

Supplemental Data

Supplemental Table 1. Unadjusted SHBG values in each subpopulation by treatment arm. SHBG: sex hormone binding globulin (nmol/L). SHBG1: SHBG level at year 1 (nmol/L). SHBGdiff: Difference in SHBG levels from year 1 to baseline (nmol/L).

Group	TX	Variable	N	Mean	SD	Minimum	Maximum
Men	ILS	SHBG	293	46.99	28.40	6.40	177.20
		SHBG1	293	39.07	17.96	10.77	139.59
		SHBGdiff	293	-7.91	22.27	-123.06	37.13
	MET	SHBG	315	44.79	25.75	4.19	152.19
		SHBG1	315	32.39	18.02	6.37	127.94
		SHBGdiff	315	-12.40	20.12	-116.61	50.91
	PLA	SHBG	278	42.93	23.62	7.56	150.96
		SHBG1	278	30.97	15.56	6.02	106.56
		SHBGdiff	278	-11.97	17.30	-87.21	30.92
Premenopausal Women	ILS	SHBGS	266	60.46	46.08	13.22	308.50
		SHBG1	266	59.85	45.98	9.34	254.04
		SHBGdiff	266	-0.61	34.24	-224.93	143.34
	MET	SHBG	246	60.59	53.54	9.70	484.28
		SHBG1	246	49.78	36.01	11.69	216.78
		SHBGdiff	246	-10.81	40.79	-359.76	122.13
	PLA	SHBG	289	59.95	48.62	7.17	388.04
		SHBG1	289	50.12	39.23	6.09	242.63
		SHBGdiff	289	-9.83	41.79	-307.10	173.70
Postmenopausal Women	ILS	SHBG	157	36.72	15.08	9.14	98.39
		SHBG1	157	45.91	23.46	6.28	188.63
		SHBGdiff	157	9.19	17.20	-34.75	155.48
	MET	SHBG	139	39.55	27.30	6.53	220.61
		SHBG1	139	39.58	23.43	5.61	176.16
		SHBGdiff	139	0.03	23.02	-180.39	110.93

Group	TX	Variable	N	Mean	SD	Minimum	Maximum
		SHBG	159	41.20	26.74	5.14	239.85
	PLA	SHBG1	159	40.32	20.15	12.18	123.94
		SHBGdiff	159	-0.88	17.25	-137.72	40.65

Supplemental Table 2. Hierarchical models of changes in SHBG by treatment arm (Adjusted Least Squares Mean with 95% CI).

	Males	Premenopausal Women	Postmenopausal Women
Model 1 – Adjusted for age at randomization, Caucasian race, smoking, alcohol intake, leisure activity, baseline SHBG			
Lifestyle	-7.06 (-8.54, -5.59)	-0.65 (-4.49, 3.18)	8.13 (5.45, 10.81)
Metformin	-12.40 (-13.81, -10.98)	-10.88 (-14.88, -6.89)	0.22 (-2.61, 3.05)
Placebo	-13.16 (-14.66, -11.67)	-10.08 (-13.78, -6.39)	0.11 (-2.54, 2.77)
Model 2 – Model 1, further adjusted for sex hormones and sex hormone changes from baseline to year 1 (estradiol, changes in estradiol, estrone, changes in estrone, testosterone, changes in testosterone)			
Lifestyle	-8.55 (-9.88, -7.22)	-1.70 (-5.78, 2.38)	4.63 (1.21, 8.05)
Metformin	-11.86 (-13.11, -10.60)	-12.25 (-16.46, -8.04)	0.02 (-3.63, 3.67)
Placebo	-12.30 (-13.66, -10.95)	-9.67 (-13.52, -5.82)	1.25 (-4.73, 2.24)
Model 3 – Model 2, further adjusted for adiposity measures and changes from baseline to year 1 (waist circumference, changes in waist circumference, BMI, changes in BMI)			
Lifestyle	-10.45 (-11.88, -9.02)	-6.16 (-10.43, -1.89)	1.76 (-1.70, 5.21)
Metformin	-11.45 (-12.68, -10.22)	-11.11 (-15.26, -6.96)	0.11 (-3.38, 3.60)
Placebo	-10.79 (-12.18, -9.40)	-6.26 (-10.15, -2.37)	1.64 (-1.90, 5.18)
Model 4 – Model 3, further adjusted for glucose measures and changes in glucose measures from baseline to year 1 (glucose, change in glucose, 2-hour glucose, change in 2-hour glucose, 1/fasting insulin, change in 1/fasting insulin)			
Lifestyle	-10.79 (-12.23, -9.35)	-5.84 (-10.12, -1.57)	1.39 (-2.15, 4.94)
Metformin	-11.59 (-12.84, -10.34)	-12.45 (-16.65, -8.25)	-0.53 (-4.10, 3.05)
Placebo	-10.53 (-11.93, -9.12)	-5.87 (-9.82, -1.93)	2.57 (-1.11, 6.26)