Control	101	80	78	77	76	76	73
Exercise, kcal/kg per wk							
4	150	126	123	117	115	114	104
8	104	85	84	79	78	77	72
12	103	90	85	85	83	78	74

The mean steps calculations do not include steps accumulated during supervised exercise. The upper errors bars indicate 95% confidence intervals for the control group and the lower error bars for the 4-kcal/kg per week group. At baseline there were no differences in groups. All groups had a significant increase in steps from baseline to month 1 ($P<.05$ for each). At months 1, 2, 3, and 4, the control group had a greater number of steps than 1 or more of the exercise groups ($P<.05$ for each), but by months 5 and 6, there were no differences between any groups.

low-up testing data. This represents 6 months of data for the 4-kcal/kg per week group, the last 5 months for the 8-kcal/kg per week group, and the last 4 months for the 12-kcal/kg per week group. The 4-kcal/kg per week exercise group obtained a mean (SD) 72.2 (12.3) minutes per week over 2.6 (0.3) sessions; the 8-kcal/kg per week group, 135.8 (19.5) minutes per week during 2.8 (0.4) sessions; and the 12-kcal/kg per week group, 191.7 (33.7) minutes per week during 3.1 (0.5) sessions. The average METs during the cycle ergometer training was similar across groups at approximately 3.8. During the treadmill training, the mean (SD) METs were 3.1 (0.6) for the 4-kcal/kg, 3.3 (0.6) for the 8-kcal/kg, and 3.5 (0.8) for the 12-kcal/kg groups.

Exercise adherence across randomization groups, defined as the percentage of expended calories with respect to prescribed expended calories for the entire 6-month intervention period, ranged from a low of 89.0% in the 8-kcal/kg group to a high of 94.6% in the 4-kcal/kg group when all participants were examined. The adherence increased to more than 97% for all groups when only study completers were examined. Adherence rates did not differ significantly across treatment groups, age groups, or various racial/ethnic groups.

As depicted in FIGURE 2, at baseline all randomization groups had similar mean daily steps of approximately 5000 (range, 4741-5039). Compared with baseline, all groups had higher mean daily steps at month 1 with a range of 5291 to 5377 steps for the 3 exercise groups and a mean value of 6063 for the control group ($P<.05$ for each vs baseline). Furthermore, at month 1 the control group had more steps per day than the 3 exercise groups ($P<.05$ for each). However, by the fifth and sixth months, there were no statistically significant differences in the 4 groups. For the 3 exercise groups, there was no difference in mean daily steps for months 1 through 6.

TABLE 3 presents the primary and secondary outcome measures after intervention. All values represent the adjusted least-squares means. All measures were adjusted for baseline value, age, and ethnicity/race. The fitness measures were adjusted for baseline weight and maximal heart rate at baseline and follow-up testing. For all 3 fitness measures, each exercise dose had a significantly higher value than the control at follow-up ($P<.001$ for each). Furthermore, the linear trend across exercise groups was significant ($P<.001$) for all 3 measures of fitness. There were no differences in weight or body fat percent across the groups at follow-up but waist circumference was significantly smaller in all 3 exercise groups compared with the control group ($P<.05$ for each). There was no difference in any of the CVD risk factors across groups at follow-up. The mean (SD) energy intake at follow-up was 1970 (791) for the control group and 1879 (727) for the 4-kcal/kg, 2041 (937) for the 8-kcal/kg, and 1960 (803) for the 12 -kcal/kg per week groups, with $P=.56$ for between-group differences.

TABLE 4 presents the changes in blood pressure variables and blood pressure medication use. In an analysis adjusted for baseline value, age, ethnicity/race, change in weight, and blood pressure medication use, the analysis of variance was significant for systolic blood pressure ($P=.03$), but the only between-group difference was found in comparing the 4-kcal/kg per week group with the 12-kcal/kg per week group ($P=.02$). None of the exercise groups had significant changes in systolic blood pressure compared with the control group. The only significant within-group change (−3.3 mm Hg) in blood pressure was found in the 12-kcal/kg per week group ($P=.003$). There were no significant between-group differences in diastolic blood pressure.

The results were similar when the study population was limited to individuals who did not change blood pressure medications during the study and when limited to those who did not use blood pressure medications during the study. Although there were no significant between-group differences in the prevalence of systolic blood pressure of 140 mm Hg or higher at baseline or follow-up, in both the control (54.9% vs 43.1%, $P=.05$) and the 12-kcal/kg per week (48.5 vs 36.9%, $P=.01$) groups, the prevalence at follow-up was significantly lower than at baseline. There was no statistically significant ($P=.07$) difference in changes in blood pressure medication use across the randomization groups.

FIGURE 3 summarizes the percent change for mean $\dot{V}O_2$abs, $\dot{V}O_2$rel, and Wpeak. All values represent the least-squares means adjusted for age, ethnicity/race, weight, and peak heart rate. Compared with the control group, the $\dot{V}O_2$abs increased by 4.2% in the 4-kcal/kg, 6.0% in the 8-kcal/kg, and 8.2% in the 12-kcal/kg per week groups. Percent change across groups was similar for $\dot{V}O_2$rel: 4.7% for the 4-kcal/kg, 7.0% for the 8-kcal/kg, and 8.5% for the 12-kcal/kg per week groups. Compared to the control groups, peak power output (in Wpeak) increased by 7.6% in the 4-kcal/kg, 10.7% in the 8-kcal/kg, and 12.9% in the 12-kcal/kg per week groups. *P* values for pairwise comparisons of control with the each exercise group were significant ($P<.001$) for each measure of fitness. Linear trends across exercise groups were significant ($P<.001$) for all 3 measures of fitness.

FIGURE 4 depicts the change in fitness across exercise groups within the subgroups of age, body mass index, weight, baseline $\dot{V}O_2$abs, ethnicity/race, and baseline hormone therapy use. The data points represent the least squares mean change by subgroup and treatment condition adjusted for baseline $\dot{V}O_2$abs, age, ethnicity/race, weight, and peak heart rates. None of the *P* values for the treatment × subgroup interactions were significant, suggesting

Table 3. Primary and Secondary Outcome Measures After Intervention*

Characteristics	Control (n = 102)	Exercise Groups 4 kcal/kg (n = 155)	8 kcal/kg (n = 104)	12 kcal/kg (n = 103)	P Value†
Fitness variables					
Peak absolute $\dot{V}O_2$, L/min	1.28 (0.01)	1.33 (0.01)	1.35 (0.01)	1.39 (0.01)	<.001‡
Peak relative $\dot{V}O_2$, mL/kg per min	15.5 (0.13)	16.2 (0.11)	16.4 (0.13)	16.8 (0.13)	<.001§
Maximal power output, W	93.4 (0.9)	99.6 (0.7)	101.2 (0.9)	105.4 (0.9)	<.001‡
Anthropometrics					
Weight, kg	83.7 (0.3)	83.3 (0.3)	82.9 (0.3)	83.3 (0.3)	.39
Body fat, %	29.8 (0.5)	28.1 (0.4)	28.3 (0.5)	28.6 (0.5)	.08
Waist circumference, cm	101.2 (0.7)	98.1 (0.5)	98.6 (0.7)	98.2 (0.7)	.002∥
Cardiovascular disease risk factors					
Cholesterol					
LDL	122.3 (2.0)	121.3 (1.6)	119.3 (2.0)	120.2 (2.0)	.71
HDL	57.2 (0.7)	57.2 (0.6)	57.1 (0.7)	56.0 (0.7)	.56
Triglycerides	135.2 (6.1)	122.7 (4.9)	126.0 (6.0)	132.9 (6.1)	.35
Fasting glucose	95.8 (0.7)	94.0 (0.6)	93.6 (0.7)	93.4 (0.7)	.05

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; $\dot{V}O_2$, volume of oxygen consumed.

SI conversions: To convert LDL and HDL to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; fasting glucose to mmol/L, multiply by 0.0555.

*Values are expressed as fitted mean (SE) and all are adjusted for baseline value, age, and ethnicity/race with the fitness variables also adjusted for baseline weight and maximum heart rate during exercise testing at baseline and follow-up.

†*P* values for difference between groups, determined by analysis of variance. For a given outcome measure when the analysis of variance (last column) was statistically significant ($P<.05$), all pairwise comparisons among groups were tested for statistical significance using Tukey studentized range test. Pairwise comparisons that were significantly different from one another are indicated in the following footnotes.

‡All pairwise comparisons significant except 4-kcal/kg vs 8-kcal/kg per week groups.

§All pairwise comparisons were statistically significant except 4-kcal/kg vs 8-kcal/kg per week groups and 8-kcal/kg vs 12-kcal/kg per week groups.

∥All exercise groups were statistically significant vs control, but no significant differences existed between any exercise groups.

Table 4. Change in Blood Pressure Variables and Blood Pressure Medication Use*

Characteristics	Control (n = 102)	Weekly Energy Expenditure 4 kcal/kg (n = 155)	8 kcal/kg (n = 104)	12 kcal/kg (n = 103)	P Value†
Change in blood pressure, mean (SE), mm Hg					
Systolic	−1.7 (1.1)	0.8 (0.9)	−1.0 (1.1)	−3.3 (1.1)†	.03
Diastolic	−0.5 (0.6)	0.9 (0.5)	0.1 (0.6)	−0.4 (0.6)	.29
Systolic blood pressure ≥140 mm Hg, No. (%)‡					
Baseline	56 (54.9)	74 (47.7)	53 (51.0)	50 (48.5)	.70
Follow-up	44 (43.1)	74 (47.7)	44 (42.3)	38 (36.9)	.39
P value	.05	>.99	.09	.01	
Changes in blood pressure medication use during study, No. (%)§					
No change	83 (94.3)	125 (94.0)	75 (88.3)	78 (87.6)	.07
Started	2 (2.3)	5 (3.8)	8 (9.4)	3 (3.4)	
Discontinued	3 (3.4)	3 (2.3)	2 (2.3)	8 (9.0)	

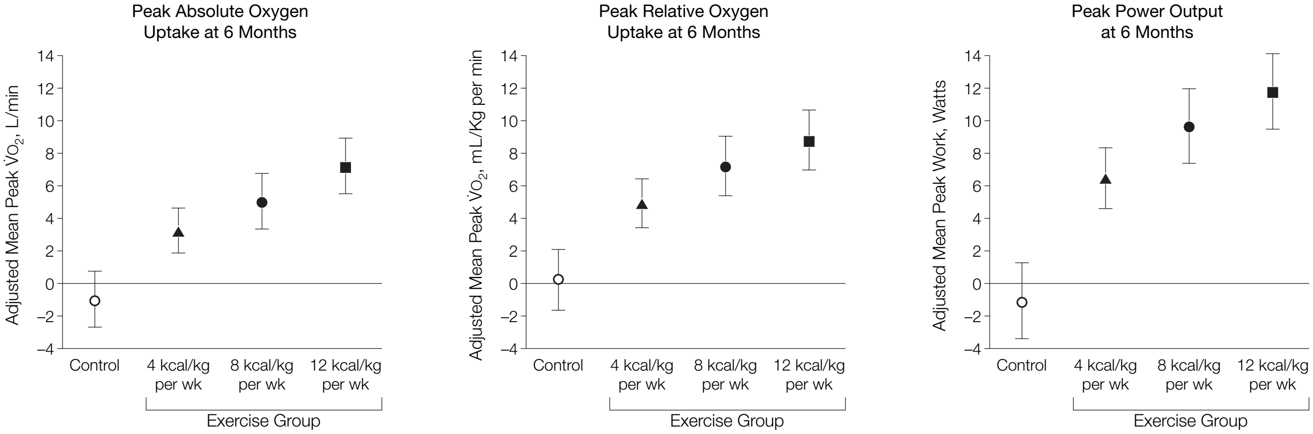
*Values are expressed as fitted mean (SE) adjusted for baseline value, age, ethnicity/race, and change in weight, blood pressure medication use at baseline and follow-up. *P* values are for group differences assessed by χ^2 tests and column *P* values are for within group differences assessed by the McNemar test. Row *P* values are for differences between groups, determined by analysis of variance. For a given outcome measure when the analysis of variance (last column) was statistically significant ($P<.05$), all pairwise comparisons among groups were tested for statistical significance using Tukey studentized range test. The pairwise comparison that was significantly different is indicated in the following footnotes.

†12 kcal/kg vs 4-kcal/kg per week, $P=.02$.

‡Column *P* values are for group differences assessed by χ^2 tests and row *P* values are for within-group differences assessed by the McNemar test.

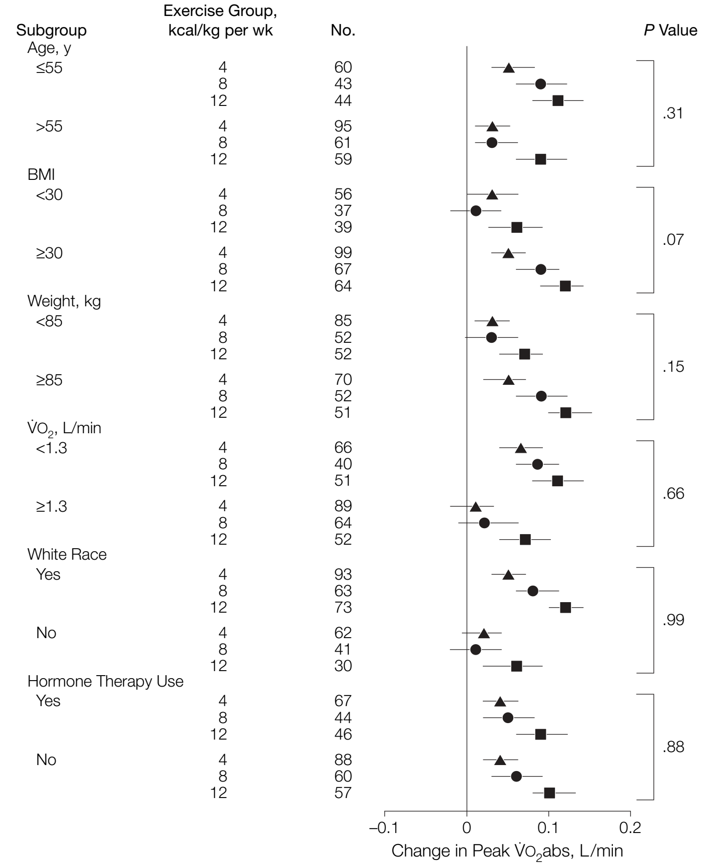
§The number of participants were 88 in the 4-kcal/kg, 133 in the 8-kcal/kg, and 85 in the 12-kcal/kg per week groups and 89 in the control group. *P* value is for differences assessed by Fisher exact test.

Figure 3. Percent Change in Fitness Data for Each Study Group



The data represent the least-squares means adjusted for age, ethnicity/race, weight, and peak heart rate. The *P* values for pairwise comparisons of control with 4-kcal/kg, 8-kcal/kg, and 12-kcal/kg per week groups are $P<.001$ for each variable. *P* for linear trend across groups $<.001$ for each outcome. Error bars indicate 95% confidence intervals.

Figure 4. Change in Peak Absolute Oxygen Uptake for Each Exercise Group



The data represent the least-squares mean change by subgroup and treatment condition adjusted for baseline value, age, ethnicity/race, weight, and peak heart rate. The specific subgroups are not adjusted for the specific variable defining the groups. For example, the age subgroup analysis is not adjusted for age. The *P* values are for treatment × subgroup interactions.

that the change in fitness across training groups was similar in all these subgroups.

COMMENT

The primary finding from this prospective, randomized, controlled exercise trial in postmenopausal women is a strong ($P<.001$) dose-response relation between the amount of exercise and change in fitness. This finding seems logical, but few reports in the literature from adequately powered studies with a tightly controlled exercise dose have evaluated the activity-fitness dose-response relation. Numerous randomized clinical trials support that accumulating at least 30 min/d of moderate-intensity physical activity on at least 5 days of the week, consistent with the 8-kcal/kg per week group in our study, has a beneficial effect on numerous physiological and clinical variables.[10,11] Observational population-based studies indicate that this same activity dose is associated with a reduced risk of several chronic diseases and with increased longevity.[22-25]

Perhaps the most striking finding of our study is that even activity at the 4-kcal/kg per week level (approximately 72 min/wk) was associated with a significant improvement in fitness compared with women in the nonexercise control group. The group exercising at 150% of the recommendation (12-kcal/kg per week) had a proportionally greater increase in fitness as compared with those in the 8-kcal/kg per week group. These improvements in fitness occurred at a modest training intensity (heart rate at 50% of peak $\dot{V}O_2$) and occurred during a time in the lifespan when fitness is decreasing at 1% to 2% per year.[17] As demonstrated by the low dropout rate and excellent adherence in all exercise groups to the 6-month caloric expenditure target in our study, the exercise prescriptions used in the DREW study were well managed by participants.

In terms of public health importance, surveys continue to show that nearly all individuals understand that there are health benefits associated with physical activity, yet approximately 1 in 5 US adults report no physical activity at all.[16,26,27] The major reason given for not engaging in more activity is lack of time.[28-30] For many years, the primary view of how much activity is enough focused on vigorous activities conducted within an exercise training model. This view began to change in the mid-1990s with the development of the NIH consensus recommendation and other reports mentioned earlier.[10,11] The recommendation to obtain at least 30 minutes a day of moderate intensity physical activity most days of the week has been called into question by recent reports, which emphasize the need for physical activity of 60 minutes or more a day to prevent weight gain or re-gain after weight loss.[31,32]

Data presented in our study show that even 72 minutes of moderate-intensity physical activity per week accumulated over about 3 days has a significant effect on fitness in previously sedentary postmenopausal women. This information can be used to support future recommendations and should be encouraging to sedentary adults who find it difficult to find the time for 150 minutes of activity per week, let alone 60 minutes per day. We emphasize that we do not recommend that the public health recommendation for physical activity be lowered to less than 150 minutes a week. However, our results should be considered, along with other new evidence on exercise dose, when revised public recommendations are developed.

The mean daily step data across the entire study provided novel insight into the physical activity behavior of previously sedentary individuals who have begun a structured exercise program. It has been suggested that some individuals who increase structured exercise compensate by reducing nonexercise activity, particularly if the exercise program is time consuming. In contrast, it has been hypothesized that initiation of a structured exercise program may make a person feel more energetic, which could result in increased nonrexercise activity. We observed neither of these 2 situations, for each exercise group had no change in mean daily steps during the 6 months of exercise training, suggesting that at least in the context of a supervised exercise trial, there is minimal link between participation in a structured exercise program and nonexercise daily physical activity levels.

Our study had a large proportion of nonwhite participants (primarily African American). Both the shape of dose-response relation and magnitude of change in fitness were similar between nonwhite participants and white participants. This suggests that for a given dose of physical activity, there are no important differences in fitness responses between ethnic/racial groups. In addition, we found the physical activity-fitness dose-response relation to be similar across age, weight, baseline fitness, and hormone therapy subgroups, providing further evidence that regular physical activity has similar benefits across a variety of individuals.

Despite the changes in fitness that we observed, there were no substantial changes in many of the CVD risk factors or weight. However, given the clinically normal baseline levels of low-density lipoprotein cholesterol, triglyceride, and fasting glucose levels and the high level of high-density lipoprotein cholesterol, it is not surprising that we did not observe change in these variables. Furthermore, we observed no changes in weight or body fat percentage, which was expected because this study was not a weight loss trial and the participants were frequently informed that the objective was not weight loss and were encouraged to keep other lifestyle habits consistent from baseline throughout the study.

However, we did observe a decrease in waist circumference. It is well documented that exercise without dietary intervention has limited effectiveness in producing substantial weight loss. It is of clinical significance that despite no differences in weight across groups, all exercise groups had a reduction in waist circumference compared with controls. This finding confirms the work of others who have suggested that exercise is an effective tool in reducing waist circumference even without substantial weight loss.[33] The reduction of waist circumference is of particular clinical importance given the increased risk of insulin resistance, diabetes, metabolic syndrome, and mortality associated with excess abdominal adiposity.[34-36]

The lack of graded dose-response systolic blood pressure changes across the exercise groups is unexpected but consistent with the findings of other large exercise and blood pressure studies that have reported exercise training to have minimal benefit to systolic blood pressure.[37,38] In a recent report with a similar study population, Stewart et al[38] reported that in 55- to 75-year-old men and women (n=104) with untreated elevated blood pressure, 6 months of supervised exercise did not reduce systolic blood pressure. Stewart et al observed a 5.3-mm Hg reduction in systolic blood pressure in the exercise group, but similar to our study, they also reported a reduction of systolic blood pressure in the control group (−4.5 mm Hg), which likely prevented detection of any between-group significant differences. The −3.3 mm Hg decrease in systolic blood pressure in the 12-kcal/kg per week group in our study is similar in magnitude to exercise associated change in systolic blood pressure reported in meta-analyses by Cornelissen and Fagard[39] (−3.0 mm Hg) and by Whelton et al[40] (−3.8 mm Hg).

There are several possible reasons exercise training did not induce significant improvements in blood pressure in this population. The training intensity may have been too low and training at higher intensity may have generated a greater blood pressure response. There was no substantial weight loss associated with the exercise training, which may have blunted the benefits to blood pressure. Aging is associated with a loss of arterial elasticity and a subsequent increase in systolic blood pressure that may not be reversible in the short term by exercise alone.[41] These findings should not dampen the enthusiasm for recommending physical activity for individuals with elevated blood pressure. We previously reported that obtaining at least moderate levels of fitness is associated with lower risk for all-cause and cardiovascular disease mortality both in individuals with elevated blood pressure and in those with a diagnosis of hypertension.[42]

Strengths and Limitations

Among the strengths of the DREW study is that it is an efficacy study, using a tightly controlled exercise dose, with all exercise completed in the laboratory and extensive monitoring of exercise energy expenditure, heart rate, and steps taken outside of the structured exercise prescription. With the efficacy of the exercise dose-response demonstrated in DREW, it will be feasible to conduct effectiveness studies to evaluate the extent to which the findings can be generalized. To our knowledge, DREW is the largest single-center, controlled efficacy trial of exercise dose-response in women. Moreover, the study participants had excellent exercise adherence and a low dropout rate. Monitoring of steps per day throughout the 6-month period indicates that outside physical activity remained constant throughout the trial for all exercise groups, thus ensuring that observed group differences were due to the prescribed exercise dose. Furthermore, the exercise doses, including intensity, are easily obtainable and are well managed by sedentary women; this has important public health implications for refining physical activity recommendations in the future.

The DREW study has limitations because its sample is limited to sedentary, overweight or obese postmenopausal women at moderately high risk of CVD. Thus, we do not know if the results will apply to other women or men. However, the study sample is a group that is likely to benefit from exercise training and represents a sizeable proportion, probably a majority, of US women in the age range of 45 to 75 years. The purpose of DREW was primarily to evaluate exercise dose-response, and it was conducted in near ideal circumstances, with relatively motivated women, well-trained personnel, extensive efforts to ensure adherence, and a well-equipped exercise facility. All maximal exercise tests took place on a cycle ergometer, which was used to reduce staff burden associated with testing, decrease the risk of falling during testing, and improve quality of exercise blood pressure measures. Observations from previous studies and our own experiences suggest that cycle ergometer tests are better tolerated than treadmill tests by unfit participants. However, most of the literature on exercise and $\dot{V}O_2$max, both from observational and intervention studies, report on fitness assessed by treadmill tests, which complicates comparison of DREW data with other reports. Noncycling men and women tend to have lower $\dot{V}O_2$max on cycle ergometer vs treadmill.[43,44]

CONCLUSIONS

In this study of previously sedentary, overweight or obese postmenopausal women, there was a graded dose-response in change in fitness across levels of exercise training. The dose-response training effect was similar across subgroups based on age, weight, baseline fitness, and ethnicity.

Author Contributions: Dr Church had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Church, Earnest, Skinner, Blair.
Acquisition of data: Church, Earnest.
Analysis and interpretation of data: Church, Blair.
Drafting of the manuscript: Church, Earnest, Blair.
Critical revision of the manuscript for important intellectual content: Church, Earnest, Skinner, Blair.
Statistical analysis: Church.
Obtained funding: Skinner, Blair.
Administrative, technical, or material support: Earnest, Blair.
Study supervision: Church, Blair.
Financial Disclosures: Dr Church reports having received honoraria for lectures from scientific, educational, and community groups; serving as a consultant for Trestle Tree Inc; and having a book in publication from which he will receive royalties. Dr Blair reports receiving book royalties from Human Kinetics; honoraria for service on the Medical Advisory Boards for Matria Health Care, Magellan Health Services, and Jenny Craig; and honoraria for lectures from scientific, educational, and community groups. Dr Blair also reports that he is paid as an Executive Lecturer by the University of North Texas. He gives these fees to the University of South Carolina Educational Foundation or to other nonprofit groups, and he reports that during the past 5-year period he has received a research grant from Jenny Craig. Dr Earnest reports having received honoraria for lectures from scientific, educational, and community groups. Dr Skinner reports having received honoraria for lectures from scientific, educational, and community groups.

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