Effect of exercise on insulin sensitivity in healthy postmenopausal women: the SHAPE study

Willemijn A van Gemert1*, Evelyn M Monninkhof1, Anne M May1, Petra H Peeters1, Albertine J Schuit2,3

1. Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
2. Department of Health Science, VU University, Amsterdam, the Netherlands
3. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands

*Corresponding author: w.vangemert@umcutrecht.nl

Running title: Effect of exercise on insulin sensitivity

Trial registration: ClinicalTrials.gov NCT00359060

Key words: exercise, insulin sensitivity, postmenopausal women, cancer risk.


Corresponding author and address of correspondence:

Willemijn A van Gemert, MD
University Medical Center Utrecht
Julius Center for Health Sciences and Primary Care, STR 6.131
Visiting address: Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
Postal address: PO Box 85500, 3508 GA Utrecht, The Netherlands
Telephone: +31 (0)88 756 8052, Fax: +31 (0)88 755 54 80
e-mail: w.vangemert@umcutrecht.nl
Conflicts of interest:

This work was supported by the Dutch Cancer Society [UU 2003-2793]. The support from the sponsor was unconditional, and the data collection, design, management, analysis, interpretation and reporting were performed without their interference. The role of the sponsor was limited to approving the scientific proposal of the study; covering salary costs of study personnel, costs for the data collection and costs for biochemical analyses.

We have no non-financial competing interests to disclose.
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 SHAPE study, 189 healthy, inactive and postmenopausal women (aged 50-69, BMI 22-40 kg/m²) were randomly assigned to a one-year aerobic and strength exercise intervention (150 min/week), 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 versus control (β) [95% confidence interval]): insulin, β=1.07 [0.96-1.19]; glucose, β=1.01 [0.99-1.02]; 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 DEXA).

Conclusions

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

Impact
Our findings suggest that 150 minutes/week of exercise, as recommended by current guidelines, is not enough to achieve improvements in insulin sensitivity and subsequent cancer risk, in healthy postmenopausal women.
INTRODUCTION

An inactive lifestyle is a recognised 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 hyperinsulinaemia, 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 IGF-1 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 hyperinsulinaemia 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 six months to one 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 which 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 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, 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 hypothesise that exercise improves insulin sensitivity, and that this association is mainly explained by concordant loss of body fat.

MATERIALS AND METHODS

The SHAPE study is a randomised controlled trial executed in 2006, comparing a one-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 programme resulted in significantly more loss of total and percentage body fat, and waist circumference versus controls, while 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 oestrogens (25). The study was approved by the Medical Ethics Committee of the UMC Utrecht. All participants provided signed informed consent.

Study participants and randomisation

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

Exercise intervention

The one-year exercise programme comprised 2.5 hours of moderate to vigorous intensity physical activity (average metabolic equivalent (MET) of 7 (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 one 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 centre 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 60-85% of the age-predicted maximum heart rate during the 30-minute aerobic exercise. The 25-minute strength training consisted of sets of 8 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 programme is described in more detail in the online Supplementary Material. Compliance to the exercise programme 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 four months by the Physical Activity Scale for the Elderly (PASE questionnaire, measuring activity pattern in the last 7 days) (29). Information regarding socio-demographic 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 analysed 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 analyser 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 oestrone levels which 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 and 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 is 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 non-compliant if they missed 30% or more of all group sessions. Noncompliance in control women was defined as having started an exercise programme or a formal weight loss programme.

To investigate if 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 randomisation, 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 non-compliant. Eleven participants in the control group started an exercise or weight loss programme 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 to other exercise intervention trials in older adults (36). Physical activity level, measured by the modified Baecke questionnaire score, at 12 months was increased in exercisers (6.9 points and 15 MET hours) and higher than in controls (increase of 1.5 points and 1.5 MET hours)(37). 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
programme 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) (24). However, declines in body fat (both in kg as in percentage) were significantly greater in the exercise group versus control (-0.33 kg, 95% CI -0.66 to 0.005 and -0.43%, 95% CI -0.74 to -0.13) (24). Furthermore, lean mass increased significantly in the exercise group and was higher when compared with the control group that showed a slight decrease (difference in lean mass between exercise and control of +0.31 kg, 95% CI 0.11 to 0.50)(24).

The intention-to-treat analysis (Table 2) showed no significant differences in changes in the one-year study period in insulin, glucose or HOMA2 levels between intervention and control participants (Treatment effect ratio ($\beta$) of exercisers versus control [95% confidence interval] of $\beta$=1.07 [95% CI 0.96-1.19], $\beta$=1.01 [95% CI 0.99-1.02] and $\beta$=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 over 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 ($\beta$=1.02 [95% CI 0.87-1.19]); glucose ($\beta$=1.02 [95% CI 0.99-1.04]); HOMA2 ($\beta$=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 favourable effects on insulin, glucose and HOMA2, known to be associated with cancer risk, of a one-year aerobic and strength exercise intervention in healthy and sedentary postmenopausal women. A per protocol analysis in
women who adhered to the study programme, and a subgroup analysis in women who lost
over 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 programmes induced substantial weight loss in
postmenopausal women, suggest that weight loss is important for favourable effects on insulin
resistance (15,16,18,21,38-40). For example, in the NEW trial, effects of weight loss induced
by diet, exercise, or a combined programme versus controls were investigated in an
overweight study population (n=439). The exercise-only group (225 min/week 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 favourable effect on these measures of insulin sensitivity (18). Another weight
loss trial, the CALERIE study, induced substantial and equal weight loss (approximately
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 over 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). While some epidemiological 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 et al. investigated exercise effects on insulin sensitivity in 154 postmenopausal women who were randomised to three groups of exercise dosages, differing in intensity, volume and duration (17). Groups included exercise programmes 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/week). 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 exercised over 150 minutes per week (16). Similarly, a comparable trial reported positive findings on insulin in women who exercised 130-190 minutes per week, 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 minutes/week, 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 hypothesised, 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 dual-energy X-ray absorptiometry 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 programme included home-based training sessions of 30 minutes per week, 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 non-diabetic fasting glucose at baseline. Achieving substantial effects in these women in both body weight as insulin levels is rather difficult, since 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)) (24) which 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 epidemiologic research (34) since the reference test is usually not feasible in these studies.

In conclusion, we did not find effects of a one-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.

Acknowledgements

We would like to thank Manon de Leeuw, Anneloes van Diemen, Claire Nollen, Karen Menninga, Lizeth Vendrig, Lara Heuveling, Jose Drijvers, Joke Metselaars and Fien Stern for their contribution to the inclusion and follow-up of the SHAPE participants.

This work was supported by the Dutch Cancer Society [UU 2003-2793]. The support from the sponsor was unconditional, and the data collection, design, management, analysis, interpretation and reporting were performed without their interference.
Reference List

   Ref Type: Report


12. Hardy OT, Czech MP, and Corvera S. What causes the insulin resistance underlying obesity? Curr Opin Endocrinol Diabetes Obes 2012:19:81-87,


limitation in older adults: a randomized controlled trial. Arch Intern Med 2009:169:122-131,

20. Ryan AS, Nicklas BJ, and Berman DM. Aerobic exercise is necessary to improve glucose utilization with moderate weight loss in women. Obesity (Silver Spring) 2006:14:1064-1072,

21. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, Klein S, and Holloszy JO. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. Am J Clin Nutr 2006:84:1033-1042,


27. Hertogh EM, Monninkhof EM, Schouten EG, Peeters PH, and Schuit AJ. Validity of the Modified Baecke Questionnaire: comparison with energy expenditure according to the doubly labeled water method. Int J Behav Nutr Phys Act 2008:5:30,


Ref Type: Electronic Citation

33. Levy JC, Matthews DR, and Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998:21:2191-2192,
34. Wallace TM, Levy JC, and Matthews DR. Use and abuse of HOMA modeling. 
Diabetes Care 2004:27:1487-1495,

longitudinal data analysis for epidemiology, pp. 179-201. Cambridge: Cambridge 

36. Martin K and Sinden A. Who will stay and who will go? A review of older adults' 
adherence to randomized controlled trials of exercise. Journal of Aging and Physical 
Activity 2001:9:91-114,

changes after a 1-yr exercise program and predictors of maintenance. Med Sci Sports 
Exerc 2010:42:886-892,

38. Camhi SM, Stefanick ML, Katzmarzyk PT, and Young DR. Metabolic syndrome and 
changes in body fat from a low-fat diet and/or exercise randomized controlled trial. 
Obesity (Silver Spring) 2010:18:548-554,

Besson H, De Lucia RE, Sleigh A, Martin HJ, Aihie SA, Cooper C, Ekelund U, 
Griffin SJ, and Wareham NJ. The effects of aerobic exercise on metabolic risk, insulin 
sensitivity and intrahepatic lipid in healthy older people from the Hertfordshire Cohort 
Study: a randomised controlled trial. Diabetologia 2010:53:624-631,

R, and Blumenthal JA. Effects of exercise and weight loss on cardiac risk factors 
associated with syndrome X. Arch Intern Med 2003:163:1889-1895,
41. Seals DR, Hagberg JM, Hurley BF, Ehsani AA, and Holloszy JO. Effects of endurance training on glucose tolerance and plasma lipid levels in older men and women. JAMA 1984:252:645-649,


45. Duvivier BM, Schaper NC, Bremers MA, van CG, Menheere PP, Kars M, and Savelberg HH. Minimal intensity physical activity (standing and walking) of longer duration improves insulin action and plasma lipids more than shorter periods of moderate to vigorous exercise (cycling) in sedentary subjects when energy expenditure is comparable. PLoS One 2013:8:e55542,

Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Exercise Group (n = 96)</th>
<th>Control Group (n = 93)</th>
<th>p for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) / Median (range)</td>
<td>Mean (SD) / Median (range)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.9 (4.6) / 58.9 (4.6)</td>
<td>58.4 (4.2) / 58.4 (4.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>8.9 (6.3) / 8.9 (6.3)</td>
<td>9.9 (6.2) / 9.9 (6.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.6 (8.2) / 73.6 (8.2)</td>
<td>74.8 (10.8) / 74.8 (10.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.5 (6.5) / 165.5 (6.5)</td>
<td>166.4 (6.0) / 166.4 (6.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.6 (2.9) / 26.6 (2.9)</td>
<td>27.3 (3.6) / 27.3 (3.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>28.3 (5.7) / 28.3 (5.7)</td>
<td>29.9 (8.0) / 29.9 (8.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>39.8 (4.5) / 39.8 (4.5)</td>
<td>40.9 (5.8) / 40.9 (5.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>7.5 (0.0-53.9) / 7.5 (0.0-53.9)</td>
<td>5.3 (0.0-75.2) / 5.3 (0.0-75.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total energy intake (kJ/d)</td>
<td>7 818 (1 946) / 7 818 (1 946)</td>
<td>8 096 (1 788) / 8 096 (1 788)</td>
<td>0.31</td>
</tr>
<tr>
<td>Physical activity (MET h/wk)³</td>
<td>4.9 (0.0-120.0) / 4.9 (0.0-120.0)</td>
<td>4.3 (0.0-70.7) / 4.3 (0.0-70.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Education number (%)</td>
<td>number (%) / number (%)</td>
<td>number (%) / number (%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Primary school</td>
<td>5 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical/professional school</td>
<td>29 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>38 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic degree</td>
<td>24 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (IQR)³ / Median (IQR)³</td>
<td>Median (IQR)³ / Median (IQR)³</td>
<td></td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>6.68 (4.78-9.60) / 6.68 (4.78-9.60)</td>
<td>7.39 (5.25-10.23) / 7.39 (5.25-10.23)</td>
<td>0.83</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.22 (4.94-5.48) / 5.22 (4.94-5.48)</td>
<td>5.11 (4.88-5.44) / 5.11 (4.88-5.44)</td>
<td>0.90</td>
</tr>
<tr>
<td>HOMA2</td>
<td>0.76 (0.54-1.11) / 0.76 (0.54-1.11)</td>
<td>0.84 (0.58-1.17) / 0.84 (0.58-1.17)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

a. MET = metabolic equivalent.
b. $IQR =$ interquartile range

Insulin, $n=189$ (100%); glucose, $n=181$ (95.8%); HOMA2, $n=181$ (95.8%).
Table 2. Means and changes in insulin, glucose and HOMA2 in exercisers versus controls

<table>
<thead>
<tr>
<th></th>
<th>Geometric mean</th>
<th>% change 0-4 months</th>
<th>% change 0-12 months</th>
<th>$\beta^*$ [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 months</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>Control</td>
<td>7.06</td>
<td>6.65</td>
<td>-5.75</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>6.74</td>
<td>7.05</td>
<td>6.76</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>Control</td>
<td>5.20</td>
<td>5.17</td>
<td>-0.39</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>5.20</td>
<td>2.53</td>
<td>5.18</td>
</tr>
<tr>
<td>HOMA2</td>
<td>Control</td>
<td>0.80</td>
<td>0.75</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>0.76</td>
<td>0.80</td>
<td>0.77</td>
</tr>
</tbody>
</table>

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

The beta ($\beta$), with 95% confidence interval, 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 antilogarithm of the original coefficient. Therefore, the antilogarithm 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

<table>
<thead>
<tr>
<th></th>
<th>Geometric mean</th>
<th>% change 0-4 months</th>
<th>% change 0-12 months</th>
<th>( \beta^a ) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin (µU/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6.95</td>
<td>6.64</td>
<td>6.80</td>
<td>-4.51 [-2.21]</td>
</tr>
<tr>
<td>Exercise</td>
<td>6.70</td>
<td>7.18</td>
<td>6.64</td>
<td>7.12 [-0.96]</td>
</tr>
<tr>
<td><strong>Glucose (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.19</td>
<td>5.18</td>
<td>1.15</td>
<td>-0.14 [-0.64]</td>
</tr>
<tr>
<td>Exercise</td>
<td>5.25</td>
<td>5.30</td>
<td>5.23</td>
<td>0.98 [-0.35]</td>
</tr>
<tr>
<td><strong>HOMA2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.79</td>
<td>0.75</td>
<td>0.77</td>
<td>-4.57 [-2.42]</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.76</td>
<td>0.82</td>
<td>0.76</td>
<td>7.33 [-0.95]</td>
</tr>
</tbody>
</table>

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 programme in the control group.

The beta (\( \beta \)), with 95% confidence interval, 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 antilogarithm of the original coefficient. Therefore, the antilogarithm 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 4. Means and changes in insulin, glucose and HOMA2 in women with >2% fat loss.

<table>
<thead>
<tr>
<th></th>
<th>Geometric mean</th>
<th>% change 0-4 months</th>
<th>% change 0-12 months</th>
<th>( \beta^a ) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 months</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td><strong>Insulin (µU/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6.83</td>
<td>6.38</td>
<td>6.67</td>
<td>-6.51</td>
</tr>
<tr>
<td>Exercise</td>
<td>7.44</td>
<td>7.32</td>
<td>6.88</td>
<td>-1.55</td>
</tr>
<tr>
<td><strong>Glucose (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.26</td>
<td>5.15</td>
<td>5.14</td>
<td>-2.13</td>
</tr>
<tr>
<td>Exercise</td>
<td>5.19</td>
<td>5.20</td>
<td>5.15</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>HOMA2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.78</td>
<td>0.72</td>
<td>0.75</td>
<td>-6.91</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.84</td>
<td>0.83</td>
<td>0.78</td>
<td>-1.50</td>
</tr>
</tbody>
</table>

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

The beta (\( \beta \)), with 95% confidence interval, 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 antilogarithm of the original coefficient. Therefore, the antilogarithm 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.
Figure 1. Flow chart of the inclusion, randomisation, and retention of the Sex Hormone And Physical Exercise (SHAPE) study participants
Invitation letters mailed to women aged 50-69 y (n=6200)

Response to invitation letter (n=1799)

Screened on eligibility criteria by phone (n=1360)

Subject information mailed to eligible women (n=310)

Invited for baseline visit (n=208)

Randomised (n=189)

Intervention group (n=96)
-Compliant (n=60)
- Attended < 70% of group sessions (n=35)
- Dropped out of the study (n=1)

Control group (n=93)
-Compliant to control status (n=77)
- Not compliant, i.e. started exercising, a weight loss programme or smoking (n=11)
- Dropped out of the study (n=5)

Blood available:
- Baseline (n=96)
- 4 months (n=94)
- 12 months (n=94)
Analysed (n=96)

Blood available:
- Baseline (n=93)
- 4 months (n=87)
- 12 months (n=88)
Analysed (n=93)
Effect of exercise on insulin sensitivity in healthy postmenopausal women: the SHAPE study

Willemijn A. van Gemert, Evelyn M. Monninkhof, Anne M. May, et al.

Cancer Epidemiol Biomarkers Prev Published OnlineFirst October 23, 2014.