SUPPLEMENTARY DATA

Annotation of statistical models analyzed in this study

For the weight loss outcomes (6-month and 2-year), the following linear model is fitted to the pooled sample if no significant interactions between SNP and treatment groups.

$$WL_i = \beta_0 + \beta_{W0} W0_i + \beta_S S_i + \beta_{LS} LS_i + \beta_{ME} ME_i + \beta_A A_i + \beta_M M_i + \beta_{AA} AA_i + \beta_H H_i + \beta_{AP} AP_i + \beta_{AI} AI_i + \varepsilon_i$$

WL_i: the weight loss outcome for the ith subject

β_0: Intercept

$W0_i$: Weight at baseline for subject i

S_i: Number of effective alleles (0,1,2) of the SNP under test in subject i

LS_i, ME_i: Indicators for subject i belonging to the Lifestyle and Metformin groups respectively

A_i: Subject i's age at baseline

M_i: Indicator for subject i being a man

AA_i, H_i, AP_i, AI_i: Indicators for subject i being an African American, Hispanic, Asian or Pacific Islander, American Indian, respectively

$\beta_{W0}, \beta_S, \beta_{LS}, \beta_{ME}, \beta_A, \beta_M, \beta_{AA}, \beta_H, \beta_{AP}, \beta_{AI}$: Regression coefficients for the corresponding covariate

ε_i: Independent random errors following a mean-zero normal distribution with constant variance.

In the presence of significant interactions between SNP and treatment groups, the following linear regression model is fitted within each treatment group

$$WL_i = \beta_0 + \beta_{W0} W0_i + \beta_S S_i + \beta_A A_i + \beta_M M_i + \beta_{AA} AA_i + \beta_H H_i + \beta_{AP} AP_i + \beta_{AI} AI_i + \varepsilon_i$$

In this case, three sets of treatment-specific coefficient estimates will be output.

For the weight regain outcome, subjects could have more than one regain rate measure at different time points during the followup after 6 month. The following two linear mixed models are fitted for each of the 16 SNPs in either the pooled sample or the treatment-specific samples.

$$WL_{ij} = \beta_0 + \beta_{W0} W0_i + \beta_S S_i + \beta_{LS} LS_i + \beta_{ME} ME_i + \beta_A A_i + \beta_M M_i + \beta_{AA} AA_i + \beta_H H_i + \beta_{AP} AP_i + \beta_{AI} AI_i + \varepsilon_{ij}$$

$$WL_{ij} = \beta_0 + \beta_{W0} W0_i + \beta_S S_i + \beta_A A_i + \beta_M M_i + \beta_{AA} AA_i + \beta_H H_i + \beta_{AP} AP_i + \beta_{AI} AI_i + \varepsilon_{ij}$$

for the jth weight regain measure in subject i. Notice the error terms within the same subject ε_{ij} are no longer independent, instead an auto-regressive covariance structure is assumed where the correlation coefficient between ε_{ij} decreases exponentially. That is, if the correlation coefficient between ε_{i1} and ε_{i2} is ρ, the correlation coefficient between ε_{i1} and ε_{i3} would be ρ^2.

SUPPLEMENTARY DATA

Genetic risk scores (GRS) and weight-regain from 6 months through study end

We constructed three GRS comprising: i) all measured SNPs coded with the effect alleles as those associated with baseline BMI in the DPP; ii) SNPs associated with weight-regain in the overall DPP cohort (as described above); iii) all SNPs showing statistically significant gene x lifestyle interactions, where the SNP effect estimate on weight-regain differed in magnitude between the lifestyle and placebo arms of the trial. As Supplemental Figure 1 illustrates, weight regain rates were comparable between the lifestyle and placebo arms for participants with a low GRS (Supplemental Figures 1A-C), but differed substantially in those with a high GRS, indicating that persons with a heavy genetic burden struggle to maintain reduced weight when engaging in programs of intensive lifestyle modification.

The first GRS model showed no overall association with rate of weight-regain (P=0.13). The second GRS yielded similar effects across three arms ($P_{interaction}$=0.70), with one unit (allele) increase conveying 0.22, 0.37 and 0.31 kg/yr/allele faster weight-regain rates in the lifestyle (P=0.04), metformin (P=0.01) and placebo (P=0.11) groups respectively (panel B). On average, the second GRS was associated with 0.28kg/yr/allele faster (P=0.0006) rate of weight-regain. The third GRS effects (panel C) differed by treatment ($P_{interaction}$=0.005), with -0.35, -0.08, and 0.40 kg/yr/allele weight-regain rates in the lifestyle (P=0.01), metformin (P=0.64), and placebo (P=0.09) groups, respectively.

Mediation analyses

Secondary analyses were performed to determine whether changes in selected behaviors mediated associations between genotypes and obesity traits. SNPs significantly affecting each of these three traits were selected. Each SNP-outcome combination was tested for potential mediators. Candidate mediators were diet adherence, leisure time physical activity (LTPA), percent calories from protein, snack frequency, sweet and dessert frequency, fruit frequency and vegetable frequency. While testing each candidate mediator, two models were fit separately with the only difference being whether or not the candidate mediator was included as a covariate in the model. The same linear or mixed model (depending on outcome) was employed. From each pair of models, the difference in the two SNP regression coefficients and the standard errors of these differences were calculated. In these analyses, a statistically significant non-zero difference represents a discrepancy between the marginal SNP effect estimate and the SNP effect estimate that is conditional on the putative mediator, thus validating the intermediate function of the mediator from genotype to the outcome.

Although a number of nominally statistically significant associations were observed between SNPs and candidate energy balance behaviors (data not shown), there was no reliable evidence that any of these factors mediated the SNP effects on weight variables after correcting for multiple statistical comparisons (data not shown).

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SUPPLEMENTARY DATA

Supplementary Table 1. Participant characteristics (max N=3,819)

Characteristic	Lifestyle	Metformin	Placebo	*Troglitazone*	*P*-value
N	1079	1073	1082	585	
Male	32%	34%	31%	34%	0.404
Baseline age (years)	51 (11)	51 (10)	50 (10)	50 (10)	0.469
Baseline weight (kg)	94 (21)	94 (20)	94 (20)	93 (19)	0.774
Baseline BMI (kg/m^2)	34 (7)	34 (7)	34 (7)	34 (6)	0.311
Baseline waist circumference (cm)	105 (15)	105 (14)	105 (14)	104 (14)	0.605
Baseline SAT L4 (cm^2)	308 (125)	301 (129)	314 (127)		0.449
Baseline SAT L5 (cm^2)	443 (152)	433 (154)	449 (151)		0.408
Baseline VAT L4 (cm^2)	200 (85)	195 (83)	199 (90)		0.701
Baseline VAT L5 (cm^2)	163 (65)	158 (65)	159 (65)		0.500
Baseline LTPA (MET hrs/wk)	16 (22)	16 (26)	17 (29)	15 (16)	0.390
Baseline energy Intake (kJ)	2137 (1071)	2144 (986)	2098 (1052)	2118 (989)	0.739
Short-term weight loss (kg) (0-6 m)	6.7 (5.6)	2.3 (4.0)	0.3 (4.0)		<0.0001
Long-term weight loss (kg) (0-24 m)	5.4 (7.6)	2.1 (5.7)	0.0 (5.5)		<0.0001
Weight regain (kg) (6m to study end)	3.0 (8.2)	2.4 (7.7)	0.8 (7.3)		<0.0001

Data are percentage or Mean (SD), stratified by treatment assignment. P-values from ANOVA F-tests and Chi-Square test of independence. LTPA: leisure-time physical activity. The sample size (N=3,819) is the maximum number used in baseline analyses and includes participants who were subsequently randomized to troglitazone treatment (in which only baseline data is available), in addition to those randomized to lifestyle, metformin, or placebo. Sample sizes for: short-term weight loss (n=3085); long-term weight loss (n=3015); weight regain (n=1411); baseline measures of VAT and SAT (n=869). We include individuals subsequently randomized to troglitazone in the baseline analyses to maximize statistical power. However, these individuals are not included in the prospective analyses as they represent a relatively small subgroup of the DPP population, which is likely underpowered for treatment stratified analyses.

SUPPLEMENTARY DATA

Supplementary Table 2. SNP identities and frequencies

Nearest gene	SNP	Minor(major) allele	Frequency of effect allele	Genotype Frequency		
MC4R	rs17782313	C(T)	n=1646 (23%)	TT (n= 2109, 60%)	CT (n= 1224, 35%)	CC (n= 211, 6%)
FTO	rs9939609	A(T)	n= 2809 (41%)	TT (n= 1235, 36%)	AT (n= 1623, 47%)	AA (n= 593, 17%)
MTCH2	rs10838738	G(A)	n= 2088 (31%)	AA (n= 1679, 49%)	GA (n= 1372, 40%)	GG (n= 358, 11%)
NEGR1	rs2815752	G(A)	n= 2437 (36%)	AA (n= 1440, 42%)	GA (n= 1529, 45%)	GG (n= 454, 13%)
TMEM18	rs6548238	T(C)	n= 1024 (15%)	CC (n= 2484, 72%)	TC (n= 866, 25%)	TT (n= 79, 2%)
SH2B1	rs7498665	C(T)	n= 2524 (37%)	TT(n= 1371, 40%)	CT (n= 1554, 46%)	CC (n= 485, 14%)
SEC16B	rs10913469	C(T)	n= 1395 (21%)	TT(n= 2058, 63%)	CT (n= 1041, 32%)	CC (n= 177, 5%)
BDNF	rs6265	T(C)	n= 1090 (16%)	CC (n= 2442, 71%)	TC (n= 890, 26%)	TT (n= 100, 3%)
FAIM2	rs7138803	A(G)	n= 2144 (32%)	GG (n= 1634, 48%)	AG (n= 1384, 41%)	AA (n= 380, 11%)
KTCD15	rs29941	A(G)	n= 2135 (31%)	GG (n= 1653, 48%)	AG (n= 1401, 41%)	AA (n= 367, 11%)
PPARG	rs1801282	Ala(Pro)	n= 585 (9%)	PP (n= 2787, 83%)	PA (n= 553, 16%)	AA (n= 16, 0%)
LYPLAL1	rs2605100	A(G)	n= 1709 (24%)	GG (n= 2016, 58%)	AG (n= 1267, 36%)	AA (n= 221, 6%)
ETV5	rs7647305	T(C)	n= 1573 (23%)	CC (n= 2091, 61%)	TC (n= 1133, 33%)	TT (n= 220, 6%)
GNPDA2	rs10938397	G(A)	n= 2614 (38%)	AA (n= 1360, 40%)	GA (n= 1546, 45%)	GG (n= 534, 16%)
TFAP2B	rs987237	G(A)	n= 1460 (21%)	AA (n= 2206, 63%)	GA(n= 1084, 31%)	GG (n= 188, 5%)
MSRA	rs7826222	G(C)	n= 1209 (17%)	CC (n= 2423, 69%)	GC (n= 953, 27%)	GG(n= 128, 4%)

SUPPLEMENTARY DATA

Supplementary Table 3. Comparison of risk increasing alleles in the published literature and the DPP for selected SNPs

Nearest gene	SNP	Published studies	Diabetes Prevention Program											
		X-sectional BMI effect allele (other)	Baseline BMI	*Weight loss at 6m*				*Weight loss at 24 m*				*Weight regain*			
			All	All	L	M	P	All	L	M	P	All	L	M	P
MC4R [1]	rs17782313	C(T)	T	C	-	-	-	T				T	-	-	-
FTO [1]	rs9939609	A(T)	A	T	-	-	-	-	A	T	T	A	-	-	-
MTCH2 [1]	rs10838738	G(A)	A	-	A	A	G	G	-	-	-	A	-	-	-
NEGR1 [1]	rs2815752	A(G)	A	G	-	-	-	-	G	G	A	G	-	-	-
TMEM18 [1]	rs6548238	C(T)	C	C	-	-	-	C	-	-	-	-	C	C	T
SH2B1 [1]	rs7498665	T(C)	T	T	-	-	-	C	-	-	-	T	-	-	-
SEC16B [1]	rs10913469	C(T)	C	C	-	-	-	C	-	-	-	C	-	-	-
BDNF [1]	rs6265	C(T)	T	T	-	-	-	C	-	-	-	C	-	-	-
FAIM2 [1]	rs7138803	A(G)	A	A	-	-	-	G	-	-	-	A	-	-	-
KTCD15 [1]	rs29941	G(A)	G	A	-	-	-	A	-	-	-	-	G	A	A
PPARG [2]	rs1801282	Ala(Pro)	Ala	Pro	-	-	-	Pro	-	-	-	Pro	-	-	-
LYPLAL1 [3]	rs2605100	G(A)	G	-	G	G	A	G	-	-	-	A	-	-	-
ETV5 [1]	rs7647305	C(T)	C	C	-	-	-	T	-	-	-	C	-	-	-
GNPDA2 [1]	rs10938397	G(A)	A	-	G	G	G	G	-	-	-	G	-	-	-
TFAP2B [3]	rs987237	G(A)	G	A	-	-	-	G	-	-	-	G	-	-	-
MSRA [3]	rs7826222	G(C)	G	C	-	-	-	C	-	-	-	C	-	-	-

Effect alleles are from: [1] Speliotes E.K., *et al*., Nat Genet. 42(11):937-48. 2010; [2] Tönjes A., *et al*. Diabetes Care, 29(11):2489-97. 2006; [3] Lindgren C.M., *et al*., PLoS Genet. 5(6):e1000508. 2009. Black boxes indicate results that did not reach a nominal level of statistical significance (P<0.05) in the DPP, whereas white boxes are those that did.
*BMI0-baseline BMI; 6m WL- 6 month weight loss; 2y WL – 2 years weight loss; WR – weight regain.

SUPPLEMENTARY DATA

Supplementary Table 4. Summary of association data for each of 16 known obesity loci with baseline weight (kg) and BMI (kg/m^2) (N=3,819)

Nearest gene	SNP	Effect(other) allele	*Weight (kg/allele)*		*BMI (kg/m^2/allele)*		*Height (m/allele)*	
			Coefficient(SE)	*P*-value	Coefficient(SE)	*P*-value	Coefficient(SE)	*P*-value
MC4R	rs17782313	C(T)	-0.63(0.52)	0.230	-0.14(0.18)	0.413	-0.30(0.18)	0.099
FTO	rs9939609	A(T)	0.91(0.46)	0.048	0.40(0.15)	0.011	-0.14(0.16)	0.389
MTCH2	rs10838738	G(A)	-0.32(0.50)	0.521	-0.23(0.17)	0.174	0.20(0.17)	0.245
NEGR1	rs2815752	A(G)	-0.35(0.47)	0.462	0.04(0.16)	0.794	-0.37(0.16)	0.025
TMEM18	rs6548238	C(T)	0.60(0.63)	0.339	0.12(0.21)	0.560	0.32(0.22)	0.145
SH2B1	rs7498665	T(C)	-0.04(0.47)	0.931	0.00(0.16)	0.996	-0.09(0.16)	0.586
SEC16B	rs10913469	C(T)	0.57(0.56)	0.303	0.26(0.19)	0.163	-0.09(0.19)	0.635
BDNF	rs6265	C(T)	-1.41(0.62)	0.024	-0.39(0.21)	0.064	-0.27(0.22)	0.214
FAIM2	rs7138803	A(G)	0.51(0.49)	0.299	0.28(0.16)	0.089	-0.24(0.17)	0.160
KTCD15	rs29941	G(A)	0.52(0.49)	0.291	0.27(0.17)	0.109	-0.21(0.17)	0.226
PPARG	rs1801282	Ala(Pro)	-1.82(0.84)	0.030	-0.50(0.28)	0.078	-0.43(0.29)	0.135
LYPLAL1	rs2605100	G(A)	-0.02(0.53)	0.970	0.01(0.18)	0.960	-0.02(0.18)	0.906
ETV5	rs7647305	C(T)	0.79(0.53)	0.136	0.28(0.18)	0.118	-0.01(0.18)	0.949
GNPDA2	rs10938397	G(A)	-1.60(0.46)	0.001	-0.47(0.15)	0.002	-0.20(0.16)	0.207
TFAP2B	rs987237	G(A)	0.16(0.55)	0.772	0.11(0.19)	0.567	-0.23(0.19)	0.244
MSRA	rs7826222	G(C)	-0.02(0.60)	0.971	0.15(0.15)	0.446	-0.41(0.21)	0.049

*Coefficients and P-values correspond to the additive allele effects adjusting for baseline age, sex and ethnicity.

SUPPLEMENTARY DATA

Supplementary Table 5. Summary of association data for each of 16 known obesity loci and rate of weight regain from 6 months through trial end (kg/yr) in non-Hispanic White and by treatment arm

Nearest gene	SNP	Effect(other) allele	SNP * TX	TX ADJUSTED coefficient (SE)	P-VAL	LIFESTYLE coefficient (SE)	P-VAL	METFORMIN coefficient (SE)	P-VAL	PLACEBO coefficient (SE)	P-VAL
MC4R	rs17782313	C(T)	N	-0.48 (0.13)	**< 0.001**	-0.59 (0.18)	**< 0.001**	-0.15 (0.21)	0.458	-0.68 (0.37)	0.067
FTO	rs9939609	A(T)	Y			0.46 (0.15)	**0.002**	-0.76 (0.19)	**< 0.001**	-0.06 (0.30)	0.837
MTCH2	rs10838738	G(A)	Y			-0.32 (0.17)	0.061	-0.04 (0.19)	0.827	0.55 (0.35)	0.114
NEGR1	rs2815752	A(G)	N	-0.38 (0.12)	**0.001**	-0.29 (0.16)	0.072	-0.50 (0.20)	**0.013**	-0.36 (0.32)	0.260
TMEM18	rs6548238	C(T)	Y			0.40 (0.21)	0.056	0.54 (0.27)	0.051	-1.13 (0.44)	**0.011**
SH2B1	rs7498665	T(C)	N	0.17 (0.12)	0.150	0.01 (0.17)	0.937	0.19 (0.19)	0.308	0.59 (0.31)	0.054
SEC16B	rs10913469	C(T)	N	0.08 (0.15)	0.592	0.00 (0.22)	0.987	0.39 (0.23)	0.094	-0.11 (0.43)	0.796
BDNF	rs6265	C(T)	Y			0.21 (0.21)	0.312	0.80 (0.22)	**< 0.001**	0.88 (0.41)	**0.035**
FAIM2	rs7138803	A(G)	N	0.13 (0.12)	0.280	0.07 (0.17)	0.688	0.50 (0.20)	**0.014**	-0.11 (0.32)	0.729
KTCD15	rs29941	G(A)	Y			0.89 (0.17)	**< 0.001**	-0.56 (0.20)	**0.007**	-0.71 (0.33)	**0.031**
PPARG	rs1801282	Ala(Pro)	N	-0.79 (0.18)	**< 0.001**	-0.91 (0.26)	**< 0.001**	-0.84 (0.28)	**0.003**	-0.60 (0.50)	0.234
LYPLAL1	rs2605100	G(A)	N	-0.02 (0.13)	0.845	0.04 (0.18)	0.807	0.06 (0.21)	0.791	-0.43 (0.33)	0.200
ETV5	rs7647305	C(T)	N	-0.13 (0.13)	0.338	-0.50 (0.18)	**0.005**	0.77 (0.23)	**< 0.001**	-0.09 (0.37)	0.805
GNPDA2	rs10938397	G(A)	N	0.01 (0.11)	0.899	-0.18 (0.16)	0.258	0.32 (0.19)	0.095	0.10 (0.29)	0.726
TFAP2B	rs987237	G(A)	N	0.19 (0.15)	0.205	0.14 (0.22)	0.528	0.38 (0.22)	0.086	-0.11 (0.35)	0.759
MSRA	rs7826222	G(C)	N	-0.22 (0.16)	0.168	-0.31 (0.22)	0.154	-0.42 (0.25)	0.095	0.47 (0.40)	0.245

SUPPLEMENTARY DATA

Supplementary Figure 1. Mean rate of weight regain from 6 months through 4.5 years (kg/yr) by treatment arm and genetic risk score (GRS) quartiles. Panel A shows a GRS comprised of all 16 SNPs; Panel B shows data for a GRS composed of only those SNPs showing statistically significant main effects for weight regain in the DPP; Panel C shows data for a GRS composed of all SNPs showing statistically significant gene x lifestyle interactions in the DPP.