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Dietary Weight-Loss and Exercise Effects on Insulin Resistance in Postmenopausal Women

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Abstract

Background—Comprehensive lifestyle interventions are effective in preventing diabetes and restoring glucose regulation; however, the key stimulus for change has not been identified and effects in older individuals are not established. The aim of the study was to investigate the independent and combined effects of dietary weight-loss and exercise on insulin sensitivity and restoration of normal fasting glucose in mid-aged and older women.

Design—Four-arm RCT, conducted between 2005 and 2009 and data analyzed in 2010.

Setting/participants—439 inactive, overweight/obese postmenopausal women. Interventions: Women were assigned to: dietary weight loss ($n=118$), exercise ($n=117$), exercise+diet ($n=117$), or control ($n=87$). The diet intervention was a group-based reduced-calorie program with a 10% weight-loss goal. The exercise intervention was 45 min/day, 5 days/week of moderate-to-vigorous intensity aerobic activity.

Main outcome measures—12-month change in serum insulin, C-peptide, fasting glucose, and whole body insulin resistance (HOMA-IR).

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Results—A significant improvement in HOMA-IR was detected in the diet (−24%, $p<0.001$) and exercise+ diet (−26%, $p<0.001$) groups, but not in the exercise (−9%, $p=0.22$) group compared to controls (−2%); these effects were similar in middle-aged (50–60 years) and older women (aged 60–75 years). Among those with impaired fasting glucose (5.6–6.9 mmol/L) at baseline ($n=143$; 33%), the odds (95% CI) of regressing to normal fasting glucose after adjusting for weight loss and baseline levels were: 2.5 (0.8, 8.4), 2.76 (0.8, 10.0), and 3.1 (1.0, 9.9) in the diet, exercise +diet, and exercise group, respectively, compared to controls.

Conclusions—Dietary weight loss, with or without exercise, significantly improved insulin resistance. Older women derived as much benefit as did the younger postmenopausal women.

Introduction

Given the high prevalence of insulin resistance¹ and its associated health burden,^{2–7} effective prevention strategies for high-risk individuals are a priority. Several trials have examined the efficacy of lifestyle interventions for preventing type 2 diabetes, but few have examined their effectiveness on restoring normal glucose homeostasis.

The Diabetes Prevention Program (DPP) demonstrated that combined diet and exercise therapy is effective for diabetes prevention,⁸ and restores normal glucose regulation more frequently than placebo.⁹ Moreover, the effect of lifestyle therapy was more pronounced in older compared with younger participants.¹⁰ Yet, because the DPP did not randomly assign each lifestyle component, the relative importance of the diet and exercise components could not be adequately examined. Furthermore, the DPP lifestyle intervention was resource-intensive, providing ongoing, individualized counseling.⁸ To our knowledge, the effectiveness of group-based adaptations of the DPP program has not been widely tested.

Since the restoration of normal glucose homeostasis is more akin to true prevention than delayed progression to overt diabetes, unraveling the relative importance of diet, exercise, and body weight in this regard has important implications for resource allocation, patient counseling, and public health.

While both obesity and diabetes risk increases with age in the U.S.,^{11,12} few studies have included older individuals in large enough numbers to determine whether lifestyle changes to reduce weight can improve insulin resistance, a major predictor of diabetes risk.¹³ Thus, the purpose of this study was to examine the independent and combined effects of 12 months of dietary weight-loss and/or aerobic exercise on insulin resistance and the restoration of normal fasting glucose among overweight postmenopausal women, and to examine whether the magnitude of these effects differed between middle-aged (50–60 years) and older women (aged 60–75 years).

The study also examined which factors, including weight loss, fat loss, or changes in cardiorespiratory fitness or physical activity, were most associated with changes in glucose homeostasis. It was hypothesized that insulin and glucose would improve in all intervention groups compared to controls, and that these changes would be mediated by the degree of weight loss. It was also hypothesized that younger women would experience greater metabolic improvements relative to older women.

Methods

Design Overview

The Nutrition and Exercise in Women (NEW) study was a 12-month RCT testing the effects of exercise and/or dietary weight loss on circulating hormones and other outcomes.¹⁴ The trial was conducted from 2005 to 2009; data were analyzed in 2010. Study procedures were

reviewed and approved by the Fred Hutchinson Cancer Research Center IRB in Seattle, WA. All participants provided informed consent.

Setting and Participants

Participants were overweight or obese ($\text{BMI} \geq 25.0$; ≥ 23.0 if Asian-American), postmenopausal women (aged 50–75 years) from the greater-Seattle area who were not meeting physical activity guidelines.¹⁵ Women were recruited through media and mass mailings (Figure 1). Specific exclusion criteria included: diagnosed diabetes, fasting blood glucose ≥ 126 mg/dL or use of diabetes medications; use of postmenopausal hormones; history of other serious medical condition(s); alcohol intake >2 drinks/day; current smoking; contraindication to the study interventions for any reason (e.g., abnormal exercise tolerance test); participation in another structured weight loss program; or use of weight loss medications.

Randomization and Interventions

Eligible women were randomized to: (1) dietary weight loss ($n=118$); (2) moderate-to-vigorous intensity aerobic exercise ($n=117$); (3) combined diet and exercise ($n=117$); or (4) control (no intervention; $n=87$). Computerized random assignment was stratified according to BMI ($\geq$ or <30 kg/m²) and participants' self-reported race/ethnicity (black, white, other). A permuted blocks randomization, wherein the control assignment was randomly eliminated from each block with a probability of approximately 1 in 4, was used to achieve a proportionally smaller control group. One participant that was randomized to diet+exercise was excluded from analysis due to missing baseline blood measures.

The exercise intervention progressed to 45 minutes of moderate-to-vigorous intensity exercise at a target heart rate of 70%–85% observed maximum, 5 days/week, by the 7th week. Participants attended three supervised sessions/week at the study facility and exercised 2 days/week at home. Participants recorded exercise mode, duration, peak heart rate, and perceived exertion at each session. Activities of ≥ 4 METs¹⁶ were counted toward the prescribed target.

The dietary weight-loss intervention involved a modification of the DPP⁸ and Look AHEAD¹⁷ lifestyle behavior change programs with goals of: 1200–2000 kcal/day, $<30\%$ calories from fat, and 10% weight loss by 6 months with maintenance thereafter. Participants met individually with a dietitian at least twice, followed by weekly group meetings (5–10 women) for 6 months. Thereafter, participants attended monthly group meetings, in addition to biweekly phone or email contact. A combination of individual and group-based approaches was used to maximize the benefits of personalized recommendations with the social support and cost effectiveness of a group setting. Women completed daily food logs for at least 6 months or until they reached their 10% weight-loss goal. Food logs were collected by the dietitian and returned with feedback. Logs, weekly weigh-ins, and session attendance were tracked to promote dietary adherence. Participants who did not meet their weight loss goal by 6 months were encouraged to continue weight loss efforts and were offered additional sessions, while women who reached their goal were allowed to continue losing but were monitored to ensure that BMI did not go below 18.5. Participants who were randomized to dietary weight loss + exercise received separate sessions and were instructed not to discuss diet during supervised exercise. The control group was instructed not to change their diet or exercise behavior for 12 months. At study completion, they were offered 4 group nutrition classes and 8 weeks of exercise training.

Outcomes and Follow-Up

All study measures were obtained and analyzed by trained personnel who were blinded to the participants' randomization status. Demographic information, medical history, dietary patterns (via 120-item self-administered food frequency questionnaire¹⁸) were collected at baseline and 12 months. At both time points, participants wore pedometers (Accusplit, Silicon Valley, CA) for 7 consecutive days to determine an average daily step count. Cardiorespiratory fitness (VO₂max) was assessed using a maximal graded treadmill test according to a modified branching protocol.¹⁹ Heart rate and oxygen uptake were continuously monitored with an automated metabolic cart (MedGraphics, St. Paul, MN).

Body mass index was calculated from weight and height, measured to the nearest 0.1 kg and 0.1cm, respectively, with a balance beam scale and stadiometer. Waist circumference was measured to the nearest 0.5cm at the minimal waist. Body composition was measured on a DXA whole-body scanner (GE Lunar, Madison, WI).

Fasting venous blood samples (50 mL) were collected during clinic visits prior to randomization and at 12 months. Participants consumed no food and drank only water for 12 hours prior and were requested not to exercise for 24 hours preceding the blood draw. Blood was processed within 1 hour and samples were stored at -70°C.

Blood samples were analyzed in batches such that each participant's samples were assayed simultaneously, the numbers of samples from each arm were approximately equal, participant randomization dates were similar, and sample order was random. All but four samples were analyzed for insulin and C-peptide in a single batch. Excluding these samples did not affect the results.

Insulin was analyzed at the University of Washington (UW) Clinical Nutrition Research Unit Laboratory, and quantified by a 48-hour, polyethylene glycol-accelerated, double antibody radioimmunoassay. The intra-assay coefficient of variation (CV) was 4.5%. C-peptide and glucose were analyzed at the UW Northwest Lipid Research Laboratories. C-peptide was analyzed using a two-site immunoenzymometric assay (Tosoh AIA 1800 auto analyzer; Tosoh Bioscience, Inc., San Francisco). Glucose was quantified using a ClinicalChemistry Autoanalyzer with the hexokinase method. The intra-assay CV for C-peptide was 4.3%. The intra- and inter-assay CVs for glucose were 1.1% and 3.5%, respectively.

The homeostasis assessment model (HOMA-IR= fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5)²⁰ was used as a surrogate measure of whole-body insulin resistance.

Statistical Analysis

In cases of missing values, no change from baseline was assumed. Repeating the main analyses using a multiple imputation method did not meaningfully affect any of the findings. Age-adjusted partial Pearson correlation coefficients were calculated between baseline anthropometric and blood measures. Generalized linear models were used to test for differences in baseline values across study arms, and a chi-square test to detect differences in the prevalence of impaired fasting glucose.

Descriptive data are presented as M (SD). Due to their non-normal distribution, blood measures were log-transformed prior to further analysis. These data are presented as geometric means (95% CIs) unless otherwise indicated. Mean changes in insulin, C-peptide, glucose, and HOMA-IR from baseline to 12 months, stratified by group, were computed; intervention effects on these variables were examined based on the assigned treatment at randomization, regardless of adherence or study retention (i.e., intent-to-treat). Mean 12-

month changes in the exercise, diet, and diet+exercise groups were compared to controls using the generalized estimating equations (GEE) modification of linear regression to account for intra-individual correlation over time. The effect of age (50–60 years vs 60–75 years) was assessed by including interaction terms in these models. Analyses were also repeated after stratification by age group. Adjustment for multiple comparisons was made using Bonferroni correction (two-sided $\alpha=0.05/3$).

Changes in body weight, body composition, pedometer steps/day, and VO_2max were similarly calculated and used to predict the observed change in metabolic variables by linear regression. These potential mediating variables were examined continuously, then categorically as: 3 clinically relevant categories of weight loss:^{21, 22} $<5\%$, $\geq 5\%–10\%$, and $\geq 10\%$ loss; change in pedometer steps/day corresponding to a decrease/no change (≤ 0 steps/day), an increase up to 2 miles/day (1–3520 steps/day), or >2 miles/day (>3520 steps/day); and tertiles of change in total body fat (kg) and VO_2max (L/min). Models included age, group assignment, and the baseline value of the outcome variable as covariates.

Participants' fasting glucose levels were classified as 'impaired' (5.6–6.9 mmol/L) or 'normal' (<5.6 mmol/L).²³ Logistic regression was used to calculate the ORs for regression from impaired to normal fasting glucose within each intervention arm compared to controls, adjusting for age, weight loss, and baseline blood glucose level. Corresponding ORs were calculated for categories of weight loss (1%–5%, $\geq 5\%–10\%$, $\geq 10\%$, relative to no change/gain) and approximate tertiles of change in VO_2max . All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

Results

Participants

At 12 months, 398 of 438 participants completed physical exams and provided a blood sample, 397 underwent a DXA scan, and 371 completed a treadmill test; 39 did not complete the study (Figure 1). There were no differences in relevant variables between groups at baseline, except the percentage of daily calories consumed as fat ($p=0.02$) (Table 1).

Adherence to Interventions

Intervention adherence and body composition changes in this sample have been recently reported.¹⁴ Briefly, women who were randomized to exercise alone participated in moderate-to-vigorous activity for a M (SD) of 163.3 (70.6) minutes/week, while women who were randomized to diet+exercise participated for 171.5 (62.9) minutes/week. Both groups significantly increased average pedometer steps/day (+2416 and +3471 steps/d, respectively) and VO_2max (+0.17 and +0.12 L/min, respectively) compared to baseline. Women who were randomized to diet+exercise increased pedometer steps/day more than women who did exercise alone ($p=0.006$).

Percentage of calories from fat decreased in both the diet alone (-18% .) and diet+exercise (-20.0%) groups. Average fiber intake and daily fruit and vegetable servings also increased in the diet alone (+3.4 g/day; +1.7 servings/day, respectively; both $p<0.001$) and diet +exercise (+2.8 g/day; +1.4 servings/day, both $p<0.0001$) groups, but not in the exercise group (+0.53 g/day; 0 servings/day, both $p>0.5$) compared to controls (-0.2 g/day; -0.9 servings/day). In both groups, women attended an average of 27 diet counseling sessions (86%). There were no significant differences in measures of adherence between mid-aged ($n=304$) and older ($n=134$) women (data not shown).

At 12 months, the mean weight loss was -2.4% ($p=0.03$) in the exercise group, -8.5% ($p<0.001$) in the diet group, and -10.8% ($p<0.001$) in the diet+exercise group, compared to -0.8% loss among controls. Weight loss was not significantly different between middle-aged and older women within each study arm (all $p > 0.2$). Women in all intervention groups significantly reduced waist circumference and % body fat (all $p<0.01$) compared to controls.¹⁴ Lean mass decreased significantly in the diet alone group ($p=0.005$) but was preserved in exercisers (both $p>0.10$).

Baseline Associations

Baseline BMI, waist circumference, and total fat mass (kg) were correlated with insulin ($r=0.39$, $r=0.47$, $r=0.25$), C-peptide ($r=0.43$, $r=0.50$, $r=0.33$), glucose ($r=0.26$, $r=0.24$, $r=0.24$), and HOMA-IR ($r=0.40$, $r=0.47$, $r=0.27$) (all $p<0.01$). $VO_2\text{max}$ and pedometer steps/day were also significantly correlated with each of the metabolic variables ($r= -0.11$ to -0.24 , all $p<0.05$).

Intervention Effects

Compared to controls, women in the diet and diet+exercise groups experienced significant reductions in serum insulin, C-peptide, and glucose (Table 2). HOMA-IR decreased by 24% ($p<0.001$) in the diet alone group and by 26% ($p<0.001$) in the diet+exercise group, compared to 2% in controls. In contrast, no overall significant treatment effects were observed for women assigned to exercise alone (-9% , $p=0.19$) (Table 2). Compared to diet alone, women receiving diet+exercise did not experience greater improvements in insulin ($p=0.69$), C-peptide ($p=0.32$), glucose ($p=0.52$), or HOMA-IR ($p=0.64$), but did have significantly greater improvements than women who were randomized to exercise alone (insulin: $p<0.001$; C-peptide: $p<0.001$; glucose: $p=0.03$; HOMA-IR: $p<0.001$). No significant age interactions were detected; the magnitude of metabolic improvement was similar between middle-aged and older women in each intervention group compared to controls (Table 3). However, within the exercise alone group, mid-aged women did experience greater improvement in insulin, C-peptide, and HOMA-IR compared to older women.

As expected, the magnitude of weight loss was associated with metabolic improvement in insulin, C-peptide, glucose and HOMA-IR (Table 4). These associations were independent of changes in cardiorespiratory fitness (Table 4) and pedometer steps/day. Greater metabolic improvement was observed with greater magnitude of change in average pedometer steps/day; however, these associations were not significant after adjusting for weight change, except for C-peptide. The magnitude of change in $VO_2\text{max}$ (L/min) was not associated with metabolic changes.

Higher baseline fasting glucose was a strong predictor of metabolic improvement in participants randomized to interventions (results not shown). In analyses limited to women with impaired fasting glucose at baseline, the odds (95% CI) of regression to fasting glucose <5.6 mmol/L at 12 months, independent of baseline level, age, and % weight change were 3.16 (1.02, 9.75) in the exercise alone group, 1.97 (0.63, 6.16) in the diet alone group, and 2.35 (0.68, 8.18) in the diet+exercise group (Table 5). The AOR of returning to normal fasting glucose in the diet+exercise group compared to diet alone was 1.17 (0.43, 3.16). Corresponding odds associated with categories of weight loss and $VO_2\text{max}$ are also shown in Table 5. Overall, the 1-year incidence of developing impaired fasting glucose among women with normal baseline values was 18% among controls, 6% in the exercise alone group, 4% in the diet alone group, and 2% in the diet+exercise group.

Discussion

A 12-month group-based modification of the DPP/LookAHEAD weight loss interventions^{8,17} resulted in significant weight loss and improved insulin resistance. However, adding a prescribed 225 minutes/week of aerobic exercise did not yield significant added benefits in these outcomes up to 12 months. Furthermore, the effect of these lifestyle interventions was similar in middle-aged and older women. Although no overall improvement in HOMA-IR was detected in women randomized to exercise alone compared to controls, 12 months of exercise training was associated with improved odds of regressing from impaired to normal fasting glucose (<5.6 mmol/L), independent of weight loss. These findings support previous reports that modest weight loss (5%–10% body weight) is associated with improved insulin sensitivity and glucose tolerance.^{8,9,24–26} They are also consistent with reports that regular exercise can improve insulin sensitivity, even in the absence of substantial weight reduction;^{27,28} however, in the current study, this effect was limited to women with impaired fasting glucose at baseline. The mechanisms postulated to account for these favorable changes include a preferential reduction in visceral fat and/or enhanced metabolic efficiency of muscle.^{29,30}

In the DPP, increasing age was associated with more physical activity, greater weight loss, and a lower incidence of diabetes, but not with reported caloric intake or reversion to normal fasting glucose.¹⁰ Other large type 2 diabetes prevention trials have not included older adults or have been unable to examine age-related differences in the response to lifestyle interventions.^{31–33} To our knowledge, no previous randomized trial has examined differences in the response to weight loss and exercise interventions in mid-aged and older women. In this study, there were no significant differences in any measure of intervention adherence between middle-aged and older women, and the magnitude of the difference between middle-aged and older women was not significantly different from controls in any of the intervention arms. Due to limited sample size, it was not possible to examine the reversion to normal fasting glucose by age group.

Although women assigned to exercise alone failed to achieve significant weight loss compared to controls, they experienced significant reductions in waist circumference and body fat. Larson-Meyer *et al.*³⁴ recently demonstrated that under conditions of equal energy deficits, overweight men and women who were randomized to caloric restriction alone or in combination with exercise showed similar reductions in body weight, total body fat and visceral fat. Yet, those who performed exercise had significantly greater improvements in insulin sensitivity and other markers of cardiovascular risk. Enhanced parasympathetic tone and endothelial function have been proposed as pathways through which exercise may influence cardiometabolic health beyond ‘traditional’ risk factors.³⁵

A limitation of the current study is that the sample was predominantly Caucasian and therefore it was not possible to examine the consistency of the current findings across racial/ethnic groups. In addition, fasting glucose was used rather than glucose tolerance testing or HgA1C, and potential differences in insulin secretion versus insulin action could not be compared between treatment arms. However, impaired fasting glucose is an important clinical marker in itself.²³ Additional strengths of the present study include its relatively large size and adequate statistical power to examine differences in insulin sensitivity between middle-aged and older women assigned to multiple interventions. Furthermore, the group-based lifestyle interventions used in this study were less staff-time intensive than those used in the DPP⁸ and many other large trials,³⁶ yet yielded substantial weight loss and improvements in glucose homeostasis. This suggests that group-based diet and exercise programs may be as effective as one-on-one counseling in eliciting favorable improvements. Future studies to determine the comparative effectiveness of these programs with larger and

more diverse groups, and in other settings would provide an important contribution to the current literature.

This study provides evidence that clinically meaningful improvements in insulin sensitivity can be achieved through caloric restriction alone or with the addition of exercise. Furthermore, a prescribed exercise dose of 225 minutes/week resulted in regression to normal glucose levels for more than half of women with impaired fasting glucose at baseline. In the DPP, individuals who were randomized to lifestyle intervention who did not achieve the desired goal of 7% reduction in body weight but attained the physical activity goal of >150 minutes/week experienced a 44% reduction in the risk of progression to diabetes.⁹ The optimal exercise dose for ‘treatment’ of impaired fasting glucose remains unknown but clearly warrants further investigation.

Weight loss among older people remains controversial, primarily due to concern over the potentially deleterious loss of muscle and bone mass. The exercise program tested in this study did not include resistance training; however resistance exercise has been shown to have favorable effects on glycemic control³⁷ and to help preserve lean mass during weight loss.²⁵ Davidson et al.²⁷ have previously shown that the combination of resistance and aerobic exercise was the optimal exercise strategy for simultaneous reduction in insulin resistance and functional limitation in obese older adults. The current findings and those of others therefore suggest that weight loss combined with exercise is likely to be the safest and most effective approach to glycemic control among older adults.

In the U.S., approximately 57 million adults have impaired fasting glucose, and up to 70% will progress to overt type 2 diabetes in their lifetime without effective intervention.³⁸ True disease prevention should be counted as the maintenance or restoration of normal glucose regulation rather than a prolonged prediabetic state, with which there remains significant health risk.² The American Diabetes Association currently recommends that people with prediabetes be referred to an effective program promoting 5%–10% body weight loss and at least 150 minutes/week of moderate physical activity.³⁹ While maximum benefit will be achieved with successful weight loss, ongoing effort to promote regular physical activity has the potential for health benefits among women with impaired fasting glucose, and to help prevent the potentially deleterious loss of lean mass in older individuals undergoing weight loss.

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Figure 1.

Flow of participants through the Nutrition and Exercise in Women (NEW) trial

Note: DXA, dual emission X-ray absorptiometry

Table 1

Selected baseline characteristics of randomized women

Variable	CONTROL M $\pm$ SD or n (%)	EXERCISE M $\pm$ SD or n (%)	DIET M $\pm$ SD or n (%)	DIET+EXERCISE M $\pm$ SD or n (%)
<i>n</i>	87	117	118	116
Age (years)	57.4 (4.4)	58.1 (5.0)	58.1 (5.9)	58.0 (4.4)
Ethnicity (%)				
Non-Hispanic white	74 (85.1)	98 (83.8)	101 (85.6)	99 (85.3)
Non-Hispanic black	6 (6.9)	15 (12.8)	9 (7.6)	5 (4.3)
Hispanic	3 (3.5)	2 (1.7)	2 (1.7)	5 (4.3)
Other (American Indian, Asian, or Unknown)	4 (4.6)	2 (1.7)	6 (5.1)	7 (6.0)
College graduate	59 (67.8)	70 (59.9)	76 (64.4)	81 (69.8)
Full-time employment	47 (63.5)	53 (55.2)	58 (55.2)	64 (62.1)
Married or living with partner	59 (73.8)	71 (60.7)	79 (67.0)	69 (60.0)
Weight (kg)	84.2 (12.5)	83.7 (12.3)	84.0 (11.8)	82.6 (10.8)
BMI	30.7 (3.9)	30.7 (3.7)	31.1 (3.9)	31.0 (4.3)
Waist circumference (cm)	94.8 (10.2)	95.1 (10.1)	94.6 (10.2)	93.7 (9.9)
Body fat (%)	47.3 (4.4)	47.3 (4.1)	47.0 (4.3)	47.4 (4.5)
Average calories consumed (kcal/day) ^a	1988 (669)	1986 (589)	1884 (661)	1894 (639)
Relative % calories from fat ^b	35.6 (6.9)	33.6 (6.9)	33.1 (6.3)	35.3 (7.3)
VO _{2max} (ml/kg/min)	23.1 (4.1)	22.5 (4.1)	22.7 (3.8)	23.6 (4.1)
Pedometer steps/day (7-day average)	5605 (2334)	5777 (2129)	5539 (2257)	5952 (2354)
Insulin (pmol/L)	93.20 (44.80)	86.95 (55.84)	91.26 (60.56)	87.23 (59.80)
C-peptide (nmol/L)	0.92 (0.31)	0.87 (0.33)	0.89 (0.36)	0.86 (0.33)
Glucose (mmol/L)	5.38 (0.46)	5.32 (0.45)	5.37 (0.48)	5.33 (0.43)
HOMA-IR	3.22 (1.65)	2.99 (2.19)	3.17 (2.25)	3.01 (2.22)

^a Daily kcal values derived from FFQ were truncated <600 kcal and >4000^b % calories from fat = (total calories derived from fat/total daily caloric intake)

No significant differences in baseline variables between groups, except in daily calories consumed as fat (p=0.02)

Table 2
Baseline, 12-month, and % change values in serum insulin, C-peptide, glucose, and HOMA-IR across four arms of the NEW trial

Variable	CONTROL				EXERCISE				DIET				DIET + EXERCISE			
	Baseline Geo M (95% CI)	12 months Geo M 95% CI	Change ^d (%)	Baseline Geo M 95% CI	12 months Geo M 95% CI	Change* (%)	<i>P</i> ^b	Baseline Geo M 95% CI	12 months Geo M 95% CI	Change* (%)	<i>P</i> ^f	Baseline Geo M 95% CI	12 months Geo M 95% CI	Change* (%)	<i>P</i> ^f	
Insulin (pmol/L)	83.27 (75.21, 92.23)	81.67 (73.83, 90.35)	-1.9	75.98 69.24, 83.34	70.08 64.17, 76.46	-7.8	0.22	76.40 68.62, 89.94	59.38 53.55, 65.91	-22.3	<0.001	74.10 67.02, 92.02	56.32 50.91, 62.37	-24.0	<0.001	
C-peptide (nmol/L)	0.87 0.81, 0.94	0.88 0.82, 0.94	1.1	0.82 0.77, 0.87	0.79 0.74, 0.84	-3.7	0.14	0.83 0.77, 0.89	0.73 0.68, 0.78	-12.0	<0.001	0.81 0.76, 0.86	0.69 0.65, 0.74	-14.8	<0.001	
Glucose (mmol/L)	5.37 5.27, 5.46	5.36 5.27, 5.45	0.2	5.30 5.22, 5.38	5.25 5.17, 5.32	-0.9	0.29	5.35 5.27, 5.44	5.22 5.14, 5.30	-2.4	0.008	5.31 5.23, 5.39	5.16 5.07, 5.22	-2.8	0.002	
HOMA-IR	2.83 2.54, 3.16	2.78 2.49, 3.09	-1.8	2.55 2.31, 2.82	2.33 2.12, 2.56	-8.6	0.19	2.59 2.31, 2.90	1.96 1.76, 2.19	-24.3	<0.001	2.50 2.24, 2.78	1.84 1.65, 2.05	-26.4	<0.001	

^a percentage change from baseline to 12 months
^b p-value comparing change from baseline to 12 months in each intervention group versus controls

Table 3

12-month changes in body weight and metabolic markers in women aged 50–60 years and 60–75 years, within each intervention arm

	Control			Exercise			Diet			Diet + Exercise		
	50–60 years	60–75 years	p	50–60 years	60–75 years	p	50–60 years	60–75 years	p	50–60 years	60–75 years	p
Body weight (%)	–0.5	–1.6		–2.0	–3.2	0.83	–9.1	–7.2	0.05	–10.4	–11.6	0.75
% Body Fat	0.1	–1.3		–2.8	–2.0	0.57	–9.9	–3.1	0.01	–12	–6.1	0.57
Insulin (%)	–1.8	–2.4		–13.6	6.1*	0.12	–21.8	–23.1	0.75	–23.1	–26.0	0.78
C-peptide (%)	0.0	0.1		–6.4	2.9*	0.26	–11.4	–13.2	0.62	–13.5	–16.3	0.52
Glucose (%)	0.5	–1.5		–1.2	–3.8	0.45	–2	–0.8	0.77	–2.6	–4.2	0.82
HOMA-IR (%)	–1.1	–3.9		–14.6	5.2*	0.11	–23.1	–26	0.80	–25	–29.3	0.82

p= age interaction effect in each intervention arm compared to controls

* p<0.01 between age groups within intervention arm

Table 4

Changes in serum insulin, C-peptide, glucose and HOMA-IR among NEW participants stratified according to 12-month weight loss, fat loss, change in cardiorespiratory fitness, and change in average pedometer steps/day

Weight Loss (%) ^a				
	<5%	≥5%–10%	≥10%	<i>p</i> trend ^c
<i>n</i>	155	74	122	
Insulin (pmol/L)	–5.83 (39.38)	–17.15 (44.52)	–29.66 (34.31)	<0.001
C-peptide (nmol/L)	0.007 (0.17)	–0.10 (0.19)	–0.19 (0.18)	<0.001
Glucose (mmol/L)	–0.01 (0.35)	–0.20 (0.34)	–0.21 (0.37)	<0.001
HOMA-IR	–0.23 (1.63)	–0.69 (1.74)	–1.10 (1.25)	<0.001

Total fat loss (kg) ^d *				
	Tertile 3	Tertile 2	Tertile 1	<i>P</i> trend ^c
<i>n</i>	117	117	117	
Insulin (pmol/L)	–1.88 (22.29)	–19.65 (51.60)	–27.99 (36.67)	<0.001
C-peptide (nmol/L)	0.01(0.12)	–0.11 (0.23)	–0.018 (0.17)	<0.001
Glucose (mmol/L)	0.008 (0.35)	–0.15 (0.36)	–0.22 (0.35)	<0.001
HOMA-IR	–0.06 (0.89)	–0.78 (2.06)	–1.06 (1.40)	<0.001

ΔVO2max (L/min) ^b ***				
	Tertile 3	Tertile 2	Tertile 1	<i>p</i> trend ^c
<i>n</i>	80	75	78	
Insulin (pmol/L)	–8.75 (36.88)	–17.36 (31.46)	–17.64 (51.88)	0.01
C-peptide (nmol/L)	–0.06 (0.18)	–0.09 (0.17)	–0.09 (0.23)	0.03
Glucose (mmol/L)	–0.04 (0.32)	–0.18 (0.40)	–0.12 (0.38)	0.08
HOMA-IR	–0.31 (1.49)	–0.67 (1.18)	–0.69 (2.09)	0.01

ΔSteps/day ^b ***				
	<1	1–3520	>3520	<i>p</i> trend ^c
<i>n</i>	68	72	93	
Insulin (pmol/L)	–9.38 (28.89)	–6.04 (28.34)	–24.72 (53.41)	0.001
C-peptide (nmol/L)	–0.03 (0.15)	–0.04 (0.16)	–0.15 (0.22)	<0.001

	Weight Loss (%) ^d			<i>p</i> trend ^c
	<5%	≥5%–10%	≥10%	
Glucose (mmol/L)	−0.07 (0.34)	−0.08 (0.367)	−0.19 (0.39)	0.01
HOMA-IR	−0.35 (1.16)	−0.25 (1.08)	−0.94 (2.15)	0.001

^a groups include women randomized to any intervention (*n*=351)

^b groups include women randomized to exercise or exercise + diet (*n*=233)

^c adjusted for age, intervention arm, and baseline value of metabolic variable of interest

^d additionally adjusted for 12-month change in pedometer steps/day;

^e additionally adjusted for 12-month % weight change

* Fat loss (group M): tertile 1=−0.06 kg; tertile 2=−4.5 kg; tertile 3=−12.0 kg

** VO₂max(group M): tertile 1=−0.12 L/minute; tertile 2=0.12 L/minute; tertile 3=0.44 L/minute

*** 3520 steps is equivalent to ≈2 miles

Table 5

Odds of regression to normal fasting glucose (NFG; <5.6 mmol/L) at 12 months among study participants with impaired fasting glucose (IFG; 5.6–6.9 mmol/L) at baseline.

	IFG	IFG	Incident IFG	Odds of returning to NFG (95% CI) ^b	
	Baseline (n)	12 mo (n)	12 mo ^d	Model 1	Model 2
Control	30	23	10/57	1.00 (ref)	1.00
Diet	43	23	3/75	3.19 (1.09, 9.28)	1.97 (0.63–6.16)
Exercise	35	17	5/82	3.64 (1.21, 11.01)	3.16 (1.02–9.75)
Diet+Exercise	35	14	2/81	5.17 (1.71–15.69)	2.35 (0.68–8.18)
Body Weight Change (%)					
≤0% loss (no change or gain)	35	25	9/81	1.00	1.00
<5% loss	43	28	4/61	1.65 (0.60–4.51)	1.62 (0.58–4.50) ^c
5%–10% loss	27	10	1/56	4.97 (1.63–15.11)	5.12 (1.65–15.86) ^c
≥10% loss	38	14	6/88	6.26 (2.14–18.29)	6.86 (2.27–20.77) ^c
ptrend=0.001					
Change in VO ₂ max (L/min) ^d					
No change or deterioration	46	24	10/154	1.00	1.00
+0.01–0.14 L/minute	50	36	4/47	1.17 (0.45–2.99)	0.78 (0.27–2.21) ^e
≥+0.14 L/minute	47	17	6/94	2.78 (1.27–6.07)	2.48 (1.11–5.57) ^e
ptrend=0.337					

^a Incident IFG = **new** cases of IFG (100–125 mg/dL) among women with values <100mg/dL at baseline

^b **Model 1:** adjusted for age, baseline serum fasting glucose; **Model 2:** additionally adjusted for % body weight change. Stratified analyses were also adjusted for group randomization.

^c Analyses additionally adjusted for change in VO₂max;

^d Groups represent approximate tertiles of change in cardiorespiratory fitness

^e Analyses additionally adjusted for change in % body weight change