

**Table S1. Study design, number of individuals and sample quality control for ExomeChip study cohorts**

Study		Study design	Ethnicity	Total sample size (N)	Sample QC		Samples in analyses (N)	BMI assessment method	References
Short name	Full name				Call rate*	Other exclusions			
<b>ARIC</b>	Atherosclerosis Risk in Communities Study	Population-based	European American (EA) African American (AA)	462	≥ 95%	1) call rate <95%, 2) PCA outliers, 3)sex mismatch , 4) inbreeding coefficient +/-6SD from mean of ancestry distribution, 5) first degree relatedness; 6) comparison with GWAS data, exclude if >40% mismatch, 7) (p10GC) genotype quality score, representing the 10th percentile of the distribution of GenCall scores across all SNPs, 8) missing leptin, adiponectin, or BMI measures (only exclude from analyses missing respective phenotype trait)	340	Measured	<b>PMID: 2646917</b> <b>PMID: 2387450</b> <b>PMCID: PMC3709915</b> <b>PMID: 12829649</b>
<b>CHS EA and AA</b>	Cardiovascular Health Study	Population-based	European American (EA) African-American (AA)	5088	≥ 95%	Following the central QC and joint variant calling, additional QC steps were applied to the CHS data using PLINK. SNPs with a missingness rate of >95% were removed and individuals meeting the following criteria were excluded from analysis. We further excluded individuals with low P10GC call, a missing genotype rate of > 97%, gender mis-matches identified by X chromosome homozygosity rates. The sample was limited to those of self-described European-ancestry (EA) and African-American (AA) participants. Principal components analysis was performed using a subset of common LD-pruned variants from the Exome Chip both for the full sample as well as in EA and AA strata. Individuals whose full-sample first principal component suggested a different ancestry from their self-reported ancestry were excluded as were individuals who were outliers for the first 10 ancestry-specific principal components. Pair-wise IBD measures were calculated and outliers with high levels of IBD were removed.	5044	Measured	<b>PMID: 23874508</b> <b>PMID: 1669507</b>
<b>CLHNS</b>	Cebu Longitudinal Health and Nutrition Survey	Population Based Longitudinal	Filipino	1799	≥98%	1) Missing study specific covariates (household assets or household income)	1,792	Measured	<b>PMID: 20507864</b>
<b>Ely</b>	Ely study	Longitudinal cohort study	European ancestry	1592	> 98%	1) Heterozygosity check, 2) Ethnic outliers, 3) Duplicate individuals, 4) Sex discrepancy, 5) Unusually high number of singleton genotypes, 6) impossible IBD values, 7) phenotype missing	1,432	Measured	<b>PMID:17257284</b>
<b>ERF study</b>	Erasmus Rucphen Family study	Family-based	White European	2963	≥ 95%	--	1146	Measured	<a href="http://www.erasmusmc.nl/klinische_genetica/research/intro/genepi/">http://www.erasmusmc.nl/klinische_genetica/research/intro/genepi/</a>
<b>FAMHS</b>	Family Heart Study	Family-based	White European	--	≥ 98%	1) Variants with missing rate > 5% (based on aggregate data) 2) p <sub>HWE</sub> <1e-6 3) Mendelian errors 4) minor allele count (MAC)<5 for variant-wise tests	1505	Measured	<b>PMID:8651220</b>
<b>Fenland-CE</b>	Fenland Study	Population-based	European ancestry	1077	> 98%	Heterozygosity check; Ethnic outliers; sex discrepancy; unusually high number of singleton genotypes; impossible IBD values; phenotype missing; excluding overlap exomechip samples	368	Measured	<b>PMID: 20519560</b>

<b>Fenland-Exomechip</b>	Fenland Study	Population-based	White European	1650	> 98%	1) heterozygosity outliers (>3.5 SDs), 2) ethnic outliers, 3) sex discrepancy, 4) unusually high number of singleton genotypes, 5) related (IBD > 0.1875)	1342	Measured	<b>PMID: 20519560</b>
<b>FHS</b>	Framingham Heart Study	Family-based	White European	8153	≥ 97%	1) Missing GWAS PCs, 2) Ethnic outlier, 3) Missing trait or covariate	7458	Measured	<b>PMID: 23874508</b>
<b>FINRISK 1997</b>	Finland National FINRISK Health Survey 1997	Population-based	White European	8325 (4006)	≥ 95%	1) Missing leptin or adiponectine levels, 2) Missing BMI, 3)Pregnancy	3917	Measured	<b>PMID: 29165699</b>
<b>FINRISK 2007</b>	Finland National FINRISK Health Survey 2007	Population-based	White European	6086 (3465)	≥ 95%	1) Missing leptin or adiponectin levels, 2) Missing BMI, height or weight, 3) Missing fat free mass or fat mass, 4) Pregnancy	2945	Measured	<b>PMID: 29158543</b>
<b>HABC AA</b>	Health, aging and body composition study	Population-based	African American ancestry	1139	> 95%	1) missing data, 2) relatedness, 3) acestry outliers, 4) heterozygosity outliers	1060	Measured	--
<b>HABC EA</b>	Health, aging and body composition study	Population-based	European ancestry	1663	> 95%	1) missing data, 2) relatedness , 3) acestry outliers, 4) heterozygosity outliers	1572	Measured	--
<b>Inter99</b>	Inter99	Population-based	European	6141	≥ 98%	1) Missing body weight and height. 2) Heterozygosity were calculated separately for maf < 1% and maf > 1% and samples were dropped judged by plots, 3) Cryptic relatedness (related to 20 or more individuals), 3) Technical duplicates , 4) Non-European population outliers from PCA plot (based on AIM SNPs), 5) Sex discrepancy	5594	Measured	<b>PMID: 14663300</b>
<b>JHS</b>	Jackson Heart Study	Population-based cohort with subset of families	African American	2803	≥ 95%	1) Missing outcome or covariate, 2) Heterozygosity, 3) PC outlier 4) Half of overlap with ARIC African Americans (coordinated with ARIC)	2312	Measured	<b>PMID: 16320381</b>
<b>KORA</b>	Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Region of Augsburg)	Population-based	White European	2921	≥98%	1) excess heterozygosity [i.e.  het_rate  >  mean+/-5sd ], 2) sex-check based on y-chromosome (remove men with <50% and women with >50% calls on y-chromosome), 3) remove of HAPMAP-samples 4) remove duplicates (keep sample with higher callrate), 5) remove samples with genetic inconsistencies with other genotyping / indication for contamination / population outliers	2916	Measured	--
<b>Leipzig-adults</b>	Leipzig Adults Study	Population-based	White European	902	≥ 99%	1) Missing phenotype, 2) Heterozygosity, 3) Non-European population outliers, 4) Technical duplicates with lower call rate 5) Sex discrepancy	902	Measured	<b>PMID: 20935630</b>
<b>MESA CAU, CHN, AFA and HIS</b>	Multi-Ethnic Study of Atherosclerosis (MESA) Cohort	Population-based	Caucasia n;Chines e;Hispani c;African-American were recruited from six field centers	6375	≥ 95%	1) Ethnic outliers, 2) duplicates, 3) gender mismatch, 4) Phenoty outliers	CAU 2497 AFA 1655 CHN 769 HIS 1435	Measured	--
<b>NEO Study</b>	The Netherlands Epidemiology of Obesity Study	Population-based	European ancestry	6.604	≥ 98%	1) remove duplicate/swap samples, 2) remove samples with gender mismatch, 3) remove outliers in PCA	6.127	Measured	<b>PMID: 23576214]</b>

<b>OMICS-Fenland</b>	Fenland Study	Population-based	White European	8994	> 97%	1) Heterozygosity check, 2) Ethnic outliers, 3) sex discrepancy, 4) unusually high number of singleton genotypes, 5) impossible IBD values, 6) phenotype missing, 7) excluding overlap exomechip samples	7845	Measured	<b>PMID: 20519560</b>
<b>PIVUS</b>	Prospective Investigation of the Vasculature in Uppsala Seniors	Population-based	White European	961	≥ 99%	1) Missing phenotype, 2) Heterozygosity, 3) Non-European population outliers, 4) technical duplicates with lower call rate 5) Sex discrepancy	961	Measured	<b>PMID: 16141402</b>
<b>RAINE Study</b>	Western Australian Pregnancy Cohort (RAINE) Study	Population-based	White European	1527	≥95%	1) Samepl discordance with GWAS data, 2) Heterozygosity 3) Missing body weight and height, 4) Did not participant in DEXA scan	1006	Measured	--
<b>RISC</b>	Relationship between Insulin Sensitivity and Cardiovascular disease	Population-based	White European	313	0.99	1) heterozygosity, 2) duplicates, 3) relatedness	313	Measured	<b>PMID:14968294</b>
<b>RSI</b>	Rotterdam Study	Population-based	White European	3163	≥ 98%	1) Heterozygosity, 2) gender-check	554	Measured	<b>PMID: 29064009</b>
<b>SHIP-TREND</b>	Study of Health in Pomerania - TREND	Population-based	White European	4270	≥ 98%	1) missing data, 2) duplicate samples (by estimated IBD), 3) reported and genotyped sex mismatch, 4) Heterozygosity	4149	Measured	<b>PMID: 20167617</b>
<b>TwinsUK</b>	TwinsUK	twin study	White European	4081	≥ 95%	1) missing phenotype, 2) sample call rate	1864	Measured	
<b>WGHS</b>	Women's Genome Health Study	population based trial	European	22618	>98%	1) Heterozygosity, 2) Batch effects, 3) see also Grove et al. (PLoS One (2013) doi: 10.1371/journal.pone.0068095)	789	Self-reported	<b>PMID: 18070814</b>
<b>WHI</b>	Women's Health Initiative	Cohort	European	21,857	≥ 95%	1) Unexpected Duplicates, 2) PC ancestry outliers, 3) Missing body weight and height	5886	Measured	<b>PMID: 9492970</b>
<b>WHI</b>	Women's Health Initiative	Cohort	African American	3,516	≥ 95%	1) Unexpected Duplicates, 2) PC ancestry outliers, 3) Missing body weight and height	884	Measured	<b>PMID: 9492970</b>
<b>YFS</b>	The Cardiovascular Risk in Young Finns Study	Population-based	White European	1998	≥ 95%	1) Pregnancy, 2) Heterozygosity, 3) Gender discrepancy, 4) MDS outliers	1681	Measured	<b>PMID: 18263651</b>

\* Call rate to exclude individuals for whom genotyping success rate is less than a certain percentage (to exclude 'bad' samples/DNA)

\*\*Exome-chip samples from this study

**Table S2. Study-specific descriptive statistics of ExomeChip cohorts.**

Study <sup>a</sup>	Trait	Men						Women					
		n	mean	SD	median	min	max	n	mean	SD	median	min	max
ARIC	Age (yrs)	249	53.8	5.7	53	45	65	342	53.2	5.6	53	44	65
	BMI (kg/m <sup>2</sup> )	249	28.7	4.04	28.2	20.4	44.9	342	28.1	5.6	26.8	18.1	49.5
	Leptin levels (ng/ml)	249	8.4	9.6	5.9	0.5	105.3	342	25.6	22.1	18.7	0.7	147.3
CHS-EA	Age (yrs)	484	72.9	5.4	72	65	91	533	72.6	4.9	72	65	92
	BMI (kg/m <sup>2</sup> )	482	26.4	3.6	26	16.9	39.4	531	26.3	4.9	25.5	15.6	47.7
	Leptin levels (ng/ml)	484	9.5	10.4	7.2	1.3	100	533	27.2	22.6	19.2	1.4	100
CHS-AA	Age (yrs)	88	73.6	5.7	73	65	89	121	73.7	5.4	73	66	90
	BMI (kg/m <sup>2</sup> )	88	26.4	3.8	26.1	18.2	37.7	121	29.6	5.3	29.3	18.3	44.5
	Leptin levels (ng/ml)	88	9.6	8.8	7.1	1.3	46.8	121	41.7	26.6	36.1	1.4	100
CLHNS	Age (yrs)	-	-	-	-	-	-	1792	48.5	6.1	47.7	35.7	69.3
	BMI (kg/m <sup>2</sup> )	-	-	-	-	-	-	1780	21.3	4.4	24.1	12.3	42.1
	Leptin levels (ng/ml)	-	-	-	-	-	-	1792	25.5	19.4	21.3	0	154.2
Ely	Age (yrs)	742	61.5	9.1	61.6	35.7	77.4	849	60.8	9.3	60.2	36.3	78.9
	BMI (kg/m <sup>2</sup> )	742	27.4	3.9	26.8	16	45.8	849	27.3	5.4	26.3	16.9	59.3
	Leptin levels (ng/ml)	658	9.2	8.1	7.1	0.1	63.1	769	33	26.7	25.7	0.7	198
ERF study	Age (yrs)	262	49.4	14.2	49.6	17.6	81.8	316	50.0	15.4	51.0	18.6	81.4
	BMI (kg/m <sup>2</sup> )	262	27.5	5.0	26.9	17.4	50.8	316	27.1	5.2	26.5	17.7	61.8
	Leptin levels (ng/ml)	262	27.7	43.8	16.8	0.6	535.9	316	91.3	89.1	60.0	0.0	599.3
FAMHS EA	Age (yrs)	737	52.5	13.9	53.9	25.2	91.0	768	52.8	13.1	53.9	25.2	88.7
	BMI (kg/m <sup>2</sup> )	737	27.8	5.0	27.0	16.0	49.6	768	28.1	6.9	26.4	16.1	55.1
	Leptin levels (ng/ml)	737	8.5	7.0	6.6	1.1	77.1	768	23.4	17.9	18.4	2.2	123.6
Fenland-CE	Age (yrs)	164	49.6	7.0	50.4	36.1	61.6	204	49.3	7.6	50.1	30.7	62.3
	BMI (kg/m <sup>2</sup> )	164	27.4	4.1	26.9	18.2	42.3	204	26.6	4.8	25.4	19.1	45.5
	Leptin levels (ng/ml)	164	7.46	7.26	5.70	0.50	57.90	204	23.69	19.80	16.75	2.20	112.00
Fenland-Exomechip	Age (yrs)	621	48.5	7.2	48.5	31.3	61.5	713	48.6	7.2	49.0	33.7	61.1
	BMI (kg/m <sup>2</sup> )	621	27.5	4.0	27.1	18.0	46.6	713	26.6	5.5	25.2	16.6	59.9

	Leptin levels (ng/ml)	621	7.7	7.5	5.9	0.1	74.5	713	24.2	21.3	17.7	0.5	169.0
Fenland-OMICS	Age (yrs)	3035	48.3	7.4	48.6	30.9	62.3	3376	48.4	7.2	48.7	30.5	62.8
	BMI (kg/m <sup>2</sup> )	3035	27.3	4.2	26.8	15.3	50.6	3376	26.4	5.2	25.4	14.5	58.7
	Leptin levels (ng/ml)	3035	7.7	7.3	5.6	0.1	72.1	3376	23.3	20.3	17.3	0.1	199.0
FHS	Age (yrs)	1800	40.3	8.9	40.0	19.0	72.0	2034	40.0	8.8	40.0	19.0	70.0
	BMI (kg/m <sup>2</sup> )	1800	27.9	4.7	27.3	16.4	56.5	2030	26.0	6.1	24.4	15.6	60.6
	Leptin levels (ng/ml)	1800	6.1	6.2	4.3	0.2	64.2	2034	18.2	17.1	12.3	0.7	110.3
FINRISK97	Age (yrs)	1786	46.1	13.1	45.3	24.2	74.1	2134.0	44.8	12.4	44.2	24.2	73.8
	BMI (kg/m <sup>2</sup> )	1783	26.6	3.9	26.1	14.7	47.1	2133.0	26.0	4.9	25.1	16.6	51.6
	Leptin levels (ng/ml)	1761	6.2	6.2	4.3	1.6	76.2	2111.0	18.0	14.0	14.0	1.6	100.0
FINRISK07	Age (yrs)	1298	52.2	13.6	53.0	25.0	74.0	1647.0	51.0	15.5	51.0	25.0	74.0
	BMI (kg/m <sup>2</sup> )	1284	26.9	4.1	26.3	15.7	62.8	1635.0	26.6	5.4	25.4	15.9	52.7
	Leptin levels (ng/ml)	1284	7.8	8.2	5.3	0.1	89.1	1602.0	19.1	15.8	14.9	0.5	100.0
HABC AA	Age (yrs)	457	73.5	2.8	73.0	69.0	79.0	603	73.3	2.9	73.0	68.0	80.0
	BMI (kg/m <sup>2</sup> )	457	27.1	4.2	26.8	14.9	43.2	603	29.4	5.6	29.0	14.6	47.5
	Leptin levels (ng/ml)	457	8.1	7.2	6.4	0.0	60.3	603	24.8	15.0	22.3	0.3	99.3
HABC EA	Age (yrs)	825	73.9	2.9	74	69	80	747	73.6	2.8	73	69	80
	BMI (kg/m <sup>2</sup> )	825	27	3.7	26.6	17.6	44.2	747	26.1	4.5	25.6	15.6	44.7
	Leptin levels (ng/ml)	825	7.7	6.8	6	0.2	59.1	747	18.9	14	14.8	0.3	86.9
Inter99	Age (yrs)	2675	46.6	7.8	45.2	29.9	61.1	2828	45.8	8.0	45.1	29.7	61.3
	BMI (kg/m <sup>2</sup> )	2674	26.8	4.0	26.3	17.1	56.9	2825	25.8	5.0	24.7	15.2	55.7
	Leptin levels (ng/ml)	2675	4.6	5.1	3.2	0.2	70.7	2828	15.1	16.1	10.3	0.4	260.6
JHS	Age (yrs)	861	51.9	12.8	51.0	21.0	81.0	1434	53.8	12.6	53.0	21.0	91.0
	BMI (kg/m <sup>2</sup> )	861	30.4	30.4	29.2	16.4	66.1	1434	31.9	6.2	31.5	16.0	91.8
	Leptin levels (ng/ml)	861	12.0	11.5	8.8	0.8	106.9	1434	36.1	21.5	32.7	1.4	291.0
KORA	Age (yrs)	1415	49.6	13.4	50.0	25.0	74.0	1506	48.4	13.2	48.0	25.0	74.0
	BMI (kg/m <sup>2</sup> )	1411	27.4	3.8	26.9	16.3	55.1	1491	26.8	5.1	25.9	15.8	51.2
	Leptin levels (ng/ml)	1410	9.4	10.3	6.3	0.0	140.0	1506	27.9	23.6	20.5	0.3	212.0
Leipzig-adults	Age (yrs)	223	42.3	17.1	40.5	18.0	99.0	276	41.5	16.6	38.0	18.0	89.0
	BMI (kg/m <sup>2</sup> )	223	35.4	12.6	32.6	18.8	120.4	276	36.1	12.6	33.6	14.7	70.0
	Leptin levels (ng/ml)	223	14.3	13.8	10.1	0.2	62.1	276	35.1	23.5	34.1	0.2	142.9

MESA CAU	Age (yrs)	395	62.6	10.2	63.0	45.0	84.0	360	62.9	9.2	62.5	45.0	84.0
	BMI (kg/m <sup>2</sup> )	395	28.2	4.0	27.6	19.9	41.1	360	27.5	5.7	26.5	16.9	45.7
	Leptin levels (ng/ml)	395	10.4	10.6	7.1	0.2	79.9	360	27.2	23.0	20.7	1.1	156.5
MESA CHN	Age (yrs)	129	62.6	10.7	63.0	45.0	82.0	115	62.3	9.7	61.0	44.0	84.0
	BMI (kg/m <sup>2</sup> )	129	24.3	2.8	23.9	16.8	32.3	115	24.4	3.2	24.6	17.8	33.0
	Leptin levels (ng/ml)	129	5.8	5.8	3.7	0.4	36.5	115	18.7	16.4	13.2	1.2	113.9
MESA AFA	Age (yrs)	158	61.7	9.7	62	45	83	180	63.6	9.6	64	46	84
	BMI (kg/m <sup>2</sup> )	158	28.6	4.5	28.3	19	46.9	180	30.3	5.7	29.4	19.7	47.3
	Leptin levels (ng/ml)	158	15.3	17.3	9.3	0.2	150	180	41.6	29.4	37.3	2.8	190.9
MESA HIS	Age (yrs)	246	60.0	9.9	59.0	44.0	82.0	242	62.3	9.2	63.0	45.0	82.0
	BMI (kg/m <sup>2</sup> )	246	29.0	4.5	28.7	19.4	45.8	242	30.1	5.5	29.6	18.3	52.5
	Leptin levels (ng/ml)	246	11.0	11.0	7.1	0.0	66.8	242	33.8	25.9	27.8	0.9	224.9
NEO study	Age (yrs)	2941	56.2	6.0	57.0	44.0	66.0	3186	55.8	5.9	56.0	44.0	66.0
	BMI (kg/m <sup>2</sup> )	2941	29.8	3.9	29.3	19.3	54.4	3186	30.3	5.5	29.8	17.2	61.2
	Leptin levels (ng/ml)	2929	12.9	9.2	10.5	0.5	98.6	3172	36.0	23.1	31.9	0.5	262.0
PIVUS	Age (yrs)	479	70.1	0.2	70.1	69.8	72.3	466	70.3	0.1	70.3	69.9	70.8
	BMI (kg/m <sup>2</sup> )	479	27.0	3.7	26.8	17.7	43.4	466	27.1	4.9	26.5	16.6	49.8
	Leptin levels (ng/ml)	479	8.0	5.6	6.5	1.1	41.8	466	19.4	11.9	17.0	1.7	90.0
RAINE Study	Age (yrs)	467	20.1	0.4	20.0	19.4	22.1	412	20.0	0.4	19.9	18.3	21.9
	BMI (kg/m <sup>2</sup> )	467	24.5	4.3	23.8	16.9	48.9	412	24.2	5.0	23.0	15.4	46.5
	Leptin levels (ng/ml)	467	6.1	9.9	3.4	0.1	162.1	412	26.2	18.7	21.5	2.2	98.2
RISC	Age (yrs)	156	44.7	8.3	-	-	-	157	45.8	7.9	-	-	-
	BMI (kg/m <sup>2</sup> )	156	26.0	3.5	26.0	17.9	39.3	157	25.2	4.5	24.3	16.9	42.9
	Leptin levels (ng/ml)	156	5.5	5.6	4.1	0.0	35.7	157	20.9	16.6	16.1	0.9	110.0
RSI	Age (yrs)	273	66.7	7.1	66.1	55.2	88.7	279	69.2	7.6	69.4	55.1	90.8
	BMI (kg/m <sup>2</sup> )	268	25.7	2.8	25.8	18.4	35.3	272	26.8	4.6	26.0	18.2	59.5
	Leptin levels (ng/ml)	273	5.6	4.5	4.0	0.4	25.2	281	17.9	13.1	15.0	0.7	61.4
SHIP-TREND	Age (yrs)	410	50.5	14.1	51.0	22.0	80.0	545	50.0	13.3	50.0	20.0	81.0
	BMI (kg/m <sup>2</sup> )	410	28.1	3.7	28.0	19.2	43.9	545	27.0	5.1	26.3	18.5	53.7
	Leptin levels (ng/ml)	410	7.4	5.6	6.2	1.0	43.1	545	21.8	15.7	18.0	1.9	165.0
TwinsUK	Age (yrs)	-	-	-	-	-	-	1015	48.8	11.2	49.1	18.4	73.5

	BMI (kg/m <sup>2</sup> )	-	-	-	-	-	-	1015	25.2	4.5	24.3	15.1	46.0
	Leptin levels (ng/ml)	-	-	-	-	-	-	1015	16.9	12.0	13.6	1.1	79.4
<b>WGHS</b>	Age (yrs)	-	-	-	-	-	-	789	58.8	8.5	58.0	45.0	87.0
	BMI (kg/m <sup>2</sup> )	-	-	-	-	-	-	789	25.9	4.7	25.0	14.6	49.9
	Leptin levels (ng/ml)	-	-	-	-	-	-	789	22.8	16.9	19.1	1.4	145.0
<b>WHI EA</b>	Age (yrs)	-	-	-	-	-	-	1901	68.3	6.4	69.0	50.0	79.0
	BMI (kg/m <sup>2</sup> )	-	-	-	-	-	-	1901	27.7	6.6	26.5	15.7	159.8
	Leptin levels (ng/ml)	-	-	-	-	-	-	1901	20.9	18.6	16.2	0.2	148.8
<b>WHI AA</b>	Age (yrs)	-	-	-	-	-	-	468	65.5	6.8	66.0	50.0	79.0
	BMI (kg/m <sup>2</sup> )	-	-	-	-	-	-	468	30.2	7.7	29.1	17.2	141.0
	Leptin levels (ng/ml)	-	-	-	-	-	-	468	33.0	20.4	29.1	2.1	117.2
<b>YFS</b>	Age (yrs)	759	32	5	33	24	39	922	32.1	5	33	24	39
	BMI (kg/m <sup>2</sup> )	755	25.7	4	25.1	15.7	47.8	919	24.4	4.6	23.5	15.7	47.2
	Leptin levels (ng/ml)	759	5.4	4.2	4.3	0.8	32.1	922	15.2	9.7	13	1.5	63.3

\* only report descriptives for the individuals included in each of the analyses

CHS NOTE: For age and BMI, I included all individuals who are included in one or more of the analyses

CHS NOTE: For leptin and adiponectin, I included all individuals in the biggest analysis (not adjusted for fat percentage or BMI)

**Table S3. Information on genotyping methods, quality control of SNPs, imputation, and statistical analysis for ExomeChip study cohorts**

Cohort	Genotyping Array	Genotype calling algorithm	Principal components		Inclusion criteria				Association analyses	
			Software	SNPs used from GWAS/ExomeCHIP/AI MS/Other	MAF	Call rate*	P-value for HWE	SNPs that met QC criteria	Polymorphic SNPs in meta-analysis	Analyses software
<b>ARIC</b>	Illumina ExomeChip V1.0	GenTrain 2.0 clustering algorithm	Eigensoft v3.0	Exomchip (MAF>5%)	≥ 0%	≥ 95%	> 10 <sup>-6</sup>	237898 **	163,162 (EA)	rvtests
<b>CHS EA and AA</b>	Illumina ExomeChip V1.0	--	R	ExomeChip	> 0%	≥ 97%	No filter	227061	--	raremetalworker
<b>CLHNS</b>	Affymetrix 500K	Birdseed v2	MACH	GWAS/ExomeCHIP	≥ 0%	≥95%	> 10 <sup>-6</sup>	2304702	28,560,246	mach2QTL
<b>Ely</b>	Illumina HumanCoreExome	GenCall	PLINK	GWAS	>0%	>95%	> 5x10 <sup>-6</sup>	231349	231349	RAREMETALWORKER
<b>ERF study</b>	Illumina HumanExome chip v1.1	GenomeStudio v1.9. and zCall	--	--	>5%	>95%	> 10 <sup>-5</sup>	--	240017	rvtests
<b>FAMHS</b>	Illumina Human Exome 12v1.0 BeadChip	Genome Studio via central CHARGE-S genotyping	EIGENSTRAT	GWAS	≥0%	≥ 98%	> 10 <sup>-6</sup>	237373 **	--	raremetalworker
<b>Fenland-CE</b>	Illumina HumanCoreExome	GenCall	PLINK v1.9beta	GWAS	>0%	>95%	> 10 <sup>-6</sup>	15083259	234201	RAREMETALWORKER
<b>Fenland-Exomechip</b>	Illumina ExomeChip v1.0	Gencall + zcall	PLINK v1.07	ExomeChip	≥ 0%	≥97%	> 10 <sup>-6</sup>	241979	240859	RAREMETALWORKER
<b>FHS</b>	Illumina Infinium HumanExome BeadChip v1.0	Illumina issued cluster file HumanExome-12v1.egt + zCall + CHARGE best practices and joint calling	EIGENSOFT	GWAS	≥ 0%	≥ 97%	No filter	237767	--	raremetalworker

<b>FINRISK 1997</b>	Illumina HumanHap 610k		PLINK	ExomeCHIP	> 0%	≥ 90%	> 10 <sup>-6</sup>	509376	495420	rvtests
<b>FINRISK 2007</b>	Illumina HumanHap 610k		PLINK	ExomeCHIP	> 0%	≥ 90%	> 10 <sup>-6</sup>	509376	495420	rvtests
<b>HABC AA</b>	Illumina ExomeChip V1.0	CHARGE protocol	eignestrat	AIMs	≥ 0%	>95%	> 10 <sup>-6</sup>	228554	228554	rvtests
<b>HABC EA</b>	Illumina ExomeChip V1.0	CHARGE protocol	eignestrat	AIMs	≥ 0%	>95%	> 10 <sup>-6</sup>	228565	228565	rvtests
<b>Inter99</b>	Illumina HumanExome-12v1	GenCall + Zcall	PLINK	AIM SNPs for outlier detection, ExomeCHIP fo adjustment	> 0%	≥ 98%	> 10 <sup>-4</sup>	137187	137187	RMW
<b>JHS</b>	Illumina ExomeChip V1.0	CHARGE joint calling (Illumina GenomeStudio v2011.1 software was utilized with the GenTrain 2.0 clustering algorithm)	Eigenstrat smartpca	Bi-allelic ExomeChip SNPs with MAF > 0.05, HWE p > 0.000001, callrate > 99%, pruned to be pairwise independent with r = 0.3 in plink.	> 0%	≥ 95%	No filter	137716	--	rvtests
<b>KORA</b>	Illumina ExomeChip V1.0	GeneCall + Zcall (CHARGE Protocol)	genomestudio	ExomeCHIP	> 0%	≥98%	≥10 <sup>-8</sup>	1409	247868	rvtests
<b>Leipzig-adults</b>	Illumina HumanExome-12v1_A	GeneCall + Zcall (Oxford Protocol)	PLINK	ExomeCHIP MAF>1%	> 0%	≥ 99%	> 10 <sup>-4</sup>	231460	--	RareMetalWorker
<b>MESA CAU, CHN, AFA, and HIS</b>	Illumina Exome Chip v1.0	Illumina GenomeStudio2011.1	EIGENSTRAT	ExomeCHIP	> 0%	≥ 90%	> 10 <sup>-6</sup>	238876	238876	rvtests
<b>NEO Study</b>	Illumina HumanCoreExomeChip-24V1.0	GeneCall (SOP v5)	PLINK	Based on LD prune	> 0%	≥ 98%	> 10 <sup>-6</sup>	209874	209874	rvtests
<b>OMICS-Fenland</b>	Affymetrix Axiom UKBiobank	Axiom GT1	PLINK v1.9beta	GWAS	> 0%	≥ 95%	> 10 <sup>-6</sup>	719871	58240	RAREMETALWORKER

<b>PIVUS</b>	Illumina HumanExome-12v1_A	GeneCall + Zcall (Oxford Protocol)	plink/MDS	AIMS	> 0%	≥ 99%	> 10 <sup>-4</sup>	233149	--	raremetalworker
<b>RAINE Study</b>	Illumina HumanExome-12v1_A	Illumina GenomeStudio GenTrain Clustering algorithm + zCall	EIGENSOFT - smartpca	AIMS	>0%	>=95%	> 10 <sup>-4</sup>	240806	240062	rvtests
<b>RISC</b>	Illumina Human Exome Beadchip v1	GenCall followed by zCall	PLINK	ExomeCHIP	≥ 0%	0.99	> 10 <sup>-4</sup>	236875	236871	RMW
<b>RSI</b>	Illumina ExomeChip V1.1	GeneCall + Zcall (CHARGE Protocol)	PLINK	GWAS	>0%	≥ 90%	> 10 <sup>-6</sup>	237766	109402	rvtests
<b>SHIP-TREND</b>	Illumina ExomeChip V1.0	GeneCall (CHARGE JointCalling Clusterfile)	Illumina GenomeStudio v2011.1	AIMs	> 0%	≥ 98% (together with SHIP)	> 10 <sup>-6</sup>	238205	--	raremetalworker
<b>TwinsUK</b>	Illumina12v1-1_A	GeneCall	Plink	GWAS	> 0%	≥ 90%	> 10 <sup>-6</sup>	222804		raremetalworker 4.13.6
<b>WGHS</b>	Illumina HumanExome Beadchip v.1.1A	genomeStudio + zCall	EIGENSTRAT	GWAS	≥ 0%	>95%	> 10 <sup>-6</sup>	235667	234710	raremetal
<b>WHI</b>	Illumina Human Exome BeadChip v1.0	GenomeStudio v2010.3	SNPRelate	ExomeCHIP	> 0%	≥ 90%	> 10 <sup>-6</sup>	246470	246,303	rvtests
<b>YFS</b>	Illumina CoreExome v1.0b	GenCall	PLINK	ExomeCHIP	> 0%	≥ 95%	> 10 <sup>-6</sup>	238194	237,852	rvtest

\* Call rate to exclude SNPs for which less than a certain percentage of individuals were successfully genotyped (i.e. to exclude 'bad' SNPs)

\*\* Includes monomorphic SNPs

**Table S4. Single-variant results in all statistical models for the leptin-associated loci**

SNP	Nearest Gene	EA	OA	EAf	Beta	SE	P value	N
<i>Leptin / Additive / All ancestries</i>								
rs1121980	<i>FTO</i>	A	G	0.424	0.050	0.006	9.4E-16	56,802
rs2340550	<i>ACTL9</i>	G	A	0.696	-0.005	0.007	4.6E-01	54,433
rs13389219	<i>COBLL1</i>	T	C	0.410	0.048	0.007	1.0E-12	50,386
rs1260326	<i>GCKR</i>	C	T	0.624	0.035	0.006	4.9E-08	56,802
rs900399	<i>CCNL1</i>	G	A	0.389	-0.036	0.007	2.5E-08	50,386
rs3799260	<i>KLHL31</i>	T	C	0.822	-0.023	0.008	3.7E-03	56,802
rs62621812	<i>ZNF800</i>	A	G	0.028	-0.097	0.018	8.0E-08	56,802
rs791600	<i>LEP</i>	A	G	0.422	-0.048	0.007	2.7E-13	49,371
rs17151919	<i>LEP</i>	A	G	0.007	-0.259	0.040	1.3E-10	49,111
rs972283	<i>KLF14</i>	G	A	0.551	-0.038	0.006	6.0E-10	56,802
<i>Leptin / Additive / European</i>								
rs1121980	<i>FTO</i>	A	G	0.432	0.055	0.007	7.7E-17	49,909
rs2340550	<i>ACTL9</i>	G	A	0.685	-0.008	0.007	2.8E-01	48,008
rs13389219	<i>COBLL1</i>	T	C	0.394	0.046	0.007	7.3E-11	43,493
rs1260326	<i>GCKR</i>	C	T	0.607	0.032	0.007	1.7E-06	49,909
rs900399	<i>CCNL1</i>	G	A	0.396	-0.033	0.007	2.4E-06	43,493
rs3799260	<i>KLHL31</i>	T	C	0.818	-0.024	0.008	3.8E-03	49,909
rs62621812	<i>ZNF800</i>	A	G	0.031	-0.098	0.018	8.2E-08	49,909
rs791600	<i>LEP</i>	A	G	0.411	-0.043	0.007	1.4E-09	42,478
rs17151919	<i>LEP</i>	A	G	0.000	0.134	0.261	6.1E-01	44,474
rs972283	<i>KLF14</i>	G	A	0.521	-0.041	0.006	1.1E-10	49,909
<i>Leptin / Additive / All ancestries / Men</i>								
rs1121980	<i>FTO</i>	A	G	0.433	0.075	0.009	9.7E-16	23,861
rs2340550	<i>ACTL9</i>	G	A	0.693	-0.027	0.010	7.5E-03	23,861
rs13389219	<i>COBLL1</i>	T	C	0.417	0.059	0.010	9.6E-09	20,822
rs1260326	<i>GCKR</i>	C	T	0.625	0.028	0.010	4.1E-03	23,861
rs900399	<i>CCNL1</i>	G	A	0.387	-0.030	0.010	2.8E-03	20,822
rs3799260	<i>KLHL31</i>	T	C	0.819	-0.007	0.012	5.7E-01	23,861
rs62621812	<i>ZNF800</i>	A	G	0.029	-0.100	0.027	2.6E-04	23,861
rs791600	<i>LEP</i>	A	G	0.406	-0.035	0.010	4.4E-04	20,822

rs17151919	LEP	A	G	0.006	-0.310	0.066	3.1E-06	22,153
rs972283	KLF14	G	A	0.544	-0.036	0.009	1.3E-04	23,861
Leptin / Additive / European / Men								
rs1121980	FTO	A	G	0.433	0.077	0.010	1.8E-15	21,921
rs2340550	ACTL9	G	A	0.684	-0.029	0.010	5.9E-03	21,921
rs13389219	COBLL1	T	C	0.395	0.057	0.011	7.0E-08	18,882
rs1260326	GCKR	C	T	0.608	0.026	0.010	8.4E-03	21,921
rs900399	CCNL1	G	A	0.395	-0.026	0.011	1.5E-02	18,882
rs3799260	KLHL31	T	C	0.819	-0.007	0.012	5.6E-01	21,921
rs62621812	ZNF800	A	G	0.031	-0.100	0.027	2.7E-04	21,921
rs791600	LEP	A	G	0.410	-0.032	0.010	2.0E-03	18,882
rs17151919	LEP	A	G	0.000	0.155	0.349	6.6E-01	20,213
rs972283	KLF14	G	A	0.522	-0.037	0.010	1.1E-04	21,921
Leptin / Additive / All ancestries / Women								
rs1121980	FTO	A	G	0.417	0.035	0.008	1.5E-05	32,940
rs2340550	ACTL9	G	A	0.697	0.010	0.009	2.5E-01	30,571
rs13389219	COBLL1	T	C	0.405	0.040	0.009	5.6E-06	29,563
rs1260326	GCKR	C	T	0.624	0.043	0.008	2.1E-07	32,940
rs900399	CCNL1	G	A	0.391	-0.049	0.008	6.2E-09	29,563
rs3799260	KLHL31	T	C	0.825	-0.041	0.010	5.6E-05	32,940
rs62621812	ZNF800	A	G	0.027	-0.102	0.024	2.2E-05	32,940
rs791600	LEP	A	G	0.434	-0.060	0.009	2.9E-12	28,548
rs17151919	LEP	A	G	0.007	-0.233	0.049	1.8E-06	26,957
rs972283	KLF14	G	A	0.555	-0.043	0.008	6.5E-08	32,940
Leptin / Additive / European / Women								
rs1121980	FTO	A	G	0.431	0.044	0.009	6.2E-07	27,987
rs2340550	ACTL9	G	A	0.685	0.007	0.010	4.6E-01	26,086
rs13389219	COBLL1	T	C	0.392	0.038	0.009	6.1E-05	24,610
rs1260326	GCKR	C	T	0.606	0.040	0.009	6.0E-06	27,987
rs900399	CCNL1	G	A	0.397	-0.048	0.009	2.5E-07	24,610
rs3799260	KLHL31	T	C	0.818	-0.043	0.011	8.9E-05	27,987
rs62621812	ZNF800	A	G	0.032	-0.103	0.024	2.1E-05	27,987
rs791600	LEP	A	G	0.413	-0.054	0.009	8.3E-09	23,595
rs17151919	LEP	A	G	0.000	-0.039	0.380	9.2E-01	24,260

rs972283	KLF14	G	A	0.521	-0.048	0.009	1.6E-08	27,987
<i>Leptin / Recessive / All ancestries</i>								
rs1121980	FTO	A	G	0.424	0.071	0.011	1.1E-10	56,802
rs2340550	ACTL9	G	A	0.696	-0.006	0.009	4.6E-01	54,433
rs13389219	COBLL1	T	C	0.410	0.062	0.012	3.2E-07	50,386
rs1260326	GCKR	C	T	0.624	0.046	0.009	2.3E-07	56,802
rs900399	CCNL1	G	A	0.389	-0.042	0.012	6.4E-04	50,386
rs3799260	KLHL31	T	C	0.822	-0.029	0.009	1.5E-03	56,802
rs62621812	ZNF800	A	G	0.021	-0.037	0.124	7.7E-01	56,802
rs791600	LEP	A	G	0.422	-0.074	0.012	6.9E-10	49,371
rs17151919	LEP	A	G	0.007	-0.527	0.190	5.6E-03	49,111
rs972283	KLF14	G	A	0.551	-0.049	0.009	2.5E-07	56,802
<i>Leptin / Recessive / European</i>								
rs1121980	FTO	A	G	0.432	0.078	0.012	3.2E-11	49,909
rs2340550	ACTL9	G	A	0.685	-0.011	0.009	2.5E-01	48,008
rs13389219	COBLL1	T	C	0.394	0.061	0.013	4.5E-06	43,493
rs1260326	GCKR	C	T	0.607	0.041	0.009	1.2E-05	49,909
rs900399	CCNL1	G	A	0.396	-0.036	0.013	6.6E-03	43,493
rs3799260	KLHL31	T	C	0.818	-0.031	0.010	1.3E-03	49,909
rs62621812	ZNF800	A	G	0.023	-0.037	0.124	7.7E-01	49,909
rs791600	LEP	A	G	0.411	-0.070	0.013	5.8E-08	42,478
rs17151919	LEP	A	G	0.000	NA	NA	NA	44,474
rs972283	KLF14	G	A	0.521	-0.054	0.010	9.5E-08	49,909
<i>Leptin / Recessive / All ancestries / Men</i>								
rs1121980	FTO	A	G	0.433	0.096	0.017	8.5E-09	23,861
rs2340550	ACTL9	G	A	0.693	-0.031	0.013	1.7E-02	23,861
rs13389219	COBLL1	T	C	0.417	0.085	0.019	7.0E-06	20,822
rs1260326	GCKR	C	T	0.625	0.031	0.014	2.4E-02	23,861
rs900399	CCNL1	G	A	0.387	-0.029	0.019	1.3E-01	20,822
rs3799260	KLHL31	T	C	0.819	-0.014	0.014	3.3E-01	23,861
rs62621812	ZNF800	A	G	0.021	-0.067	0.192	7.3E-01	23,861
rs791600	LEP	A	G	0.406	-0.065	0.019	4.6E-04	20,822
rs17151919	LEP	A	G	0.005	-0.725	0.260	5.3E-03	22,153
rs972283	KLF14	G	A	0.544	-0.050	0.015	6.0E-04	23,861

<i>Leptin / Recessive / European / Men</i>								
rs1121980	<i>FTO</i>	A	G	0.433	0.100	0.017	7.6E-09	21,921
rs2340550	<i>ACTL9</i>	G	A	0.684	-0.035	0.014	1.1E-02	21,921
rs13389219	<i>COBLL1</i>	T	C	0.395	0.080	0.020	7.1E-05	18,882
rs1260326	<i>GCKR</i>	C	T	0.608	0.027	0.014	6.0E-02	21,921
rs900399	<i>CCNL1</i>	G	A	0.395	-0.023	0.020	2.6E-01	18,882
rs3799260	<i>KLHL31</i>	T	C	0.819	-0.015	0.014	2.9E-01	21,921
rs62621812	<i>ZNF800</i>	A	G	0.023	-0.067	0.192	7.3E-01	21,921
rs791600	<i>LEP</i>	A	G	0.410	-0.065	0.019	8.7E-04	18,882
rs17151919	<i>LEP</i>	A	G	0.000	NA	Inf	NA	20,213
rs972283	<i>KLF14</i>	G	A	0.522	-0.052	0.015	5.6E-04	21,921
<i>Leptin / Recessive / All ancestries / Women</i>								
rs1121980	<i>FTO</i>	A	G	0.417	0.058	0.015	6.8E-05	32,940
rs2340550	<i>ACTL9</i>	G	A	0.697	0.011	0.012	3.6E-01	30,571
rs13389219	<i>COBLL1</i>	T	C	0.405	0.052	0.016	9.4E-04	29,563
rs1260326	<i>GCKR</i>	C	T	0.624	0.059	0.012	3.9E-07	32,940
rs900399	<i>CCNL1</i>	G	A	0.391	-0.061	0.016	1.5E-04	29,563
rs3799260	<i>KLHL31</i>	T	C	0.825	-0.047	0.012	8.4E-05	32,940
rs62621812	<i>ZNF800</i>	A	G	0.019	-0.149	0.162	3.6E-01	32,940
rs791600	<i>LEP</i>	A	G	0.434	-0.088	0.016	1.9E-08	28,548
rs17151919	<i>LEP</i>	A	G	0.007	-0.195	0.280	4.9E-01	26,957
rs972283	<i>KLF14</i>	G	A	0.555	-0.055	0.012	8.5E-06	32,940
<i>Leptin / Recessive / European / Women</i>								
rs1121980	<i>FTO</i>	A	G	0.431	0.068	0.016	1.4E-05	27,987
rs2340550	<i>ACTL9</i>	G	A	0.685	0.006	0.013	6.5E-01	26,086
rs13389219	<i>COBLL1</i>	T	C	0.392	0.055	0.018	2.1E-03	24,610
rs1260326	<i>GCKR</i>	C	T	0.606	0.055	0.013	1.3E-05	27,987
rs900399	<i>CCNL1</i>	G	A	0.397	-0.057	0.017	9.9E-04	24,610
rs3799260	<i>KLHL31</i>	T	C	0.818	-0.049	0.013	1.5E-04	27,987
rs62621812	<i>ZNF800</i>	A	G	0.022	-0.149	0.162	3.6E-01	27,987
rs791600	<i>LEP</i>	A	G	0.413	-0.083	0.017	1.8E-06	23,595
rs17151919	<i>LEP</i>	A	G	0.000	NA	NA	NA	24,260
rs972283	<i>KLF14</i>	G	A	0.521	-0.062	0.014	5.6E-06	27,987
<i>LeptinAdjBMI / Additive / All ancestries</i>								

rs1121980	FTO	A	G	0.424	0.003	0.006	5.7E-01	56,708
rs2340550	ACTL9	G	A	0.695	-0.014	0.007	3.2E-02	54,339
rs13389219	COBLL1	T	C	0.410	0.053	0.007	3.0E-15	50,297
rs1260326	GCKR	C	T	0.624	0.050	0.006	2.7E-15	56,708
rs900399	CCNL1	G	A	0.389	-0.041	0.007	5.2E-10	50,297
rs3799260	KLHL31	T	C	0.822	-0.036	0.008	4.0E-06	56,708
rs62621812	ZNF800	A	G	0.028	-0.127	0.018	2.0E-12	56,708
rs791600	LEP	A	G	0.422	-0.066	0.007	1.1E-23	49,282
rs17151919	LEP	A	G	0.007	-0.333	0.040	1.5E-16	49,034
rs972283	KLF14	G	A	0.550	-0.053	0.006	6.3E-18	56,708
<i>LeptinAdjBMI / Additive / European</i>								
rs1121980	FTO	A	G	0.432	0.005	0.007	4.5E-01	49,830
rs2340550	ACTL9	G	A	0.685	-0.016	0.007	2.6E-02	47,929
rs13389219	COBLL1	T	C	0.394	0.053	0.007	1.1E-13	43,419
rs1260326	GCKR	C	T	0.607	0.048	0.007	4.3E-13	49,830
rs900399	CCNL1	G	A	0.396	-0.040	0.007	9.2E-09	43,419
rs3799260	KLHL31	T	C	0.818	-0.038	0.008	3.8E-06	49,830
rs62621812	ZNF800	A	G	0.031	-0.127	0.018	2.8E-12	49,830
rs791600	LEP	A	G	0.411	-0.063	0.007	5.4E-19	42,404
rs17151919	LEP	A	G	0.000	-0.187	0.261	4.7E-01	44,401
rs972283	KLF14	G	A	0.521	-0.056	0.006	3.8E-18	49,830
<i>LeptinAdjBMI / Additive / All ancestries / Men</i>								
rs1121980	FTO	A	G	0.433	0.028	0.009	2.6E-03	23,822
rs2340550	ACTL9	G	A	0.693	-0.050	0.010	8.5E-07	23,822
rs13389219	COBLL1	T	C	0.417	0.052	0.010	3.8E-07	20,787
rs1260326	GCKR	C	T	0.624	0.043	0.010	8.4E-06	23,822
rs900399	CCNL1	G	A	0.387	-0.036	0.010	4.3E-04	20,787
rs3799260	KLHL31	T	C	0.819	-0.023	0.012	6.0E-02	23,822
rs62621812	ZNF800	A	G	0.029	-0.148	0.027	7.0E-08	23,822
rs791600	LEP	A	G	0.406	-0.054	0.010	6.8E-08	20,787
rs17151919	LEP	A	G	0.006	-0.399	0.066	1.2E-09	22,119
rs972283	KLF14	G	A	0.544	-0.045	0.009	1.8E-06	23,822
<i>LeptinAdjBMI / Additive / European / Men</i>								
rs1121980	FTO	A	G	0.433	0.026	0.010	6.4E-03	21,883

rs2340550	ACTL9	G	A	0.684	-0.053	0.010	4.1E-07	21,883
rs13389219	COBLL1	T	C	0.395	0.048	0.011	5.2E-06	18,848
rs1260326	GCKR	C	T	0.608	0.042	0.010	2.1E-05	21,883
rs900399	CCNL1	G	A	0.395	-0.033	0.011	2.1E-03	18,848
rs3799260	KLHL31	T	C	0.819	-0.025	0.012	4.3E-02	21,883
rs62621812	ZNF800	A	G	0.031	-0.146	0.028	1.1E-07	21,883
rs791600	LEP	A	G	0.410	-0.049	0.010	2.5E-06	18,848
rs17151919	LEP	A	G	0.000	-0.225	0.352	5.2E-01	20,180
rs972283	KLF14	G	A	0.522	-0.048	0.010	4.8E-07	21,883
<i>LeptinAdjBMI / Additive / All ancestries / Women</i>								
rs1121980	FTO	A	G	0.417	-0.013	0.008	1.2E-01	32,886
rs2340550	ACTL9	G	A	0.697	0.007	0.009	4.2E-01	30,517
rs13389219	COBLL1	T	C	0.405	0.052	0.009	2.0E-09	29,510
rs1260326	GCKR	C	T	0.624	0.059	0.008	6.2E-13	32,886
rs900399	CCNL1	G	A	0.391	-0.054	0.008	1.2E-10	29,510
rs3799260	KLHL31	T	C	0.825	-0.055	0.010	1.0E-07	32,886
rs62621812	ZNF800	A	G	0.027	-0.125	0.024	2.2E-07	32,886
rs791600	LEP	A	G	0.434	-0.079	0.009	4.1E-20	28,495
rs17151919	LEP	A	G	0.007	-0.291	0.050	5.7E-09	26,915
rs972283	KLF14	G	A	0.555	-0.063	0.008	3.7E-15	32,886
<i>LeptinAdjBMI / Additive / European / Women</i>								
rs1121980	FTO	A	G	0.431	-0.009	0.009	3.2E-01	27,947
rs2340550	ACTL9	G	A	0.685	0.008	0.009	4.1E-01	26,046
rs13389219	COBLL1	T	C	0.392	0.055	0.009	3.8E-09	24,571
rs1260326	GCKR	C	T	0.606	0.057	0.009	9.4E-11	27,947
rs900399	CCNL1	G	A	0.398	-0.058	0.009	3.4E-10	24,571
rs3799260	KLHL31	T	C	0.818	-0.057	0.011	2.2E-07	27,947
rs62621812	ZNF800	A	G	0.032	-0.126	0.024	1.9E-07	27,947
rs791600	LEP	A	G	0.413	-0.080	0.009	2.9E-17	23,556
rs17151919	LEP	A	G	0.000	-0.310	0.375	4.1E-01	24,221
rs972283	KLF14	G	A	0.521	-0.066	0.009	1.3E-14	27,947
<i>LeptinAdjBMI / Recessive / All ancestries</i>								
rs1121980	FTO	A	G	0.424	0.000	0.011	9.8E-01	56,708
rs2340550	ACTL9	G	A	0.695	-0.014	0.009	9.8E-02	54,339

rs13389219	COBLL1	T	C	0.410	0.080	0.012	7.0E-11	50,297
rs1260326	GCKR	C	T	0.624	0.057	0.009	1.8E-10	56,708
rs900399	CCNL1	G	A	0.389	-0.057	0.012	4.3E-06	50,297
rs3799260	KLHL31	T	C	0.822	-0.044	0.009	1.7E-06	56,708
rs62621812	ZNF800	A	G	0.021	-0.145	0.124	2.4E-01	56,708
rs791600	LEP	A	G	0.422	-0.099	0.012	2.4E-16	49,282
rs17151919	LEP	A	G	0.007	-0.795	0.190	2.9E-05	49,034
rs972283	KLF14	G	A	0.550	-0.071	0.009	6.1E-14	56,708
LeptinAdjBMI / Recessive / European								
rs1121980	FTO	A	G	0.432	-0.005	0.012	6.8E-01	49,830
rs2340550	ACTL9	G	A	0.685	-0.018	0.009	5.7E-02	47,929
rs13389219	COBLL1	T	C	0.394	0.081	0.013	1.4E-09	43,419
rs1260326	GCKR	C	T	0.607	0.053	0.009	1.9E-08	49,830
rs900399	CCNL1	G	A	0.396	-0.054	0.013	3.8E-05	43,419
rs3799260	KLHL31	T	C	0.818	-0.047	0.010	1.3E-06	49,830
rs62621812	ZNF800	A	G	0.023	-0.145	0.124	2.4E-01	49,830
rs791600	LEP	A	G	0.411	-0.099	0.013	2.7E-14	42,404
rs17151919	LEP	A	G	0.000	NA	Inf	NA	44,401
rs972283	KLF14	G	A	0.521	-0.079	0.010	8.0E-15	49,830
LeptinAdjBMI / Recessive / All ancestries / Men								
rs1121980	FTO	A	G	0.433	0.024	0.017	1.6E-01	23,822
rs2340550	ACTL9	G	A	0.693	-0.065	0.013	6.5E-07	23,822
rs13389219	COBLL1	T	C	0.417	0.082	0.019	1.4E-05	20,787
rs1260326	GCKR	C	T	0.624	0.046	0.014	7.9E-04	23,822
rs900399	CCNL1	G	A	0.387	-0.036	0.019	6.2E-02	20,787
rs3799260	KLHL31	T	C	0.819	-0.030	0.014	2.9E-02	23,822
rs62621812	ZNF800	A	G	0.021	-0.293	0.192	1.3E-01	23,822
rs791600	LEP	A	G	0.406	-0.095	0.019	4.2E-07	20,787
rs17151919	LEP	A	G	0.005	-0.942	0.258	2.5E-04	22,119
rs972283	KLF14	G	A	0.544	-0.058	0.015	6.2E-05	23,822
LeptinAdjBMI / Recessive / European / Men								
rs1121980	FTO	A	G	0.433	0.021	0.017	2.2E-01	21,883
rs2340550	ACTL9	G	A	0.684	-0.071	0.014	2.0E-07	21,883
rs13389219	COBLL1	T	C	0.395	0.072	0.020	3.3E-04	18,848

rs1260326	GCKR	C	T	0.608	0.045	0.014	1.6E-03	21,883
rs900399	CCNL1	G	A	0.395	-0.032	0.020	1.1E-01	18,848
rs3799260	KLHL31	T	C	0.819	-0.034	0.015	2.0E-02	21,883
rs62621812	ZNF800	A	G	0.023	-0.293	0.192	1.3E-01	21,883
rs791600	LEP	A	G	0.410	-0.092	0.019	2.1E-06	18,848
rs17151919	LEP	A	G	0.000	NA	NA	NA	20,180
rs972283	KLF14	G	A	0.522	-0.065	0.015	2.0E-05	21,883
<i>LeptinAdjBMI / Recessive / All ancestries / Women</i>								
rs1121980	FTO	A	G	0.417	-0.016	0.015	2.6E-01	32,886
rs2340550	ACTL9	G	A	0.697	0.016	0.012	1.8E-01	30,517
rs13389219	COBLL1	T	C	0.405	0.080	0.016	4.3E-07	29,510
rs1260326	GCKR	C	T	0.624	0.068	0.012	4.4E-09	32,886
rs900399	CCNL1	G	A	0.391	-0.083	0.016	2.3E-07	29,510
rs3799260	KLHL31	T	C	0.825	-0.063	0.012	1.3E-07	32,886
rs62621812	ZNF800	A	G	0.019	-0.241	0.162	1.4E-01	32,886
rs791600	LEP	A	G	0.434	-0.112	0.016	5.7E-13	28,495
rs17151919	LEP	A	G	0.007	-0.570	0.284	4.5E-02	26,915
rs972283	KLF14	G	A	0.555	-0.086	0.012	2.5E-12	32,886
<i>LeptinAdjBMI / Recessive / All ancestries / Women</i>								
rs1121980	FTO	A	G	0.431	-0.022	0.015	1.5E-01	27,947
rs2340550	ACTL9	G	A	0.685	0.015	0.012	2.3E-01	26,046
rs13389219	COBLL1	T	C	0.392	0.093	0.018	1.7E-07	24,571
rs1260326	GCKR	C	T	0.606	0.062	0.013	7.0E-07	27,947
rs900399	CCNL1	G	A	0.398	-0.085	0.017	9.2E-07	24,571
rs3799260	KLHL31	T	C	0.818	-0.066	0.013	2.2E-07	27,947
rs62621812	ZNF800	A	G	0.022	-0.241	0.162	1.4E-01	27,947
rs791600	LEP	A	G	0.413	-0.118	0.017	1.4E-11	23,556
rs17151919	LEP	A	G	0.000	NA	NA	NA	24,221
rs972283	KLF14	G	A	0.521	-0.096	0.014	1.4E-12	27,947

**Table S5. Comparison of BMI-adjusted and BMI-unadjusted results for leptin associated loci**

SNP	Chr	Position	Gene	Meta-analysis	Annotation	EA	OA	Beta AdjBMI	Beta	SE AdjBMI	SE	P AdjBMI	P	N AdjBMI	N
<b>Novel loci</b>															
rs3799260	6	53519605	<i>KLHL31</i>	Additive / All ancestries / Women	missense	C	T	0.055	0.041	0.010	0.010	1.0E-07	5.6E-05	32,886	32,940
rs62621812	7	127015083	<i>ZNF800</i>	Additive / All ancestries	missense	G	A	0.127	0.097	0.018	0.018	2.0E-12	8.0E-08	56,708	56,802
rs17151919	7	127894592	<i>LEP</i>	Additive / All ancestries	missense	G	A	0.333	0.259	0.040	0.040	1.5E-16	1.1E-10	49,034	49,111
rs972283	7	130466854	<i>KLF14</i>	Additive / European	intergenic	A	G	0.056	0.041	0.006	0.006	3.8E-18	1.1E-10	49,830	49,909
rs2340550	19	8808942	<i>ACTL9</i>	Recessive / European / Men	missense	A	G	0.071	0.035	0.014	0.014	2.0E-07	1.1E-02	21,883	21,921
<b>Previously identified loci</b>															
rs1260326	2	27730940	<i>GCKR</i>	Additive / All ancestries	missense	C	T	0.050	0.035	0.006	0.006	2.7E-15	4.9E-08	56,708	56,802
rs13389219	2	165528876	<i>COBLL1</i>	Additive / All ancestries	intronic	T	C	0.053	0.048	0.007	0.007	3.0E-15	1.0E-12	50,297	50,386
rs900399	3	156798732	<i>CCNL1</i>	Additive / All ancestries / Women	intergenic	A	G	0.054	0.049	0.008	0.008	1.2E-10	6.2E-09	29,510	29,563
rs791600	7	127865816	<i>LEP</i>	Additive / All ancestries	intergenic	G	A	0.066	0.048	0.007	0.007	1.1E-23	2.7E-13	49,282	49,371
rs1121980	16	53809247	<i>FTO</i>	Additive / European	intronic	A	G	0.005	0.055	0.007	0.007	4.5E-01	7.7E-17	49,830	49,909

The chromosomal positions are based on hg19.

Chr, chromosome; EA, Effect allele; OA, Other allele; EAF, Effect allele frequency; LeptinAdjBMI, leptin adjusted for body mass index

**Table S6. Examination of collider bias with BMI among the exome-array significant loci associated with leptin adjusted for BMI**

Locus	MarkerName	EA	EAF	xL	pL	xLadjB	pLadjB	xLadjBa	xB	pB
<i>FTO</i>	rs1121980	A	0.4316428	0.05486291	7.71E-17	0.004952214	4.47E-01	0.04153	0.07481	6.70E-225
<i>ACTL9*</i>	rs2340550	G	0.6846579	-0.007649348	2.79E-01	-0.01562951	2.62E-02	-0.01394	0.00345	1.51E-01
<i>COBLL1</i>	rs13389219	T	0.3938886	0.04618875	7.30E-11	0.05254237	1.13E-13	0.05871	0.01261	8.16E-08
<i>GCKR</i>	rs1260326	C	0.6070448	0.03182518	1.71E-06	0.04773787	4.32E-13	0.04993	0.00449	5.24E-02
<i>CCNL1</i>	rs900399	G	0.3961604	-0.03304733	2.43E-06	-0.04024503	9.25E-09	-0.04198	-0.00355	1.24E-01
<i>KLHL31*</i>	rs3799260	T	0.8183081	-0.02397769	3.79E-03	-0.03820487	3.83E-06	-0.03499	0.00657	1.71E-02
<i>ZNF800</i>	rs62621812	A	0.03142557	-0.09769461	8.18E-08	-0.1273454	2.80E-12	-0.11685	0.02147	1.24E-03
<i>LEP</i>	rs791600	A	0.4110841	-0.04264698	1.36E-09	-0.06262022	5.35E-19	-0.06034	0.00466	4.54E-02
<i>LEP*</i>	rs17151919	A	0.000166917	0.1342779	6.07E-01	-0.1868478	4.73E-01	-0.18299	0.00789	9.20E-01
<i>KLF14</i>	rs972283	G	0.5211696	-0.04137304	1.12E-10	-0.05554037	3.84E-18	-0.05942	-0.00793	2.68E-04

xL, Effect size for leptin

pL, P value for leptin

xLadjB, Effect size for leptin adjusted for BMI

pLadjB, P value for leptin adjusted for BMI

xLadjBa, Corrected effect size for leptin adjusted for BMI

xB, Effect size for BMI

pB, P value for BMI

\* The *ACTL9*, *KLHL31*, and *LEP* rs17151919 loci reached array-wide significance ( $P < 2 \times 10^{-7}$ ) in meta-analyses of European-ancestry men (recessive model), all-ancestry women, and African-ancestry men and women combined, respectively. The results shown are from meta-analyses of European ancestry individuals only.

**Table S7. Ancestry-specific results for the Val94Met (rs17151919) missense variant in *LEP***

Ancestry	Trait	Chr:Position	EA	OA	N	EAF	N <sub>GG</sub>	N <sub>GA+AG</sub>	N <sub>AA</sub>	beta	se	Pvalue	I2
All	LeptinAdjBMI	7:127894592	A (Met94)	G (Val94)	49034	0.0067	40075	609	28	-0.333	0.040	1.53E-16	76%
European	LeptinAdjBMI	7:127894592	A (Met94)	G (Val94)	44401	0.0002	36065	15	0	-0.187	0.261	4.73E-01	0%
African	LeptinAdjBMI	7:127894592	A (Met94)	G (Val94)	3901	0.0800	3302	571	27	-0.343	0.042	2.40E-16	94%
Hispanic	LeptinAdjBMI	7:127894592	A (Met94)	G (Val94)	488	0.0221	464	23	1	-0.209	NA	2.85E-01	NA
East Asian	LeptinAdjBMI	7:127894592	A (Met94)	G (Val94)	244	NA	NA	NA	NA	NA	NA	NA	NA

EA, effect allele; OA, other allele; EAF, effect allele frequency

**Table S8. Gene-based results in all statistical models for leptin-associated genes**

Gene	Method	N	P value	beta	se	N variants
<i>Leptin / Additive / All ancestries</i>						
<i>CNTD1</i>	SKAT broad	49,597	9.1E-04	0.350	0.094	6
<i>CNTD1</i>	SKAT strict	48,582	7.0E-02	1.043	0.330	1
<i>CNTD1</i>	VT broad	49,597	3.9E-06	0.746	0.149	4
<i>CNTD1</i>	VT strict	48,582	7.0E-02	1.043	0.330	1
<i>DNAJC18</i>	SKAT broad	56,013	2.2E-02	0.062	0.057	7
<i>DNAJC18</i>	SKAT strict	49,597	5.1E-05	0.466	0.135	2
<i>DNAJC18</i>	VT broad	56,013	4.3E-03	0.323	0.096	5
<i>DNAJC18</i>	VT strict	49,597	1.1E-03	0.466	0.135	2
<i>Leptin / Additive / European</i>						
<i>CNTD1</i>	SKAT broad	42,704	1.4E-05	0.580	0.126	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA
<i>CNTD1</i>	VT broad	42,704	1.1E-05	0.720	0.153	4
<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA
<i>DNAJC18</i>	SKAT broad	49,120	3.1E-02	0.045	0.060	7
<i>DNAJC18</i>	SKAT strict	42,704	5.3E-05	0.478	0.140	2
<i>DNAJC18</i>	VT broad	49,120	8.4E-03	0.360	0.112	5
<i>DNAJC18</i>	VT strict	42,704	1.3E-03	0.478	0.140	2
<i>Leptin / Additive / All ancestries / Men</i>						
<i>CNTD1</i>	SKAT broad	20,822	2.0E-05	0.580	0.137	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA
<i>CNTD1</i>	VT broad	20,822	6.4E-06	1.026	0.209	3
<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA
<i>DNAJC18</i>	SKAT broad	23,861	5.3E-01	-0.061	0.086	6
<i>DNAJC18</i>	SKAT strict	20,822	2.0E-01	0.034	0.223	2
<i>DNAJC18</i>	VT broad	23,861	3.4E-01	-0.569	0.360	2
<i>DNAJC18</i>	VT strict	20,822	1.3E-01	-0.896	0.499	1
<i>Leptin / Additive / European / Men</i>						
<i>CNTD1</i>	SKAT broad	18,882	1.3E-07	0.898	0.165	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA
<i>CNTD1</i>	VT broad	18,882	1.4E-07	0.898	0.165	5
<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA

<i>DNAJC18</i>	SKAT broad	21,921	5.3E-01	-0.059	0.087	6
<i>DNAJC18</i>	SKAT strict	18,882	2.0E-01	0.034	0.223	2
<i>DNAJC18</i>	VT broad	21,921	6.4E-01	-0.566	0.446	2
<i>DNAJC18</i>	VT strict	18,882	1.3E-01	-0.896	0.499	1
<i>Leptin / Additive / All ancestries / Women</i>						
<i>CNTD1</i>	SKAT broad	29,563	5.5E-01	0.178	0.123	6
<i>CNTD1</i>	SKAT strict	28,548	7.3E-02	0.981	0.297	1
<i>CNTD1</i>	VT broad	29,563	3.2E-02	0.553	0.211	4
<i>CNTD1</i>	VT strict	28,548	7.3E-02	0.981	0.297	1
<i>DNAJC18</i>	SKAT broad	32,940	1.3E-02	0.151	0.075	7
<i>DNAJC18</i>	SKAT strict	29,563	1.9E-05	0.717	0.166	2
<i>DNAJC18</i>	VT broad	32,940	5.8E-04	0.452	0.117	5
<i>DNAJC18</i>	VT strict	29,563	3.3E-05	0.717	0.166	2
<i>Leptin / Additive / European / Women</i>						
<i>CNTD1</i>	SKAT broad	24,610	2.7E-01	0.233	0.188	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA
<i>CNTD1</i>	VT broad	24,610	1.3E-01	0.478	0.240	4
<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA
<i>DNAJC18</i>	SKAT broad	27,987	1.9E-02	0.132	0.081	6
<i>DNAJC18</i>	SKAT strict	24,610	1.3E-05	0.767	0.177	2
<i>DNAJC18</i>	VT broad	27,987	8.1E-04	0.557	0.146	4
<i>DNAJC18</i>	VT strict	24,610	2.8E-05	0.767	0.177	2
<i>LeptinAdjBMI / Additive / All ancestries</i>						
<i>CNTD1</i>	SKAT broad	49,508	4.6E-02	0.242	0.093	6
<i>CNTD1</i>	SKAT strict	48,493	9.1E-02	0.969	0.330	1
<i>CNTD1</i>	VT broad	49,508	9.0E-04	0.560	0.149	4
<i>CNTD1</i>	VT strict	48,493	9.1E-02	0.969	0.330	1
<i>DNAJC18</i>	SKAT broad	55,919	4.3E-03	0.083	0.057	7
<i>DNAJC18</i>	SKAT strict	49,508	1.2E-07	0.485	0.136	2
<i>DNAJC18</i>	VT broad	55,919	1.8E-02	0.279	0.096	5
<i>DNAJC18</i>	VT strict	49,508	7.1E-04	0.485	0.136	2
<i>LeptinAdjBMI / Additive / European</i>						
<i>CNTD1</i>	SKAT broad	42,630	3.8E-03	0.430	0.126	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA
<i>CNTD1</i>	VT broad	42,630	2.0E-03	0.525	0.153	4

<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA
<i>DNAJC18</i>	SKAT broad	49,041	8.4E-03	0.063	0.060	7
<i>DNAJC18</i>	SKAT strict	42,630	2.3E-07	0.474	0.141	2
<i>DNAJC18</i>	VT broad	49,041	6.4E-02	0.286	0.113	5
<i>DNAJC18</i>	VT strict	42,630	1.6E-03	0.474	0.141	2
<i>LeptinAdjBMI / Additive / All ancestries / Men</i>						
<i>CNTD1</i>	SKAT broad	20,787	7.1E-02	0.313	0.138	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA
<i>CNTD1</i>	VT broad	20,787	1.5E-02	0.606	0.210	3
<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA
<i>DNAJC18</i>	SKAT broad	23,822	2.6E-01	-0.124	0.086	6
<i>DNAJC18</i>	VT broad	23,822	1.6E-01	-0.713	0.359	2
<i>DNAJC18</i>	SKAT strict	20,787	9.6E-02	0.036	0.223	2
<i>DNAJC18</i>	VT strict	20,787	4.2E-02	-1.138	0.498	1
<i>LeptinAdjBMI / Additive / European / Men</i>						
<i>CNTD1</i>	SKAT broad	18,848	7.4E-03	0.565	0.165	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA
<i>CNTD1</i>	VT broad	18,848	2.6E-03	0.565	0.165	5
<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA
<i>DNAJC18</i>	SKAT broad	21,883	2.6E-01	-0.109	0.087	6
<i>DNAJC18</i>	SKAT strict	18,848	9.6E-02	0.036	0.223	2
<i>DNAJC18</i>	VT broad	21,883	2.5E-01	-0.838	0.446	2
<i>DNAJC18</i>	VT strict	18,848	4.2E-02	-1.138	0.498	1
<i>LeptinAdjBMI / Additive / All ancestries / Women</i>						
<i>CNTD1</i>	SKAT broad	29,510	3.0E-01	0.238	0.124	6
<i>CNTD1</i>	SKAT strict	28,495	7.7E-02	0.972	0.305	1
<i>CNTD1</i>	VT broad	29,510	1.3E-02	0.620	0.212	4
<i>CNTD1</i>	VT strict	28,495	7.7E-02	0.972	0.305	1
<i>DNAJC18</i>	SKAT broad	32,886	7.6E-04	0.234	0.075	7
<i>DNAJC18</i>	SKAT strict	29,510	5.5E-08	0.757	0.169	2
<i>DNAJC18</i>	VT broad	32,886	4.4E-04	0.460	0.118	5
<i>DNAJC18</i>	VT strict	29,510	1.5E-05	0.757	0.169	2
<i>LeptinAdjBMI / Additive / European / Women</i>						
<i>CNTD1</i>	SKAT broad	24,571	1.7E-01	0.373	0.186	5
<i>CNTD1</i>	SKAT strict	NA	NA	NA	NA	NA

<i>CNTD1</i>	VT broad	24,571	6.3E-02	0.554	0.239	4
<i>CNTD1</i>	VT strict	NA	NA	NA	NA	NA
<i>DNAJC18</i>	SKAT broad	27,947	2.4E-03	0.207	0.081	6
<i>DNAJC18</i>	SKAT strict	24,571	7.9E-08	0.774	0.179	2
<i>DNAJC18</i>	VT broad	27,947	4.1E-03	0.496	0.147	4
<i>DNAJC18</i>	VT strict	24,571	3.2E-05	0.774	0.179	2

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**Table S9. Association of the leptin-decreasing Met94 allele of *LEP* Val94Met (rs1715919) with BMI z-score in African-ancestry children from the CHOP cohort.**

Age Bin	N	Allele freq.	Beta	SE	P
2	2726	0.089	0.079	0.055	0.153
3	2570	0.089	0.123	0.056	0.029
4	2572	0.093	0.160	0.054	0.003
5	2381	0.089	0.154	0.060	0.010
6	2030	0.091	0.204	0.066	0.002
7	1769	0.092	0.143	0.070	0.041
8	1583	0.092	0.029	0.074	0.694
9	1476	0.099	0.017	0.078	0.824
10	1446	0.095	0.017	0.080	0.832
11	1500	0.095	-0.004	0.079	0.964
12	1455	0.096	-0.036	0.075	0.631
13	1460	0.101	-0.007	0.075	0.928
14	1417	0.104	0.004	0.074	0.959
15	1355	0.099	0.048	0.077	0.537
16	1287	0.093	-0.006	0.081	0.937
17	1098	0.102	0.055	0.087	0.527
18	451	0.085	-0.009	0.135	0.946

**Table S10. Association of the leptin-decreasing C allele of rs10487505 near *LEP* with BMI z-score in a meta-analysis of African-ancestry and European ancestry children from the CHOP cohort.**

Age Bin	N	Allele freq.	Beta	SE	<i>P</i>
2	3681	0.462	0.033	0.026	0.203
3	3618	0.467	0.026	0.026	0.334
4	3681	0.469	0.058	0.026	0.027
5	3557	0.471	-0.002	0.027	0.929
6	3166	0.473	-0.044	0.029	0.132
7	2869	0.469	-0.006	0.031	0.835
8	2711	0.465	-0.021	0.032	0.504
9	2571	0.465	-0.035	0.033	0.290
10	2608	0.468	-0.033	0.033	0.317
11	2705	0.462	-0.028	0.032	0.380
12	2685	0.454	-0.021	0.032	0.502
13	2697	0.459	0.004	0.031	0.898
14	2679	0.454	-0.027	0.032	0.389
15	2604	0.451	-0.009	0.031	0.777
16	2463	0.458	0.012	0.033	0.719
17	2130	0.465	-0.004	0.036	0.917
18	663	0.456	-0.003	0.062	0.959

**Table S11. Predicted change in leptin protein stability upon the Val94Met change (Val73Met in the mature leptin protein) in the amino acid sequence**

Tool	Protein (PDB-ID)	WT/MT	Chain	Overall stability	Predicted $\Delta\Delta G$
CUPSAT	LEP (1AX8)	VAL/MET	A	Decreased	-0.22
I-Mutant v2.0	LEP (1AX8)	VAL/MET	A	Decreased	--
SDM	LEP (1AX8)	VAL/MET	A	Decreased	-0.72

Table S12. Colocalization of METSIM subcutaneous adipose tissue eQTLs at GWAS loci for leptin

SNP	Chr	Position	MAF	Probeset	Allele 1 / EA	Allele 2	eQTL gene	GWAS variant association with expression level				Lead eSNP association with expression level						LD r <sup>2</sup>
								Beta initial	P initial	Beta conditional	P conditional	Lead eSNP	Allele 1/ Allele 2	Beta initial	P initial	Beta conditional	P conditional	
rs62621812	7	127,015,083	0.06	11736419_a_at	G	A	ZNF800	-0.871	2.40E-16	0.000	3.18E-01	rs62621812	A/G	0.871	2.40E-16	0.000	3.2E-01	1.00
rs972283	7	130,466,854	0.45	11737563_at	A	G	KLF14	0.233	4.14E-06	-0.322	4.46E-01	rs6467315	G/C	-0.238	2.26E-06	-0.552	1.9E-01	0.98
rs1260326	2	27,730,940	0.36	11729870_x_at	C	T	EMILIN1	-0.230	9.22E-06	0.166	5.23E-01	rs780094	C/T	-0.240	3.33E-06	-0.407	1.1E-01	0.96
rs900399	3	156,798,732	0.32	11717399_a_at	A	G	TIPARP	-0.905	2.99E-72	-0.213	1.57E-01	rs13322435	G/A	0.922	9.57E-77	0.715	2.0E-06	0.91

LD r2 calculated using 770 METSIM samples (Finnish males) included in eQTL data

A1 (column E) is the leptin raising allele from the Exome Chip analysis. A1 is also the effect allele for the effect sizes listed in columns H and J. Allele 1 in column O is the effect allele for the effect in columns O/Q.

FDR<1% ( P < 2.37 x 10<sup>-4</sup>)

**Table S13. PASCAL gene set enrichment analysis results for leptin unadjusted for BMI using coding variants only.**

(A) Leptin not adjusted for BMI, European, additive model, sex-combined analysis. Coding variants included. SUM method used (Bonferroni correction for 1000 gene sets and 2 traits: $P < 2.5E-05$ for both $\chi^2 P$ value and $emp P$ value)			
Name	$\chi^2 P$ value	$emp P$ value	Annotation
GO:2000243	1.30E-04	8.80E-05	positive regulation of reproductive process
MP:0005501	3.40E-04	0.000284	abnormal skin physiology
ENSG00000204713	4.31E-04	0.000389	TRIM27 PPI subnetwork
ENSG00000112448	4.31E-04	0.000397	ENSG00000112448 PPI subnetwork
ENSG00000215641	4.31E-04	0.000404	TRIM27 PPI subnetwork
GO:0032769	4.85E-04	0.000335	negative regulation of monooxygenase activity
MP:0002769	5.05E-04	0.000492	abnormal vas deferens morphology
ENSG00000008853	8.38E-04	0.000432	RHOB2 PPI subnetwork
ENSG00000081019	9.58E-04	0.00058	RSBN1 PPI subnetwork
GO:0072527	1.37E-03	9.70E-04	pyrimidine-containing compound metabolic process
ENSG00000143344	1.56E-03	0.00076	RGL1 PPI subnetwork
(B) Leptin not adjusted for BMI, European, additive model, sex-combined analysis. Coding variants included. MAX method used (Bonferroni correction for 1000 gene sets and 2 traits: $P < 2.5E-05$ for both $\chi^2 P$ value and $emp P$ value)			
Name	$\chi^2 P$ value	$emp P$ value	Annotation
GO:2000243	1.53E-05	1.59E-05	positive regulation of reproductive process
ENSG00000143344	4.85E-04	1.56E-04	RGL1 PPI subnetwork
ENSG00000215641	1.95E-04	1.69E-04	TRIM27 PPI subnetwork
ENSG00000204713	1.95E-04	1.94E-04	TRIM27 PPI subnetwork
ENSG00000112448	1.95E-04	1.96E-04	ENSG00000112448 PPI subnetwork
MP:0002769	2.23E-04	2.33E-04	abnormal vas deferens morphology
GO:0032769	2.57E-04	2.93E-04	negative regulation of monooxygenase activity
ENSG00000074211	3.57E-04	4.03E-04	PPP2R2C PPI subnetwork
ENSG00000008853	1.30E-03	4.40E-04	RHOB2 PPI subnetwork
ENSG00000169682	6.59E-04	5.50E-04	SPNS1 PPI subnetwork
ENSG00000081019	8.20E-04	5.60E-04	RSBN1 PPI subnetwork
GO:0004715	7.77E-04	5.70E-04	non-membrane spanning protein tyrosine kinase activity
GO:0010458	7.32E-04	6.00E-04	exit from mitosis
ENSG00000090054	2.10E-03	9.00E-04	SPTLC1 PPI subnetwork
ENSG00000113578	6.06E-04	9.50E-04	FGF1 PPI subnetwork
MP:0008347	1.09E-03	9.70E-04	decreased gamma-delta T cell number

**Table S14. PASCAL gene set enrichment analysis for leptin adjusted for BMI using coding variants only.**

(A) Leptin adjusted for BMI, European, additive model, sex-combined analysis. Coding variants included. SUM method used (Bonferroni correction for 1000 gene sets and 2 traits: $P < 2.5E-05$ for both $\chi^2$ Pvalue and empPvalue)			
Name	$\chi^2$ Pvalue	empPvalue	Pathway/Gene-set
ENSG00000175575	3.69E-05	7.90E-06	TRIM39PPI subnetwork
ENSG00000204599	3.69E-05	7.90E-06	PAAF1 PPI subnetwork
ENSG00000206495	3.69E-05	8.80E-06	ENSG00000206419 PPI subnetwork
ENSG00000206419	3.69E-05	1.03E-05	ENSG00000105972 PPI subnetwork
ENSG00000105972	7.14E-05	1.13E-05	mitochondrial large ribosomal subunit
GO:0005762	1.62E-04	2.66E-05	organellar large ribosomal subunit
GO:0000315	1.62E-04	2.76E-05	KLF1 PPI subnetwork
ENSG00000105610	1.96E-04	2.78E-05	negative regulation of monooxygenase activity
GO:0032769	1.58E-04	5.20E-05	BCL10 PPI subnetwork
ENSG00000142867	6.84E-05	6.10E-05	CHD2 PPI subnetwork
ENSG00000173575	1.20E-04	6.20E-05	UBE3B PPI subnetwork
ENSG00000151148	6.91E-05	6.70E-05	abnormal skin physiology
MP:0005501	8.97E-05	6.70E-05	CCDC33 PPI subnetwork
ENSG00000140481	3.61E-04	9.70E-05	abnormal cell migration
ENSG00000198925	1.53E-04	2.13E-04	HSPA12A PPI subnetwork
MP:0003091	2.13E-04	1.59E-04	SV2A PPI subnetwork
ENSG00000159164	5.38E-04	1.61E-04	MTHFD1L PPI subnetwork
ENSG00000120254	4.09E-04	1.75E-04	REACTOME_REGULATION_OF_ACTIVATED_PAK:2P34_BY_PROTEASOME_MEDIATED_DEGRADATION
REACTOME_REGULATION_OF_ACTIVATED_PAK:2P34_BY_PROTEASOME_MEDIATED_DEGRADATION	3.32E-04	1.79E-04	ATG9A PPI subnetwork
ENSG00000165868	7.61E-04	2.16E-04	ENO2 PPI subnetwork
ENSG00000178363	2.21E-04	4.50E-04	EEF1A2 PPI subnetwork
ENSG00000111674	8.97E-04	2.31E-04	RHOBTB2 PPI subnetwork
ENSG00000008853	6.23E-04	2.49E-04	exit from mitosis
GO:0010458	5.32E-04	2.67E-04	ZNF462 PPI subnetwork
ENSG00000148143	8.18E-04	2.78E-04	TOP2B PPI subnetwork
ENSG00000077097	5.67E-04	2.82E-04	RSBN1 PPI subnetwork
ENSG00000081019	6.96E-04	3.13E-04	HLA-G PPI subnetwork
ENSG00000204632	1.21E-03	3.16E-04	ENSG00000206443 PPI subnetwork
ENSG00000206443	1.21E-03	3.21E-04	HLA-G PPI subnetwork
ENSG00000206506	1.21E-03	3.22E-04	acanthosis

MP:0001874	3.68E-04	3.41E-04	REACTOME_AUTODEGRADATION_OF_CDH1_BY_CDH1APCC
REACTOME_AUTODEGRADATION_OF_CDH1_BY_CDH1APCC	5.20E-04	3.43E-04	SBF1 PPI subnetwork
ENSG00000100241	9.96E-04	3.67E-04	ENSG00000206413 PPI subnetwork
ENSG00000206413	1.46E-03	3.75E-04	NIPSNAP1 PPI subnetwork
ENSG00000184117	1.14E-03	3.78E-04	abnormal CD4-positive T cell differentiation
MP:0008076	7.62E-04	3.81E-04	HLA-E PPI subnetwork
ENSG00000206493	1.46E-03	3.85E-04	REACTOME_P53:INDEPENDENT_G1S_DNA_DAMAGE_CHECKPOINT
REACTOME_P53:INDEPENDENT_G1S_DNA_DAMAGE_CHECKPOINT	8.27E-04	4.13E-04	ZNF317 PPI subnetwork
ENSG00000130803	5.25E-04	4.35E-04	REACTOME_P53:INDEPENDENT_DNA_DAMAGE_RESPONSE
REACTOME_P53:INDEPENDENT_DNA_DAMAGE_RESPONSE	8.27E-04	4.40E-04	PDE1A PPI subnetwork
ENSG00000198838	4.45E-04	5.70E-04	TOMM34 PPI subnetwork
ENSG00000115252	1.34E-03	4.46E-04	FBNP1 PPI subnetwork
ENSG00000187239	1.01E-03	4.47E-04	CALML3 PPI subnetwork
ENSG00000101210	5.88E-04	4.50E-04	REACTOME_MYD88_DEPENDENT_CASCADE_INITIATED_ON_ENDOSOME
REACTOME_MYD88_DEPENDENT_CASCADE_INITIATED_ON_ENDOSOME	8.42E-04	4.55E-04	REACTOME_UBIQUITIN_MEDIATED_DEGRADATION_OF_PHOSPHORYLATED_CDC25A
REACTOME_UBIQUITIN_MEDIATED_DEGRADATION_OF_PHOSPHORYLATED_CDC25A	8.27E-04	4.62E-04	cellular defense response
GO:0006968	9.97E-04	4.76E-04	macrolide binding
GO:0005527	6.63E-04	4.91E-04	REACTOME_TOLL_LIKE_RECEPTOR_78_TLR78_CASCADE
REACTOME_TOLL_LIKE_RECEPTOR_78_TLR78_CASCADE	8.42E-04	5.10E-04	RPN1 PPI subnetwork
ENSG00000163902	1.62E-03	5.10E-04	FK506 binding
GO:0005528	6.63E-04	5.20E-04	ARID5B PPI subnetwork
ENSG00000150347	7.60E-04	5.20E-04	SEC31A PPI subnetwork
ENSG00000138674	1.23E-03	5.20E-04	SEPT3 PPI subnetwork
ENSG00000100167	1.37E-03	5.20E-04	ROGDI PPI subnetwork
ENSG00000067836	1.31E-03	5.30E-04	NAPB PPI subnetwork
MP:0004957	5.34E-04	8.00E-04	DCLK1 PPI subnetwork
ENSG00000125814	1.34E-03	5.50E-04	ADARB2 PPI subnetwork
ENSG00000185736	8.02E-04	5.60E-04	abnormal cardinal vein morphology
MP:0004783	1.81E-03	5.60E-04	RYR3 PPI subnetwork
ENSG00000025772	1.35E-03	5.80E-04	columnar/cuboidal epithelial cell differentiation
GO:0002065	1.43E-03	5.90E-04	RTN3 PPI subnetwork
ENSG00000133318	1.50E-03	6.00E-04	LIN7B PPI subnetwork
ENSG00000104863	1.80E-03	6.00E-04	AMOTL1 PPI subnetwork
ENSG00000166025	1.02E-03	6.10E-04	REACTOME_UBIQUITIN:DEPENDENT_DEGRADATION_OF_CYCLIN_D1
REACTOME_UBIQUITIN:DEPENDENT_DEGRADATION_OF_CYCLIN_D1	1.62E-03	6.10E-04	USP11 PPI subnetwork

ENSG00000102226	1.28E-03	6.20E-04	ATP2B1 PPI subnetwork
ENSG00000070961	9.08E-04	6.50E-04	ENSG00000186979 PPI subnetwork
ENSG00000186979	9.97E-04	6.70E-04	ZNF174 PPI subnetwork
ENSG00000103343	1.81E-03	6.90E-04	REACTOME_ANTIGEN_PRESENTATION_FOLDING_ASSEMBLY_AND_PEPTIDE_LOADING_OF_CLASS_I_MHC
REACTOME_ANTIGEN_PRESENTATION_FOLDING_ASSEMBLY_AND_PEPTIDE_LOADING_OF_CLASS_I_MHC	1.25E-03	7.10E-04	abnormal vascular development
MP:0000259	1.29E-03	7.10E-04	KIF21A PPI subnetwork
ENSG00000139116	1.80E-03	7.70E-04	REACTOME_CDK:MEDIATED_PHOSPHORYLATION_AND_REMOVAL_OF_CD6
REACTOME_CDK:MEDIATED_PHOSPHORYLATION_AND_REMOVAL_OF_CD6	1.59E-03	7.90E-04	testis tumor
MP:0006262	1.72E-03	7.90E-04	abnormal blastocyst morphology
ENSG00000133083	2.15E-03	8.40E-04	APPBP2 PPI subnetwork
ENSG00000062725	1.08E-03	8.60E-04	PDE1B PPI subnetwork
ENSG00000123360	1.95E-03	8.60E-04	abnormal body weight
MP:0001259	1.22E-03	8.70E-04	REACTOME_REGULATION_OF_MRNA_STABILITY_BY_PROTEINS_THAT_BIND_AU:RICH_ELEMENTS
REACTOME_REGULATION_OF_MRNA_STABILITY_BY_PROTEINS_THAT_BIND_AU:RICH_ELEMENTS	1.13E-03	8.90E-04	REACTOME_APCCDC20_MEDIATED_DEGRADATION_OF_SECURIN
REACTOME_APCCDC20_MEDIATED_DEGRADATION_OF_SECURIN	1.33E-03	8.90E-04	STXBP5 PPI subnetwork
ENSG00000164506	1.05E-03	9.10E-04	embryonic digestive tract morphogenesis
GO:0048557	1.86E-03	9.10E-04	REACTOME_DESTABILIZATION_OF_MRNA_BY_AUF1_HNRNP_D0
REACTOME_DESTABILIZATION_OF_MRNA_BY_AUF1_HNRNP_D0	1.94E-03	9.10E-04	HLA-F PPI subnetwork
ENSG00000204642	2.31E-03	9.50E-04	REACTOME_ACTIVATED_TLR4_SIGNALLING
REACTOME_ACTIVATED_TLR4_SIGNALLING	1.92E-03	9.60E-04	REACTOME_UBIQUITIN:DEPENDENT_DEGRADATION_OF_CYCLIN_D
REACTOME_UBIQUITIN:DEPENDENT_DEGRADATION_OF_CYCLIN_D	1.62E-03	9.90E-04	REACTOME_ACTIVATION_OF_CHAPERONES_BY_IRE1ALPHA
REACTOME_ACTIVATION_OF_CHAPERONES_BY_IRE1ALPHA	2.20E-03	9.90E-04	CAMK1 PPI subnetwork
ENSG00000134072	3.14E-03	9.90E-04	COPE PPI subnetwork
(B) Leptin adjusted for BMI, European, additive model, sex-combined analysis. Coding variants included. MAX method used (Bonferroni correction for 1000 gene sets and 2 traits: P<2.5E-05 for both chi2Pvalue and empPvalue)			
Name	chi2Pvalue	empPvalue	Pathway/Gene-set
GO:0032769	6.37E-05	1.93E-05	negative regulation of monooxygenase activity
MP:0005501	3.04E-05	4.62E-05	abnormal skin physiology
ENSG00000206495	1.68E-04	4.71E-05	TRIM39 PPI subnetwork
ENSG00000204599	1.68E-04	5.40E-05	TRIM39 PPI subnetwork
ENSG00000206419	1.68E-04	6.00E-05	ENSG00000206419 PPI subnetwork
ENSG00000198925	7.30E-05	9.60E-05	ATG9A PPI subnetwork
ENSG00000105972	3.12E-04	1.70E-04	ENSG00000105972 PPI subnetwork
MP:0003091	3.86E-04	1.87E-04	abnormal cell migration
ENSG00000142867	8.77E-04	3.36E-04	BCL10 PPI subnetwork

GO:0033273	3.51E-04	5.01E-04	response to vitamin
ENSG00000163902	1.19E-03	4.91E-04	RPN1 PPI subnetwork
ENSG00000138674	1.06E-03	5.09E-04	SEC31A PPI subnetwork
GO:0002065	1.32E-03	6.10E-04	columnar/cuboidal epithelial cell differentiation
ENSG00000120254	9.48E-04	6.40E-04	MTHFD1L PPI subnetwork
REACTOME_TOLL_LIKE_RECEPTOR_78_TLR78_CASCADE	1.39E-03	6.40E-04	REACTOME_TOLL_LIKE_RECEPTOR_78_TLR78_CASCADE
REACTOME_MYD88_DEPENDENT_CASCADE_INITIATED_ON_ENDOSOME	1.39E-03	6.40E-04	REACTOME_MYD88_DEPENDENT_CASCADE_INITIATED_ON_ENDOSOME
ENSG00000165699	2.08E-03	7.60E-04	TSC1 PPI subnetwork
ENSG00000164506	1.09E-03	7.80E-04	STXBP5 PPI subnetwork
ENSG00000185825	1.38E-03	9.00E-04	BCAP31 PPI subnetwork
GO:0071299	2.22E-03	9.80E-04	cellular response to vitamin A