Sex Differences in Diabetes Risk and the Effect of Intensive Lifestyle Modification in the Diabetes Prevention Program

LEIGH PERREAULT, MD[1]
YONG MA, MS[2]
SAM DAGOGO-JACK, MD[3]
EDWARD HORTON, MD[4]
DAVID MARRERO, MD[5]
JILL CRANDALL, MD[6]
ELIZABETH BARRETT-CONNOR, MD[7]
FOR THE DIABETES PREVENTION PROGRAM

OBJECTIVE — In participants of the Diabetes Prevention Program (DPP) randomized to intensive lifestyle modification (ILS), meeting ILS goals strongly correlated with prevention of diabetes in the group as a whole. Men met significantly more ILS goals than women but had a similar incidence of diabetes. Therefore, we explored sex differences in risk factors for diabetes and the effect of ILS on risk factors.

RESEARCH DESIGN AND METHODS — Baseline risk factors for diabetes and percent change in risk factors over the first year in men versus women were compared using Wilcoxon's rank-sum tests.

RESULTS — At baseline, men were older and had a larger waist circumference; higher fasting plasma glucose concentration, caloric intake, and blood pressure; and lower HDL cholesterol and corrected insulin response than women, who were less physically active and had a higher BMI ($P < 0.01$ for all comparisons). Over the first year of the DPP, no sex difference in risk factors for diabetes was observed for those who lost <3% body weight. Weight loss of 3–7% body weight yielded greater decreases in 2-h glucose ($P < 0.01$), insulin concentration ($P < 0.04$), and insulin resistance ($P < 0.03$) in men than in women. Weight loss of >7% body weight resulted in greater decreases in 2-h glucose ($P < 0.01$), triglyceride level ($P < 0.01$), and A1C ($P < 0.03$) in men than in women.

CONCLUSIONS — Weight loss >3% body weight yielded greater reduction in risk factors for diabetes in men than in women. Despite the more favorable effects of ILS in men, baseline risk factors were more numerous in men and likely obscured any sex difference in incident diabetes.

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The global epidemic of type 2 diabetes has led to a number of large clinical trials examining the feasibility and efficacy of prevention strategies, including both lifestyle modification and drug therapy (1–4). Despite their large number of participants, none of these trials were specifically designed to compare sex differences in adherence to or benefit from the interventions. The Malmo Study (1) included only men. The Da Xing Study included equal numbers of men and women with impaired glucose tolerance, but no sex-specific comparisons were reported (3). The Finnish Diabetes Prevention Study reported a 63% reduction in the incidence of diabetes among men versus a 54% reduction among women with impaired glucose tolerance in a comparison of intensive lifestyle modification (ILS) to no lifestyle intervention (4). However, the authors do not report whether this sex difference was statistically different or whether men met more lifestyle goals than women. The U.S. Diabetes Prevention Program (DPP) also studied adults with impaired glucose tolerance and found that men were significantly more physically active, lost more weight, and met more of the goals of ILS than women; nevertheless, reduction in incidence of diabetes in the lifestyle group did not differ significantly by sex (2). Results from the DPP suggest that sexual dimorphism may exist with regard to adherence to or benefit from ILS, but its magnitude or mechanism has not been explored. The aim of this paper was to examine sex differences in risk factors for diabetes and compare the effect of lifestyle changes on cardiometabolic and diabetes risk in men versus women.

RESEARCH DESIGN AND METHODS

— The DPP was a randomized clinical trial conducted at 27 sites enrolling individuals who were at high risk for diabetes. Detailed methodology has been reported (5), and the protocol is available at http://www.bsc.gwu.edu/dpp. The institutional review board at each center approved the protocol, and all participants gave written informed consent before participation.

Eligibility criteria included age ≥25 years, BMI ≥24 kg/m^2 (≥22 kg/m^2 in Asians), and plasma glucose concentration 5.3–6.9 mmol/l (≤6.9 mmol/l in the American Indian clinics) in the fasting state and 7.8–11.0 mmol/l 2 h after a 75-g oral glucose tolerance test (OGTT). Individuals were excluded if they were taking medicines known to alter glucose tolerance or had significant illness.

Interventions

Eligible participants were randomly assigned to one of three interventions: *1*) placebo twice daily and standard lifestyle recommendations; *2*) metformin, at a dose of 850 mg twice daily, and standard lifestyle recommendations; or *3*) ILS. This paper considers sex differences only in the lifestyle and placebo groups.

The goals for the participants assigned to ILS were to achieve and main-

From the [1]University of Colorado Health Sciences Center, Aurora, Colorado; the [2]Coordinating Center, George Washington University, Rockville, Maryland; the [3]University of Tennessee, Memphis, Tennessee; the [4]Joslin Diabetes Center, Boston, Massachusetts; [5]Indiana University, Indianapolis, Indiana; the [6]Albert Einstein College of Medicine, Bronx, New York; and the [7]University of California, San Diego, La Jolla, California.

Corresponding author: The Diabetes Prevention Program Coordinating Center, dppmail@biostat.bsc.gwu.edu.

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tain a weight reduction of at least 7% in initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 min per week.

Outcome measures

The primary outcome was diabetes, diagnosed on the basis of a confirmed value for plasma glucose of ≥7.0 mmol/l in the fasting state or ≥11.1 mmol/l 2 h after a 75-g OGTT. Self-reported levels of leisure physical activity were assessed semi-annually with the Modifiable Activity Questionnaire (5). The physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week) weighted by an estimate of the metabolic equivalent of that activity (MET) and summed for all activities performed, with the result expressed as the average MET-hours per week for the previous year. Usual daily caloric intake during the previous year, including calories from fat, carbohydrate, protein, and other nutrients, was assessed at baseline and at 1 year with the use of a modified version of the Block food frequency questionnaire (5). Weight was measured semi-annually and compared with previous measures to calculate weight change.

Venous blood was obtained and processed at each DPP clinical site following DPP protocol (available at https://www.bsc.gwu.edu/dpp/protocol.htmlvdoc). Serum and plasma samples were stored at −20°C for several days and then shipped in batches on dry ice to the same central laboratory. Measurement methods for glucose, insulin, triglyceride, HDL cholesterol, and A1C have been published (5).

Measures of insulin secretion (corrected insulin response [CIR]) and insulin action (homeostasis model assessment of insulin resistance [HOMA-IR]) were calculated and compared between men and women using validated indexes (6,7). These indexes were calculated as follows:

CIR = [100 × 30 min insulin]/[30 min glucose × (30 min glucose − 70)] and

HOMA-IR = 1/{22.5/[fasting insulin × (fasting glucose/18.01)]}.

Statistical analysis

Wilcoxon's rank-sum tests were used to compare continuous baseline characteristics between the sexes, and data were reported as median ± interquartile ranges because of their nonnormal distribution. Pearson's χ^2 tests were used to compare categorical baseline characteristics between the sexes. The effect of sex on the development of diabetes was modeled using Cox proportional hazards models. Wilcoxon's rank-sum tests were also used to compare changes in continuous variables from baseline to the end of year 1. Pearson's χ^2 test was used to compare manners of progression to diabetes (fasting vs. 2-h glucose concentration vs. both) at time of diagnosis. All analyses were conducted using SAS software (version 9.1; SAS Institute, Cary, NC).

RESULTS

Demographics

There were twice as many women as men in both the ILS (734 women and 345 men) and placebo (747 women and 335 men) groups, reflecting the demographic of the overall cohort. Ethnic distribution was generally similar in men and women. At baseline, men were older, had a larger waist circumference, and had higher caloric intake and blood pressure than women, who were less physically active and had a higher BMI ($P < 0.01$ for all comparisons) (Table 1). Obesity (BMI >30 kg/m^2) was present in 56.5% of men and 73% of women ($P < 0.0001$). Men and women were comparable in terms of socioeconomic status (estimated from employment status, education, annual family income, marital status, and number of individuals in household). The dropout rate during the trial was less than 10% in both men and women.

Meeting goals

In the ILS group, men lost more absolute weight (6.0 vs. 4.6 kg, $P < 0.01$), a greater percentage of body weight (8 vs. 7%, $P = 0.02$), and more absolute and percentage of waist circumference (5.6 cm [5.2%] vs. 4.6 cm [4.4%], $P < 0.05$ for all comparisons) than women. Overall, more men than women achieved the 7% weight loss goal (46.8 vs. 37.4%, $P = 0.0004$). Men also reported higher levels of leisure (11.5 vs. 3.2 MET h/week, $P = 0.001$) and recreational (10.6 vs. 6.8 MET h/week, $P = 0.05$) activity than women. Neither the absolute daily reduction in calories ($P = 0.11$) nor the percentage of change in reported caloric intake ($P = 0.07$) differed by sex. In the placebo group, no sex differences were observed with respect to change in weight, BMI, waist circumference, or caloric intake (Table 2).

Sex and ILS effect on cardiometabolic and diabetes risk

As previously reported, the DPP showed a 58% reduction in conversion to diabetes among participants randomized to ILS compared with those randomized to placebo (2), and the overall treatment effect did not differ by sex ($P = 0.71$). However, despite the fact that men in the ILS group met more of the lifestyle goals than women, the percentage of diabetes risk reduction (61.6 vs. 51.8% higher than placebo, men versus women; $P = 0.25$) and of participants achieving normal glucose tolerance (37.7 vs. 36.5%, men versus women; $P = 0.72$) did not differ by sex.

Baseline measures

We considered whether the lack of greater benefit in the men in the ILS group could be related to sex differences at baseline. Baseline fasting plasma glucose concentration was higher in men than in women (5.9 ± 0.7 vs. 5.8 ± 0.6 mmol/l, respectively; $P < 0.01$) with no sex difference in postchallenge glucose concentration (2-h post-OGTT glucose 9.0 ± 1.6 vs. 8.9 ± 1.5 mmol/l, $P = 0.60$) or A1C (5.9 ± 0.5% for both, $P = 0.94$). Despite their higher fasting glucose levels, men did not have higher fasting insulin levels at baseline (138 ± 102 vs. 144 ± 105 pmol/l, $P = 0.23$). This apparent sex difference in the insulinotropic response to ambient glycemia was corroborated by calculation of the CIR (0.49 ± 0.4 vs. 0.56 ± 0.41, $P < 0.01$). In contrast, men had similar whole-body insulin action as assessed by HOMA-IR (6.0 ± 4.6 vs. 6.0 ± 4.9, $P = 0.73$). Men also had higher blood pressure (124/80 ± 18/13 vs. 121/78 ± 21/13 mmHG, $P < 0.01$) and lower HDL cholesterol than women at baseline (39 ± 13 vs. 47 ± 16 mg/dl, $P < 0.01$). Comparable sex differences were observed in the placebo group at baseline (Table 1).

Measures at the end of year 1

It was further considered whether lack of greater benefit from ILS in men may have been due to a weaker effect of ILS on risk factors for cardiovascular disease and diabetes in men. To examine the effect of ILS on risk factors for cardiovascular disease and diabetes, groups were stratified by weight loss (<3%, 3–7%, and >7%), as weight loss is more closely related to diabetes prevention than the manner in which it occurs (8). Within each weight loss stratum, changes in activity, calorie intake, BMI, and percentage of weight loss

Table 1—*Baseline characteristics and risk factors for cardiovascular disease and/or diabetes of study participants randomized to ILS or placebo*

	ILS		Placebo	
	Men	Women	Men	Women
n (%)	345 (32)	734 (68)*	335 (31)	747 (69)*
Age (years)	54.0 ± 17.4	47.8 ± 14.5*	53.1 ± 15.2	48.3 ± 12.9*
Race/ethnic group (*n* [%])				
White	199 (57.7)	381 (51.9)	184 (54.9)	402 (53.8)
African American	50 (14.5)	154 (21.0)	57 (17.0)	163 (21.8)
Hispanic	58 (16.8)	120 (16.3)	57 (17.0)	111 (14.9)
American Indian	31 (9.0)	26 (3.5)	7 (2.1)	52 (7.0)
Asian	7 (2.0)	53 (7.2)	30 (9.0)	19 (2.5)
Cardiometabolic risk factors				
Fasting glucose (mmol/l)	5.9 ± 0.7	5.8 ± 0.6*	6.0 ± 0.7	5.8 ± 0.6*
TG (mmol/l)	2.01 ± 1.45	1.76 ± 1.29*	2.01 ± 1.32	1.94 ± 1.36
HDL (mmol/l)	1.01 ± 0.7	1.22 ± 0.41*	1.01 ± 0.26	1.16 ± 0.39*
BP (mmHg)	124/80 ± 18/13	121/78 ± 20/13*	125/80 ± 18/13	121/77 ± 20/13*
Waist circumference (cm)	106.5 ± 17.7	101.8 ± 19.0*	105.9 ± 17.2	103.0 ± 20.4*
BMI (kg/m^2)	30.9 ± 6.2	33.6 ± 8.6*	30.9 ± 7.1	34.1 ± 9.6*
Activity				
Leisure(MET/h)	13.8 ± 22.4	8.1 ± 12.8*	15.6 ± 24.1	8.1 ± 14.8*
Recreational (MET/h)	70.5 ± 57.0	57.4 ± 52.3*	70.9 ± 53.6	55.5 ± 48.8*
Caloric intake (kcal)	2,065 ± 1,149	1,789 ± 1,041*	1,990 ± 1,178	1,851 ± 1,019*
% on meds for TG or BP	22.0	17.8	21.2	15.7†
% women on HRT	–	24.4	–	20.6
Diabetes risk factors				
2-h glucose (mmol/l)	9.0 ± 1.6	8.9 ± 1.5	9.0 ± 1.6	9.0 ± 1.6
A1C (%)	5.9 ± 0.6	5.9 ± 0.6	5.9 ± 0.7	5.9 ± 0.6
Insulin (pmol/l)	138 ± 102	144 ± 108	144 ± 90	144 ± 102
Index of insulin secretion				
CIR	0.49 ± 0.4	0.56 ± 0.41*	0.52 ± 0.49	0.57 ± 0.44*
Index of insulin action				
HOMA-IR	6.0 ± 4.6	6.0 ± 4.9	6.4 ± 4.2	6.2 ± 4.7

Data are medians ± interquartile range unless otherwise indicated. Twenty Pacific Islanders were included in the "Asian" group. Physical activity data are based on responses to the Modifiable Activity Questionnaire. MET-hours represent the average amount of time engaged in specified physical activities multiplied by the MET value of each activity. BP, blood pressure; HRT, hormone replacement therapy; TG, triglyceride. *$P < 0.01$, men vs. women; †$P < 0.05$, men vs. women.

were not different between men and women. Over year 1 of DPP, as weight loss increased, fasting and 2-h glucose, triglycerides, blood pressure, waist circumference, BMI, A1C, insulin level, and insulin resistance (HOMA-IR) decreased, whereas HDL cholesterol and insulin secretion (CIR) increased in both sexes. No sex difference in any risk factor for diabetes was observed for those who lost <3% body weight (including the placebo group). Weight loss of 3–7% yielded greater decreases in 2-h glucose ($P < 0.01$), insulin concentration ($P < 0.04$), and insulin resistance ($P < 0.03$) in men than women. Weight loss of >7% resulted in greater decreases in 2-h glucose ($P < 0.01$), triglyceride level ($P < 0.01$), and A1C ($P < 0.03$) in men than women (Table 3).

Progression to diabetes

Sequential Cox proportional hazards models revealed no independent effect of sex on diabetes risk in ILS or placebo group participants after adjustment for baseline and time-dependent variables (data not shown). However, among those who progressed to diabetes during the DPP, we observed significant differences with respect to the manner in which men and women were diagnosed. Although a similar proportion of men (15.6%) and women (14.5%) were diagnosed by fasting glucose criteria alone, women were more likely than men to convert by 2-h glucose alone (66.1 vs. 54.4%, respectively) and men were more likely to convert on the basis of fasting and 2-h glucose together (30.0 vs. 19.4%) ($P \leq 0.02$ for all).

CONCLUSIONS — In the DPP lifestyle cohort, meeting the 7% weight loss goal via a hypocaloric low-fat diet and 150 min per week of moderate-intensity physical activity was strongly correlated with the prevention of diabetes in both sexes. Although men in the ILS group lost significantly more weight and reported more physical activity than women, their rate of progression to diabetes (or regression to normal glucose tolerance) was the same. The present analyses suggest that the lack of greater benefit in the men may have been caused by a greater load of baseline risk factors. Of the cardiometabolic and diabetes risk factors assessed at baseline, women had higher risk in two (higher BMI and less physical activity), whereas men had higher risk in six (older age; higher fasting glucose level, waist circumference, and blood pressure; and lower HDL and insulin secretion). We explored the possibility that lack of greater benefit in the men could be due to a weaker effect of ILS on risk factors for diabetes in men versus women. To control for sex difference in levels of success with ILS, groups were stratified by weight loss as an objective measure of adherence (since diet and activity information was

Table 2—*Percent change in risk factors for cardiovascular disease and diabetes over year 1 in those randomized to placebo*

	Men	Women
n	335	747
Cardiometabolic risk factors		
Fasting glucose	0.0 ± 11.9	−0.9 ± 11.9
TG	−5.1 ± 46.8	−5.1 ± 40.8
HDL	0.0 ± 15.6	0.0 ± 17.6
BP	−0.8/−1.3 ± 13/14	−0.9/−1.3 ± 13/16
Waist circumference	−0.2 ± 4.8	−0.5 ± 6.1
Weight	0.0 ± 3.7	0.1 ± 4.5
BMI	0.0 ± 3.8	0.1 ± 5.2
Physical activity	12.5 ± 125	6.6 ± 162
Caloric intake	−8.5 ± 42.7	−9.7 ± 36.9
% on meds for TG or BP	0.5	8.3
Diabetes risk factors		
2-h glucose	−6.9 ± 30.4	−4.8 ± 27.5†
A1C	0.02 ± 0.06	0.00 ± 0.06
Insulin	5.0 ± 53.2	0.0 ± 57.1
Index of insulin secretion		
CIR	−4.1 ± 57.1	−2.3 ± 59.4
Index of insulin action		
HOMA-IR	5.3 ± 61.0	0.2 ± 64.9

Data are medians ± interquartile range. BP, blood pressure; TG, triglyceride. †$P < 0.05$, men vs. women.

based on self-report) and also because weight loss is more closely related to diabetes prevention than the manner in which it occurs (8). When stratified by weight loss, reduction in cardiometabolic and diabetes risk factors was actually greater in men than in women. Nevertheless, fasting glucose was only slightly modified by ILS and appeared to be more important in the development of diabetes in men than the development of diabetes in women. Greater success with ILS did not translate into reduced incidence of diabetes in men versus women, in part because of the higher baseline risk factors, especially fasting glucose concentration, in men in the DPP.

With more numerous risk factors at baseline, men conceivably had a greater risk for diabetes than women from the outset of the DPP. Cox proportional hazards modeling adjusted for age and ethnicity demonstrated a nonsignificant trend toward a 20% higher risk of diabetes in male than in female placebo participants in the DPP ($P = 0.08$). Several large trials, including the Strong Heart Study (9) and the Women's Health Study (10), contend that the type and/or potency of cardiometabolic and diabetes risk factors may be different in men and women. In particular, older age, higher blood pressure, and the presence of metabolic syndrome have been shown to convey greater cardiometabolic and/or diabetes risk in women (11,12). Certainly, diabetes itself has long been appreciated as a stronger relative risk factor for cardiovascular disease in women (13). Therefore, the fact that older age, higher plasma fasting glucose, and features of metabolic syndrome were more common in men than women at baseline in the DPP makes it worth considering whether the more numerous baseline risk factors in men actually conferred greater diabetes risk or simply equalized the risk between the sexes. A meta-analysis of 16 trials comparing the impact of sex with that of risk factors for cardiovascular disease revealed that cardiometabolic risk could be predicted by cardiometabolic risk factors but not by sex per se (14). In sum, men in the DPP had more numerous risk factors than women, presumably making their baseline risk for diabetes higher. Whether these risk factors modified disease risk differently in men versus women in the DPP remains speculative.

Higher fasting glucose concentration in men versus women in the DPP is consistent with repeated observations in population studies (15,16). Although both fasting and 2-h glucose concentrations are positively associated with diabetes risk, diabetes incidence rises exponentially as fasting glucose levels increase but only linearly when 2-h glucose levels increase (17). Therefore, when participants were enrolled in the DPP (requiring elevation of both fasting and 2-h glucose values), the men started with higher diabetes risk due to higher initial fasting glucose values. Strong evidence exists that those with high fasting and 2-h glucose values progress to diabetes more rapidly than those with only one or the other (18,19). Although no overall sex difference was observed in incident diabetes in the DPP, sex difference in manner of diagnosis was observed. More women than men progressed to diabetes based on 2-h glucose criteria, whereas more men than women progressed based on the combination of fasting and 2-h glucose criteria. Together, these observations highlight the importance of fasting hyperglycemia as a risk factor and route of progression to diabetes in men.

Strengthening its role as a pivotal risk factor, fasting glucose was only modestly affected by lifestyle intervention. ILS improved many risk factors for diabetes among participants of the DPP but appeared to be more robust in lowering 2-h than fasting glucose levels. In those randomized to ILS, 2-h glucose concentration during the OGTT fell 5–26%, whereas fasting glucose concentration fell only 1–8%. Two-hour glucose concentration decreased steadily in response to increased success with ILS in both men and women; however, among those who lost >3% body weight, the decrease was greater in men. Although no weight change was noted among placebo participants in the DPP, a decrease in 2-h glucose at year 1 was seen in men but not women. This may relate to the fact that men were more physically active than women upon entry and throughout the DPP. Consistent with the recently published AusDiab study (20), 2-h glucose appears to be more strongly modified by physical activity than fasting glucose, and the effect may be independent of weight loss.

The greater decline in 2-h glucose in men versus women who lost >3% body weight in the DPP might be explained by sex differences in glucose uptake and oxidation during physical activity (21). Clinical studies suggest that men rely proportionately more on carbohydrate and women proportionately more on lipid during submaximal physical activity (21,22). This is evidenced by a higher respiratory exchange ratio in men (21,22) during exercise at a similar intensity. The preferential use of carbohydrate as a fuel

Table 3—*Percent change in risk factors for cardiovascular disease and diabetes over year 1 in those randomized to ILS*

	<3% weight loss		3–7% weight loss		>7% weight loss	
	Men	Women	Men	Women	Men	Women
n	48	159	86	181	178	322
Cardiometabolic risk factors						
Fasting glucose	−3.8 ± 15.1	−1.0 ± 10.7	−4.4 ± 10.5	−3.9 ± 9.8	−6.8 ± 11	−7.6 ± 9.1
TG	−4.3 ± 42.9	1.5 ± 37.5	−13.3 ± 43	−11.1 ± 38	−28 ± 43	−19 ± 40*
HDL	0.0 ± 16.1	−2.0 ± 17.5	2.8 ± 21	2.0 ± 17	6.5 ± 18	4.6 ± 20
BP	1.2/0.0 ± 12/12	0.8/0.0 ± 12/14	−1.1/−3.6 ± 15/15	−2.1/−4.1 ± 14/15	−6.4/−8.9 ± 13/14	−4.9/−7.6 ± 12/14
Waist circumference	−2.1 ± 5.4	−1.3 ± 5.2	−4.9 ± 4.0	−4.7 ± 5.2	−9.3 ± 6.5	8.7 ± 6.9
BMI	−0.8 ± 2.5	−0.6 ± 2.7	−5.4 ± 1.8	5.0 ± 2.2	−10.2 ± 5.5	−11.1 ± 5.7
Physical activity	51 ± 167	30 ± 187	43 ± 162	42 ± 230	67 ± 221	92 ± 281
Caloric intake	−8.4 ± 40	−19.2 ± 38	−17.5 ± 47	−22.4 ± 36	−18.7 ± 36	−21.1 ± 39
% on meds for TG or BP	0.0	0.0	0.0	0.0	0.0	0.0
Diabetes risk factors						
2-h glucose	−6.9 ± 30	−5.2 ± 27	−22 ± 29	−13 ± 27*	−26 ± 30	−19 ± 26*
A1C	−0.02 ± 0.05	0.00 ± 0.07	−0.02 ± 0.05	−0.02 ± 0.05	−0.03 ± 0.06	−0.02 ± 0.05†
Insulin	−2.9 ± 49	−5.9 ± 52	−19 ± 50	−11 ± 49†	−39 ± 41	−33 ± 40
Index of insulin secretion						
CIR	−0.9 ± 65	2.7 ± 61	0.9 ± 69	−3.1 ± 65	3.6 ± 68	4.3 ± 66
Index of insulin action						
HOMA-IR	−4.4 ± 70	−6.0 ± 61	−25 ± 49	−15 ± 51†	−40–5 ± 44	−39 ± 37

Data are medians ± interquartile range. BP, blood pressure; TG, triglyceride. *$P < 0.01$, men vs. women; †$P < 0.05$, men vs. women.

during physical activity in men would mandate postexercise repletion of glucose stores and might explain the greater lowering of 2-h glucose among men with >3% weight loss in the DPP. In addition to 2-h glucose concentration, numerous diabetes and cardiometabolic risk factors were favorably modified by weight loss from ILS. Among those who lost >3% body weight, men appeared to have greater risk factor reduction with respect to insulin concentration and insulin resistance (at 3–7% weight loss), as well as triglyceride concentration and A1C (at >7% weight loss). Although the trends were not consistent between strata of weight loss (as with 2-h glucose), they cumulatively represent improved insulin action, which also likely relates to greater active lean mass in men compared with women.

Several limitations of the current study are worth noting. First, although randomized, the study was not balanced with respect to sex or powered to examine sex differences a priori. Post hoc analyses may yield erroneous results, especially when making multiple comparisons. Second, data on physical activity and dietary intake were self-reported and lack the robustness of a supervised intervention. Finally, the physiological or behavioral basis for the greater success in meeting ILS goals among men versus women is unknown.

In summary, meeting the 7% weight loss goal through ILS strongly correlated with the prevention of diabetes in the DPP participants. Surprisingly, in the ILS group, men lost significantly more weight and were more active than women and yet incident diabetes (or return to normal glucose tolerance) did not differ significantly by sex. The present analyses suggest that the lack of greater benefit in the men may have been obscured by their more numerous and/or more severe baseline risk factors, especially fasting glucose concentration, which was modified only modestly by ILS. Fasting and 2-h glucose concentration may impart different risk for diabetes in men and in women, in that progression to diabetes appeared more dependent on fasting glucose in men and more dependent on 2-h glucose in women. Prospective studies powered to examine sex-specific consequences of different prevention strategies would be useful.

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