Genetic variation near *IRS1* associates with reduced adiposity and an impaired metabolic profile

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Supplementary Table 1 Stage 1 results for the 14 SNPs that reached an association *P* value < 10^{-6} with body fat percentage in the stage 1 genome-wide association meta-analysis and were taken forward for follow-up

				Alleles		**Stage 1** **All individuals** (n=36,626) (includes 7,557 Indian Asians)				**Stage 1** **Europeans** (n=29,069)				**Stage 1** **Men** (n=19,815) (includes 6,535 Indian Asians)				**Stage 1** **Women** (n=16,811) (includes 1,022 Indian Asians)			
Chr	**Nearby Gene**	**Lead SNP**	**Position (bp)**	**Effect**	**Other**	**n**	**Freq (%)**	**beta**	***P***	**n**	**Freq (%)**	**beta**	***P***	**n**	**Freq (%)**	**beta**	***P***	**n**	**Freq (%)**	**beta**	***P***
1	*GRIK3*	rs12739617	36,945,244	G	C	35803	86	0.048	3.2x10^{-5}	28246	90	0.069	8.6x10^{-7}	19388	86	0.046	2.4x10^{-3}	16415	89	0.042	2.4x10^{-2}
2	*IRS1*	rs2943650	226,814,165	C	T	36574	36	0.044	7.9x10^{-9}	29017	37	0.039	3.1x10^{-6}	19751	35	0.059	4.1x10^{-8}	16823	36	0.034	2.7x10^{-3}
2	*SNED1*	rs7425888	241,575,678	A	G	33997	15	0.029	7.1x10^{-3}	26713	13	0.016	2.2x10^{-1}	18859	16	0.077	1.4x10^{-7}	15138	14	-0.027	1.1x10^{-1}
5	*HTR1A*	rs7736910	63,076,529	G	A	32629	50	0.039	5.9x10^{-7}	27275	48	0.045	2.0x10^{-7}	16706	52	0.029	1.0x10^{-2}	15924	49	0.048	4.0x10^{-5}
5	*MARCH3*	rs7738021	126,230,059	G	T	32629	68	0.033	1.9x10^{-4}	27275	71	0.036	2.6x10^{-4}	16706	66	0.009	4.5x10^{-1}	15924	69	0.065	9.9x10^{-7}
6	*WISP3*	rs6909893	112,466,236	A	G	34831	26	0.045	7.6x10^{-7}	27274	28	0.043	9.9x10^{-6}	18908	25	0.059	6.5x10^{-6}	15923	27	0.028	3.6x10^{-2}
8	*PPP1R3B*	rs17706711	9,116,692	A	T	29050	81	0.060	1.5x10^{-7}	27274	81	0.060	1.5x10^{-7}	13240	82	0.070	9.4x10^{-5}	15811	82	0.051	1.4x10^{-3}
8	*RP1L1*	rs9657518	10,504,999	C	T	34558	39	0.038	1.9x10^{-5}	27274	34	0.050	7.4x10^{-7}	18635	41	0.035	3.4x10^{-3}	15923	35	0.036	8.3x10^{-3}
8	*FDFT1*	rs17149412	11,719,247	C	T	32628	28	0.044	8.8x10^{-7}	27274	27	0.054	7.5x10^{-8}	16705	29	0.032	1.1x10^{-2}	15923	27	0.054	6.3x10^{-5}
8	*SLC39A14*	rs12674913	22,319,562	G	C	36612	69	0.043	1.6x10^{-7}	29055	72	0.035	1.4x10^{-4}	19777	68	0.046	4.0x10^{-5}	16835	71	0.043	6.0x10^{-4}
10	*GFRA1*	rs180585	117,797,907	C	T	36603	84	0.049	7.9x10^{-7}	29046	84	0.054	1.1x10^{-6}	19726	84	0.026	6.5x10^{-2}	16830	84	0.074	6.7x10^{-7}
13	*SPRY2*	rs534870	79,857,208	G	A	36488	33	0.036	3.2x10^{-6}	28931	31	0.044	7.9x10^{-7}	19726	35	0.034	1.6x10^{-3}	16763	32	0.039	9.0x10^{-4}
16	*FTO*	rs8050136	52,373,776	A	C	36537	39	0.063	3.9x10^{-17}	28980	41	0.067	4.6x10^{-16}	19739	38	0.058	2.5x10^{-8}	16798	40	0.063	1.2x10^{-8}
18	*MC4R*	rs590215	56,055,068	T	C	36571	31	0.034	1.9x10^{-5}	29014	29	0.025	5.4x10^{-3}	19752	32	0.055	4.6x10^{-7}	16820	29	0.013	2.8x10^{-1}

Body fat percentage was inverse normal transformed to approximate normality (mean = 0, sd = 1) in men and women separately. Alleles, effect is the fat % increasing allele, other is the fat % decreasing allele; beta, change in inverse normal transformed body fat percentage per effect alelle; Chr/Position: the chromosome and position (in Build 36) of the SNP; Freq, frequency of the effect allele; Nearby Gene, gene nearest the SNP used in analyses.

Supplementary Table 2 Association of the 14 SNPs that were taken forward for replication from stage 1 with body fat percentage in a meta-analysis of stage 2 follow-up studies

				Alleles				**Stage 2 All individuals**				**Stage 2 Men**				**Stage 2 Women**			
Chr	**Nearby Gene**	**Lead SNP**	**Position (bp)**	**Effect**	**Other**	**Proxy SNP**	**r^2 between lead and proxy**	**n**	**Freq (%)**	**beta**	***P***	**n**	**Freq (%)**	**beta**	***P***	**n**	**Freq (%)**	**beta**	***P***
1	*GRIK3*	rs12739617	36,945,244	G	C	rs7554980 rs12063010	1 1	34,254	88	0.015	1.8x10^{-1}	20,490	88	0.009	5.2x10^{-1}	13,764	89	0.026	1.7x10^{-1}
2	*IRS1*	rs2943650	226,814,165	C	T	rs2972143 rs2943634	1 0.83	39,576	36	0.025	1.9x10^{-4}	24,047	36	0.035	3.4x10^{-5}	15,529	36	0.008	4.7x10^{-1}
2	*SNED1*	rs7425888	241,575,678	A	G	rs4521036	1	34,392	14	0.021	4.1x10^{-2}	20,562	13	0.016	2.3x10^{-1}	13,830	14	0.029	7.9x10^{-2}
5	*HTR1A*	rs7736910	63,076,529	G	A	rs10805383	1	24,407	55	0.015	7.9x10^{-2}	15,506	57	0.010	1.6x10^{-1}	8,901	50	0.015	2.9x10^{-1}
5	*MARCH3*	rs7738021	126,230,059	G	T			24,437	64	-0.003	7.5x10^{-1}	15,543	62	0.004	6.8x10^{-1}	8,894	67	-0.018	2.4x10^{-1}
6	*WISP3*	rs6909893	112,466,236	A	G	rs2280153	0.85	34,428	26	0.022	6.9x10^{-3}	20,555	24	0.023	3.1x10^{-2}	13,873	28	0.021	1.0x10^{-1}
8	*PPP1R3B*	rs17706711	9,116,692	A	T	rs2929313	1	34,403	83	-0.003	7.6x10^{-1}	20,550	84	0.001	9.2x10^{-1}	13,853	82	-0.009	5.5x10^{-1}
8	*R1P1L1*	rs9657518	10,504,999	C	T			34,556	45	0.004	6.3x10^{-1}	20,632	49	0.006	5.0x10^{-1}	13,924	62	-0.001	9.4x10^{-1}
8	*FDFT1*	rs17149412	11,719,247	C	T			24,435	33	-0.005	5.7x10^{-1}	15,534	34	-0.005	6.7x10^{-1}	8,901	27	-0.017	2.9x10^{-1}
8	*SLC39A14*	rs12674913	22,319,562	G	C	rs2293145 rs13256933	1 1	31,715	71	0.013	9.9x10^{-2}	17,804	70	0.017	1.1x10^{-1}	13,911	72	0.008	5.2x10^{-1}
10	*GFRA1*	rs180585	117,797,907	C	T	rs180566	1	34,405	84	0.012	2.2x10^{-1}	20,574	83	0.010	4.3x10^{-1}	13,831	84	0.015	3.3x10^{-1}
13	*SPRY2*	rs534870	79,857,208	G	A			34,342	30	0.023	2.6x10^{-3}	20,537	30	0.030	2.1x10^{-3}	13,805	30	0.012	3.4x10^{-1}
16	*FTO*	rs8050136	52,373,776	A	C	rs9939609 rs1121980	1 0.85	34,105	40	0.047	4.4x10^{-11}	20,624	41	0.045	6.0x10^{-7}	13,481	40	0.051	1.6x10^{-5}
18	*MC4R*	rs590215	56,055,068	T	C	rs17782313	0.71	33,826	24	0.017	4.2x10^{-2}	20,244	22	0.024	3.1x10^{-2}	13,582	26	0.008	5.8x10^{-1}

All individuals were of white European descent. Body fat percentage was inverse normal transformed to approximate normality (mean = 0, sd = 1) in men and women separately. Alleles, effect is the fat % increasing allele, other is the fat % decreasing allele; beta, change in inverse normal transformed body fat percentage per effect allele; Chr/Position, the chromosome and position (in Build 36) of the SNP; Freq, frequency of the effect allele; Nearby Gene, gene nearest the SNP used in analyses

Supplementary Table 3 Association of the 14 SNPs that were taken forward for replication from stage 1 with body fat percentage in the combined meta-analysis of stage 1 and stage 2

				Alleles		**Stage 1 + 2 All individuals** (includes 7,557 Indian Asians)				**Stage 1 + 2 Europeans**				**Stage 1 + 2 Men** (includes 6,535 Indian Asians)				**Stage 1 + 2 Women** (includes 1,022 Indian Asians)			
Chr	**Nearby Gene**	**SNP**	**Position (bp)**	**Effect**	**Other**	**n**	**Freq (%)**	**beta**	***P***	**n**	**Freq (%)**	**beta**	***P***	**N**	**Freq (%)**	**beta**	***P***	**n**	**Freq (%)**	**beta**	***P***
1	*GRIK3*	rs12739617	36,945,244	G	C	70,057	87	0.031	1.2×10^{-4}	62,500	89	0.036	4.2×10^{-5}	39,878	86	0.025	1.3×10^{-3}	30,179	89	0.034	1.0×10^{-2}
2	*IRS1*	rs2943650	226,814,165	C	T	76,150	36	0.034	3.8×10^{-11}	68,593	36	0.031	6.0×10^{-9}	43,798	36	0.044	2.9×10^{-11}	32,352	36	0.021	9.0×10^{-3}
2	*SNED1*	rs7425888	241,575,678	A	G	68,389	14	0.025	8.9×10^{-4}	61,105	13	0.019	1.9×10^{-2}	39,421	15	0.044	9.3×10^{-6}	28,968	14	0.002	8.8×10^{-1}
5	*HTR1A*	rs7736910	63,076,529	G	A	57,036	52	0.028	1.5×10^{-6}	51,682	51	0.030	1.2×10^{-6}	32,212	55	0.021	6.0×10^{-3}	24,825	50	0.034	1.2×10^{-4}
5	*MARCH3*	rs7738021	126,230,059	G	T	57,066	66	0.015	1.7×10^{-2}	51,712	67	0.014	3.2×10^{-2}	32,249	64	0.006	4.2×10^{-1}	24,818	68	0.030	3.2×10^{-3}
6	*WISP3*	rs6909893	112,466,236	A	G	69,259	26	0.033	8.7×10^{-8}	61,702	27	0.031	9.5×10^{-7}	39,463	24	0.038	5.5×10^{-6}	29,796	28	0.024	8.4×10^{-3}
8	*PPP1R3B*	rs17706711	9,116,692	A	T	63,453	82	0.023	1.6×10^{-3}	61,677	82	0.023	1.6×10^{-3}	33,790	83	0.024	2.1×10^{-2}	29,664	82	0.019	7.9×10^{-2}
8	*R1P1L1*	rs9657518	10,504,999	C	T	69,114	42	0.018	1.9×10^{-3}	61,830	41	0.019	1.1×10^{-3}	39,267	46	0.017	2.1×10^{-2}	29,847	37	0.016	8.5×10^{-2}
8	*FDFT1*	rs17149412	11,719,247	C	T	57,063	30	0.018	5.3×10^{-3}	51,709	30	0.019	4.2×10^{-3}	32,239	32	0.011	1.8×10^{-1}	24,824	27	0.025	1.7×10^{-2}
8	*SLC39A14*	rs12674913	22,319,562	G	C	68,327	70	0.028	1.1×10^{-6}	60,770	71	0.023	1.7×10^{-4}	37,581	69	0.030	6.5×10^{-5}	30,746	72	0.026	3.5×10^{-3}
10	*GFRA1*	rs180585	117,797,907	C	T	71,008	84	0.030	1.6×10^{-5}	63,451	84	0.030	3.7×10^{-5}	40,300	84	0.017	7.0×10^{-2}	30,661	84	0.046	2.0×10^{-5}
13	*SPRY2*	rs534870	79,857,208	G	A	70,831	32	0.030	6.5×10^{-8}	63,273	30	0.032	3.2×10^{-8}	40,263	32	0.032	1.1×10^{-5}	30,568	31	0.026	2.2×10^{-3}
16	*FTO*	rs8050136	52,373,776	A	C	70,642	40	0.055	2.7×10^{-26}	63,085	41	0.056	5.6×10^{-25}	40,363	40	0.051	1.3×10^{-13}	30,279	40	0.058	1.1×10^{-12}
18	*MC4R*	rs590215	56,055,068	T	C	70,397	28	0.026	6.2×10^{-6}	62,840	26	0.021	7.5×10^{-4}	39,996	27	0.040	3.2×10^{-7}	30,402	28	0.011	2.4×10^{-1}

Body fat percentage was inverse normal transformed to approximate normality (mean = 0, sd = 1) in men and women separately. Alleles, effect is the fat % increasing allele, other is the fat % decreasing allele; beta, change in inverse normal transformed body fat percentage per effect allele; Chr/Position: the chromosome and position (in Build 36) of the SNP; Freq, frequency of the effect allele; Nearby Gene, gene nearest the SNP used in analyses

Supplementary Table 4 Comparison of the combined stage 1 and stage 2 results for the rs2943650 SNP near *IRS1*, rs534870 SNP near *SPRY2*, and rs8050136 SNP in *FTO* in meta-analyses of ‘European individuals only’ vs. ‘Europeans and Indian-Asians combined’

Locus	Meta-analysis	N	Freq (%)	beta	*P*	I^2
rs2943650 (near *IRS1*) Chr2: 226,814,165 bp Effect allele: T	All, European + Indian Asian	76,150	64	-0.034	$3.8x10^{-11}$	22%
	All, European	68,593	64	-0.031	$6.0x10^{-9}$	21%
	All, Indian Asian	7,557	71	-0.065	$2.7x10^{-4}$	0%
	Men, European + Indian Asian	43,798	64	-0.044	$2.9x10^{-11}$	22%
	Men, European	37,263	64	-0.042	$5.8x10^{-9}$	21%
	Women, European + Indian Asian	32,352	64	-0.021	$9.0x10^{-3}$	8%
	Women, European	31,330	64	-0.018	0.030	1%
rs534870 (near*SPRY2*) Chr13: 79,857,208 bp Effect allele: A	All, European + Indian Asian	70,831	68	-0.030	$6.5x10^{-8}$	14%
	All, European	63,273	70	-0.032	$3.2x10^{-8}$	15%
	All, Indian Asian	7,557	58	-0.011	0.52	0%
	Men, European + Indian Asian	40,263	68	-0.032	$1.1x10^{-5}$	23%
	Men, European	33,727	70	-0.041	$3.6x10^{-7}$	23%
	Women, European + Indian Asian	30,568	69	-0.026	0.0022	0%
	Women, European	29,546	69	-0.024	0.0064	0%
rs8050136 (*FTO*) Chr16: 52,373,776 bp Effect allele: C	All, European + Indian Asian	70,642	60	-0.055	$2.7x10^{-26}$	17%
	All, European	63,085	59	-0.056	$5.6x10^{-25}$	17%
	All, Indian Asian	7,557	68	-0.044	0.012	0%
	Men, European + Indian Asian	40,363	60	-0.051	$1.3x10^{-13}$	29%
	Men, European	33,828	59	-0.050	$1.9x10^{-11}$	29%
	Women, European + Indian Asian	30,279	60	-0.058	$1.1x10^{-12}$	0%
	Women, European	29,257	60	-0.057	$2.9x10^{-12}$	9%

Indian-Asian individuals were only available for the stage 1 meta-analysis. Body fat percentage was inverse normal transformed to approximate normality (mean = 0, sd = 1) in men and women separately. The effect allele for each locus is the body fat percentage decreasing (major) allele. Chromosomal positions are indicated according to Build 36 and allele coding based on the positive strand.

beta, change in inverse normal transformed body fat percentage per effect allele in the combined stage 1 and stage 2 meta-analysis; bp, base pairs; Freq, frequency of the effect allele

Supplementary Table 5 Association of the body fat percentage decreasing (T) allele of rs2943650 near *IRS1* with anthropometric traits in a meta-analysis of stage 2 follow-up studies

	All individuals			**Men**			**Women**			
Trait	**n**	**beta (se)**	***P***	**n**	**beta (se)**	***P***	**n**	**beta (se)**	***P***	P_{diff}
BMI , kg/m	43,291	-0.026 (0.026)	0.32	24,731	-0.046 (0.032)	0.16	18,560	0.012 (0.045)	0.79	0.30
Height, m	43,205	-0.018 (0.044)	0.68	24,692	0.014 (0.060)	0.82	18,513	-0.055 (0.064)	0.39	0.43
Weight, kg	43,208	-0.076 (0.085)	0.37	24,688	-0.156 (0.113)	0.17	18,520	0.029 (0.129)	0.82	0.28
Waist circumference, cm	21,850	0.063 (0.098)	0.52	10,609	0.062 (0.134)	0.65	11,241	0.065 (0.143)	0.65	0.99
Hip circumference, cm	21,834	-0.040 (0.072)	0.58	10,604	-0.026 (0.088)	0.76	11,230	-0.068 (0.128)	0.59	0.77
Waist-to-hip ratio	21,832	0.0009 (0.0006)	0.13	10,602	0.0007 (0.0008)	0.40	11,230	0.0011 (0.0008)	0.19	0.72
	n	**OR (95% CI)**	***P***	**n**	**OR (95% CI)**	***P***	**n**	**OR (95% CI)**	***P***	P_{diff}
Obesity (BMI ≥30 vs. BMI <25)	26,009	0.98 (0.94-1.02)	0.36	13,518	0.94 (0.89-1.00)	0.044	12,491	1.03 (0.96-1.10)	0.40	0.048
Overweight (BMI ≥25 vs. BMI <25)	42,551	1.01 (0.98-1.04)	0.67	24,557	0.99 (0.95-1.03)	0.56	17,994	1.03 (0.99-1.08)	0.19	0.18

All models were adjusted for age and age squared. The meta-analyses on BMI, height, weight, obesity, and overweight included all 11 stage 2 cohorts whereas the meta-analyses on waist circumference, hip, circumference, and waist-to-hip ratio included three cohorts (EPIC-Norfolk, Fenland, and MRC Ely) (**Supplementary Note**). beta, change in phenotype per each fat percentage decreasing (T) allele of rs2943650; P_{diff}, *P* value for the difference between sexes

Supplementary Table 6 Association of the body fat percentage decreasing (T) allele of rs2943650 near *IRS1* with blood lipids, insulin sensitivity traits, leptin and adiponectin in a meta-analysis of stage 2 and stage 3 follow-up studies.

	All individuals			**Men**			**Women**			
Trait	**n**	**beta (se)**	***P***	**n**	**beta (se)**	***P***	**n**	**beta (se)**	***P***	**P_{diff}**
HDL cholesterol	20,596	-0.054 (0.010)	1.0x10^{-7}	9,937	-0.077 (0.015)	1.7x10^{-7}	10,659	-0.033 (0.014)	0.019	0.027
LDL cholesterol	20,596	0.020 (0.010)	0.045	9,937	0.031 (0.015)	0.033	10,659	0.010 (0.013)	0.44	0.26
Triglycerides	21,168	0.042 (0.010)	2.0x10^{-5}	10,320	0.066 (0.014)	5.8x10^{-6}	10,848	0.022 (0.013)	0.11	0.025
M/I-ratio	1,953	-0.032 (0.031)	0.30	1,410	-0.035 (0.037)	0.34	543	-0.025 (0.058)	0.67	0.88
Ins-AUC / Glu-AUC	9,572	0.047 (0.015)	0.0014	8,376	0.051 (0.016)	0.0011	1,196	0.017 (0.042)	0.69	0.45
Matsuda index	13,520	-0.036 (0.012)	0.0043	11,333	-0.035 (0.014)	0.010	2,187	-0.037 (0.030)	0.22	0.95
Gutt index	13,815	-0.033 (0.012)	0.0083	11,472	-0.033 (0.014)	0.015	2,343	-0.029 (0.028)	0.31	0.89
Leptin [a]	4,641	-0.027 (0.021)	0.21	3,530	-0.027 (0.024)	0.26	1,111	-0.026 (0.044)	0.55	0.98
Adiponectin [b]	9,769	-0.061 (0.015)	4.7x10^{-5}	8,681	-0.072 (0.016)	6.1x10^{-6}	1,088	0.024 (0.044)	0.58	0.040

All traits were inverse normal transformed to approximate normality (mean = 0, sd = 1) in men and women separately. All models were adjusted for age and age squared. The meta-analyses on blood lipids included three cohorts (EPIC-Norfolk, Fenland, and MRC Ely). The meta-analyses on Matsuda index and Gutt index included five cohorts (METSIM, MRC Ely, RISC, ULSAM, and Whitehall) of which all but Whitehall II had also data available on Ins-AUC / Glu-AUC. The M/I-ratios were available only from the RISC and ULSAM cohorts. The meta-analysis on adiponectin levels included four cohorts (METSIM, MRC Ely, MrOS, and RISC), of which all but METSIM had also data on leptin (**Supplementary Note**). Beta, change in phenotype per each body fat percentage decreasing (T) allele of rs2943650; M/I-ratio, glucose infused (M) derived by the circulating insulin concentration (I); Ins-AUC / Glu-AUC, insulin area under the curve / glucose area under the curve; P_{diff}, *P* value for the difference between sexes. [a] Analyses for leptin had smaller sample size and thus statistical power than analyses for adiponectin. Assuming the beta-coefficient in the meta-analysis of all individuals represents the true effect size, a sample of more than 11,000 individuals would be needed to show a significant association ($P < 0.05$) between rs2943650 and leptin. [b] As the adiponectin sample consists mainly (89%) of men, the analysis in women is underpowered. Nevertheless, the beta-coefficient in women is different than in men and does not suggest any association between the near-*IRS1* locus and adiponectin.

Supplementary Table 7 Significant associations ($P < 0.05$)* of the rs2943650 SNP near *IRS1* and the rs534870 SNP near *SPRY2* with *cis* gene expression (*cis*-eQTLs) in subcutaneous adipose tissue, omental adipose tissue, blood, liver, and brain from three populations[a, b, c]

SNP	Tissue	Sample	Gene	n	Effect [d]	P*	P_{adj} [e]	Peak SNP [f]	r^2 [g]	P	P_{adj} [h]
All individuals											
rs2943650	Subcutaneous fat	Surgery patients[a]	*IRS1*	590	-	$4.2\text{x}10^{-4}$	0.93	rs2943653	0.81	$6.3\text{x}10^{-6}$	0.37
			BC018684	607	+	0.0017	NA	NA	NA	NA	NA
			Contig24493_RC	605	-	$4.9\text{x}10^{-4}$	0.98	rs2943653	0.81	$5.3\text{x}10^{-5}$	0.64
			Contig50189_RC	600	-	0.0098	NA	NA	NA	NA	NA
			ENST00000272907	609	+	0.032	NA	NA	NA	NA	NA
	Subcutaneous fat	General population[b]	*IRS1*	604	-	$9.6\text{x}10^{-10}$	0.63	rs2176040	1.00	$9.6\text{x}10^{-10}$	0.62
			Contig 50189_RC	604	-	$7.1\text{x}10^{-5}$	0.72	rs2943653	0.79	$3.7\text{x}10^{-5}$	0.25
	Omental fat	Surgery patients[a]	*IRS1*	714	-	$2.3\text{x}10^{-8}$	0.97	rs908252	0.89	$3.0\text{x}10^{-9}$	0.74
			Contig24493_RC	738	-	$2.6\text{x}10^{-4}$	0.85	rs10933137	0.66	$5.9\text{x}10^{-5}$	0.51
			Contig39389_RC	739	-	0.024	NA	NA	NA	NA	NA
			Contig50189_RC	735	-	0.013	0.0087	rs3769647	0.00	$1.6\text{x}10^{-5}$	$1.1\text{x}10^{-5}$
			ENST00000272907	740	-	0.0080	NA	NA	NA	NA	NA
	Blood	General population[b]	*COL4A4*	745	-	0.03	0.16	rs13398103	0.00	$5.4\text{x}10^{-30}$	$3.2\text{ x}10^{-29}$
rs534870	Blood	General population[b]	*SPRY2*	745	-	$3.7\text{x}10^{-4}$	$7.9\text{x}10^{-4}$	rs7995973	0.00	$4.2\text{x}10^{-14}$	$9.1\text{x}10^{-14}$
Men											
rs2943650	Subcutaneous fat	Surgery patients[a]	*IRS1*	171	-	0.017	0.52	rs2943653	0.82	$5.7\text{x}10^{-5}$	0.20
			Contig24493_RC	175	-	0.010	0.49	rs2943653	0.82	0.0012	0.37
			Contig50189_RC	174	-	0.0095	NA	NA	NA	NA	NA
	Subcutaneous fat	General population[b]	*IRS1*	252	-	$2.2\text{x}10^{-8}$	0.61	rs2943645	0.97	$2.1\text{x}10^{-8}$	0.59
			Contig 50189_RC	252	-	0.0091	0.0084	rs11694119	0.01	$2.9\text{x}10^{-4}$	$2.7\text{x}10^{-4}$
	Omental fat	Surgery patients[a]	*IRS1*	188	-	$9.7\text{x}10^{-4}$	0.92	rs908252	0.85	$4.5\text{x}10^{-5}$	0.60
			COL4A4	192	-	0.014	0.066	rs6706802	0.02	$3.5\text{x}10^{-6}$	$2.1\text{x}10^{-5}$
			Contig39389_RC	192	-	0.0070	NA	NA	NA	NA	NA
rs534870	Omental fat	Surgery patients[a]	*HSS00006179*	193	+	$8.6\text{x}10^{-4}$	NA	NA	NA	NA	NA
			XM_090673	192	+	0.035	NA	NA	NA	NA	NA
	Blood	General population[b]	*ARF4*	312	-	0.022	0.031	rs12583018	0.01	0.002	0.0028
Women											
rs2943650	Subcutaneous fat	Surgery patients[a]	*IRS1*	416	-	0.017	0.91	rs2943653	0.80	0.011	0.73
			BC018684	430	+	0.011	NA	NA	NA	NA	NA
			Contig24493_RC	427	-	0.015	0.89	rs2943653	0.80	0.0088	0.76
	Subcutaneous fat	General population[b]	*IRS1*	352	-	$2.7\text{x}10^{-4}$	0.0010	rs1190117	0.01	$1.1\text{x}10^{-4}$	$4.4\text{x}10^{-4}$
			Contig50189_RC	352	-	0.0019	0.88	rs2138157	0.89	0.0019	0.87
	Omental fat	Surgery patients[a]	*Contig24493_RC*	543	+	0.0024	0.73	rs10933137	0.69	$7.3\text{x}10^{-4}$	0.57
			Contig50189_RC	539	-	0.037	0.45	rs3769647	0.00	$3.0\text{x}10^{-4}$	$3.7\text{x}10^{-4}$
			ENST00000272907	545	-	0.0094	NA	NA	NA	NA	NA
	Liver	Surgery patients[a]	*HSS00339567*	405	+	0.045	NA	NA	NA	NA	NA
	Blood	General population[b]	*SPRY2*	433	-	0.0012	0.0083	rs518627	0.01	$1.0\text{x}10^{-9}$	$7.3\text{x}10^{-9}$

The gene transcripts that were tested for rs2943650 were BC014369, BC018685, BC035052, Contig24493_RC, Contig39389_RC, Contig50189_RC, ENST00000272907, hCT1970673, HSS00207461, HSS00339567, *COL4A3* (NM_000091 and NM_031362), *COL4A4* (NM_000092), *IRS1* (NM_005544), and *RHBDD1* (NM_032276).

The gene transcripts that were tested for the rs534870 SNP were AB032991, BC036310, BC039360, HSS00006179, HSS00020342, HSS00085876, HSS00097095, HSS00303580, *SPRY2* (NM_005842), *RBM26* (HM_022118), and XM_090673. NA, data not reported as the body fat percentage associated SNP and the most significant SNP for the gene transcript were the same.

*Only associations with P value <0.05 with gene expression are reported. As altogether 26 genes were tested in the gene expression analyses, the threshold for a statistically significant association with Bonferroni correction is P=0.0019; [a] Tissue samples from patients who underwent bariatric surgery (see Supplementary Note - Methods); [b] Tissue samples from general population (see Supplementary Note - Methods); [c] Neutopathologically normal cortical brain samples from 193 individuals (mean age 81 years) of European descent (see Supplementary Note – Methods). No significant associations with brain expression were found. [d] Direction of effect for the body fat percentage decreasing allele; [e] P value for the body fat percentage SNP after conditioning on the most significant SNP for the gene transcript; [f] Most significant SNP associated; [g] Correlation between the body fat percentage SNP and the peak SNP with the gene transcript; [h] P value for the peak SNP after conditioning on the body fat percentage SNP.

Supplementary Table 8 Association of the body fat percentage decreasing (A) allele of rs534870 near *SPRY2* with anthropometric traits, blood lipids, and insulin sensitivity traits in a meta-analysis of stage 2 follow-up studies.

	All individuals			Men			Women			
Trait	**n**	**beta (se)**	***P***	**n**	**beta (se)**	***P***	**n**	**beta (se)**	***P***	P_{diff}
BMI, kg/m²	43,132	-0.087 (0.027)	0.0014	24,694	-0.073 (0.034)	0.031	18,438	-0.114(0.046)	0.014	0.47
Height, m	43,047	-0.034 (0.046)	0.46	24,656	0.083 (0.062)	0.18	18,391	-0.169 (0.067)	0.012	0.0060
Weight, kg	43,049	-0.284 (0.089)	0.0014	24,652	-0.138 (0.118)	0.24	18,397	-0.473 (0.134)	0.043	0.060
Waist circumference, cm	21,607	-0.119 (0.102)	0.24	10,516	-0.078 (0.139)	0.57	11,091	-0.167 (0.150)	0.26	0.66
Hip circumference, cm	21,591	-0.070 (0.074)	0.35	10,510	0.025 (0.092)	0.78	11,081	-0.259 (0.129)	0.045	0.031
Waist-to-hip ratio	20,431	-0.0003 (0.0006)	0.62	10,602	-0.0011 (0.0009)	0.20	9,829	0.0005 (0.0009)	0.55	0.18
HDL cholesterol	20,351	0.010 (0.011)	0.36	9,847	-0.006 (0.015)	0.69	10,504	0.025 (0.015)	0.10	0.15
LDL cholesterol	20,351	0.005 (0.010)	0.62	9,847	0.000 (0.015)	0.99	10,504	0.009 (0.014)	0.50	0.65
Triglycerides	20,897	-0.014 (0.010)	0.16	10,311	-0.000 (0.015)	0.97	10,803	-0.026 (0.014)	0.060	0.21
M/I-ratio	1,974	0.052 (0.034)	0.13	1,410	0.069 (0.041)	0.094	564	0.015 (0.060)	0.81	0.46
Ins-AUC / Glu-AUC	9,454	-0.010 (0.016)	0.54	8,308	-0.000 (0.017)	0.98	1,146	-0.072 (0.044)	0.10	0.13
Matsuda index	11,379	0.013 (0.014)	0.33	9,777	0.003 (0.015)	0.82	1,612	0.100 (0.037)	0.0062	0.014
Gutt index	11,569	0.032 (0.014)	0.032	9,917	0.021 (0.015)	0.18	1,754	0.089 (0.035)	0.011	0.072
	n	**OR (95% CI)**	***P***	**n**	**OR (95% CI)**	***P***	**n**	**OR (95% CI)**	***P***	P_{diff}
Obesity (BMI ≥30 vs. BMI <25)	25,940	0.93 (0.89-0.97)	0.0010	13,521	0.92 (0.87-0.98)	0.0095	12,419	0.93 (0.87-1.00)	0.041	0.79
Overweight (BMI ≥25 vs. BMI <25)	42,371	0.98 (0.95-1.01)	0.16	24,520	0.99 (0.95-1.03)	0.61	17,851	0.96 (0.92-1.01)	0.12	0.42

Anthropometric traits were non-transformed, whereas blood lipid and insulin sensitivity traits were inverse normal transformed to approximate normality (mean = 0, sd = 1) in men and women separately. All models were adjusted for age and age squared. The meta-analyses on BMI, height, weight, obesity, and overweight included all 11 stage 2 studies whereas the meta-analyses on waist circumference, hip, circumference, waist-to-hip ratio, and blood lipids included three studies (EPIC-Norfolk, Fenland, and MRC Ely) (**Supplementary Note**). The meta-analyses on Matsuda index and Gutt index included five cohorts (METSIM, MRC Ely, RISC, ULSAM, and Whitehall) of which all but Whitehall II had also data available on Ins-AUC / Glu-AUC. The M/I-ratios were available only from the RISC and ULSAM cohorts. beta, change in phenotype per each body fat percentage decreasing (A) allele of rs534870; M/I-ratio, glucose infused (M) derived by the circulating insulin concentration (I); Ins-AUC / Glu-AUC, insulin area under the curve / glucose area under the curve; P_{diff}, *P* value for the difference between sexes

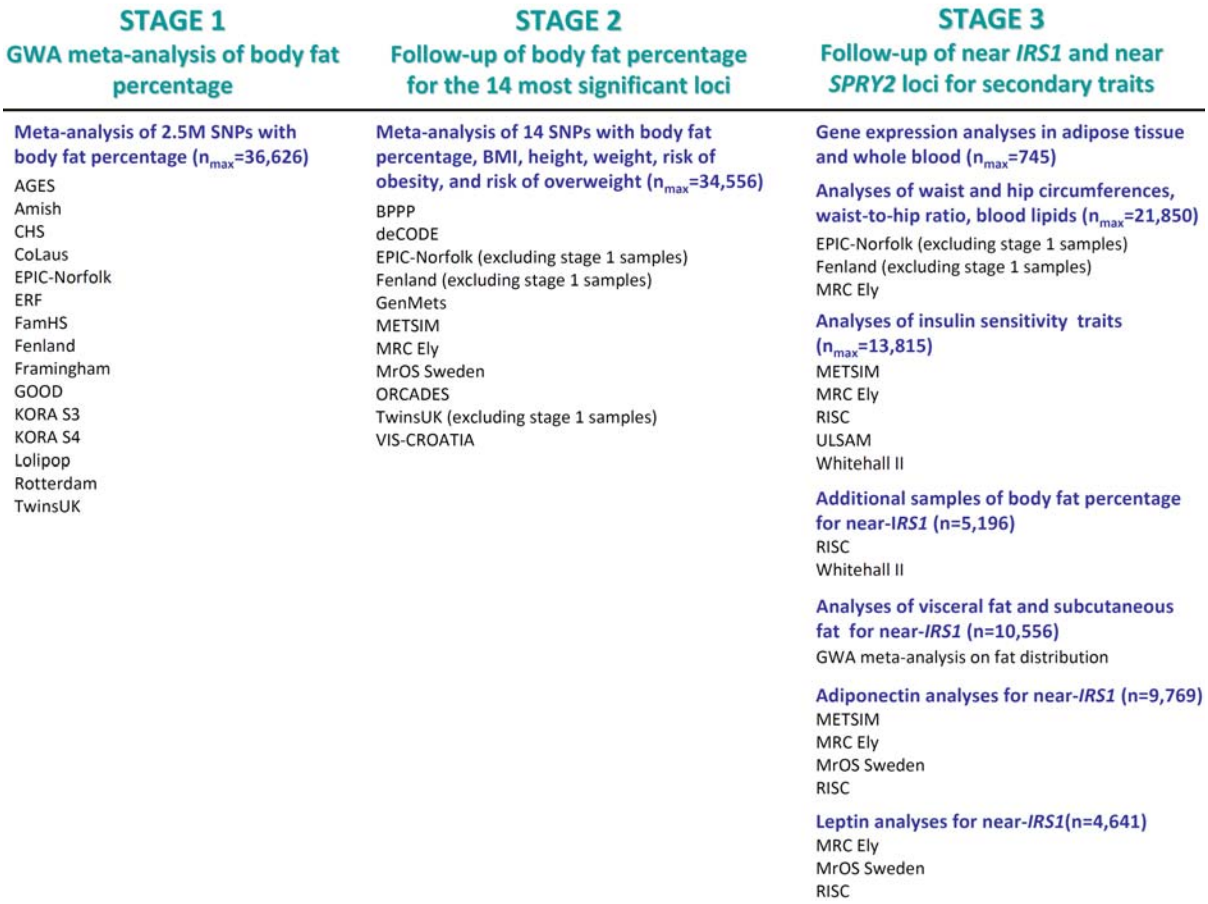
Supplementary Table 9 Association of established susceptibility loci for BMI, waist circumference, extreme obesity, and waist-to-hip ratio with body fat percentage in the stage 1 genome-wide association meta-analysis

Chr	Nearest gene	SNP	Effect allele	Other allele	N	Freq (%)	β	*P*	Established trait	Original reference
1	*TNNI3K*	rs1514175	A	G	36,563	44	0.009	2.4×10^{-1}	BMI	8
1	*PTBP2*	rs10489741	A	G	36,568	57	0.020	7.8×10^{-3}	BMI	8
1	*NEGR1*	rs2815752	A	G	36,602	62	0.022	4.3×10^{-3}	BMI	6,7
1	*SEC16B*	rs10913469	C	T	36,580	19	0.030	1.5×10^{-3}	BMI	6
2	*LRP1B*	rs2890652	C	T	29,035	18	0.001	9.4×10^{-1}	BMI	8
2	*FANCL*	rs887912	T	C	29,049	29	0.019	3.4×10^{-2}	BMI	8
2	*RBJ*	rs713586	C	T	36,542	47	0.015	4.7×10^{-2}	BMI	8
2	*TMEM18*	rs7561317	G	A	36,351	66	0.032	9.3×10^{-4}	BMI	6,7
3	*CADM2*	rs13078807	G	A	27,275	20	0.018	7.8×10^{-2}	BMI	8
3	*ETV5*	rs7647305	C	T	36,546	79	0.013	1.5×10^{-1}	BMI	6
4	*SLC39A8*	rs13107325	T	C	27,275	8	0.027	1.2×10^{-1}	BMI	8
4	*GNPDA2*	rs10938397	G	A	36,610	43	0.026	1.2×10^{-3}	BMI	7
5	*ZNF608*	rs4836133	A	C	27,274	47	0.032	2.4×10^{-4}	BMI	8
5	*FLJ35779*	rs2112347	T	G	36,600	59	0.003	6.9×10^{-1}	BMI	8
6	*NUDT3*	rs206936	G	A	36,620	24	0.010	2.7×10^{-1}	BMI	8
6	*TFAP2B*	rs987237	G	A	36,614	18	0.025	8.2×10^{-3}	BMI	8
9	*LRRN6C*	rs10968576	G	A	36,618	29	0.015	7.4×10^{-2}	BMI	8
11	*RPL27A*	rs4929949	C	T	32,629	50	0.007	3.7×10^{-1}	BMI	8
11	*MTCH2*	rs10838738	G	A	36,587	34	0.017	3.0×10^{-2}	BMI	7
11	*BDNF*	rs4923461	A	G	36,599	77	0.023	6.4×10^{-3}	BMI	6
12	*FAIM2*	rs7138803	A	G	36,572	37	0.025	1.0×10^{-3}	BMI	6
13	*MTIF3*	rs4771122	G	A	34,832	22	0.011	2.3×10^{-1}	BMI	8
14	*PRKD1*	rs11847697	T	C	27,872	5	0.061	5.2×10^{-3}	BMI	8
14	*NRXN3*	rs10146997	G	A	29,012	20	0.003	8.1×10^{-1}	BMI	8
15	*MAP2K5*	rs2241423	G	A	29,064	78	0.013	2.0×10^{-1}	BMI	8
16	*GPRC5B*	rs12444979	C	T	29,021	87	0.016	2.0×10^{-1}	BMI	8
16	*SH2B1*	rs7498665	G	A	36,598	36	0.029	2.3×10^{-4}	BMI	6,7
16	*FTO*	rs8050136	A	C	36,537	39	0.063	3.9×10^{-17}	BMI	3,5
18	*MC4R*	rs17782313	C	T	35,798	28	0.039	2.1×10^{-6}	BMI	4
19	*TMEM160*	rs3810291	A	G	34,832	62	0.001	9.4×10^{-1}	BMI	8
19	*QPCTL*	rs2287019	C	T	22,188	82	0.036	5.0×10^{-3}	BMI	8
19	*KCTD15*	rs29941	G	A	34,408	66	0.013	1.0×10^{-1}	BMI	6,7
6	*TFAP2B*	rs987237	G	A	36,613	18	0.025	8.2×10^{-3}	Waist	26
8	*MSRA*	rs7826222	G	C	18,566	23	0.012	3.8×10^{-1}	Waist	26
14	*NRXN3*	rs10146997	G	A	29012	20	0.003	8.1×10^{-1}	Waist	25
1	*SDCCAG8*	rs12145833	T	G	36,342	84	0.014	1.7×10^{-1}	Extreme obesity	28
8	*TNKS/MSRA*	rs473034	T	C	34,832	11	0.012	4.5×10^{-2}	Extreme obesity	28
10	*PTER*	rs10508503	C	T	26,034	91	0.018	3.1×10^{-1}	Extreme obesity	27
16	*MAF*	rs1424233	T	C	36,309	52	0.005	4.8×10^{-1}	Extreme obesity	27
18	*NPC1*	rs1805081	T	C	33,460	60	0.016	4.5×10^{-2}	Extreme obesity	27
1	*TBX15*	rs984222	G	C	36,596	58	-0.006	4.2×10^{-1}	WHR adj BMI	29
1	*LYPLAL1*	rs4846567	G	T	36,591	73	-0.024	4.4×10^{-3}	WHR adj BMI	26,29
1	*DNM3*	rs1011731	G	A	36,522	43	-0.005	5.1×10^{-1}	WHR adj BMI	29
2	*GRB14*	rs10195252	T	C	34,832	60	-0.025	1.3×10^{-3}	WHR adj BMI	29
3	*ADAMTS9*	rs6795735	C	T	36,603	51	-0.011	1.4×10^{-1}	WHR adj BMI	29
3	*NISCH*	rs6784615	T	C	34,291	94	0.003	8.5×10^{-1}	WHR adj BMI	29
5	*CPEB4*	rs6861681	A	G	32,628	29	-0.012	1.8×10^{-1}	WHR adj BMI	29
6	*RSPO3*	rs9491696	G	C	36,564	49	-0.009	2.1×10^{-1}	WHR adj BMI	29
6	*VEGFA*	rs6905288	A	G	36,332	59	0.000	9.8×10^{-1}	WHR adj BMI	29
6	*LY86*	rs1294421	G	T	36,604	58	-0.005	5.5×10^{-1}	WHR adj BMI	29
7	*NFE2L3*	rs1055144	T	C	36,548	24	-0.013	1.4×10^{-1}	WHR adj BMI	29
12	*ITPR2*	rs718314	G	A	36,339	24	-0.011	2.0×10^{-1}	WHR adj BMI	29
12	*HOXC13*	rs1443512	A	C	35,670	25	0.006	5.1×10^{-1}	WHR adj BMi	29
22	*KREMEN1*	rs4823006	A	G	36,475	54	-0.011	1.3×10^{-1}	WHR adj BMI	29

Effect allele is the BMI, waist circumference, extreme obesity risk, or waist-to-hip ratio increasing allele. Chr, chromosome; Freq, frequency of the effect allele; WHR adj BMI, waist-to-hip ratio adjusted for BMI

1.2. SUPPLEMENTARY FIGURES

Supplementary Figure 1	Study design and participating cohorts.
Supplementary Figure 2	Manhattan plots showing the significance of association with body fat percentage for all SNPs in the stage 1 meta-analysis in all individuals (n=36,626), individuals of European descent (n=29,069), men (n=19,815), and women (n=16,811).
Supplementary Figure 3	Association of the rs2943650 SNP (near-*IRS1*) body fat percentage decreasing (T) allele with body fat percentage and insulin sensitivity (measured with the Matsuda index) among 6,489 men from the METSIM (Metabolic Syndrome in Men) study with and without adjustment of each trait with the other.
Supplementary Figure 4	Association of SNPs within ±1 Mb from the rs2943650 SNP and ±1 Mb from the rs534870 SNP with the expression of *IRS1* and *SPRY2*, respectively, in omental and subcutaneous adipose tissue.
Supplementary Figure 5	Expression of the *IRS1* gene in isolated adipocytes from visceral and subcutaneous adipose tissues of male and female mice.
Supplementary Figure 6	Expression of the *IRS1* gene in visceral and subcutaneous adipose tissues of men and women.
Supplementary Figure 7	Quantile-quantile plots and genomic control parameters (λ) for the association with body fat percentage in all individuals (n=36,626), individuals of European descent (n=29,069), men (n=19,815), and women (n=16,811).



STAGE 1

GWA meta-analysis of body fat percentage

Meta-analysis of 2.5M SNPs with body fat percentage (n_{max}=36,626)

AGES
Amish
CHS
CoLaus
EPIC-Norfolk
ERF
FamHS
Fenland
Framingham
GOOD
KORA S3
KORA S4
Lolipop
Rotterdam
TwinsUK

STAGE 2

Follow-up of body fat percentage for the 14 most significant loci

Meta-analysis of 14 SNPs with body fat percentage, BMI, height, weight, risk of obesity, and risk of overweight (n_{max}=34,556)

BPPP
deCODE
EPIC-Norfolk (excluding stage 1 samples)
Fenland (excluding stage 1 samples)
GenMets
METSIM
MRC Ely
MrOS Sweden
ORCADES
TwinsUK (excluding stage 1 samples)
VIS-CROATIA

STAGE 3

Follow-up of near *IRS1* and near *SPRY2* loci for secondary traits

Gene expression analyses in adipose tissue and whole blood (n_{max}=745)

Analyses of waist and hip circumferences, waist-to-hip ratio, blood lipids (n_{max}=21,850)

EPIC-Norfolk (excluding stage 1 samples)
Fenland (excluding stage 1 samples)
MRC Ely

Analyses of insulin sensitivity traits (n_{max}=13,815)

METSIM
MRC Ely
RISC
ULSAM
Whitehall II

Additional samples of body fat percentage for near-*IRS1* (n=5,196)

RISC
Whitehall II

Analyses of visceral fat and subcutaneous fat for near-*IRS1* (n=10,556)

GWA meta-analysis on fat distribution

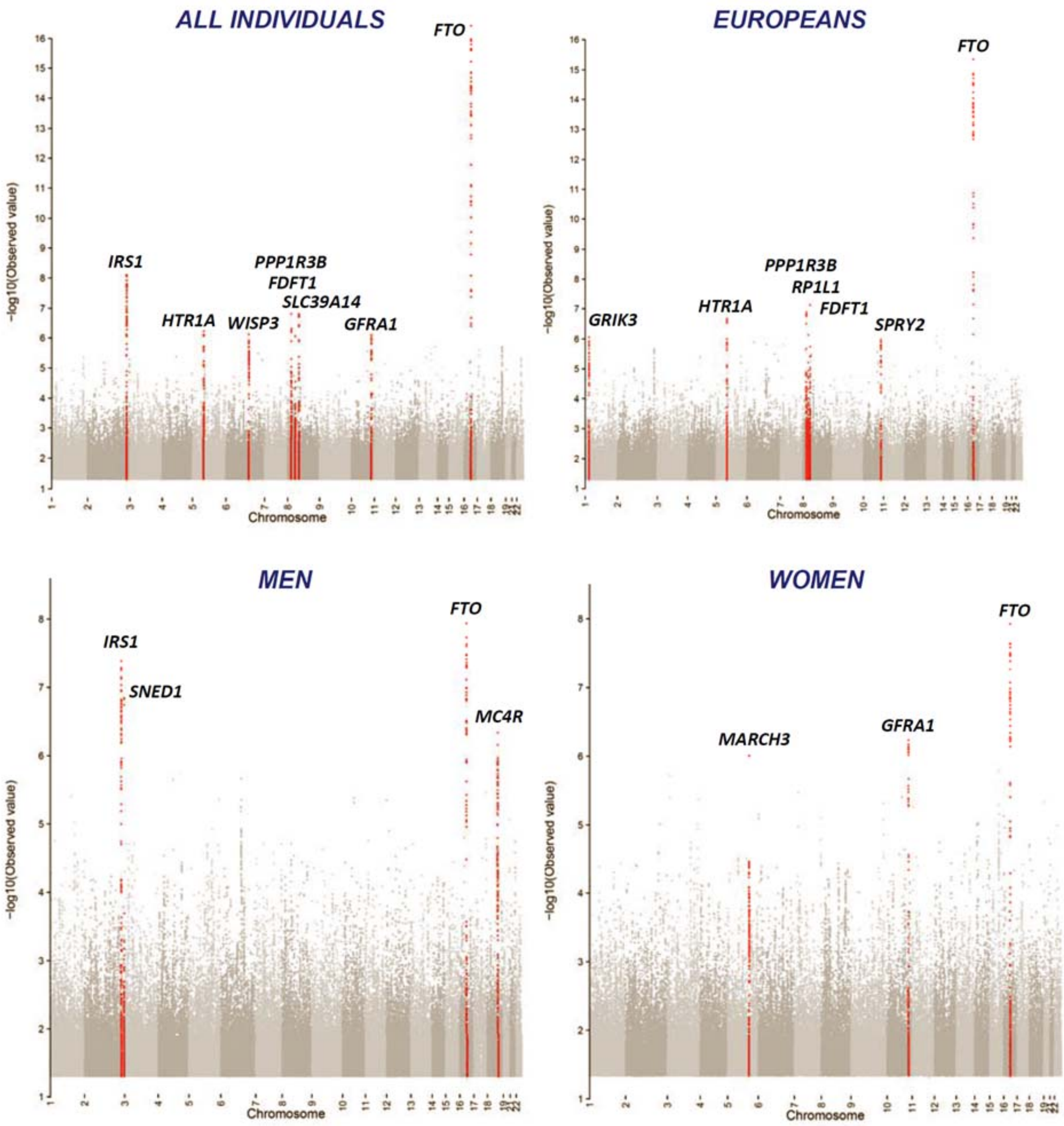
Adiponectin analyses for near-*IRS1* (n=9,769)

METSIM
MRC Ely
MrOS Sweden
RISC

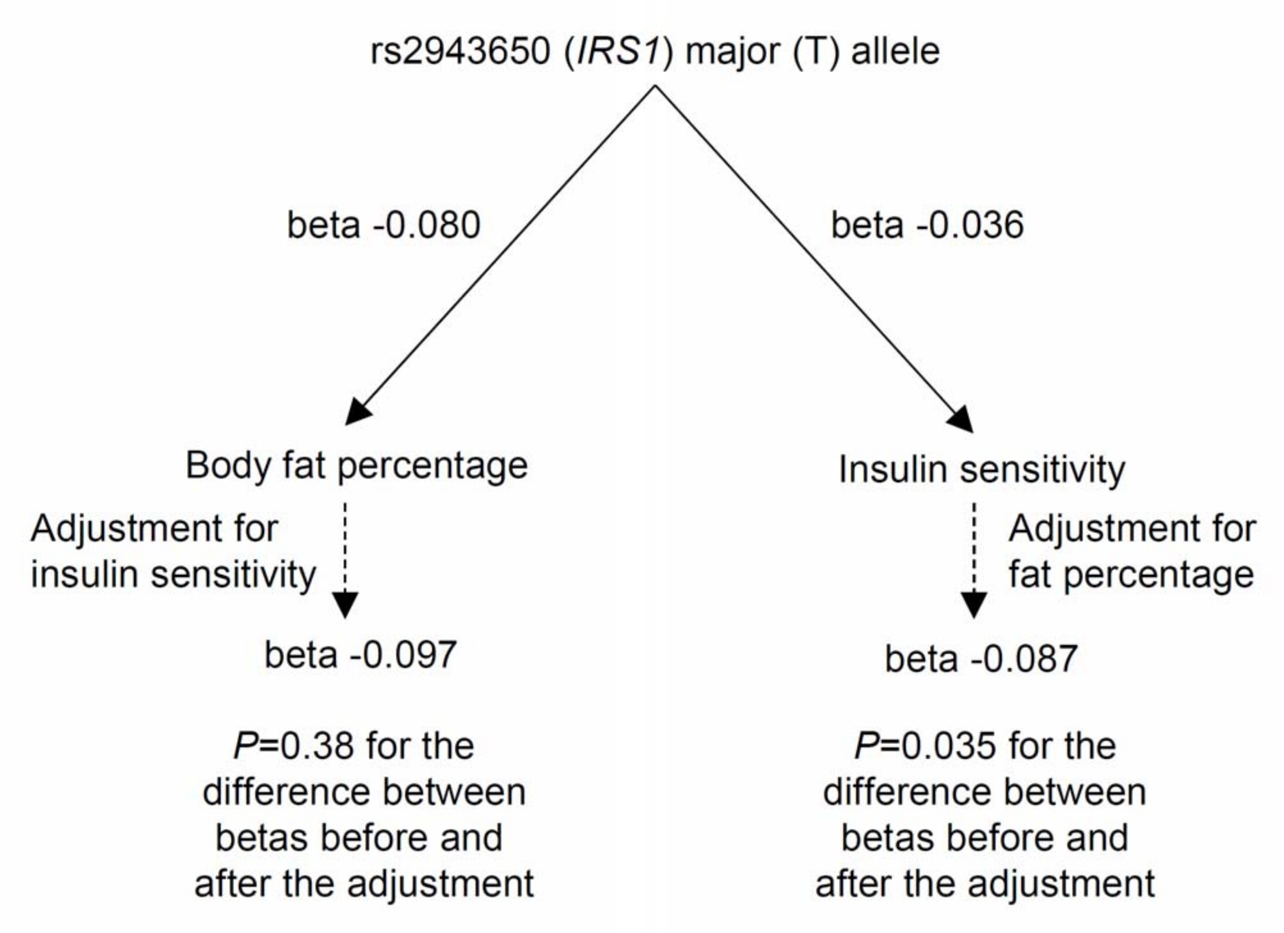
Leptin analyses for near-*IRS1*(n=4,641)

MRC Ely
MrOS Sweden
RISC

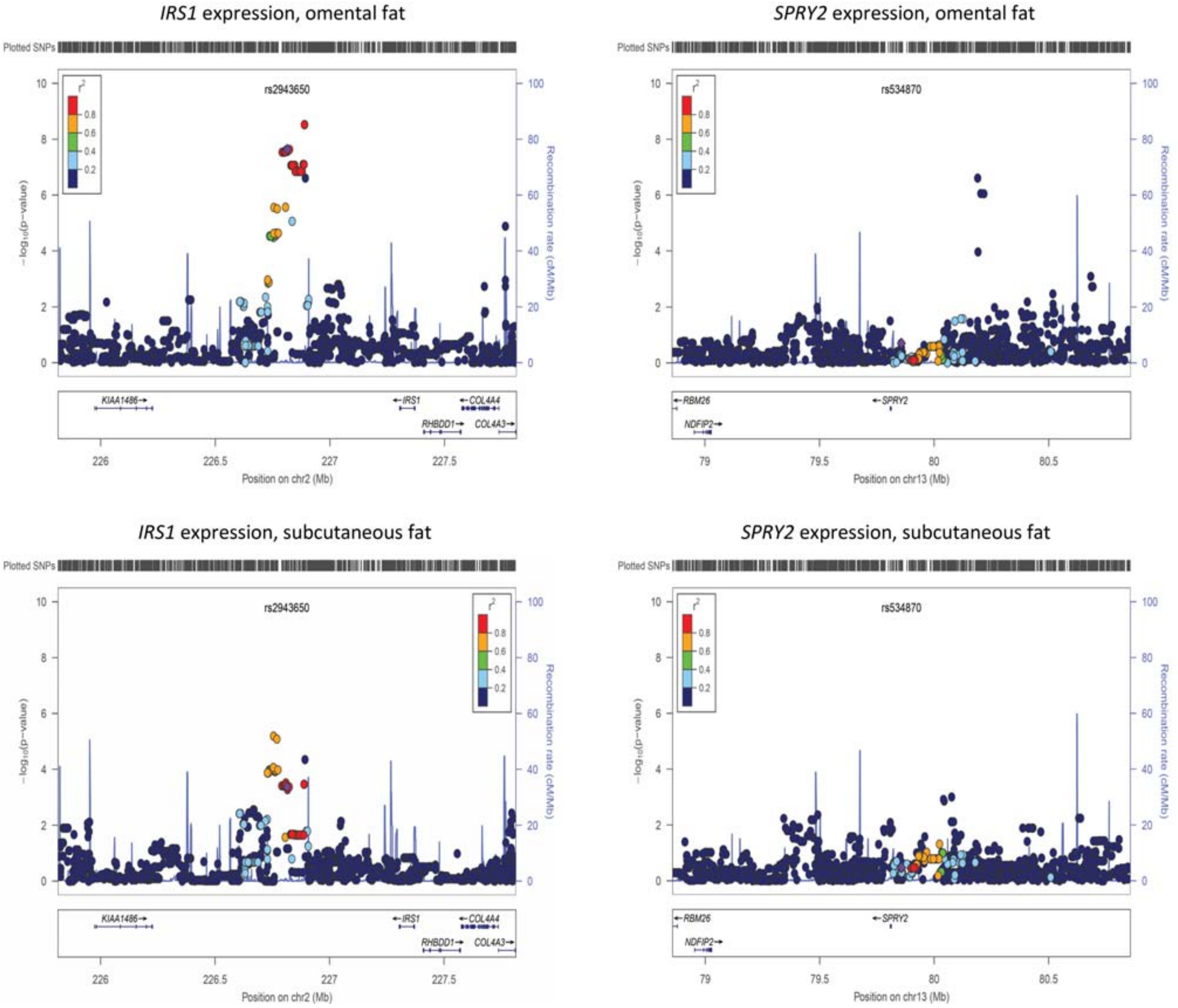
Supplementary Figure 1 Study design and participating cohorts. Stage 1 - Meta-analysis of genome-wide association data was performed in stage 1 across 15 studies of white European ancestry and a total of 14 SNPs representing the best associating ($P < 10^{-6}$) loci were taken forward for replication. Stage 2 – The 14 SNPs were genotyped in 11 studies of adults of European ancestry, and tested for association with body fat percentage, as well as with BMI, height, weight, risk of obesity, and risk of overweight. Stage 3 - Additional follow-up analyses were performed for the newly identified adiposity loci near the *IRS1* and *SPRY2* genes.



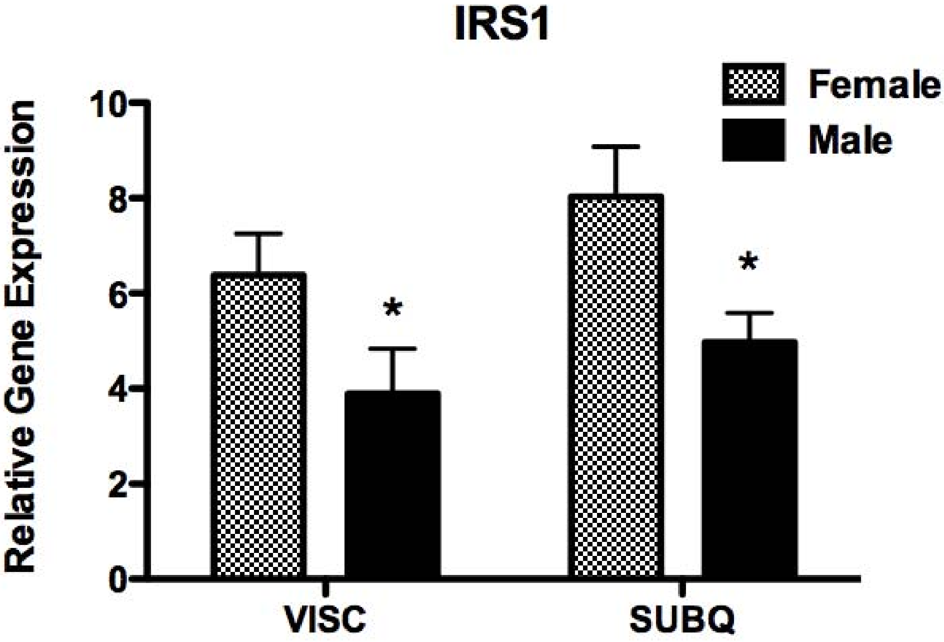
Supplementary Figure 2 Manhattan plots showing the significance of association with body fat percentage for all SNPs in the stage 1 meta-analysis in all individuals (n=36,626), individuals of European descent (n=29,069), men (n=19,815), and women (n=16,811). The $-\log_{10}P$ values for the association of each single nucleotide polymorphism with BMI are shown on the y-axis. SNPs are plotted on the x-axis according to their position on each chromosome against association with body fat percentage on the y-axis (shown as $-\log_{10}$ *P*-value). The loci coloured in red reached a *P* value $<10^{-6}$ in stage 1 meta-analysis and were taken forward for follow-up.



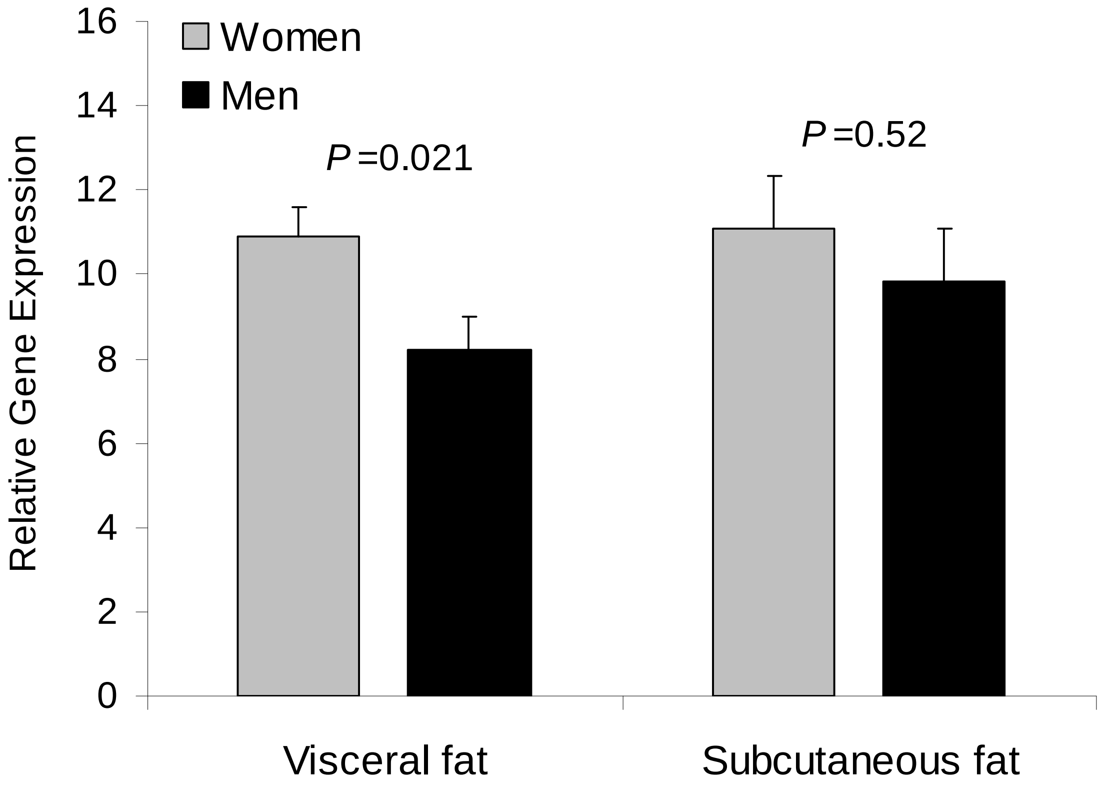
Supplementary Figure 3 Association of the rs2943650 SNP (near-*IRS1*) body fat percentage decreasing (T) allele with body fat percentage and insulin sensitivity (measured with the Matsuda index) among 6,489 men from the METSIM (Metabolic Syndrome in Men) study with and without adjustment of each trait with the other. Beta, change in phenotype per each body fat percentage decreasing (T) allele of rs2943650.



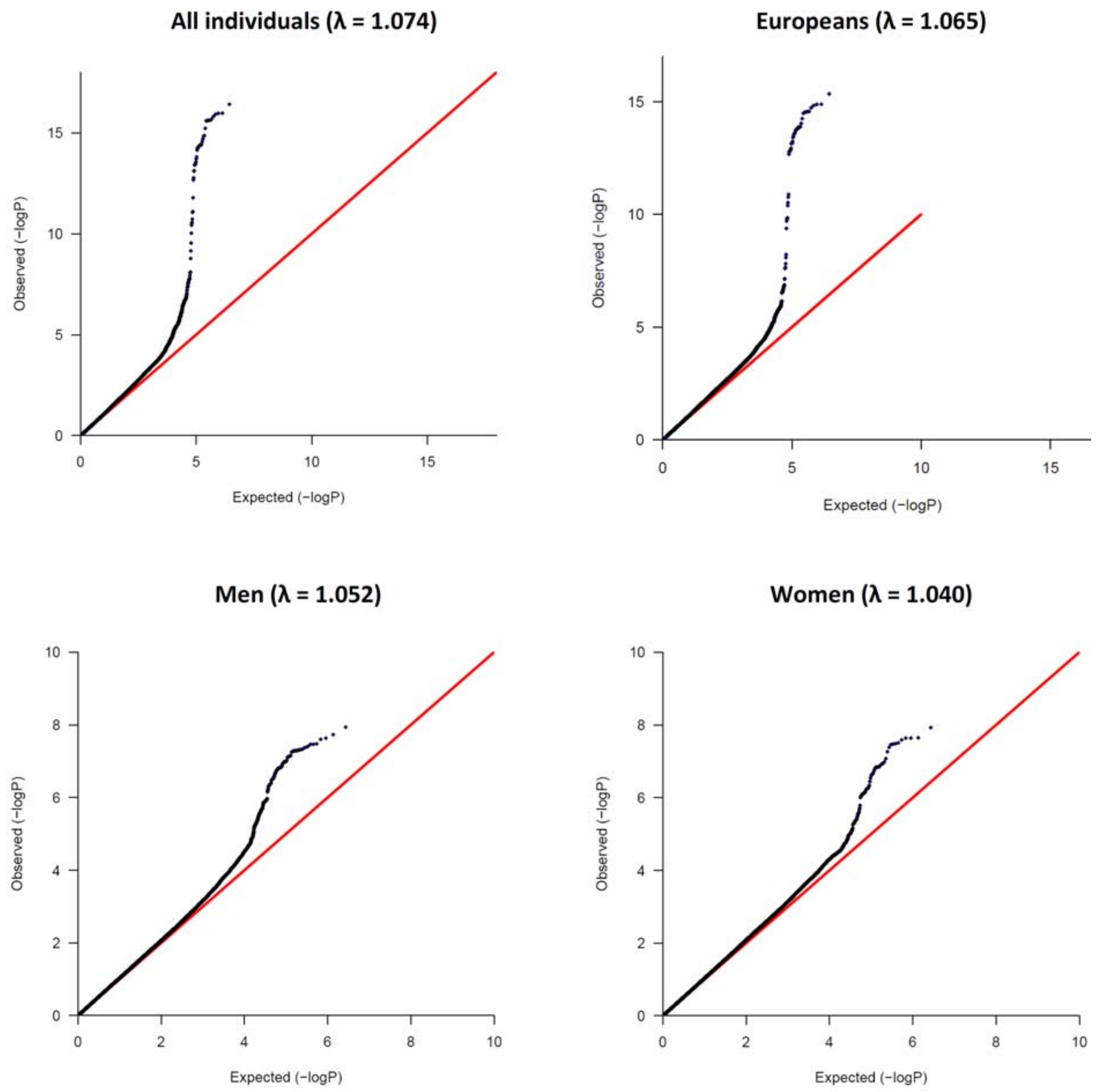
Supplementary Figure 4 Association of SNPs within ±1 Mb from the rs2943650 SNP and ±1 Mb from the rs534870 SNP with the expression of *IRS1* and *SPRY2*, respectively, in omental and subcutaneous adipose tissue from patients who underwent bariatric surgery (see Supplementary Note - Methods). The plot was generated using LocusZoom (http://csg.spg.umic.edu/locuszoom)[44].



Supplementary Figure 5 Expression of the *IRS1* gene in isolated adipocytes from visceral and subcutaneous adipose tissues of male and female mice. VISC, adipocytes from visceral adipose tissue. SUBQ, adipocytes from subcutaneous adipose tissue. *A statistically significant ($P<0.05$) difference in *IRS1* expression between females and males.



Supplementary Figure 6 Expression of the *IRS1* gene in visceral and subcutaneous adipose tissues of men and women. *P* values indicate the difference in *IRS1* expression between men and women. The analyses on visceral fat included 26 men and 75 women whereas the analyses on subcutaneous fat included 19 men and 49 women.



Supplementary Figure 7 Quantile-quantile plots and genomic control parameters (λ) for the association with body fat percentage in all individuals (n=36,626), individuals of European descent (n=29,069), men (n=19,815), and women (n=16,811). The plots shown were corrected for population stratification by applying a genomic control correction.

2. SUPPLEMENTARY NOTE

2.1. SUPPLEMENTARY NOTE - TABLES

Supplementary Note - Table 1	Number of individuals and sample quality control for genome-wide association studies of stage 1.
Supplementary Note - Table 2	Information on genotyping methods, quality control of SNPs, imputation, and statistical analysis for genome-wide association studies of stage 1.
Supplementary Note - Table 3	Study-specific descriptive statistics for genome-wide association studies of stage 1.
Supplementary Note - Table 4	Number of individuals and sample quality control for stage 2 and stage 3 follow-up studies with *de novo* genotyping.
Supplementary Note - Table 5	Information on genotyping methods, quality control of SNPs, and association analysis software for stage 2 and stage 3 follow-up studies with *de novo* genotyping.
Supplementary Note - Table 6	Number of individuals and sample quality control for stage 2 and stage 3 follow-up studies with *in silico* genotyping.
Supplementary Note - Table 7	Information on genotyping methods, quality control of SNPs, imputation, and association analysis software for stage 2 and stage 3 follow-up studies with *in silico* genotyping.
Supplementary Note - Table 8	Study-specific descriptive statistics for stage 2 and stage 3 follow-up studies.
Supplementary Note - Table 9	Samples and assays used for the measurement of circulating levels of glucose, insulin, leptin, and adiponectin in the stage 3 follow-up studies.

Supplementary Note - Table 1 Number of individuals and sample quality control for genome-wide association studies of stage 1

Study		**Total sample size (N)**	**Sample QC**		**Samples in analyses (N)**	**Fat % assessment method**	**Instrument**	**References**
Short name	**Full name**		**Call rate***	**other exclusions**				
AGES	Age, Gene/Environment Susceptibility-Reykjavik Study	3,219	≥ 97%	1) mismatch with previous genotypes 2) remove A/T & G/C SNPs 3) remove SNPs not in HapMap	2,375	Bioimpedance	A Xitron HYDRA ECF/ICF, Model 4200	**[PMID: 17351290]** Harris T, et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. American Journal of Epidemiology 165, 1076–1087 (2007).
Amish	The Old Order Amish	1,186	≥ 96%	1) failed Mendelian check 2) failed duplicate check 3) missing body fat percentage data	850	DEXA	Hologic QDR-4500W	**[PMID: PMC2443415]** Mitchell BD, et al. The genetic response to short-term interventions affecting cardiovascular function: Rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. Am Heart J 823, 828 (2008).
CHS	Cardiovascular Health Study	3,980	≥ 95%	1) prevalent clinical CVD 2) African-American 3) sex discordant 4) discordant prior genotyping 5) no DEXA scan done	921	DEXA	Hologic QDR-2000 Bone densitometer	**[PMID: 11454111]** Robbins J, et al. The association of bone mineral density and depression in an older population. J Am Geriatr Soc 49, 732-736 (2001). **[PMID: 1669507]** Fried LP, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1, 263-276 (1991).
CoLaus	Cohort Lausannoise	6,188	≥ 90%	1) ethnic outliers 2) related individuals and duplicates 3) missing body fat percentage data	5,389	Bioimpedance	Bodystat 1500 Analyzer	**[PMID: 18366642]** Firmann M, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovasc Dis, 8, 6 (2008).
EPIC-Obesity	European Prospective Investigation into Cancer and Nutrition - Obesity Study	2,566	≥ 94%	1) Heterozygosity <23% or >30% 2) >5.0% discordance in SNP pairs with r^2= 1 in HapMap 3) ethnic outliers 4) related individuals and duplicates 5) missing body fat percentage data	2,543	Bioimpedance	Tanita BC-531 Body Composition Monitor	**[PMID: 10466767]** Day, N.E. et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. British Journal of Cancer 80, 95-103 (1999). **[PMID: 18454148]** Loos, R.J. et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 40, 768-775 (2008).
ERF	Erasmus Rucphen Family	2,315	> 95%	1) gender mismatch 2) ethnic outliers 3) missing body fat percentage data	2,087	DEXA	GE Lunar Prodigy	**[PMID: 10466767]** Aulchenko YS. et al. Linkage disequilibrium in young genetically isolated Dutch population. Eur J Hum Genet 12, 527-534 (2004).
FamHS	Family Heart Study	974	≥ 98%	1) technical errors 2) discrepancies between reported sex and sex-diagnostic markers	809	Bioimpedance	RJL bioelectric impedance meter	**[PMID: 8651220]** Higgins, M. et al., NHLBI Family Heart Study: objectives and design, Am J Epidemiol 143, 1219–1228 (1996).
Fenland	Fenland Study	1,500	≥ 95%	1) failed heterozygosity check: upperbound 0.2882, lowerbound 0.2735 2) failed relatedness check (sample with lower call rate in related samples) 3) failed duplicate check (sample with lower call rate in duplicates) 4) missing body fat percentage data	1,402	DEXA	GE Lunar Prodigy	**[PMID: 20519560]** De Lucia Rolfe, E. et al. Association between birth weight and visceral fat in adults. Am J Clin Nutr (2009) Jun 2 [Epub ahead of print]. **[PMID: 19079261]** Willer CJ, Speliotes EK, Loos RJ, et al. Siz new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 41, 25-34 (2009)

Study		Total sample size (N)	Sample QC		Samples in analyses (N)	Fat % assessment method	Instrument	References
Short name	Full name		Call rate*	other exclusions				
Framingham	Framingham Heart Study	3,780	≥ 97%	1) autosomal heterozygosity <0.33 or >0.37 2) ethnic outliers (using Eigenstrata) 3) missing body fat percentage data	2,748	DEXA	GE Lunar DPX-L	**[PMID: 10466767]** Visser, M . et al. Body fat and skeletal muscle mass in relation to physical disability in very old men and women of the Framingham Heart Study. J Gerontol 53A, M214-M221 (1998).
GOOD	Gothenburg Osteoporosis and Obesity Determinants Study	1,056	≥ 97.5%	1) heterozygosity >33% 2) ethnic outliers 3) related individuals and duplicates	940	DEXA	GE Lunar Prodigy	**[PMID: 16007330]** Lorentzon, M. et al Free testosterone is a positive whereas free estradiol is a negative predictor of cortical bone size in young Swedish men-The GOOD Study. J Bone Miner Res 20, 1334-1341 (2005).
KORA S3	Cooperative Health Research in the Augsburg Region	NA	≥ 93%	1) gender mismatch 2) missing body fat percentage data	1,560	Bioimpedance	DATA-INPUT GmbH BIA 2000-S	**[PMID: 20031538]** Heid IM, et al. Genome-wide association analysis of high-density lipoprotein cholesterol in the population-based KORA study sheds new light on intergenic regions. Circ Cardiovasc Genet 1, 10-20 (2008).
KORA S4/F4	Cooperative Health Research in the Augsburg Region	NA	≥ 93%	1) gender mismatch 2) missing body fat percentage data	1,794	Bioimpedance	DATA-INPUT GmbH BIA 2000-S	**[PMID: 16032514]** Wichmann HE, et al. KORA-gen - resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen, 67 Suppl 1, S26-30 (2005).
LOLIPOP	London Life Sciences Population Study	12,248	≥ 95%	1) ethnic outliers 2) related individuals and duplicates 3) wrong genders 4) missing body fat percentage data	8,999	Bioimpedance	Tanita TBF-401	**[PMID: 18193046]** Kooner, J.S. et al. Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides. Nat Genet 40, 149-151 (2008). **[PMID: 18454146]** Chambers, J.C. et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nat Genet 40, 716-718 (2008). **[PMID: 19820698]** Chambers, J.C. et al. Genome-wide assocaition study identifies variants in TMPRSS6 associated with hemoglobin. Nat Genet 41, 1170-1172 (2009).
ROTTERDAM	Rotterdam Study	7,983	≥ 97.5%	1) missing DNA 2) gender mismatch with typed X-linked markers 3) excess autosomal heterozygosity >0.336~FDR>0.1% 4) duplicates and/or 1st or 2nd degree relatives using IBS probabilities >97% from PLINK 5) ethnic outliers using IBS distances >3SD from PLINK 6) missing phenotype	2,438	DEXA	Lunar Prodigy, GE Healthcare	**[PMID: 19700477]** Estrada, K. et al. GRIMP: a web- and grid-based tool for high speed analysis of large-scale genome-wide association using imputed data. Bioinformatics 25, 2750-2752 (2009). **[PMID: 19728115]** Hofman, A. et al. The Rotterdam Study: 2010 objectives and design update. Eur J Epidemiol 24, 553-572 (2009). **[PMID: 1833235]** Hofman, A. et al. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 7, 403-422 (1991).
TWINS UK	Twins UK	5,654	≥ 98%	1) failed ethnicity check 2) failed relatedness check 3) failed zygosity check 4) failed population stratification check 5) missing body fat percentage data	1,688	DEXA	Hologic Discovery W' - QDR software version 12.6	**[PMID: 19343178]** Soranzo, N. et al. Meta-analysis of genome-wide scans for human adult stature identifies novel Loci and associations with measures of skeletal frame size. PLoS Genet 5(4):e1000445 (2009)

* Sample genotyping success rate; i.e. minimum percentage of successfully genotyped SNPs per sample

Supplementary Note - Table 2 Information on genotyping methods, quality control of SNPs, imputation, and statistical analysis for genome-wide association studies of stage 1

Study	Platform	Genotyping				Imputation			Association analyses			
		Genotype calling algorithm	Inclusion criteria		SNPs that met QC criteria	Imputation software	Imputation quality*	SNPs in meta-analysis	λ_{GC}			Analysis software
			Call rate*	p for HWE					All	Men	Women	
AGES	Illumina 370K	BeadStudio	≥ 95%	> 10^{-6}	315,410	MACH	r2-hat ≥ 0.30	2,465,997	-	1.020	1.029	ProbABEL
Amish	Affymetrix 500K	BRLMM	≥ 96%	> 10^{-6}	382,935	MACH	r2-hat ≥ 0.30	2,302,463	1.049	1.018	1.077	ITSNBN
CHS	Illumina 370-CNV	BeadStudio	> 97%	> 10^{-5}	306,655	BimBam	observed/expected variance ≥ 0.30	2,195,299	-	1.014	1.020	R
CoLaus	Affymetrix 500K	BRLMM	> 70%	> 10^{-7}	390,631	IMPUTE	proper-info ≥ 0.40	2,439,888	-	1.020	1.022	QUICKTEST
EPIC-Obesity (obese cases)	Affymetrix 500K	BRLMM	≥ 90%	> 10^{-6}	397,438	IMPUTE	proper-info ≥ 0.40	2,381,011	-	1.170	0.994	SNPtest
EPIC-Cohort (controls)	Affymetrix 500K	BRLMM	≥ 90%	> 10^{-6}	397,438	IMPUTE	proper-info ≥ 0.40	2,428,445	-	0.992	0.995	SNPtest
ERF	Illumina 318K and 370K Affymetrix 250K	BeadStudio, BRLMM	≥ 96%	>10^{-6}	487,573	MACH	r2-hat ≥ 0.30	2,468,052	1.017	1.001	1.017	ProbABEL
FamHS	Illumina 1 Million	BeadStudio	≥ 98%	> 10^{-6}	874,830	MACH	r2-hat ≥ 0.30	2,375,698	1.031	1.035	1.043	SAS
Fenland	Affymetrix 500K	BRLMM	≥ 90%	> 10^{-6}	362,055	IMPUTE	proper-info ≥ 0.40	2,427,084	-	1.014	1.006	SNPtest
Framingham	Affymetrix 500K Affymetrix 50K supplemental	BRLMM	≥ 97%	> 10^{-6}	378,163	MACH	r2-hat ≥ 0.30	2,455,944	0.991	1.020	1.012	R
GOOD	Illumina 610K	BeadStudio	≥ 98%	> 10^{-6}	521,160	MACH	r2-hat ≥ 0.30	2,503,211	-	1.015	-	MACH2QTL
KORAS3	Affymetrix 500K	BRLMM	≥ 90%	-	490,032	MACH	r2-hat ≥ 0.30	2,416,530	-	1.002	1.010	MACH2QTL
KORAS4/F4	Affymetrix 6.0	Birdseed2	-	-	909,622	IMPUTE	proper-info ≥ 0.40	2,040,316	-	1.023	0.993	SNPtest
LOLIPOP	Affymetrix 500K (Caucasians)	BRLMM	> 90%	> 10^{-6}	374,773	MACH	r2-hat ≥ 0.30	2,444,407	-	1.018	0.989	MACH2QTL
LOLIPOP	Illumina 317K (Indian-Asians)	Beadstudio	> 90%	> 10^{-6}	245,892	MACH	r2-hat ≥ 0.30	1,896,366	-	1.003	-	MACH2QTL
LOLIPOP	Illumina 610K (Indian-Asians)	Beadstudio	> 90%	> 10^{-6}	544,390	MACH	r2-hat ≥ 0.30	2,147,795	-	1.027	1.014	MACH2QTL
LOLIPOP	Perlegen (Caucasians)	Custom	> 90%	> 10^{-6}	202,544	MACH	r2-hat ≥ 0.30	2,398,436	-	1.007	-	MACH2QTL
LOLIPOP	Perlegen (Indian-Asians)	Custom	> 90%	> 10^{-6}	170,055	MACH	r2-hat ≥ 0.30	1,546,962	-	0.979	-	MACH2QTL
Rotterdam	Illumina Infinium 550	BeadStudio	≥ 97.5%	> 10^{-6}	512,349	MACH	r2-hat ≥ 0.30	2,488,215	-	1.010	1.019	MACH2QTL
Twins UK	Illumina 317K	BeadStudio	≥ 95%	> 10^{-6}	307,040	IMPUTE	proper-info ≥ 0.40	2,278,608	-	-	1.052	Merlin

* SNP genotyping success rate; i.e. minimum percentage of successfully genotyped samples per SNP

Supplementary Note - Table 3 Study-specific descriptive statistics for genome-wide association studies of stage 1

Study	Men							Women						
	N	Age, yrs mean (sd)	BMI, kg/m² mean (sd)	Height, m mean (sd)	Weight, kg mean (sd)	Total fat mass, kg mean (sd)	Fat% mean (sd)	N	Age, yrs mean (sd)	BMI, kg/m² mean (sd)	Height, m mean (sd)	Weight, kg mean (sd)	Total fat mass, kg mean (sd)	Total body fat% mean (sd)
AGES	1,019	49.7 (5.9)	25.6 (3.1)	1.78 (0.06)	81.3 (11.4)	-	22.0 (5.5)	1,356	52.0 (6.5)	24.9 (3.8)	1.64 (0.05)	67.1 (10.5)	-	34.0 (5.0)
Amish	406	50.7 (15.0)	26.5 (3.4)	1.72 (0.06)	78.2 (12.1)	15.9 (7.5)	19.7 (6.5)	444	52.2 (14.4)	28.4 (5.4)	1.60 (0.06)	72.4 (14.4)	25.8 (8.9)	35.4 (6.5)
CHS	349	77.6 (5.0)	26.5 (3.4)	1.73 (0.06)	79.4 (10.9)	23.1 (7.7)	29.4 (6.6)	572	(76.9 (4.3)	26.1 (4.4)	1.59 (0.06)	66.2 (12.1)	28.4 (9.6)	42.6 (7.5)
CoLaus	2,539	52.9 (10.8)	26.6 (4.2)	1.75 (0.07)	81.5 (13.4)	-	23.9 (6.0)	2,850	53.9 (10.7)	25.2 (4.9)	1.62 (0.07)	66.4 (13.0)	-	34.4 (8.2)
EPIC-Obesity	1,121	63.2 (8.9)	28.4 (3.9)	1.74 (0.07)	85.9 (13.0)	19.9 (7.6)	26.4 (7.1)	1,422	62.2 (8.7)	28.5 (5.2)	1.61 (0.06)	74.1 (13.8)	28.4 (11.1)	43.8 (10.5)
ERF	900	48.8 (14.5)	27.2 (3.97)	1.75 (0.07)	82.8 (13.5)	22.0 (8.6)	26.9 (7.1)	1187	47.7 (14.5)	26.4 (4.8)	1.61 (0.07)	69.1 (13.1)	26.4 (9.7)	38.7 (7.6)
FamHS	388	59.9 (12.3)	29.6 (4.8)	1.76 (0.07)	91.8 (15.8)	30.7 (10.5)	27.9 (7.6)	421	64.6 (9.8)	28.7 (6.3)	1.60 (0.06)	74.4 (17.6)	33.6 (12.8)	38.7 (7.7)
Fenland	615	44.5 (7.4)	27.6 (3.9)	1.77 (0.07)	86.8 (13.9)	24.7 (8.6)	28.0 (6.7)	787	45.3 (7.2)	26.7 (5.5)	1.64 (0.06)	71.5 (15.3)	27.4 (10.7)	37.6 (7.7)
Framingham	1,003	64.1 (11.2)	26.7 (2.9)	1.73 (0.07)	80.1 (10.2)	22.8 (6.1)	28.2 (5.5)	1745	64.3 (11.4)	26.3 (4.3)	1.60 (0.07)	67.1 (11.6)	27.9 (8.8)	41.1 (7.3)
GOOD	940	18.9 (0.6)	22.4 (3.2)	1.82 (0.07)	73.9 (11.6)	13.2 (7.9)	17.1 (7.4)	0	-	-	-	-	-	-
KORAF3	773	62.5 (10.0)	28.2 (3.5)	1.73 (0.07)	84.9 (12.1)	24.3 (7.3)	28.1 (5.0)	787	61.6 (9.9)	27.9 (5.0)	1.61 (0.06)	71.9 (13.2)	28.1 (8.5)	38.4 (5.2)
KORAS4/F4	874	54.1 (8.9)	28.4 (4.2)	1.74 (0.07)	86.5 (14.1)	24.3 (7.6)	28.0 (4.9)	920	53.6 (8.8)	27.9 (5.3)	1.61 (0.06)	72.6 (13.7)	27.3 (8.6)	37.5 (5.4)
Lolipop - Europeans	1,238	55.0 (9.7)	28.3 (4.7)	1.75 (0.07)	86.8 (15.7)	24.8 (11.3)	27.5 (7.8)	204	51.3 (10.4)	27.2 (5.7)	1.63 (0.06)	72.5 (15.5)	28.0 (10.9)	37.3 (7.0)
Lolipop - Indian-Asians	6,535	54.0 (10.9)	27.0 (4.1)	1.70 (0.07)	78.4 (13.4)	22.2 (9.3)	27.5 (7.3)	1,022	56.9 (10.0)	28.8 (5.3)	1.56 (0.06)	69.5 (12.7)	27.8 (9.1)	39.1 (6.4)
Rotterdam	1,043	63.9 (5.6)	25.9 (2.8)	1.76 (0.06)	80.5 (10.0)	23.4 (7.6)	28.9 (6.2)	1,395	64.2 (6.0)	26.3 (3.8)	1.63 (0.06)	70.2 (10.7)	28.4 (8.8)	29.0 (6.6)
Twins UK	0	-	-	-	-	-	-	1,688	47.5(12.4)	24.9(4.5)	1.63(0.06)	65.7(12.3)	-	33.4(7.4)

Supplementary Note - Table 4 Number of individuals and sample quality control for stage 2 and stage 3 follow-up studies with *de novo* genotyping

Study **Short name**	 **Full name**	**Total sample size (N)**	**Exclusions**	**Samples in analyses (N)**	**Fat % assessment method**	**Instrument**	**References**
BPPP	Botnia Prevalence, Prediction and Prevention of Diabetes study	1,889	1) Missing phenotypes 2) Missing DNA	1,870	Bioimpedance	Tanita BF-350	**[PMID: 20454776]** Isomaa B. et al. A family history of diabetes is associated with reduced physical fitness in the Prevalence, Prediction, and Prevention of Diabetes (PPP)-Botnia study. Diabetologia 53, 1709-1713 (2010).
EPIC-Norfolk	European Prospective Investigation into Cancer and Nutrition - Obesity Study	25,663	1) Missing phenotypes 2) Missing DNA	10,282	Bioimpedance	Tanita BC-531 Body Composition Monitor	**[PMID: 10466767]** Day, N.E. et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. British Journal of Cancer 80, 95-103 (1999). **[PMID: 18454148]** Loos, R.J. et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 40, 768-775 (2008).
METSIM	Metabolic Syndrome In Men Study	8,740	1.)Missing phenotypes 2) Missing DNA	7,470	Bioimpedance	Akern Bioimpedance Analyzer Model BIA101	**[PMID: 19223598]** Stančáková, A. et al. Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6,414 Finnish Men. Diabetes 58, 1212-1221 (2009).
MrOS Sweden - Hologic	Osteoporotic Fracture in Men Study - Sweden	1,010	1) Missing phenotypes 2) Missing DNA	917	DEXA	Hologic QDR, 4500/A-Delphi	**[PMID: 16598372]** Mellström, D.. et al. Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. J Bone Miner Res 21, 529-535 (2006).
MrOS Sweden - Lunar	Osteoporotic Fracture in Men Study - Sweden	2,004	1) Missing phenotypes 2) Missing DNA	1,946	DEXA	GE Lunar Prodigy	**[PMID: 16598372]** Mellström, D.. et al. Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. J Bone Miner Res 21, 529-535 (2006).
RISC	Relationship between Insulin Sensitivity and Cardiovascular Disease	1,308	1) Missing DNA 2) Missing phenotypes	1,247	Bioimpedance	Tanita TBF-300 Body Composition Analyser	**[PMID: 14968294]** Hills, S.A. et al. The EGIR-RISC STUDY (The European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease risk): methodology and objectives. Diabetologia 47, 566-570 (2004).
ULSAM	Uppsala Longitudinal Study of Adult Men	1,221	1) Missing DNA 2) Missing phenotypes 3) Prevalent diabetes (FG>=7.0 mmol/L or Rx)	960	BMI	-	**[PMID: 16030278]** Ingelsson, E. et al. Insulin resistance and risk of congestive heart failure. JAMA 294, 334-341 (2005).

* Sample genotyping success rate; i.e. minimum percentage of successfully genotyped SNPs of GWAs per sample

Supplementary Note - Table 5. Information on genotyping methods, quality control of SNPs, and association analysis software for stage 2 and stage 3 follow-up studies with *de novo* genotyping

Study	**Genotyping Platform**	**Inclusion criteria** **Call rate***	 **Duplicate concordance**	 **p for HWE**	**Analysis software**
EPIC-Norfolk	Custom TaqMan® SNP Genotyping Assays (Applied Biosystems, Warrington, UK) iPLEX™ Sequenom MassARRAY®	≥ 93%	≥ 97%	> 0.05	SAS
BPPP	iPLEX™ Sequenom MassARRAY®	≥ 99%	NA	>0.0001	PLINK
METSIM	Custom TaqMan® SNP Genotyping Assays (Applied Biosystems, Warrington, UK)	≥ 95%	≥ 96%	>0.05	SPSS
MrOS Sweden - Hologic	iPLEX™ Sequenom MassARRAY®	≥ 98%	≥ 97%	> 0.45	SAS
MrOS Sweden - Lunar	iPLEX™ Sequenom MassARRAY®	≥ 98%	≥ 97%	> 0.42	SAS
RISC	Fluorescence-based competitive allele-specific PCR (Kbiosciences, Hoddesdon, UK)	≥ 98%	≥ 98%	> 0.05	SAS
ULSAM	Single-base extension with fluorescence polarization detection	≥ 99%	100%	> 0.05	STATA

NA, data not available

* SNP genotyping success rate; i.e. minimum percentage of successfully genotyped samples per SNP

Supplementary Note - Table 6. Number of individuals and sample quality control for stage 2 and stage 3 follow-up studies with *in silico* genotyping

Study		**Total sample size**	**Sample QC**		**Samples in analyses**	**Fat % assessment method**	**Instrument**	**References**
Short name	**Full name**	**(N)**	**Call rate***	**Other exclusions**	**(N)**			
deCODE	deCODE genetics sample set	38,446	≥ 98%	1) missing phenotype 2) missing genotype	2,547	DEXA	Hologic QDR4500A	**[PMID: 19079260]** Thorleifsson, G. et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 41, 18-24 (2009).
Fenland	Fenland Study	-	≥ 95%	1) gender check 2) duplicates check 3) missing phenotype	3,132	DEXA	GE Lunar Prodigy	**[PMID: 20519560]** De Lucia Rolfe, E. et al. Association between birth weight and visceral fat in adults. Am J Clin Nutr (2009) Jun 2 [Epub ahead of print]. **[PMID: 19079261]** Willer CJ, Speliotes EK, Loos RJ, et al. Siz new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 41, 25-34 (2009)
Genmets	Health2000 GenMets MS Cases and Controls	2,124	>95%	1) heterozygosity check 2) gender check 3) cryptic relatedness 4) missing phenotypes	1,726	Bioimpedance	InBody 3.0	**[PMID: 19554302]** Perttilä J, et al. OSBL10, a novel candidate gene for high triglyceride trait in dyslipidemic Finnish subjects, regulates cellular lipid metabolism. J Mol Med 87, 825-835 (2009)
MRC Ely	MRC Ely Study	-	≥ 95%	1) gender check 2) duplicates check 3) missing phenotype	1,582	DEXA	GE Lunar Prodigy	**[PMID: 17257284]** Forouhi, N.G. et al. Incidence of type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990-2000. Diabet Med 24, 200-207 (2007)
ORCADES	Orkney Complex Disease Study	~1,000	≥ 97%	1) ethnic outliers 2) missing phenotype 3) missing genotype 4) genotypes not imputed 5) duplicate samples	719	Bioimpedance	Tanita TBF-300 Body Composition Analyser	**[PMID: 18952825]** Johansson, A. et al. Common variants in the JAZF1 gene associated with height identified by linkage and genome-wide association analysis. Hum Mol Genet 18, 373-380 (2009). **[PMID: 19798445]** Hicks, A.A. et al. Genetic determinants of circulating sphingolipid concentrations in European populations. PLoS Genet 5(10):e1000672 (2009).
Twins UK	Twins UK	5,654	≥ 98%	1) ethnic outlier 2) failed relatedness 3) failed zygosity 4) failed population stratification check 5) missing phenotype	1,691	DEXA	Hologic Discovery W’ - QDR software version 12.6	**[PMID: 19343178]** Soranzo, N. et al. Meta-analysis of genome-wide scans for human adult stature identifies novel Loci and associations with measures of skeletal frame size. PLoS Genet 5(4):e1000445 (2009)
VIS	VIS-CROATIA	1,056	≥ 97%	1) ethnic outliers 2) missing phenotype 3) missing genotype 4) genotypes not imputed 5) duplicate samples	781	Bioimpedance	Akern Soft-Tissue-Analyzer-STA	**[PMID: 18952825]** Johansson, A. et al. Common variants in the JAZF1 gene associated with height identified by linkage and genome-wide association analysis. Hum Mol Genet 18, 373-380 (2009). **[PMID: 19798445]** Hicks, A.A. et al. Genetic determinants of circulating sphingolipid concentrations in European populations. PLoS Genet 5(10):e1000672 (2009).
Whitehall II	Whitehall II	5,592	≥ 98%	1) non-white ethnicity 2) outliers in Plink 3) missing phenotype	3,949	Bioimpedance	Tanita TBF-300 Body Composition Analyser	**[PMID: 15576467]** Marmot, M. et al. Cohort Profile: The Whitehall II Study. Int J Epidemiol 34, 251-256 (2005).

* Sample genotyping success rate; i.e. minimum percentage of successfully genotyped SNPs of GWAs per sampl

Supplementary Note - Table 7. Information on genotyping methods, quality control of SNPs, imputation, and association analysis software for stage 2 and stage 3 follow-up studies with *in silico* genotyping

Study	Genotyping						Imputation			Association analyses	
	Platform	Genotype calling algorithm	Inclusion criteria			SNPs that met QC criteria	Imputation software	Inclusion criteria		SNPs for analysis	Analysis software
			MAF	Call rate*	p for HWE			MAF	Imputation quality*		
deCODE	Illumina HumanHap 300 370CNV	BeadStudio	≥ 1%	≥ 96%	> 10-6	290,449	IMPUTE	≥ 1%	proper-info ≥ 0.40	14	SNPtest
Fenland	Illumina MetaboChip	GeneCall	-	≥ 90%	$> 10^{-6}$	167,085	-	-	-	14	Plink
Genmets	Ilumina 610K	Illuminus	≥ 1%	≥ 95%	$> 10^{-6}$	555,388	MACH 1.0.10	≥ 1%	r2-hat ≥ 0.83	14	Probabel
MRC Ely	Illumina MetaboChip	GeneCall	-	≥ 90%	$> 10^{-6}$	149,302	-	-	-	14	Plink
ORCADES	Illumina Hap300v2	BeadStudio	≥ 2%	≥ 98%	$> 10^{-6}$	294,123	MACH	≥ 1%	r2-hat ≥ 0.30	14	ProbABEL
Twins UK	Illumina HumanHap 300 Illumina HumanHap 610Q Illumina 1M-Duo Illumina 1.2M Duo	BRLMM	≥ 1%	≥97% for MAF>5% ≥99% for 1<MAF<5%	$> 10^{-6}$	874,733	IMPUTE v2	-	proper-info ≥ 0.40	33	Merlin, PLINK
VIS	Illumina Hap300v1	BeadStudio	≥ 2%	≥ 95%	$> 10^{-6}$	308,996	MACH	≥ 1%	r2-hat ≥ 0.30	14	ProbABEL
Whitehall II	Illumina HumanCVD BeadChip, 50K	Beadstudio	≥ 1%	≥ 98%	$> 10^{-6}$	48,032	-	-	-	1	SAS

* SNP genotyping success rate; i.e. minimum percentage of successfully genotyped samples per SNP

Supplementary Note - Table 8. Study-specific descriptive statistics for stage 2 and stage 3 follow-up studies.

Study	Men							Women						
	N	Age, yrs mean (sd)	BMI, kg/m^2 mean (sd)	Height, m mean (sd)	Weight, kg mean (sd)	Total fat mass, kg mean (sd)	Fat% mean (sd)	N	Age, yrs mean (sd)	BMI, kg/m^2 mean (sd)	Height, m mean (sd)	Weight, kg mean (sd)	Total fat mass, kg mean (sd)	Total body fat% mean (sd)
BPPP	927	48.4 (15.8)	26.8 (3.8)	1.77(0.07)	84.0 (13.1)	20.8 (6.7)	24.3 (6.7)	943	48.3 (15.5)	26.3 (4.7)	1.64 (0.06)	70.7 (12.8)	34.4 (7.5)	25.1 (9.4)
deCODE	533	62.5 (15.2)	27.1 (4.0)	1.76 (0.08)	83.9 (14.8)	23.9 (8.8)	26.6 (6.0)	2,014	56.9 (15.9)	25.8 (4.8)	1.64 (0.07)	69.9 (13.3)	27.2 (9.2)	37.0 (6.8)
EPIC-Norfolk	5,210	59.1 (9.0)	25.8 (2.7)	1.74 (0.06)	78.5 (9.7)	18.2 (6.2)	22.9 (5.7)	5,072	58.1 (8.9)	25.1 (3.3)	1.61 (0.06)	65.4 (9.4)	25.7 (8.4)	38.7 (8.3)
Fenland	1,465	46.9 (7.2)	27.0 (4.1)	1.78 (0.07)	85.4 (14.1)	-	23.7 (5.7)	1,667	46.9 (7.0)	26.5 (5.4)	1.64 (0.06)	71.1 (15.3)	-	35.7 (7.2)
GenMets cases	422	49.2 (10.4)	25.4 (3.1)	1.76 (0.06)	78.0 (10.4)	15.9 (5.7)	19.8 (5.0)	447	52.0 (11.6)	25.1 (4.1)	1.64 (0.06)	65.3 (10.4)	20.5 (7.8)	29.9 (6.7)
GenMets controls	425	49.2 (10.4)	29.4 (3.6)	1.78 (0.07)	91.2 (12.6)	23.9 (7.7)	25.3 (5.4)	432	52.4 (11.7)	29.7 (4.9)	1.64 (0.06)	76.6 (13.4)	28.9 (9.4)	36.1 (6.0)
METSIM	7,470	57.5 (7.0)	27.2 (4.1)	1.76 (0.06)	84.3 (13.9)	20.8 (8.0)	24.1 (6.5)	-	-	-	-	-	-	-
MRC Ely	737	61.5 (9.1)	27.4 (4.0)	1.74 (0.07)	83.1 (13.3)	22.4 (7.0)	26.6 (5.2)	845	60.8 (9.2)	27.3 (5.4)	1.61 (0.06)	71.1 (14.4)	29.0 (10.2)	39.9 (6.5)
MrOS Sweden - Hologic	917	75.2 (3.2)	25.9 (3.2)	1.76 (0.06)	80.2 (11.2)	18.5 (5.7)	22.7 (4.8)	-	-	-	-	-	-	-
MrOS Sweden - Lunar	1,946	75.5 (3.2)	26.5 (3.6)	1.74 (0.07)	80.7 (12.1)	23.7 (7.9)	28.7 (6.5)	-	-	-	-	-	-	-
ORCADES	334	54.0 (15.6)	28.1 (4.1)	1.75 (0.06)	85.8 (13.0)	23.3 (8.6)	26.5 (6.8)	385	52.5 (15.7)	27.3 (5.3)	1.61 (0.06)	70.6 (13.8)	26.5 (10.2)	36.2 (7.3)
RISC	560	43.4 (8.6)	26.4 (3.5)	1.78 (0.07)	83.9 (12.6)	22.1 (6.6)	22.1 (6.6)	687	44.3 (8.1)	24.8 (4.4)	1.65 (0.06)	67.5 (12.4)	22.6 (9.2)	32.3 (7.7)
Twins UK	137	49.1 (12.8)	26.0 (3.1)	1.75 (0.06)	80.0 (10.0)	-	22.0 (6.0)	1,554	49.0 (12.9)	25.4 (4.6)	1.62 (0.06)	66.8 (12.5)	-	34.3 (7.5)
ULSAM	960	71.0 (0.6)	26.0 (3.2)	1.75 (0.06)	79.7 (10.8)	-	-	-	-	-	-	-	-	-
VIS	315	55.7 (14.8)	27.5 (3.7)	1.76 (0.07)	85.5 (13.4)	31.7 (8.1)	37.2 (7.9)	466	56.4 (16.1)	27.2 (4.7)	1.62 (0.07)	71.3 (12.8)	26.1 (7.6)	36.7 (8.4)
Whitehall II	2,958	60.5 (5.8)	26.4 (3.7)	1.76 (0.06)	81.6 (12.4)	20.0 (7.2)	23.9 (5.5)	991	60.4 (5.9)	26.6 (5.2)	1.62 (0.06)	69.7 (14.2)	25.6 (9.8)	35.7 (7.0)

Supplementary Note - Table 9. Samples and assays used for the measurement of circulating levels of glucose, insulin, leptin, and adiponectin in the stage 3 follow-up studie

Study	Glucose Sample	Glucose Assay	Insulin Sample	Insulin Assay	Leptin Sample	Leptin Assay	Adiponectin Sample	Adiponectin Assay
METSIM	Fasting plasma, OGTT (30,120 mins)	Enzymatic hexokinase photometric assay (Konelab System Reagents, Thermo Fischer Scientific, Vaasa, Finland)	Fasting plasma, OGTT (30,120 mins)	Immunoassay (ADVIA Centaur Insulin RIA, no. 02230141, Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA)	NA	NA	Fasting plasma	Enzyme immunoassay (ELISA) kit (Linco Research, St. Charles, MI, USA)
MRC Ely	Fasting plasma, OGTT (30,60,120 mins)	Hexokinase assay	Fasting plasma, OGTT (30,60,120 mins)	Immunometric assay	Fasting blood	Two-step time-resolved fluorometric assays of the 1235 AutoDELFIA (PerkinElmer Lifesciences, Boston, MA) automatic immunoassay system	Fasting blood	Two-step time-resolved fluorometric assays of the 1235 AutoDELFIA (PerkinElmer Lifesciences, Boston, MA) automatic immunoassay system
MrOS Sweden	NA	NA	NA	NA	Fasting serum (Uppsala centre, n=956) Non-fasting serum (Malmö and Uppsala centres n=1,926)	Commercially available kit (Diagnostics Systems Laboratories, Webster, TX, USA)	Fasting plasma	Enzyme immunoassay (ELISA) kit (Linco Research, St. Charles, MI, USA)
RISC	Euglycemic-Hyperinsulinemic-clamp; OGTT (0, 30, 60, 90, 120 mins)	Glucose oxidase method (Cobas Integra; Roche Diagnostics, Basel, Switzerland)	Euglycemic-Hyperinsulinemic-clamp; OGTT (0, 30, 60, 90, 120 mins)	Specific time-resolved fluoroimmunoassay (AutoDELFIA Insulin Kit; Wallac Oy, Turku, Finland)	Fasting blood	Two-step time-resolved fluorometric assays of the 1235 AutoDELFIA (PerkinElmer Lifesciences, Boston, MA) automatic immunoassay system	Fasting blood	In-house time-resolved immunofluorometric assay (TR-IFMA) on the basis of two antibodies and reombinant human adiponectin (R&D Systems, Abingdon, UK)
ULSAM	Euglycemic-Hyperinsulinemic-clamp; OGTT (0, 30, 60, 90, 120 mins)	Glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany)	Euglycemic-Hyperinsulinemic-clamp; OGTT (0, 30, 60, 90, 120 mins)	Enzymatic-immunological assay (Enzymun, Boehringer Mannheim, Germany)	NA	NA	NA	NA
Whitehall II	Fasting plasma, OGTT (0, 120 mins)	Electrochemical glucose oxidase method	Fasting plasma, OGTT (120 mins)	Double antibody ELISA	NA	NA	NA	NA

NA, not available for analyses

2.2. AUTHOR CONTRIBUTIONS

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2.4. COMPETING INTERESTS STATEMENT

Inês Barroso and spouse own stock in Incyte Ltd and GlaxoSmithKline.
Kari Stefansson, Gudmar Thorleifsson, Unnur Throsteinsdottir, and Unnur Styrkarsdottir are employed by deCODE Genetics.
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