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Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program

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Running Title: Effect of sex on diabetes risk

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ABSTRACT

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

*Research Design And Methods***:** Baseline RFs for diabetes, and percent change in RFs over the first year, were compared using Wilcoxon rank-sums in men vs. women.

Results: At baseline, men were older, had a larger waist circumference, higher fasting plasma glucose concentration, caloric intake, and blood pressure, as well as lower HDL cholesterol and corrected insulin response than women, who were less physically active and had a higher body mass index (BMI) ($p<0.01$ for all comparisons). Over the first year of DPP, no sex difference in RFs for diabetes was observed for those who lost <3% body weight. Weight loss of 3-7% yielded greater decreases in 2-hour glucose ($p<0.01$), insulin concentration ($p<0.04$) and insulin resistance ($p<0.03$) in men vs. women. Weight loss of >7% resulted in greater decreases in 2-hour glucose ($p<0.01$), triglyceride level ($p<0.01$) and HbA1C ($p<0.03$) in men vs. women.

Conclusions: Weight loss >3% yielded greater reduction in RFs for diabetes in men vs. women. Despite the more favorable effects of ILS in men, baseline RFs was more numerous in men, and likely obscured any sex difference in incident diabetes.

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 a 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 in women with impaired glucose tolerance comparing lifestyle modification 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 intensive lifestyle modification compared to 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, and benefit from, lifestyle modification, but its magnitude or mechanism have 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 in men versus women relevant to cardiometabolic and diabetes risk.

METHODS

The DPP was a randomized clinical trial conducted at 27 sites enrolling persons 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 prior to participation.

Participants - Eligibility criteria included age at least 25 years, body-mass index (kg/m^2) of 24 or higher (22 or higher in Asians), fasting plasma glucose concentration of 5.3 to 6.9 mmol/l (≤6.9 mmol/l in the American Indian clinics) and 7.8 to 11.0 mmol/l two hours after a 75-g oral glucose load (OGTT). Persons 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) an intensive program of lifestyle modification (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 maintain 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 minutes 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 two hours after a 75 g oral glucose load. 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 one year with the use of a modified version of the Block food frequency questionnaire (5). Weight was measured semi-annually and compared to previous measures to calculate weight change. Venous blood was obtained and processed at each DPP clinical site following a standardized manual of operations (https://www.bsc.gwu.edu/dpp/CBLMOO05-05.pdf). Serum and plasma samples were stored at – 20^{o}C for several days and then shipped in batches on dry ice to the same central laboratory. Measurement methods for glucose, insulin, triglyceride, high-density cholesterol (HDL) and glycosylated hemoglobin (HbA1C) 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 indices (6; 7). These indices were calculated as:

CIR = (100 x 30 minute insulin)/ (30 minute glucose x (30 minute glucose -70))

HOMA-IR = 1/[22.5/(fasting insulin x (fasting glucose/18.01))]

Statistical Analysis **-** Wilcoxon rank-sum tests were used to compare continuous baseline characteristics between the sexes, and data reported as median ± inter-quartile ranges due to their non-normal distribution. Pearson’s chi-square 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 hazard models. Wilcoxon tests were also used to compare changes in continuous variables from baseline to the end of year 1. Pearson’s chi-square test was used to compare manner of progression to diabetes (fasting vs. 2-hour glucose concentration vs. both) at time of diagnosis. All analyses were conducted using SAS software (Version 8.01; SAS Institute, Cary, NC).

RESULTS

Demographics **-** There were twice as many women as men in both the ILS (n=734 women and 345 men) and placebo (n= 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, higher caloric intake, and blood pressure than women, who were less physically active and had a higher body mass index (BMI) (p<0.01 for all comparisons; Table 1). Obesity (BMI > 30 kg/m^2) was present in 56.5% of men and 73.0% 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 percent of body weight (8% vs. 7%, p=0.02), and waist circumference (5.6 cm (5.2%) vs. 4.6 cm (4.4%), p<0.05 for all comparisons) compared to women. Overall, more men than women achieved the 7% weight loss goal (46.8 vs. 37.4%, men vs. women, p=0.0004). Men also reported higher levels of leisure (11.5 vs. 3.2 MET-hr/week, p=0.001) and recreational (10.6 vs. 6.8 MET-hr/week, p=0.05) activity than women. Neither the absolute daily reduction in calories (p=0.11), nor the percent 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 on Cardiometabolic and Diabetes Risk - As previously reported, the DPP showed a 58% reduction in conversion to diabetes among participants randomized to ILS compared to 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 percent diabetes risk reduction (61.6% vs. 51.8%, vs. placebo, men vs. women, p=0.25) and percent of participants achieving normal glucose tolerance (37.7% vs. 36.5%, men vs. 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 women (5.9 ± 0.7 vs. 5.8 ± 0.6 mmol/l, men vs. women, p<0.01) with no sex difference in post-challenge glucose concentration (2-hour post-OGTT glucose 9.0 ± 1.6 vs. 8.9 ± 1.5 mmol/l, p=0.60) or glycosylated hemoglobin (HbA1C, 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, men vs. women, p=0.23). This apparent sex difference in the insulinotropic response to ambient glycemia was corroborated by calculation of the corrected insulin response (CIR; 0.49 ± 0.4 vs. 0.56 ± 0.41, men vs. women, p<0.01). In contrast, men had similar whole-body insulin action as assessed by the homeostasis model assessment of insulin resistance (HOMA-IR, men vs. women, p=0.73). Men also had higher blood pressure (124/80 ± 18/13 vs. 121/78 ± 21/13, 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 diabetes in men. In order 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 strata, changes in activity, calorie intake, BMI and % weight loss were not different between men and women. Over year 1 of DPP, as weight loss increased, fasting and 2-hour glucose, triglycerides, blood pressure waist circumference, BMI, HbA1C, 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 in the placebo group). Weight loss of 3-7% yielded greater decreases in 2-hour glucose (p<0.01), insulin concentration (p<0.04) and insulin resistance (p<0.03) in men vs. women. Weight loss of >7% resulted in greater decreases in 2-hour glucose (p<0.01), triglyceride level (p<0.01) and HbA1C (p<0.03) in men vs. women (Table 3).

Progression to Diabetes - Sequential Cox proportional hazards models revealed no independent effect of sex on diabetes risk in ILS or placebo 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 sex 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 to convert by 2-hour glucose alone (66.1 vs. 54.4%), and men were more likely to convert on the basis of both fasting and 2-hour glucose together (30.0 vs. 19.4%) ($p \leq 0.02$ for all).

DISCUSSION

In the DPP lifestyle cohort, meeting the 7% weight loss goal via a hypocaloric low-fat diet and 150 minutes 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 compared to women, their progression to diabetes (or regression to normal glucose tolerance) did not differ from the progression rate observed in women. The present analyses suggest the lack of greater benefit in the men may have been obscured by a greater load of baseline risk factors. Of the cardiometabolic and diabetes risk factors assessed at baseline, women fared worse than men in two (higher BMI and less physical activity), whereas men fared worse than women in six (older age, higher fasting glucose level, waist circumference and blood pressure, as well as 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 vs. women. To control for sex difference in success with ILS, groups were stratified by weight loss as an objective measure of adherence to ILS (since diet and activity information was 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 vs. women. Nevertheless, fasting glucose was only slightly modified by ILS, and appeared to be more important in the development of diabetes in men as compared to women. Together, greater success with ILS did not translate into reduced incidence of diabetes in men vs. women due, in part, to 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 DPP. Cox proportional hazards modeling adjusted for age and ethnicity demonstrated a non-significant trend toward a 20% higher risk of diabetes in male vs. female placebo participants in DPP ($p=0.08$). Nevertheless, several large trials, including Strong Heart (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, age, blood pressure and 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 (CVD) 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 DPP makes it worth considering if the more numerous baseline risk factors in men actually conferred greater diabetes risk in men, or simply equalized the risk between the sexes. A meta-analysis of 16 trials specifically focused on the impact of sex vs. risk factors on CVD revealed that cardiometabolic risk could be predicted by cardiometabolic risk factors, but not 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 vs. women in DPP remains speculative.

Higher fasting glucose concentration in men vs. women in the DPP is consistent with repeated observations in population studies (15; 16). Although both fasting and 2-hour glucose concentrations are positively associated with diabetes risk, diabetes incidence rises exponentially as fasting glucose levels increase, whereas risk rises linearly with 2-hour glucose values (17). Therefore, when participants were enrolled in DPP (requiring elevation of both fasting and 2-hour 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-hour glucose values progress to diabetes more rapidly than those with one or the other (18; 19). Although no overall sex difference was observed in incident diabetes in DPP, sex difference in manner of diagnosis was observed. More women than men progressed to diabetes based on 2-hour glucose criteria, whereas more men than women progressed based on the combination of fasting and 2-hour 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. Intensive lifestyle modification improved many risk factors for diabetes among participants of the DPP, but appeared to be more robust in lowering 2-hour vs. fasting glucose levels. In those randomized to ILS, 2-hour 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 DPP, a decrease in 2-hour 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 DPP. Consistent with the recently published AusDiab Study (20), 2-hour glucose appears more strongly modified by physical activity than does fasting glucose, and the effect may be independent of weight loss.

The greater decline in 2-hour glucose men vs. women who lost >3% body weight in 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 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 as women. The preferential use of carbohydrate as a fuel during physical activity in men would mandate post-exercise repletion of glucose stores, and might explain the greater lowering of 2-hour glucose among men with >3% weight loss in DPP. In addition to 2-hour 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 HbA1C (at >7% weight loss). Although the trends were not consistent between strata of weight loss (as with 2-hour glucose), they cumulatively represent improved insulin action, which also likely relates to greater active lean mass in men compared to women.

Several limitations of the current study are worth noting. First, although randomized, the study was not balanced with respect to sex, nor was it 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 compared to women is unknown.

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

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REFERENCES

1. Eriksson KF, Lindgarde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia* 34:891-898, 1991
2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002
3. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537-544, 1997
4. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343-1350, 2001
5. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care* 22:623-634, 1999
6. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412-419, 1985
7. Phillips DI, Clark PM, Hales CN, Osmond C: Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med* 11:286-292, 1994
8. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, Hoskin M, Kriska AM, Mayer-Davis EJ, Pi-Sunyer X, Regensteiner J, Venditti B, Wylie-Rosett J: Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 29:2102-2107, 2006
9. Howard BV, Cowan LD, Go O, Welty TK, Robbins DC, Lee ET: Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. The Strong Heart Study. *Diabetes Care* 21:1258-1265, 1998
10. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347:1557-1565, 2002
11. Alexander CM, Landsman PB, Teutsch SM, Haffner SM: NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 52:1210-1214, 2003
12. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 364:937-952, 2004
13. Gregg EW, Gu Q, Cheng YJ, Narayan KM, Cowie CC: Mortality trends in men and women with diabetes, 1971 to 2000. *Ann Intern Med* 147:149-155, 2007
14. Kanaya AM, Grady D, Barrett-Connor E: Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 162:1737-1745, 2002
15. Li CL, Tsai ST, Chou P: Relative role of insulin resistance and beta-cell dysfunction in the progression to type 2 diabetes--The Kinmen Study. *Diabetes Res Clin Pract* 59:225-232, 2003

16. Williams JW, Zimmet PZ, Shaw JE, de Courten MP, Cameron AJ, Chitson P, Tuomilehto J, Alberti KG: Gender differences in the prevalence of impaired fasting glycaemia and impaired glucose tolerance in Mauritius. Does sex matter? *Diabet Med* 20:915-920, 2003
17. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF: Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 46:701-710, 1997
18. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096-1105, 2006
19. Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R: The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. *Diabetes* 52:1475-1484, 2003
20. Healy GN, Dunstan DW, Shaw JE, Zimmet PZ, Owen N: Beneficial associations of physical activity with 2-h but not fasting blood glucose in Australian adults: the AusDiab study. *Diabetes Care* 29:2598-2604, 2006
21. Tarnopolsky MA: Gender differences in substrate metabolism during endurance exercise. *Can J Appl Physiol* 25:312-327, 2000
22. Carter SL, Rennie CD, Hamilton SJ, Tarnopolsky: Changes in skeletal muscle in males and females following endurance training. *Can J Physiol Pharmacol* 79:386-392, 2001

TABLE 1. Baseline Characteristics and Risk Factors for Cardiovascular Disease and/or Diabetes of Study Participants Randomized to intensive Lifestyle Modification (ILS) or Placebo

	ILS		Placebo	
	Men	Women	Men	Women
Number (%)	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 – no. (%)				
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*
Triglyceride (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*
Blood pressure (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*
Body mass index (kg/m^2)	30.9 ± 6.2	33.6 ±8.6*	30.9 ± 7.1	34.1 ±9.6*
Activity:				
Leisure(MET/hr)	13.8 ± 22.4	8.1 ± 12.8*	15.6 ± 24.1	8.1 ± 14.8*
Recreational (MET/hr)	70.5 ± 57.0	57.4 ± 52.3*	70.9 ± 53.6	55.5 ± 48.8*
Caloric intake (kcal)	2065 ± 1149	1789 ± 1041*	1990 ± 1178	1851 ±1019*
% 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-hour glucose (mmol/l)	9.0 ± 1.6	8.9 ± 1.5	9.0 ± 1.6	9.0 ± 1.6
HbA1C (%)	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:				
Corrected insulin response (CIR)	0.49 ± 0.4	0.56 ± 0.41*	0.52 ± 0.49	0.57 ± 0.44*
Index of insulin action:				
Homeostasis model assessment of insulin resistance (HOMA-IR)	6.0 ± 4.6	6.0 ± 4.9	6.4 ± 4.2	6.2 ± 4.7

*p<0.01, men vs. women
†p<0.05, men vs. women
Plus-minus values are medians ± inter-quartile range
Twenty Pacific Islanders were included in the “asian” group
HDL = high-density cholesterol
Physical activity data are based on responses to the Modifiable Activity Questionnaire. MET denotes metabolic equivalent. MET-hours represent the average amount of time engaged in specified physical activities multiplied by the MET value of each activity.
TG= triglyceride
BP = blood pressure
HRT = hormone replacement therapy
CIR = (100 x 30 minute insulin)/(30 minute glucose x (30 minute glucose -70))
HOMA-IR = 1/[22.5/(fasting insulin x (fasting glucose/18.01))]

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
Triglyceride	-5.1 ± 46.8	-5.1 ± 40.8
HDL	0.0 ± 15.6	0.0 ± 17.6
Blood pressure	-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
Body mass index	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-hour glucose	-6.9 ± 30.4	-4.8 ± 27.5†
HbA1C	0.02 ± 0.06	0.00 ± 0.06
Insulin	5.0 ± 53.2	0.0 ± 57.1
Index of insulin secretion:		
Corrected insulin response (CIR)	-4.1 ± 57.1	-2.3 ± 59.4
Index of insulin action:		
Homeostasis model assessment of insulin resistance (HOMA-IR)	5.3 ± 61.0	0.2 ± 64.9

*p<0.01, men vs. women
†p<0.05, men vs. women
Plus-minus values are medians ± inter-quartile range

TABLE 3. Percent Change in Risk Factors for Cardiovascular Disease and Diabetes over Year 1 in Those Randomized to Intensive Lifestyle Modification

	<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
Triglyceride	-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
Blood pressure	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
Body mass index	-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-hour glucose	-6.9±30	-5.2±27	-22±29	-13±27*	-26±30	-19±26*
HbA1C	-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:						
Corrected insulin response (CIR)	-0.9±65	2.7±61	0.9±69	-3.1±65	3.6±68	4.3±66
Index of insulin action:						
Homeostasis model assessment of insulin resistance (HOMA-IR)	-4.4±70	-6.0±61	-25±49	-15±51†	-40-5±44	-39±37

*p<0.01, men vs. women
†p<0.05, men vs. women
Plus-minus values are medians ± inter-quartile range