

Body Size and Shape Changes and the Risk of Diabetes in the Diabetes Prevention Program (DPP)

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The Diabetes Prevention Program Research Group

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## Abstract

### OBJECTIVE

To test the hypothesis that risk of type 2 diabetes is less following reductions in body size and central adiposity.

### RESEARCH DESIGN AND METHODS

The Diabetes Prevention Program (DPP) recruited and randomized individuals with impaired glucose tolerance to treatment with placebo, metformin, or lifestyle modification. Height, weight, waist circumference, and subcutaneous and visceral fat at L2-L3 and L4-L5 by computed tomography (CT) were measured at baseline and at 1 year. Cox proportional hazards models assessed by gender the effect of change in these variables over the first year of intervention upon development of diabetes over subsequent follow-up in a subset of 758 participants.

### RESULTS

Lifestyle reduced visceral fat at L2-L3 (men -24.3%, women -18.2%) and at L4-L5 (men -22.4%, women -17.8%), subcutaneous fat at L2-L3 (men -15.7%, women -11.4%) and at L4-L5 (men -16.7%, women -11.9%), weight (men -8.2%, women -7.8%), body mass index (BMI, men -8.2%, women -7.8%), and waist (men -7.5%, women -6.1%). Metformin reduced weight (-2.9%) and BMI (-2.9%) in men and subcutaneous fat (-3.6% at L2-L3 and -4.7% at L4-L5), weight (-3.3%), BMI (-3.3%), and waist (-2.8%) in women. Decreased diabetes risk by lifestyle intervention was associated with reductions of body weight, BMI, and central body fat distribution after adjustment for age and self-reported ethnicity.

### CONCLUSIONS

Reduced diabetes risk with lifestyle intervention may have been through effects upon both overall body fat and central body fat but with metformin appeared to be independent of body fat.

Key Words: Body mass index, Computed tomography, Impaired glucose tolerance, Lifestyle, Metformin, Visceral fat, Waist circumference

## Introduction

Type 2 diabetes has rapidly become a global health problem (1). Moreover, diabetes is a major cause of morbidity and mortality from coronary artery, cerebrovascular, retinal, neurological, and renal complications (2,3). One solution may be to prevent or delay diabetes in at-risk populations (4-6). The Diabetes Prevention Program (DPP), a multi-center randomized clinical trial, showed that this could be accomplished with lifestyle intervention or metformin among individuals with impaired glucose tolerance (IGT). At the end of 3.2 years, diabetes incidence rates were 10.8, 7.7, and 5.0 per 100 person-years in the placebo, metformin, and lifestyle groups (this average duration of follow-up is four months longer than reported in the primary outcome paper [6]). Treatment effects were consistent by sex and race/ethnicity.

Individuals who have type 2 diabetes usually are overweight or obese. Moreover, a central pattern of body fat distribution, particularly an increased amount of intra-abdominal or visceral fat, is an independent risk factor for type 2 diabetes (7-17). The effect of lifestyle and metformin on body size and central obesity was assessed in the DPP by both anthropometric measurements and computed tomography (CT).

In this paper, we tested the hypothesis that reductions in body size and central adiposity over the first year are associated with a decreased risk in developing type 2 diabetes over subsequent follow-up. This was done in a subset of 758 participants who had measurements of body fat and body fat distribution both at baseline and

one year and who remained nondiabetic at one year.

## Methods and Materials

**Subject Eligibility and Recruitment:** Because the design and methods of the DPP (18), the baseline characteristics of the cohort (19), and the primary outcomes (6) have been previously described in detail, they are briefly summarized here. Participants were recruited across 27 clinical centers located throughout the United States. Key eligibility requirements were age > 25 yrs, BMI > 24 kg/m<sup>2</sup> (> 22 kg/m<sup>2</sup> for Asian Americans), a fasting plasma glucose level of 5.3 to 7.0 mmol/L (95 to 125 mg/dL) [ $\leq$  7.0 mmol/L ( $\leq$  125 mg/dL) in the American Indian Centers], and a 2-hour plasma glucose level of 7.8 to 11.1 mmol/L (140 to 199 mg/dL) following 75 g glucose by mouth. Individuals were excluded if they had diabetes, any condition likely to limit life span or increase risk from the interventions, or any condition that would likely affect the ability to conduct the trial as designed, or if they were taking any medication or had any medical condition likely to confound the assessment of diabetes status.

**Intervention Groups:** Participants were randomized to placebo, metformin (850 mg twice daily), or an intensive lifestyle modification program. At baseline and annually thereafter, all participants received written information and an individual session with their case manager to address the importance of a healthy lifestyle for the prevention of type 2 diabetes.

The intensive lifestyle intervention goals were to: 1) achieve and maintain a weight reduction of at least 7% of initial body

weight through healthy eating and physical activity; and, 2) achieve and maintain a level of physical activity of at least 150 min/week (equivalent to about 700 kcal/week) through moderate intensity activity (such as walking or bicycling). Key elements included training in diet, exercise and behavior modification skills, frequent contact with the interventionist (at least monthly), and cultural sensitivity. The weight-loss goal was attempted initially through a reduction in dietary fat intake to <25% of calories and if this was not successful, caloric restriction was added. Details are available at <http://www.bsc.gwu.edu/dpp/index.html> doc (20).

Because CT was not initiated at the very start of the DPP, the subset of participants who are in this report was followed for an average 2.5 years, compared to 3.2 years for all DPP participants.

**Anthropometry:** Each measurement was recorded twice during the baseline screening visit and averaged. A third measurement was taken if the variability was greater than a predefined value. Staff members performing these measurements were certified annually. Height was measured on a stadiometer to the nearest 0.5 cm., body weight was measured on a calibrated balance scale to the nearest 0.1 kg, and BMI ( $\text{kg}/\text{m}^2$ ) was computed from body weight and height. Waist was defined as the midpoint between the highest point of the iliac crest and the lowest point of the costal margin at the mid-axillary line and waist circumference was measured with a cloth tape. Hip circumference was measured at the level of the greater femoral trochanters. The waist-to-hip ratio (WHR) was the waist

circumference divided by the hip circumference.

**Measurements of Adipose Tissue by CT:** Baseline measurement of adipose tissue by CT was done in 1106 participants from 18 of the 27 sites. Of these, 159 had a poor quality scan at baseline, 113 had a poor quality scan at follow-up, and 59 did not return for a second scan, resulting in 777 participants who had CT scans at both baseline and follow-up of acceptable quality. Among the participants who had acceptable CT scans at baseline, those who did not have follow-up scans were larger in terms of hip circumference, BMI, and waist circumference ( $p < 0.001$ ) than those who did receive follow-up scans. The instruments used included GE High Speed Advantage (5 centers), Picker PQ 5000 (5 centers), Siemens and Siemens Somatom Plus (2 centers), GE 9800 (3 centers), and GE Highlite (2 centers). The clinic variability of measurement for both subcutaneous and visceral adipose tissue at L2-L3 and L4-L5 for men and women was considerably smaller than the residual variance indicating that different clinic CT methods did not have an important influence upon the scan measurements.

An antero-posterior scout and two 10 mm thick axial images at the L2-L3 and the L4-L5 disc spaces were submitted to a central reading facility at the University of Colorado Health Sciences Center by tape or optical disc. Each subject was used as his/her own control to create a bimodal histogram depicting the distribution of Hounsfield units in the image, resulting in separate peaks for muscle and fat. The area under the fat peak (number of fat pixels) multiplied by area of one pixel equals fat area for that CT slice. This peak also defines the range of fat density for a patient. Four such measurements were

obtained (two at L2-L3 and two at L4-L5). Averages and SD were reported for each level. A line drawn manually through the body wall divided the subcutaneous and visceral compartments and subcutaneous fat area was calculated by subtracting visceral fat area from total fat area. Those analyzing the CT scans were blinded as to treatment assignment.

**Statistical Analysis:** Of the 777 participants who had CT at baseline and one year, 19 diagnosed with diabetes at 6 months or one year were excluded from the analyses reported here, leaving a final sample size of 758.

Descriptive statistics of baseline and year one body composition variables were computed by sex, race, and treatment groups. Differences between treatment groups in baseline and year one body fat measurements were tested for each sex using general linear models adjusted for self-reported race/ethnicity and age. The Holm's procedure (21) was used to control type 1 error rate between treatment comparisons. A p-value of  $\leq 0.05$  was considered statistically significant. Cox regression models were used to assess effect of change in body fat variables (visceral fat area at L2-L3 and L4-L5, subcutaneous fat area at L2-L3 and L4-L5, weight, waist, BMI, and WHR) over the first year (year 1 measurement minus baseline measurement) on the subsequent risk of developing diabetes. Hazard ratios are reported per 1 standard deviation of the change in body fat measurements. Models were run separately for each treatment group adjusted for age and self-reported ethnicity and a test of heterogeneity was used to see if the effect of change in a body fat variable differed across treatment groups. Madalla's

likelihood ratio  $R^2_{LR}$  (22) was computed to determine the approximate variation explained by addition of a body fat measurement to a Cox model with age and race/ethnicity. The SAS analysis system version 8.2 was used for all analyses (SAS Institute, Inc., Cary, NC).

## Results

None of the baseline measurements of body fat differed significantly by treatment group (Table 1). On average, participants were obese with a mean BMI of 32.1 ( $\pm 5.2$ ) kg/m<sup>2</sup> in men and 33.0 ( $\pm 5.5$ ) kg/m<sup>2</sup> in women. The waist circumference was large. Waist girth and visceral fat area were larger in men than women while the subcutaneous fat area at both L2-L3 and L4-L5 was larger in women than men. There was more visceral fat and sex differences appeared to be greater at the L2-L3 level than the L4-L5 level. All body fat measurements differed significantly by sex at a  $p < 0.01$ , except BMI ( $p = 0.03$ ).

Every anthropometric measurement decreased from baseline in both sexes in both the metformin and lifestyle arms (Table 2 and Figure 1). Reductions in visceral fat observed with lifestyle intervention in both men (-24.3% at L2-L3 and -22.4% at L4-L5, Fig 1) and women (-18.2% at L2-L3 and -17.8 at L4-L5, Fig 2) were especially dramatic. Much smaller reductions in subcutaneous fat, waist, BMI, and weight were found after 1 year of lifestyle intervention.

Cox regression models predicting diabetes were run separately for each treatment group (Table 3). In men, reductions in all of the fat variables were significant predictors of decreased diabetes risk in the lifestyle arm while in women, weight,

BMI, and waist reduction were significant predictors. Visceral fat reduction was nearly significant as a predictor in women. In the placebo group only subcutaneous fat reduction predicted decreased diabetes risk, and only in men. In both men and women, none of the fat variables predicted diabetes in the metformin group.

## Discussion

A central pattern of body fat distribution has been associated with both insulin resistance and risk for diabetes independent of BMI (8-17). A central pattern of body fat distribution may be identified by waist or WHR or by skinfold thickness on the trunk as compared to the extremities. In the DPP, weight, BMI, waist girth, hip girth, and WHR each significantly predicted the development of diabetes in the placebo and lifestyle groups in both sexes (23). Skinfolts were less predictive. In the metformin group none of these measurements predicted the future risk of diabetes and the reduction in diabetes incidence was much less than with lifestyle modification. We have now shown that reduction of diabetes risk with lifestyle was closely associated with reduction of body size and central adiposity. Reduction of diabetes risk with metformin, however, appeared independent of changes in body size or central adiposity.

Increased subcutaneous abdominal fat, increased visceral fat, or a combination of the two may underlie central adiposity. Techniques such as CT or magnetic resonance imaging are necessary to distinguish between subcutaneous and visceral abdominal fat (24). Greater visceral adiposity and not subcutaneous fat was shown by CT to precede the development of diabetes in a prospective

study among Japanese Americans (15,17). But there appear to be racial differences in the relationship between the amount of visceral fat and diabetes as well as in the amount of visceral fat at similar levels of overall obesity. African-American men, despite higher risk for type 2 diabetes, were shown to have less visceral fat than white men (25). Pima Indians also have less visceral fat than whites at similar levels of obesity (26). Although others have argued that subcutaneous fat has as important a role in insulin resistance as does visceral fat (27), most studies have shown the visceral adipose depot to be more important. Although comprising only a small portion of total body fat stores, visceral fat shows rapid turnover and, during weight loss attributable to diet and physical activity, there is a proportionately greater reduction of visceral fat than of total body fat stores (27-30).

We found that in both men and women lifestyle intervention dramatically reduced visceral fat whereas metformin had no effect. There were, however, some sex differences in the response of other body fat variables. Both lifestyle and metformin reduced weight and BMI in both men and women. In women, both lifestyle and metformin also reduced waist circumference and subcutaneous fat while in men, lifestyle but not metformin reduced both of these. However, where lifestyle and metformin both had an effect, that of lifestyle was far greater in both men and women. In men, changes in subcutaneous fat predicted time to develop diabetes in the placebo group while in the lifestyle group, decreases in all the fat variables predicted diabetes independent of age and self-reported race/ethnicity. It is not surprising that changes in subcutaneous fat predicted

diabetes in the placebo group since this was the measure that changed the most while both visceral fat and total body fat remained relatively constant. For this group, measures of body fatness at baseline were strong predictors of diabetes.

These results suggest that lifestyle decreases diabetes risk in men through reductions in overall as well as central body fat. In women, no fat measurement predicted diabetes in the placebo group and only changes in weight, BMI, and waist circumference were predictive in the lifestyle group. Change in visceral fat, which is highly correlated with change in waist circumference, was nearly significant. In contrast while diabetes risk reduction appears to be mediated through changes in body fat and body fat distribution in both sexes, the reduction of diabetes risk by metformin appears to be through a mechanism independent of such changes.

The Da Qing Study (4) and the Finnish Diabetes Prevention Study (5), which also demonstrated prevention of type 2 diabetes through diet and exercise interventions, examined a limited number of adipose variables that did not include CT. Both studies showed a significant reduction in body weight, while in the Finnish Study there was also significant reduction in waist circumference.

In the DPP, improvements at one year in insulin sensitivity and preservation of insulin secretion were associated with lower hazard rates for diabetes (31). Lifestyle had the greatest improvement, there was no significant change in the placebo group, and metformin was intermediate.

In a small lifestyle modification study among Japanese Americans with IGT, dietary restriction of saturated fat plus participation in physical activity for 24 months resulted in significant weight loss, reduced percent body fat, decreased visceral and subcutaneous abdominal fat by CT, and increased insulin sensitivity (32,32). Improvement of insulin sensitivity was the result of changes in visceral rather than subcutaneous fat when examined with multiple regression analyses.

A strength of our study is the large number of participants in whom we were able to obtain baseline and follow-up measurements of body fat and body fat distribution. A limitation is that we assessed body fat change over only the first year of intervention whereas diabetes risk was assessed over the subsequent mean 1.5 years of follow-up. The relationship between body fat change and change in diabetes risk may have been greatly improved if we had assessed the former over 2.5 years. Another limitation is that because not all DPP participants were in the CT sub-study, there were some differences in results between this study and other DPP publications. For example, weight did not predict diabetes among the metformin participants in this sub-study. Such differences may be due to the smaller number of participants in the sub-study but are more likely due to differences in baseline characteristics such as lower body weight, BMI, and hip and waist circumferences in the sub-study participants than in the entire DPP cohort ( $p < 0.001$ ). Although we focused specifically upon body fat and its distributional change, differential lean body mass change by treatment arm and

gender is possible but was not examined. Since muscle is a major glucose clearance site, change in muscle mass could influence diabetes risk. Although the physical activity program was predominantly aerobic, strength training activities were not prohibited.

In conclusion, lifestyle intervention was associated with dramatic reductions in visceral fat as well as smaller but still

significant decreases in subcutaneous fat, body weight, BMI, and waist in both men and women. Moreover, reduction in the risk of developing diabetes was associated with decreases in both body fat and central adiposity only in the lifestyle group, suggesting that these changes in body fat were important in determining the benefit seen with the DPP lifestyle intervention.

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Table 1. Baseline Characteristics by Treatment Group in Men and Women\*

Baseline Characteristics	Men Overall (n = 259)	Placebo (n = 80)	Metformin (n = 96)	Lifestyle (n = 83)	Women Overall (n = 499)	Placebo (n = 164)	Metformin (n = 165)	Lifestyle (n = 170)
Self-reported ethnicity								
Caucasian	161 (62.2)	51 (63.8)	63 (65.6)	47 (56.6)	270 (54.1)	86 (52.4)	86 (52.1)	98 (57.6)
African American	38 (14.7)	13 (16.3)	17 (17.7)	8 (9.6)	124 (24.8)	43 (26.2)	45 (27.3)	36 (21.2)
Hispanic	44 (17.0)	13 (16.3)	11 (11.5)	20 (24.1)	81 (16.2)	27 (16.5)	28 (17.0)	26 (15.3)
Asian/Pacific Islander	16 (6.2)	3 (3.8)	5 (5.2)	8 (9.6)	17 (3.4)	6 (3.7)	3 (1.8)	8 (4.7)
American Indian					7 (1.4)	2 (1.2)	3 (1.8)	2 (1.2)
Age (years)	54.2 ± 11.4	52.9 ± 12.0	52.6 ± 11.0	57.3 ± 10.9	50.8 ± 9.7	50.1 ± 9.5	51.3 ± 9.2	51.2 ± 10.4
Visceral L2-L3	262 ± 82.9	270 ± 94.0	252 ± 78.2	267 ± 86.1	162 ± 61.3	159 ± 59.4	161 ± 66.4	165 ± 58.0
Visceral L4-L5	180 ± 73.1	179 ± 67.3	178 ± 72.8	183 ± 79.4	145 ± 53.9	141 ± 51.6	143 ± 57.6	150 ± 52.2
Subcutaneous L2-L3	246 ± 105	256 ± 107	241 ± 108	241 ± 98.9	320 ± 113	324 ± 121	314 ± 109	322 ± 111
Subcutaneous L4-L5	345 ± 125	363 ± 135	337 ± 121	339 ± 119	472 ± 134	478 ± 141	463 ± 131	476 ± 131
Weight (kg)	99 ± 16	100 ± 18	98 ± 16	98 ± 16	87 ± 16	86 ± 16	87 ± 15	88 ± 15

BMI (kg/m <sup>2</sup> )	32.1 ± 5.2	32.7 ± 6.5	31.7 ± 4.4	31.8 ± 4.7	33.0 ± 5.6	32.8 ± 5.8	32.9 ± 5.6	33.2 ± 5.3
Waist (cm)	108 ± 11.6	109 ± 12.6	108 ± 10.7	108 ± 11.5	99.2 ± 12.0	98.4 ± 11.9	99.4 ± 12.7	99.8 ± 11.5
WHR (cm)	1.00 ± 0.06	0.99 ± 0.06	1.00 ± 0.07	1.00 ± 0.05	0.88 ± 0.07	0.87 ± 0.06	0.88 ± 0.08	0.88 ± 0.07

\* Plus-minus values are means ±SD

Table 2. Change in Body Fat Measurement (Year 1 minus Baseline) by Treatment Group in Men and Women\*

Body measurement	Men (n=259)**			Women (n=499)**			
	fat	Placebo	Metformin	Lifestyle	Placebo	Metformin	Lifestyle
Men							
Visceral L2-L3 (cm <sup>2</sup> )		0.2 (48.2) <sup>*†</sup>	-8.9 (49.8) <sup>*</sup>	-55.5 (76.4) <sup>†</sup>	0.0 (30.8) <sup>*†</sup>	-7.5 (27.3) <sup>*‡</sup>	-23.9 (45.1) <sup>‡</sup>
Visceral L4-L5 (cm <sup>2</sup> )		-1.9 (35.1) <sup>*†</sup>	-3.1 (40.2) <sup>*</sup>	-35.6 (51.3) <sup>†</sup>	-0.3 (30.2) <sup>*†</sup>	-8.7 (31.1) <sup>*‡</sup>	-25.1 (42.0) <sup>‡</sup>
Subcutaneous L2-L3 (cm <sup>2</sup> )		3.9 (30.9) <sup>*†</sup>	-5.2 (42.2) <sup>*</sup>	-32.9 (53.6) <sup>†</sup>	1.8 (48.7) <sup>*†</sup>	-11.8 (61.9) <sup>*‡</sup>	-31.1 (68.3) <sup>‡</sup>
Subcutaneous L4-L5 (cm <sup>2</sup> )		11.2 (30.9) <sup>*†</sup>	-12 (42.2) <sup>*‡</sup>	-47.6 (53.6) <sup>†‡</sup>	-4.6 (48.7) <sup>*†</sup>	-24.4 (61.9) <sup>*‡</sup>	-47.2 (68.3) <sup>‡</sup>
Weight (kg)		-0.3± 5.1 <sup>*†</sup>	-2.8± 4.5 <sup>*‡</sup>	-8.3± 7.1 <sup>†‡</sup>	-0.1± 3.9 <sup>*†</sup>	-3.0± 5.1 <sup>*‡</sup>	-7.0± 7.1 <sup>†‡</sup>
Waist (cm)		-0.1± 1.6 <sup>*†</sup>	-0.9± 1.5 <sup>*‡</sup>	-2.7± 2.3 <sup>†‡</sup>	0.0± 1.5 <sup>*†</sup>	-1.1± 1.9 <sup>*‡</sup>	-2.6± 2.7 <sup>†‡</sup>
BMI (kg/m <sup>2</sup> )		-0.7± 5.0 <sup>*†</sup>	-2.1± 4.4 <sup>*</sup>	-8.2± 6.5 <sup>†</sup>	-0.4± 5.2 <sup>*†</sup>	-3.0± 5.6 <sup>*‡</sup>	-6.2± 6.7 <sup>†‡</sup>
WHR (cm)		0.00± 0.04 <sup>*†</sup>	-0.01± 0.04 <sup>*</sup>	-0.04± 0.04 <sup>†</sup>	-0.00± 0.05 <sup>*</sup>	-0.01± 0.05	-0.02± 0.05 <sup>*</sup>

\* Plus-minus values are means ±SD; all others are median (interquartile range)

\*\* Within either sex if the same superscript is shown between treatment groups, the changes in body fat measurements are significantly different between those treatment groups at p ≤ 0.05. For example, in men, change in visceral fat at L2-L3 is significantly different between the placebo group and the metformin group, and significantly different between the placebo group and the lifestyle group. Comparisons between treatment groups are significant at the 0.05 level after adjusting for multiple comparisons in general linear models adjusted for race and age.

Table 3. Cox Regression Models Estimating Hazard Ratios for Change in Body Fat Measurement (Year 1 minus Baseline) in Predicting Diabetes by Treatment Group and Gender\*

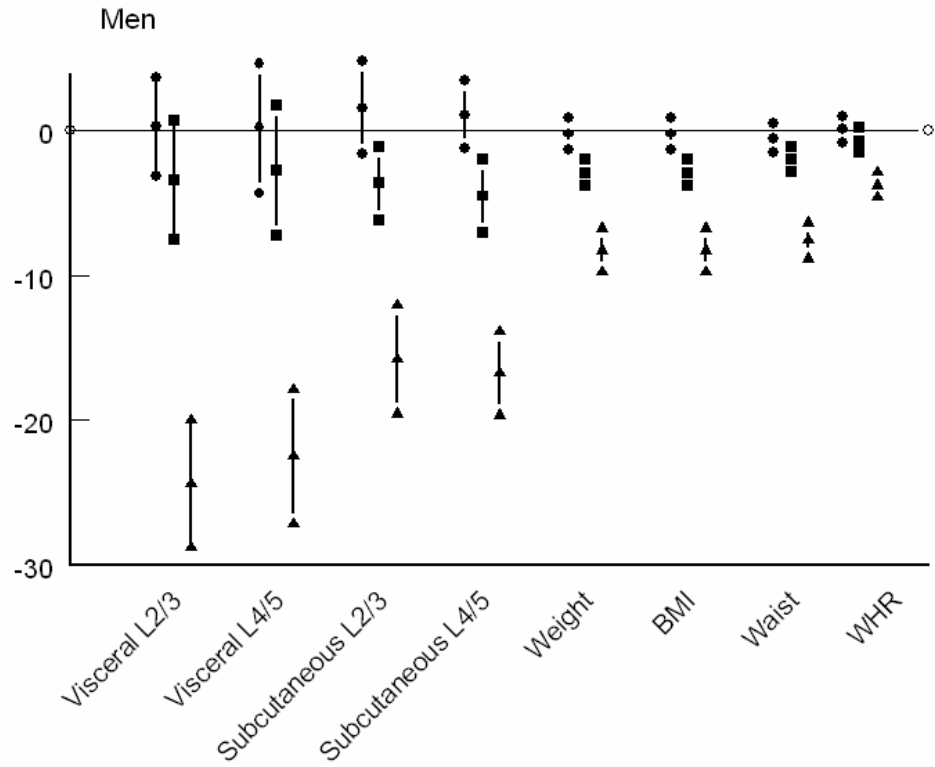
Baseline minus Year 1	Placebo				Metformin				Lifestyle			
	R <sup>2</sup>	HR	95% CI	P	R <sup>2</sup>	HR	95% CI	P	R <sup>2</sup>	HR	95% CI	P
Men												
Visceral L2-L3 (cm <sup>2</sup> )	3.9	0.54	(0.27- 1.09)	0.08	0.2	0.86	(0.45- 1.66)	0.65	10.4	0.16	(0.03- 0.81)	0.03
Visceral L4-L5 (cm <sup>2</sup> )	1.3	0.71	0.38- 1.35	0.30	0.0	0.97	0.50- 1.9	0.94	10.5	0.13	0.03- 0.63	0.01
Subcutaneous L2-L3 (cm <sup>2</sup> )	13.4	0.37	0.19- 0.71	<0.01	0.2	0.90	0.52- 1.55	0.70	8.5	0.18	0.04- 0.81	0.03
Subcutaneous L4-L5 (cm <sup>2</sup> )	10.0	0.40	0.19- 0.82	0.01	0.5	1.28	0.66- 2.51	0.47	10.4	0.15	0.03- 0.65	0.01
Weight (kg)	3.4	0.31	0.33- 1.13	0.11	0.6	1.36	0.64- 2.88	0.42	9.3	0.22	0.06- 0.78	0.02
Waist (cm)	2.3	0.67	0.36- 1.26	0.19	0.5	1.38	0.64- 2.95	0.50	12.7	0.19	0.05- 0.72	0.02
BMI (kg/m <sup>2</sup> )	2.1	0.65	0.34- 1.23	0.22	0.7	1.33	0.58- 3.05	0.41	9.9	0.10	0.01- 0.75	0.01
WHR (cm)	0.0	1.03	0.58- 1.84	0.92	0.3	1.21	0.59- 2.50	0.60	5.9	0.22	0.05- 1.08	0.06
Women												
Visceral L2-L3 (cm <sup>2</sup> )**	0.7	0.77	0.47- 1.26	0.30	0.0	1.09	0.62- 1.90	0.77	2.2	0.71	0.49- 1.03	0.07
Visceral L4-L5 (cm <sup>2</sup> )	0.6	0.77	0.48- 1.26	0.30	1.5	0.66	0.39- 1.09	0.10	2.3	0.71	0.50- 1.02	0.06

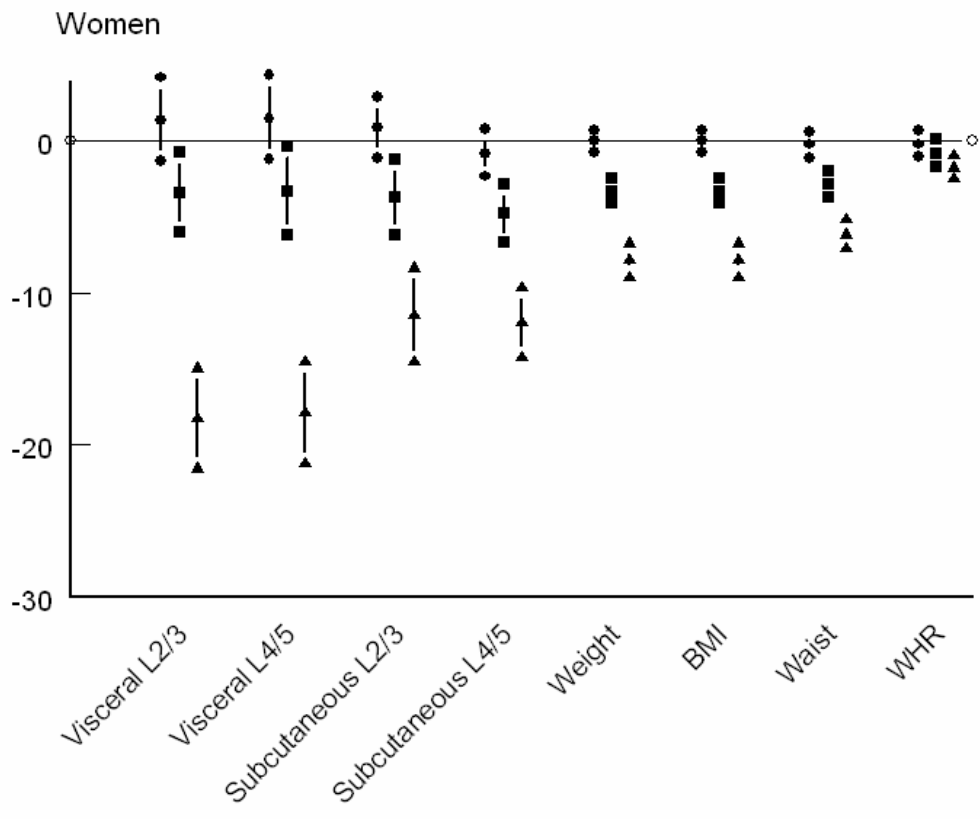
Subcutaneous L2-L3 (cm <sup>2</sup> )	1.0	0.71	0.40-1.25	0.23	0.0	0.93	0.56-1.56	0.79	0.7	0.81	0.58-1.15	
Subcutaneous L4-L5 (cm <sup>2</sup> )	1.3	0.72	0.46-1.12	0.15	0.5	0.79	0.49-1.29	0.35	1.5	0.68	0.41-1.14	0.14
Weight (kg)	1.2	0.66	0.38-1.14	0.14	0.6	0.75	0.43-1.32	0.31	6.0	0.40	0.21-0.74	<0.01
Waist (cm)	0.6	0.68	0.40-1.17	0.26	0.0	0.76	0.43-1.34	0.99	3.5	0.41	0.22-0.74	0.02
BMI (kg/m <sup>2</sup> )	1.0	0.74	0.44-1.24	0.17	0.6	1.0	0.59-1.70	0.35	6.4	0.50	0.28-0.90	<0.01
WHR (cm)	0.2	0.87	0.59-1.29	0.50	0.0	1.02	0.63-1.65	0.93	0.0	1.03	0.65-1.64	0.90

\* R-squares are treatment group specific and measure the percent of variation explained when the body fat measurement is added to a model with baseline body fat, age and self-reported race/ethnicity as independent variables. Hazard ratios are per 1 SD.

\*\* Significant differences between treatment groups

Figure 1. Percent Change (Mean and 95% Confidence Limits) in Body Fat Measurement Year minus Baseline by Treatment Group in Men and Women





Legend  
 Circle=Placebo, Square=Metformin, Triangle= Life Style