

Effect of Exercise on Insulin Sensitivity in Healthy Postmenopausal Women: The SHAPE Study

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Abstract

Background: An inactive lifestyle is a risk factor for several types of cancer. A proposed pathway through which exercise influences cancer risk is via insulin. We aim to investigate the effect of a one-year exercise intervention on insulin sensitivity, and the role of body fat in this association, in healthy, normal to overweight/obese, postmenopausal women.

Methods: In the Sex Hormones And Physical Exercise (SHAPE) study, 189 healthy, inactive and postmenopausal women [ages, 50–69 years; body mass index (BMI), 22–40 kg/m²] were randomly assigned to a one-year aerobic and strength exercise intervention (150 min/wk), or a control group. Between-group differences in fasting insulin, glucose, and homeostatic model assessment of insulin resistance (HOMA2) over time were estimated using linear mixed models.

Results: Follow-up measurements of insulin sensitivity were available for 181 (95.8%) and 182 (96.3%) women at 4 and 12

months, respectively. The intention-to-treat analysis showed no significant differences between the two study groups [treatment effect ratio of the exercise group vs. control (β ; 95% confidence interval): insulin, β , 1.07 (0.96–1.19); glucose, β , 1.01 (0.99–1.02); and HOMA2, β , 1.07 (0.96–1.20)]. Similar results were found in a per protocol analysis in compliant women, and in a subgroup of women who lost >2% body fat [measured by dual-energy X-ray absorptiometry (DEXA)].

Conclusions: Participation in a one-year aerobic and strength exercise intervention program did not result in changes in insulin sensitivity in healthy postmenopausal and inactive women.

Impact: Our findings suggest that 150 min/wk of exercise, as recommended by current guidelines, is not enough to achieve improvements in insulin sensitivity and subsequent cancer risk, in healthy postmenopausal women. *Cancer Epidemiol Biomarkers Prev*; 24(1); 81–87. ©2014 AACR.

Introduction

An inactive lifestyle is a recognized risk factor for several cancers, with the largest body of evidence for colorectal and postmenopausal breast cancer (1, 2). The mechanism through which a lack of physical activity affects cancer risk is not fully understood. A commonly proposed pathway is via a decrease in insulin sensitivity (3).

Physical activity, insulin, and cancer are closely linked in a causal network, where energy balance plays a key role (4, 5). Chronic hyperinsulinemia, as a result of a decreased insulin sensitivity, might influence cancer risk through different mechanisms, including activation of inflammatory mediators, as well as

increase of bioavailable insulin-like growth factor-I (IGFI) and increase of sex hormone levels (6).

Meta-analyses of cohort and case-control studies showed that women with diabetes mellitus have a significant 16% to 23% increase in postmenopausal breast cancer risk (7, 8) and a 26% to 35% increased risk of colon cancer (8, 9). In addition, a large case-cohort and nested case-control study found that hyperinsulinemia is an independent risk factor for breast cancer (10, 11).

For long-term and chronic effects on insulin, exercise-induced reduction of body weight and body fat plays an important role. The way by which excess body weight influences cancer risk, mediated by insulin resistance, is complex and multifactorial (12). Besides insulin mediated, obesity is also an independent risk factor for different cancer types (1, 13).

Several exercise intervention studies have investigated the effect of 6-months to 1-year endurance and/or strength training on insulin resistance in healthy postmenopausal women (14–21). Results show that aerobic exercise mainly results in improvements in insulin sensitivity but not resistance training alone that was investigated in one study (19). One of the above trials investigated three aerobic interventions varying in intensity and duration (17). The researchers found that longer total endurance exercise duration resulted in a larger improvement in insulin sensitivity. However, in the above trials, exercisers lost more weight than their controls. After adjusting for weight loss, the exercise effect disappeared in some (15, 18, 19), but not all studies (16, 17, 22).

To gain more insight in the pathways whereby physical activity influences cancer risk, and the role of body fat in this association,

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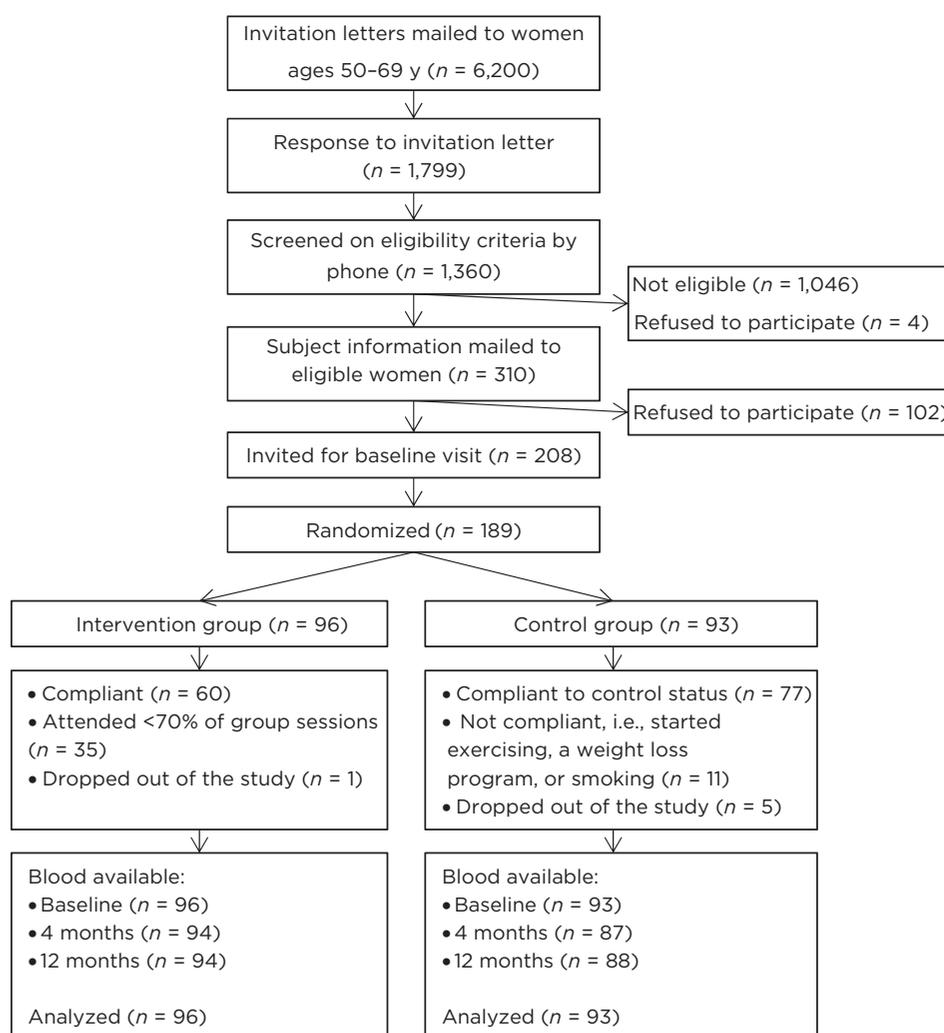


Figure 1. Flow chart of the inclusion, randomization, and retention of the SHAPE study participants.

we studied the effect of a 1-year combined aerobic and strength exercise intervention on insulin sensitivity in healthy, normal to overweight/obese, postmenopausal women. We hypothesize that exercise improves insulin sensitivity, and that this association is mainly explained by concordant loss of body fat.

Materials and Methods

The Sex Hormones And Physical Exercise (SHAPE) study is a randomized controlled trial executed in 2006, comparing a 1-year exercise intervention to control. The detailed study design is described elsewhere (23). Primary outcomes of the study were serum sex hormone levels and body composition. In short, the exercise program resulted in significantly more loss of total and percentage body fat, and waist circumference versus controls, whereas lean mass increased (24). Sex hormone levels decreased in women who lost more than 2% of body fat, where significant differences between groups were found for androgens, but not for estrogens (25). The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (Utrecht, the Netherlands). All participants provided signed informed consent.

Study participants and randomization

Study participants were recruited from the general population. Eligible women were of ages 50 to 69 years, postmenopausal and sedentary. Postmenopausal was defined as ≥ 12 months since last menses. Being sedentary was defined as being engaged in less than 2 h/wk of moderate or vigorous physical activities. Furthermore, women had to be nonsmokers and had to have nondiabetic fasting glucose levels (<7 mmol/L). Main exclusion criteria were having diabetes (type I or II), ever diagnosed with cancer in the 5 years preceding recruitment, and use of exogenous hormones. In total, 189 women were randomly assigned (Fig. 1). Randomization was blocked on two categories of waist circumference ($<$ and ≥ 92 cm) and was performed by using a computer-generated sequence.

Exercise intervention

The 1-year exercise program comprised 2.5 hours of moderate to vigorous intensity physical activity [average metabolic equivalent (MET) of 7; ref. 26] per week. Women were strictly advised to perform the 2.5 hours of exercise in addition to their usual physical activity pattern. Supervised group sessions of 1 hour combined aerobic and strength exercise were provided twice a

week. In addition, participants were instructed to perform one 30-minute home-based session of individual aerobic exercise. The group sessions were provided in a nearby fitness center by qualified sports instructors. Fifteen to 20 women were included in one group. Classes started with a 10-minute warming-up and ended with a 5-minute cooling down. Heart rate monitors were worn to ensure an intensity of 60% to 85% of the age-predicted maximum heart rate during the 30-minute aerobic exercise. The 25-minute strength training consisted of sets of eight to 12 repetitions of exercises for each major muscle group. The intensity and number of sets were gradually increased during the study period. The exercise program is described in more detail in the Supplementary Data. Compliance to the exercise program was monitored by the sports instructors, who registered attendance, and by study personnel who visited the exercise sites regularly. Women were asked to record their home-based exercise activities (type, duration, and average heart rate) in an exercise diary.

Controls were asked to maintain their habitual physical activity level. All participants were asked to maintain their usual diet.

Outcome measures

Study measures were obtained by research nurses at baseline, 4, and 12 months. Blood samples and anthropometric measurements of body weight, height, and waist and hip circumference were taken. Body mass index (BMI) was calculated by weight divided by height squared. Total and percentage body fat were estimated from a total body dual-energy X-ray absorptiometry (DEXA). At each visit, habitual (last year) physical activity was measured by the modified Baecke questionnaire (27), dietary intake by a food frequency questionnaire (28), and medication use was assessed. Current physical activity level was assessed every 4 months by the Physical Activity Scale for the Elderly (PASE questionnaire, measuring activity pattern in the last 7 days; ref. 29). Information about sociodemographic characteristics, reproductive factors, medical history, smoking history, and past physical activity levels was assessed by questionnaires at baseline only.

Blood sampling

Blood samples were drawn after an overnight fast between 9:00 and 11:00 a.m. and stored at -70°C . Participating women were asked not to perform any moderate to vigorous physical activity in the 48 hours preceding the blood sampling. Serum insulin and glucose were determined in the laboratory "Stichting Huisartsenlaboratorium Oost," in Velp, the Netherlands. Laboratory technicians performing the analyses were blinded to the intervention status. All samples of one individual were analyzed in the same batch.

Insulin was measured by radioimmunoassay [Diagnostic Systems Laboratories, Webster, TX (DSL-1600)], with a mean intra-assay coefficient of variation (CV) of 9%. Glucose was measured using the hexokinase method (Hitachi High Tech, clinical analyzer 7600). Homeostatic model assessment for insulin resistance (HOMA2) is a surrogate measure for whole-body insulin sensitivity, based on insulin and glucose levels (30, 31). We calculated HOMA2 by computer software (32) according to an updated model (33, 34). A decrease in HOMA2 represents a beneficial increase in insulin sensitivity.

Statistical analyses

The SHAPE study was powered on serum estrone levels that was the primary outcome (23). For the outcome insulin, we had a power of over 80% to detect a between-group difference of up to 2% on a significance level of $\alpha = 0.05$ with the current sample size, based on findings from previous trials (15, 16). Descriptive data are presented as means and standard deviations (SD), medians, range or frequencies, and percentages. The primary analysis was performed according to the intention-to-treat principle. Metabolic variables were log-transformed to achieve a normal distribution. Mean changes in insulin, glucose, and calculated HOMA2 between exercisers and controls were computed. Intervention effects were evaluated using linear mixed models for repeated measurements. Mixed models are a suitable technique for repeated measurements over time while it considers within individual correlations.

Insulin, glucose, and HOMA2 at 4 and 12 months were taken as dependent, and study group as key independent variable. Models were adjusted for baseline levels of metabolic factors. Adjustment for baseline leads to equal starting points for both groups, and therefore, the intervention effect over time (including changes from 0 to 4 months and 4 to 12 months) is presented by the coefficient of study group (35).

Second, a per protocol analysis was performed. Exercisers were considered noncompliant if they missed 30% or more of all group sessions. Noncompliance in control women was defined as having started an exercise program or a formal weight loss program.

To investigate whether body fat moderates the effect of exercise, we tested the interaction between body fat percentage and study group. Furthermore, we performed an analysis stratified by change in body fat percentage (i.e., $<2\%$ and $>2\%$ fat loss).

Results

At baseline, women in intervention ($n = 96$) and control ($n = 93$) groups were comparable with respect to age, years since menopause, body composition, and alcohol use (Table 1). Despite randomization, slightly higher baseline levels were observed for BMI, body fat, and education in the control group. Baseline levels of glucose were similar in both study groups (Table 1). However, baseline levels of insulin and HOMA2 were slightly higher in the exercise group.

Six women did not complete the study (3.2%; 1 in the intervention group and 5 controls). Insulin and glucose were available for all women at baseline ($n = 189$), for 181 (95.8%) at 4 months, and 182 (96.3%) women at 12 months. Overall, 46 (24%) women who completed the trial were noncompliant. Eleven participants in the control group started an exercise or weight loss program and 35 participants in the intervention group missed 30% or more of all group sessions. The median attendance rate of sports hours in the exercise group was 76%, which is comparable with other exercise intervention trials in older adults (36). Physical activity level measured by the modified Baecke questionnaire increased in exercisers on average by 6.9 points and 15-MET hours, and by 1.5 points and 1.5-MET hours in control women (37). Adverse events as a result of the exercise program were not reported. Body weight did not change in both study groups (-0.66 kg and -0.34 kg in the exercise and control group, respectively; ref. 24). However,

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Table 1. Baseline characteristics of the study population

	Exercise group (n = 96)	Control group (n = 93)	P _{difference}
	Mean (SD)/median (range)	Mean (SD)/median (range)	
Age, y	58.9 (4.6)	58.4 (4.2)	0.45
Years since menopause	8.9 (6.3)	9.9 (6.2)	0.30
Weight, kg	73.6 (8.2)	74.8 (10.8)	0.39
Height, cm	165.5 (6.5)	166.4 (6.0)	0.33
BMI, kg/m ²	26.6 (2.9)	27.3 (3.6)	0.14
Fat mass, kg	28.3 (5.7)	29.9 (8.0)	0.13
Body fat, %	39.8 (4.5)	40.9 (5.8)	0.13
Alcohol, g/d	7.5 (0.0–53.9)	5.3 (0.0–75.2)	0.27
Total energy intake, kJ/d	7,818 (1,946)	8,096 (1,788)	0.31
Physical activity, MET h/wk	4.9 (0.0–120.0)	4.3 (0.0–70.7)	0.36
Education	n (%)	n (%)	0.03
Primary school	5 (5)	5 (5)	
Technical/professional school	29 (30)	29 (31)	
Secondary school	38 (40)	20 (22)	
Academic degree	24 (25)	39 (42)	
	Median (IQR)	Median (IQR)	
Insulin, μ U/mL	6.68 (4.78–9.60)	7.39 (5.25–10.23)	0.83
Glucose, mmol/L	5.22 (4.94–5.48)	5.11 (4.88–5.44)	0.90
HOMA2	0.76 (0.54–1.11)	0.84 (0.58–1.17)	0.83

NOTE: Insulin, n = 189 (100%); glucose, n = 181 (95.8%); HOMA2, n = 181 (95.8%).
Abbreviation: IQR, interquartile range.

declines in body fat (both in kg as in percentage) were significantly greater in the exercise group versus control [−0.33 kg, 95% confidence interval (CI), −0.66 to 0.005 and −0.43%, 95% CI, −0.74 to −0.13; ref. 24]. Furthermore, lean mass increased significantly in the exercise group.

The intention-to-treat analysis (Table 2) showed no significant differences in changes in the 1-year study period in insulin, glucose, or HOMA2 levels between intervention and control participants [treatment effect ratio (β) of exercisers vs. control (95% CI): β , 1.07 (95% CI, 0.96–1.19); β , 1.01 (95% CI, 0.99–1.02); and β , 1.07 (95% CI, 0.96–1.20), respectively; Table 2].

The per protocol analysis showed similar results and did not show significant differences between the study groups either (Table 3).

No significant interaction was found between body fat percentage and study group for insulin, glucose, and HOMA2. In women who lost more than 2% of body fat, levels of all three metabolic factors declined in both study groups (Table 4); however, not different between the study groups [insulin (β , 1.02; 95% CI, 0.87–1.19); glucose (β , 1.02; 95% CI, 0.99–1.04); and HOMA2 (β , 1.02; 95% CI, 0.88–1.19)]. In the group of women who did not lose body fat, also no significant effects were found.

Discussion

In the SHAPE study, we did not observe favorable effects on insulin, glucose, and HOMA2, known to be associated with cancer risk, of a 1-year aerobic and strength exercise intervention in healthy and sedentary postmenopausal women. A per protocol analysis in women who adhered to the study program, and a subgroup analysis in women who lost more than 2% of body fat, showed similar results.

Our null results on glucose are in line with other exercise intervention studies (16–18, 38). However, our results on insulin and HOMA2 are contradictory with our hypothesis that exercise would lower insulin levels and, thereby, decrease cancer risk. Several other studies found statistically significant effects of exercise on insulin and HOMA levels. Possible explanations for these differences could be that the dose of exercise in the SHAPE study was not high enough and/or that the exercise effect on insulin sensitivity is dependent on concordant (substantial) weight loss, which was not aimed and achieved in our trial.

Comparable trials, where exercise programs induced substantial weight loss in postmenopausal women, suggest that weight loss is important for favorable effects on insulin resistance (15, 16, 18, 21, 38–40). For example, in the NEW trial, effects of weight

Table 2. Means and changes in insulin, glucose, and HOMA2 in exercisers versus controls

	Geometric mean			% change (0–4 mo)	% change (0–12 mo)	β^a (95% CI)
	Baseline	4 mo	12 mo			
Insulin, μ U/mL						
Control	7.06	6.65	6.79	−5.75	−3.81	1.07 (0.96–1.19)
Exercise	6.74	7.05	6.76	4.66	0.39	
Glucose, mmol/L						
Control	5.20	5.17	5.17	−0.39	−0.58	1.01 (0.99–1.02)
Exercise	5.20	2.53	5.18	0.58	−0.29	
HOMA2						
Control	0.80	0.75	0.77	−5.84	−3.97	1.07 (0.96–1.19)
Exercise	0.76	0.80	0.77	4.76	0.36	

NOTE: Measures were available for all women at baseline (n = 189). Data were missing for 8 women at 4 months, and for 7 women at 12 months.

^aThe β (95% CI) is the treatment effect ratio representing the overall intervention effect on metabolic variable (adjusted for baseline), including changes from baseline to 4 months and 4 to 12 months. Because metabolic variables were log-transformed for the analysis, the regression coefficient is the anti-logarithm of the original coefficient. Therefore, the anti-logarithm of the coefficient is a ratio that indicates whether the hormone level is, on average, higher in the intervention group compared with controls (>1) or lower (<1); e.g., 1.01 indicates that the metabolic variable is on average 1% higher in the intervention group compared with controls.

Table 3. Means and changes in insulin, glucose, and HOMA2 in women adherent to the study protocol

	Geometric mean			% change 0-4 mo	% change 0-12 mo	β^a (95% CI)
	Baseline	4 mo	12 mo			
Insulin, $\mu\text{U/mL}$						
Control	6.95	6.64	6.80	-4.51	-2.21	1.06 (0.93-1.20)
Exercise	6.70	7.18	6.64	7.12	-0.96	
Glucose, mmol/L						
Control	5.19	5.18	1.15	-0.14	-0.64	1.01 (0.99-1.03)
Exercise	5.25	5.30	5.23	0.98	-0.35	
HOMA2						
Control	0.79	0.75	0.77	-4.57	-2.42	1.06 (0.93-1.21)
Exercise	0.76	0.82	0.76	7.33	-0.95	

NOTE: In total, 137 women were considered in this analysis ($n = 60$ in the intervention, and $n = 77$ in the control group). Follow-up data of three women in the control group were missing.

Adherence is defined as >70% presence in sports classes for the exercise group, and not started a formal exercise or weight loss program in the control group.

^aThe β (95% CI) is the treatment effect ratio representing the overall intervention effect on metabolic variable (adjusted for baseline), including changes from baseline to 4 months and 4 to 12 months. Because metabolic variables were log-transformed for the analysis, the regression coefficient is the anti-logarithm of the original coefficient. Therefore, the anti-logarithm of the coefficient is a ratio that indicates whether the hormone level is, on average, higher in the intervention group compared with controls (>1) or lower (<1); e.g., 1.01 indicates that the metabolic variable is on average 1% higher in the intervention group compared with controls.

loss induced by diet, exercise, or a combined program versus controls were investigated in an overweight study population ($n = 439$). The exercise-only group (225 min/wk vigorous aerobic exercise) failed to lose a significant amount of body fat (-3.3%) and weight (-2.4%) in contrast to the diet and combined intervention groups (18). Subsequently, the exercise-only group showed no changes in insulin, glucose, or HOMA, whereas both other intervention groups did. Furthermore, compared with diet alone, the combined diet plus exercise group had no additional favorable effect on these measures of insulin sensitivity (18). Another weight loss trial, the CALERIE study, induced substantial and equal weight loss (~9.5%) in both a caloric restriction and exercise group, in 48 older men and women during 12 months (21). Women in the caloric restriction group were prescribed a diet with a deficit of 20% of total calories and women in the exercise group were prescribed 90 minutes of exercise daily, corresponding to an energy deficit of 20%. Insulin improved equally in both groups.

These, and our findings, suggest that changes in insulin sensitivity may seem to result largely from concurrent changes in body weight/fat instead of directly from physical activity. The fact that in our study insulin and glucose levels improved more, however not significantly, in the subgroup of women who lost more than 2% of body fat compared with women who did not lose fat mass, also supports this hypothesis that weight loss is necessary for long-

term beneficial exercise effects on metabolic factors. However, also some trials found an exercise effect independent of weight loss (16, 17, 20, 22).

So far, it is not evident which exercise dose is optimal for insulin improvement and cancer risk (3). Although some epidemiologic studies suggest that exercise intensity (i.e., vigorous vs. light to moderate) is the determinant for causing effects on insulin (41, 42), others provide evidence that total time spent in physical activity is most important (15-17, 43-45). Houmard and colleagues (17) investigated exercise effects on insulin sensitivity in 154 postmenopausal women who were randomized to three groups of exercise dosages, differing in intensity, volume, and duration. Groups included exercise programs of a low-volume/moderate intensity/170 min/wk, a low-volume/high-intensity/115 min/wk, and a high-volume/high-intensity/170 min/wk. The relative increases in insulin sensitivity were greatest in the exercise groups who spent the most time being physically active (i.e., 170 vs. 115 min/wk). Hence, the authors concluded that the total exercise duration rather than intensity is the most important factor in influencing insulin levels. These effects were also seen when change in body mass was made equivalent across all exercise groups. In addition, a secondary analysis in a large exercise intervention study, the ALPHA trial, found a significant linear dose-response relationship between exercise duration and improvement of insulin and HOMA levels in women who

Table 4. Means and changes in insulin, glucose, and HOMA2 in women with >2% fat loss

	Geometric mean			% change 0-4 mo	% change 0-12 mo	β^a (95% CI)
	Baseline	4 mo	12 mo			
Insulin, $\mu\text{U/mL}$						
Control	6.83	6.38	6.67	-6.51	-2.36	1.02 (0.87-1.19)
Exercise	7.44	7.32	6.88	-1.55	-7.49	
Glucose, mmol/L						
Control	5.26	5.15	5.14	-2.13	-2.35	1.02 (0.99-1.04)
Exercise	5.19	5.20	5.15	0.15	-0.71	
HOMA2						
Control	0.78	0.72	0.75	-6.91	-2.92	1.02 (0.88-1.19)
Exercise	0.84	0.83	0.78	-1.50	-7.57	

NOTE: In total, 69 women were considered in this analysis ($n = 39$ in the intervention and $n = 30$ in the control group). Data were missing for 2 women (1 control, 1 intervention) at 4 months, and for 1 woman (intervention) at 12 months.

^aThe β (95% CI) is the treatment effect ratio representing the overall intervention effect on metabolic variable (adjusted for baseline), including changes from baseline to 4 months and 4 to 12 months. Because metabolic variables were log-transformed for the analysis, the regression coefficient is the anti-logarithm of the original coefficient. Therefore, the anti-logarithm of the coefficient is a ratio that indicates whether the hormone level is, on average, higher in the intervention group compared with controls (>1) or lower (<1); e.g., 1.01 indicates that the metabolic variable is on average 1% higher in the intervention group compared with controls.

exercised more than 150 min/wk (16). Similarly, a comparable trial reported positive findings on insulin in women who exercised 130 to 190 min/wk, but not in women who spent less time exercising (15). These results suggest that the effects on insulin resistance are dose-dependent. In the SHAPE study, women exercised 150 min/wk, of which 120 minutes were supervised. Therefore, the second explanation for our null results on insulin sensitivity could be that the total time of exercise in our study was too low to enhance effects.

More pathways whereby physical activity may influence cancer risk have been hypothesized, as via endogenous sex hormones, adipokines, and inflammatory markers (3). Regarding breast cancer risk, in a previous analysis of the SHAPE study, we found effects on sex hormones in women who also lost >2% of body fat. Thus, even though no effect was observed on insulin sensitivity, we can conclude that the intervention influenced breast cancer risk via other biomarkers. Although it is likely that these pathways interact at a certain level, changes in some biomarkers can be observed irrespective of the lack of changes in other outcomes.

Strengths of this study include the relatively large study population and the substantial contrast in the level of physical activity between the intervention and control group that was achieved after 12 months (37). The combined aerobic and strength training comprised an exercise level achievable by postmenopausal women. Furthermore, the comprehensive measurement of body composition using DEXA allowed us to address the effect of changes in insulin sensitivity in relation to body fat.

There were also some limitations in our study. The exercise program included home-based training sessions of 30 min/wk, making it more difficult to achieve adherence. Participants of our trial were postmenopausal women, the stage of life with the highest (breast) cancer risk. However, a rather healthy selection was recruited, including women with normal body weights and nondiabetic fasting glucose at baseline. Achieving substantial effects in these women in both body weight as insulin levels is rather difficult, because there is little room for improvements. Furthermore, women in the control group also lost a modest amount of weight (−0.34 kg) and their dietary intake decreased during the study compared with the exercise group [−445 kJ/day (−106 kcal) vs. −27 kJ/day (−6 kcal); ref. 24] that might have influenced our findings. Furthermore, insulin sensitivity was estimated by glucose, insulin, and HOMA2, which are alternatives for the reference test: hyperinsulinemic-euglycemic clamp (46). However, HOMA2 is proven to be a good measure of insulin sensitivity in epi-

miologic research (34) because the reference test is usually not feasible in these studies.

In conclusion, we did not find effects of a 1-year combined aerobic and strength exercise intervention on insulin sensitivity and fasting glucose, in a population of healthy and sedentary, postmenopausal women. Possible explanations are that the exercise dosage was not high enough or the effect of exercise on insulin sensitivity depends on substantial concurrent weight loss. Future intervention studies are needed to give more insight in the optimal dosage of exercise and possible additional effects of exercise when weight loss is reached, on insulin sensitivity and subsequent cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.M. Monninkhof, P.H. Peeters, A.J. Schuit

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