

SUPPLEMENTARY DATA

Genome-wide and abdominal MRI-imaging data provides evidence that a genetically determined favourable adiposity phenotype is characterized by lower ectopic liver fat and lower risk of type 2 diabetes, heart disease and hypertension.

Yingjie Ji^{*1}, Andrianos M. Yiorkas^{*2,3}, Francesca Frau^{*4}, Dennis Mook-Kanamori^{*5,6}, Harald Staiger^{*7,8,9}, E. Louise Thomas¹⁰, Naeimeh Atabaki-Pasdar¹¹, Archie Campbell¹², Jessica Tyrrell¹, Samuel E. Jones¹, Robin N. Beaumont¹, Andrew R. Wood¹, Marcus A. Tuke¹, Katherine S. Ruth¹, Anubha Mahajan¹³, Anna Murray¹, Rachel M. Freathy¹, Michael N. Weedon¹, Andrew T. Hattersley¹⁴, Caroline Hayward¹⁵, Jürgen Machann^{7,8}, Hans-Ulrich Häring^{7,8,16}, Paul Franks^{11,17,18}, Renée de Mutsert⁵, Ewan Pearson¹⁹, Norbert Stefan^{*7,8,16}, Timothy M. Frayling^{*1}, Karla V. Allebrandt^{*4}, Jimmy D. Bell^{*10}, Alexandra I. Blakemore^{*2,3}, Hanieh Yaghootkar^{*#1}

* Contributed equally

Corresponding author

1- Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, RILD Level 3, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

2- Section of Investigative Medicine, Imperial College London, London W12 0NN, UK

3- Department of Life Sciences, Brunel University London, Uxbridge UB8 3PH, UK

4- Translational Medicine and Early Development, TMED Translational Informatics, Sanofi, Frankfurt am Main, Germany

5- Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

6- Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

7- Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Otfried Müller Strasse 10, 72076 Tübingen, Germany

8- German Center for Diabetes Research (DZD), Otfried-Müller-Strasse 10, 72076 Tübingen, Germany

9- Institute of Pharmaceutical Sciences, Department of Pharmacy and Biochemistry, Eberhard Karls University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany

10- Research Centre for Optimal Health, School of Life Sciences, University of Westminster, London, UK

11- Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University, Skåne University Hospital Malmö, SE-21741, Malmö, Sweden.

12- Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

13- Wellcome Centre for Human Genetics, University of Oxford, Oxford, UK.

14- Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter EX2 5DW, UK

15- Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

16- Department of Internal Medicine IV, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, Eberhard Karls University Tübingen, Otfried-Müller-Strasse 10, 72076 Tübingen, Germany

17- Department of Public Health & Clinical Medicine, Umeå University, Umeå, Sweden.

18- Department of Nutrition, Harvard School of Public Health, Boston, MA, USA.

19- Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital, Dundee, UK

Corresponding author: Hanieh Yaghootkar

University of Exeter Medical School, RILD building Level 3, Royal Devon & Exeter Hospital, Barrack Road, Exeter, EX2 5DW

E-mail: h.yaghootkar@exeter.ac.uk

SUPPLEMENTARY DATA

Supplementary Table 1. Summary characteristics of participating studies. N: total number of sample size.

Variable	Statistics	Unit	UK Biobank	NEO	Tübingen Family Study for Type-2 Diabetes (TÜF)	IMI-DIRECT	EXTEND	GenScotland
Age	N	years	451099	5744	2679	3029	7537	19988
	mean [min to max] (sd)		57.3 [39.7, 73.7] (8)	56.0 [44, 66] (5.9)	42.8 [18, 82] (14.2)	61.7 [30, 75] (6.9)	56.3 [18, 98] (15.21)	47.4 [18, 99] (14.98)
Sex	males / females	NA	206,251 / 244,848	2,757 / 2,987	970 / 1709	2,142 / 887	3,140 / 4,397	8,220 / 11,774
Body fat %	N	%	443,000	5,714	2,553	NA	6,958	19,438
	mean [min to max] (sd)		31.4 [5, 69.8] (8.5)	35.8 [9.3, 67.5] (8.9)	34.2 [0.9, 74.9] (13.0)		32 [1.2, 59] (8.71)	30 [1,62] (9.63)
BMI (kg m-2)	N	kg/m ²	449359	5744	2679	2871	7498	19781
	mean [min to max] (sd)		27.4 [12.1, 74.7] (4.8)	30.0 [17.2, 61.2] (4.8)	31.0 [16.3, 86.5] (9.4)	28.7 [16.9, 50.4] (4.4)	27.2 [14.3, 48.6] (4.97)	26.6 [10.49, 47.69] (5.00)
WHR	N	NA	450232	5739	2645	2979	7509	19630
	mean [min to max] (sd)		0.87 [0.2, 3] (0.09)	0.92 [0.59, 1.25] (0.08)	0.88 [0.41, 1.38] (0.10)	0.97 [0.72, 1.26] (0.08)	0.87 [0.578, 1.27] (0.10)	0.86 [0.51, 1.23] (0.09)
Hip circumference	N	cm	450276	5739	2645	2979	7476	19586
	mean [min to max] (sd)		103.4 [30, 195] (9.2)	110 [74, 177] (10)	111 [65, 201] (18)	104.1 [84, 153] (8.7)	104 [65.4, 144] (9.46)	103.3 [62, 145] (9.95)
Waist circumference	N	cm	450323	5739	2648	2985	7512	19651
	mean [min to max] (sd)		90.3 [20, 197] (13.5)	102 [57, 165] (13)	98 [48, 185] (20)	101 [65, 146] (11.8)	90.3 [54, 150] (14.57)	89.15 [45, 145] (13.85)
Adiponectin	N	mg/L	NA	5718	1270	NA	NA	NA
	mean [min to max] (sd)			8.4 [0.5, 41.8] (4.4)	13.9 [0.4, 56.0] (7.4)			
Alanine transaminase	N	U/L	NA	5731	1815	NA	5943	NA
	mean [min to max] (sd)			28.3 [4.7, 229.0] (14.7)	29.6 [3.0, 161.0] (17.0)		22.3 [3.9, 110] (11.08)	
Fasting insulin	N	mU/L	NA	5731	2665	2834	NA	NA
	mean [min to max] (sd)			12.8 [0.05, 299.0] (11.0)	14.6 [1.3, 137.2] (11.8)	33.42 [1.1, 471.8] (53.9)		
HDL-C	N	mmol/L	NA	5727	2584	2869	5932	19157
	mean [min to max] (sd)			1.43 [0.24, 4.26] (0.41)	1.61 [0.72, 4.14] (0.43)	1.28 [0.1, 3.45] (0.37)	1.72 [0.62, 4.43] (0.49)	1.46 [0.4, 3.1] (0.40)
Triglycerides	N	mmol/L	NA	5727	2601	2869	4906	NA
	mean [min to max] (sd)			1.46 [0.16, 20.40] (0.96)	1.23 [0.15, 32.02] (1.11)	1.42 [0.14, 6.52] (0.7)	1.17 [0.27, 6.99] (0.65)	
Subcutaneous adipose tissue	N	litres	5045	2236 (cm ²)	833 (Kg)	1320 (Kg)	NA	NA
	mean [min to max] (sd)		7.03 [0.65-23.48] (3.20)	300 [21, 783] (113)	11.3 [0.0, 44.0] (6.1)	6.64 [0.9, 21.9] (3.10)		
Visceral	N		5045	2236 (cm ²)	906 (Kg)	1323 (Kg)	NA	NA

SUPPLEMENTARY DATA

adipose tissue	mean [min to max] (sd)	litres	3.74 [0.12-14.41] (2.25)	123 [7, 426] (67)	3.51[0.22,12.75] (2.16)	5.49 [0.2, 14.5] (2.35)		
VAT/SAT ratio	N		5045	2236	833	1320	NA	NA
	mean [min to max] (sd)	ratio	0.57 [0.07-2.39] (0.34)	0.45 [0.05, 5.92] (0.30)	0.35 [0.00, 1.70] (0.25)	0.94 [0.06, 3.21] (0.47)		
Liver fat	N		5045	1821	911	1433	NA	NA
	mean [min to max] (sd)	%	4.13 [0.45-34.5] (4.6)	8.85 [0.2, 62.9] (10.0)	6.55[0.09,43.14] (6.87)	6.19 [0.3, 37.6] (5.8)		
Pancreatic fat	N		NA	NA	NA	1359	NA	NA
	mean [min to max] (sd)					12.55 [0.2, 37.9] (8.6)		
Type 2 diabetes	N cases / N controls	NA	14,371 / 428,017	580 / 5132	0 / 2679	795 / 2234	1424 / 6113	597 / 18985
Systolic blood pressure (mmHg)	N	mmHg	450075	5735	2041	2736	7532	19929
	mean [min to max] (sd)		144.2 [72, 252.5] (24)	133 [85, 222] (17)	133 [82, 218] (18)	131.1 [90.1,199] (15.4)	134[78,219] (20.34)	132.8[74,209] (19.02)
Diastolic blood pressure (mmHg)	N	mmHg	449322	5736	2039	2736	7532	19944
	mean [min to max] (sd)		86.4 [36.5, 147] (13.5)	85 [45, 145] (10)	83 [40, 140] (12)	79.6 [52, 117] (9.3)	77.9[47,121] (10.96)	80.61[42,124] (11.03)
Hypertension	N cases / N controls	NA	241,691 / 206,525	392 / 5330	NA	1385 / 1416	1767 / 5770	2640 / 16942
Heart disease	N cases / N controls	NA	37,741 / 318,892	2339 / 3997	NA	675 / 2349	498 / 7039	713 / 18869

SUPPLEMENTARY DATA

Supplementary Table 2. Fourthin variants associated with "favorable adiposity". The imputation information is for the UK Biobank study. BETA, SE and P-value are reported for the GWAS of body fat % in UK Biobank. SE: standard error; HWE: Hardy–Weinberg equilibrium.

RSID	Chr_pos	Effect allele	Other allele	BETA (SD)	SE	p-value	HWE p-value	Imputation info	MetaCCA p-value	Gene context	Association with other traits/diseases
rs11118306	1:219627486	A	G	0.0202	0.0015	2E-40	0.38	0.99	3.16E-21	LYPLAL1---[]---SLC30A10	WHR, Insulin sensitivity, Fasting insulin,
rs13389219	2:165528876	T	C	0.0169	0.0015	2E-29	0.75	0.99	5.01E-41	GRB14---[]---COBLL1	Triglycerides, Fasting insulin, WHR, Insulin sensitivity
rs2943653	2:227047771	C	T	0.0158	0.0016	7E-24	0.65	0.99	1.58E-43	NYAP2---[]---IRS1	HDL-C, Fasting insulin, Insulin sensitivity
rs1801282	3:12393125	G	C	0.0289	0.0023	3E-37	0.09	1	2E-10	[PPARG]	Insulin sensitivity, Fasting insulin
rs2276936	4:89726283	A	C	0.0122	0.0015	1E-16	0.72	0.99	2.51E-20	[FAM13A]	WHR, Insulin sensitivity, Fasting insulin,
rs40271	5:55796319	C	T	0.0116	0.0017	6E-12	0.03	0.99	1E-12	ANKRD55---[]---MAP3K1	Insulin sensitivity, Fasting insulin
rs632057	6:139834012	G	T	0.0087	0.0015	2E-8	0.62	1	3.16E-10	CITED2---[]	
rs998584	6:43757896	C	A	0.009	0.0015	3E-9	0.74	0.99	5E-11	VEGFA---[]---C6orf223	WHR
rs972283	7:130466854	A	G	0.0143	0.0015	5E-22	0.68	1	1.26E-19	KLF14---[]---MKLN1	HDL-C, Insulin sensitivity
rs2980888	8:126507308	C	T	0.0119	0.0016	9E-14	0.39	0.99	1.26E-35	TRIB1---[]	Adiponectin, ALT, HDL-C, Triglycerides, Insulin sensitivity
rs7133378	12:124409502	A	G	0.019	0.0016	2E-33	0.63	0.99	2E-17	[DNAH10]	Adiponectin, HDL-C, WHR, Insulin sensitivity
rs11045172	12:20470221	C	A	0.0108	0.0019	8E-9	0.32	0.99	3.98E-9	AEBP2---[]---PDE3A	Adiponectin
rs7258937	19:33938800	T	C	0.0157	0.0015	5E-26	0.52	0.99	5E-12	[PEPD]	Insulin sensitivity, Fasting insulin
rs2267373	22:38600542	C	T	0.0169	0.0015	4E-29	0.56	0.99	7.94E-14	[MAFF]	

SUPPLEMENTARY DATA

Supplementary Table 3. Genetic variants associated with body fat % (GWAS in UK Biobank individuals) and a multivariate GWAS of 7 metabolic biomarkers (from published GWASs). SE: standard error; HWE: Hardy–Weinberg equilibrium.

RSID	Chr_pos	Effect allele	Other allele	BETA	SE	p-value	HWE p-value	Imputation info	MetaCCA p-value	Gene context	r2_UKB	Lead SNP from UKB
rs2943653	2:227047771	C	T	0.0158	0.0016	7E-24	0.65	0.99	1.58E-43	NYAP2---[]---IRS1	1	LEAD
rs13389219	2:165528876	T	C	0.0169	0.0015	2E-29	0.75	0.99	5.01E-41	GRB14---[]---COBLL1	1	LEAD
rs2980888	8:126507308	C	T	0.0119	0.0016	9E-14	0.39	0.99	1.26E-35	TRIB1---[]	0.68	rs183929111
rs11118306	1:219627486	A	G	0.0202	0.0015	2E-40	0.38	0.99	3.16E-21	LYPLAL1---[]---SLC30A10	0.99	1:219665643_ACTGGTGTAA_GAATT_A
rs2276936	4:89726283	A	C	0.0122	0.0015	1E-16	0.72	0.99	2.51E-20	[FAM13A]	0.92	rs548008292
rs972283	7:130466854	A	G	0.0143	0.0015	5E-22	0.68	1	1.26E-19	KLF14---[]---MKLN1	1	LEAD
rs7133378	12:124409502	A	G	0.019	0.0016	2E-33	0.63	0.99	2.00E-17	[DNAH10]	1	LEAD
rs2267373	22:38600542	C	T	0.0169	0.0015	4E-29	0.56	0.99	7.94E-14	[MAFF]	0.99	rs4820325
rs40271	5:55796319	C	T	0.0116	0.0017	6E-12	0.03	0.99	1.00E-12	ANKRD55---[]---MAP3K1	0.99	rs30351
rs7258937	19:33938800	T	C	0.0157	0.0015	5E-26	0.52	0.99	5.01E-12	[PEPD]	1	LEAD
rs998584	6:43757896	C	A	0.009	0.0015	3E-9	0.74	0.99	5.01E-11	VEGFA---[]---C6orf223	1	LEAD
rs1801282	3:12393125	G	C	0.0289	0.0023	3E-37	0.09	1	2.00E-10	[PPARG]	1	LEAD
rs632057	6:139834012	G	T	0.0087	0.0015	2E-8	0.62	1	3.16E-10	CITED2---[]	0.92	rs143770783
rs11045172	12:20470221	C	A	0.0108	0.0019	8E-9	0.32	0.99	3.98E-09	AEBP2---[]---PDE3A	1	LEAD
rs12940684	17:7453919	C	T	0.0111	0.0016	2E-11	0.56	0.99	1.26E-43	[TNFSF12-TNFSF13]	1	LEAD
rs1558902	16:53803574	A	T	0.0413	0.0015	4E-164	0.48	0.99	1.26E-19	[FTO]	0.99	PROXY
rs4497915	2:48690596	G	T	0.0081	0.0015	3E-8	0.52	0.99	3.16E-19	[PPP1R21]	1	LEAD
rs6024001	20:36842836	C	T	0.0086	0.0015	4E-9	0.75	0.99	1.58E-17	[KIAA1755]	0.94	PROXY
rs10496731	2:135597628	T	G	0.0097	0.0015	4E-10	0.11	0.99	2.51E-12	[ACMSD]	1	LEAD
rs7239114	18:45921214	A	G	0.009	0.0015	3E-9	0.59	0.99	6.31E-12	ZBTB7C---[]---CTIF	1	LEAD
rs340025	15:60908307	C	T	0.0089	0.0015	2E-9	0.93	0.99	3.98E-11	[RORA]	1	LEAD
rs17207196	7:75101065	C	T	0.0131	0.0015	2E-18	0.51	1	2.51E-10	[POM121C]	0.99	PROXY

SUPPLEMENTARY DATA

rs7903146	10:114758349	C	T	0.0109	0.0016	3E-11	0.5	1	2.51E-10	[TCF7L2]	0.89	PROXY
rs9435341	1:107616641	T	C	0.0105	0.0016	2E-11	0.0004	0.99	2.51E-10	PRMT6--[]--NTNG1	1	LEAD
rs10779835	1:230299949	T	C	0.0093	0.0015	3E-10	0.77	0.99	5.01E-10	[GALNT2]	0.99	PROXY
rs8074454	17:3981148	C	G	0.0105	0.0016	3E-11	0.59	0.99	5.01E-10	[ZZEF1]	1	LEAD
rs9538162	13:59265043	T	C	0.0087	0.0015	6E-9	0.36	0.99	7.94E-10	PCDH17---[]---DIAPH3	0.98	PROXY
rs11096549	2:16607101	T	C	0.0095	0.0017	8E-9	0.32	0.99	7.94E-09	MYCN---[]---FAM49A	1	LEAD
rs7621025	3:136272246	C	T	0.0091	0.0017	3E-8	0.65	0.99	2.51E-08	[STAG1]	0.98	PROXY
rs6752378	2:25150116	A	C	0.023	0.0015	3E-55	0.09	0.99	2.51E-08	ADCY3--[]--DNAJC27	1	LEAD
rs2298117	10:70346740	T	C	0.0098	0.0015	3E-10	0.46	0.99	2.51E-08	[TET1]	0.92	PROXY
rs79011	22:41866938	A	G	0.0144	0.0019	1E-14	0.28	0.99	3.16E-08	[ACO2]	0.99	PROXY
rs7124681	11:47529947	A	C	0.0225	0.0015	4E-50	0.14	1	3.98E-08	CELF1--[]--PTPMT1	1	LEAD

SUPPLEMENTARY DATA

Supplementary Table 4. The association of genetic variants with 6 metabolic biomarkers. A1: effect allele; A0: other allele; P: p-value; Adipo: adiponectin; ALT: alanine transaminase; HDL: HDL-cholesterol; SHBG: Sex-hormone binding globulin; TG: triglycerides; FIadjBMI: fasting insulin adjusted for BMI.

RSID	Chr:Position	GENE CONTEXT	A1	A0	Beta Adipo	P Adipo	Beta ALT	P ALT	Beta HDL	P HDL	Beta SHBG	P SHBG	Beta TG	P TG	Beta FIadjBMI	P FIadjBMI
rs12940684	17:7453919	[TNFSF12-TNFSF13]	C	T	0.007	0.17	0.0031	0.172	0.0068	0.2	0.079	3E-56	-8E-4	0.5009	-7E-4	0.8
rs2943653	2:227047771	NYAP2---[]---IRS1	C	T	0.022	4E-6	-0.0034	0.033	0.0312	5E-9	0.014	0.005	-0.026	8E-8	-0.021	5E-14
rs13389219	2:165528876	GRB14---[]---COBLL1	T	C	0.019	3E-5	-0.0041	0.001	0.0254	2E-7	0.016	4E-4	-0.029	3E-10	-0.018	7E-11
rs2980888	8:126507308	TRIB1---[]	C	T	0.033	4E-8	-0.0104	5E-9	0.0407	8E-12	0.003	0.5	-0.067	2E-31	-0.0019	0.55
rs11118306	1:219627486	LYPLAL1---[]---SLC30A10	A	G	0.019	4E-5	-0.0031	0.113	0.0203	0.0004	0.006	0.18	-0.016	0.002	-0.014	5E-7
rs2276936	4:89726283	[FAM13A]	A	C	0.020	8E-6	-0.0018	0.084	0.0219	1E-5	7E-4	0.86	-0.013	0.024	-0.012	2E-5
rs972283	7:130466854	KLF14---[]---MKLN1	A	G	-0.006	0.2	-9E-4	0.31	0.0377	6E-15	0.004	0.36	-0.021	1E-5	-0.013	4E-6
rs1558902	16:53803574	[FTO]	A	T	0.0033	0.47	0.0029	0.045	-0.021	5E-6	0.007	0.1	0.014	0.008	-0.003	0.22
rs4497915	2:48690596	[PPP1R21]	G	T	0.0058	0.2	0.0049	0.0001	-0.01	0.054	0.015	4E-4	0.007	0.115	-0.005	0.08
rs6024001	20:36842836	[KIAA1755]	C	T	-0.009	0.04	0.0048	0.0003	-0.013	0.002	-5E-4	0.9	0.004	0.378	0.0072	0.0066
rs7133378	12:124409502	[DNAH10]	A	G	0.0297	1E-9	-4E-4	0.83	0.031	4E-9	0.008	0.1	-0.023	6E-6	-0.008	0.009
rs7958691	12:124440743	[CCDC92]	T	G	0.0268	1E-8	0.0016	0.59	0.032	6E-10	0.007	0.15	-0.027	9E-8	-0.007	0.01
rs2267373	22:38600542	[MAFF]	C	T	-0.0004	0.9	-0.0039	0.07	0.015	0.003	-0.005	0.23	-0.024	5E-7	-0.008	0.004
rs40271	5:55796319	ANKRD55---[]---MAP3K1	C	T	-0.0059	0.26	-0.003	0.02	0.02	0.0003	0.018	5E-4	-0.023	4E-5	-0.012	5E-5
rs10496731	2:135597628	[ACMSD]	T	G	0.0059	0.22	0.0051	0.007	-0.02	0.006	-0.002	0.65	0.006	0.26	0.0052	0.067
rs7258937	19:33938800	[PEPD]	T	C	0.0188	2E-5	8E-4	0.95	0.016	0.001	0.006	0.19	-0.009	0.097	-0.008	0.002
rs7239114	18:45921214	ZBTB7C---[]---CTIF	A	G	-0.0065	0.2	0.0053	0.002	-0.014	0.02	-0.005	0.34	0.005	0.278	-0.005	0.12
rs340025	15:60908307	[RORA]	C	T	0.0023	0.6	0.005	0.001	0.0045	0.42	0.001	0.82	3E-4	0.864	-0.001	0.7
rs998584	6:43757896	VEGFA---[]---C6orf223	C	A	0.0296	6E-8	0.0025	0.58	0.024	2E-5	0.012	0.02	-0.03	4E-7	-0.006	0.04
rs1801282	3:12393125	[PPARG]	G	C	0.0034	0.6	-0.005	0.21	0.021	0.004	0.018	0.003	-0.02	0.0027	-0.022	8E-9

SUPPLEMENTARY DATA

rs17207196	7:75101065	[POM121C]	C	T	-0.0009	0.87	0.0037	0.29	-0.009	0.077	0.007	0.1	0.0096	0.189	0.011	0.0002
rs7903146	10:114758349	[TCF7L2]	C	T	-0.0022	0.66	-0.001	0.51	0.0033	0.78	0.004	0.4	-0.01	0.038	0.014	5E-6
rs9435341	1:107616641	PRMT6--[]--NTNG1	T	C	0.0106	0.026	0.0018	0.34	-0.009	0.04	0.025	3E-8	0.005	0.286	0.006	0.027
rs632057	6:139834012	CITED2---[]	G	T	0.0203	1E-5	-0.0014	0.25	0.024	5E-7	0.001	0.77	-0.023	9E-6	-0.006	0.026
rs10779835	1:230299949	[GALNT2]	T	C	0.0078	0.085	0.0011	0.65	-0.043	6E-20	4E-4	0.9	0.036	1E-13	-9E-4	0.748
rs8074454	17:3981148	[ZZEF1]	C	G	-0.0058	0.23	-0.0052	0.006	-0.009	0.07	0.005	0.3	6E-4	0.97	-0.0016	0.57
rs9538162	13:59265043	PCDH17---[]---DIAPH3	T	C	0.001	0.82	-0.0047	0.031	0.009	0.14	0.005	0.2	-0.0045	0.24	-0.0025	0.36
rs11045172	12:20470221	AEBP2---[]--PDE3A	C	A	0.0365	5E-8	-0.007	0.007	0.029	3E-6	0.007	0.3	-0.019	0.0033	-0.003	0.39
rs11096549	2:16607101	MYCN---[]---FAM49A	T	C	0.0017	0.7	-0.002	0.2	-0.006	0.19	0.012	0.01	0.006	0.2	0.011	0.0002
rs7621025	3:136272246	[STAG1]	C	T	-0.0035	0.49	0.0065	0.0003	-0.026	4E-6	-0.023	1E-5	0.026	1E-6	0.0044	0.16
rs6752378	2:25150116	ADCY3-[]--DNAJC27	A	C	0.0082	0.07	0.0027	0.6	-0.011	0.03	0.006	0.17	0.002	0.89	-0.0037	0.16
rs2298117	10:70346740	[TET1]	T	C	-0.0043	0.35	-0.0012	0.49	-0.008	0.11	-0.009	0.04	0.01	0.027	0.01	0.0002
rs79011	22:41866938	[ACO2]	A	G	0.0085	0.12	0.0057	0.001	0.002	0.89	0.009	0.08	7E-4	0.83	-0.0025	0.44

SUPPLEMENTARY DATA

Supplementary Table 5. The association of "favourable adiposity" polygenic score with measures of adiposity and biomarkers from independent studies. The effects are in SD. P: p-value; N: total sample size; Adipo: adiponectin; ALT: alanine transaminase; BF%: body fat percentage; HDL: HDL-cholesterol; TG: triglycerides.

		NEO			EXTEND			GenScotland			TUF			DIRECT			Meta-analysis			
	Trait	Beta	P	N	Beta	P	N	Beta	P	N	Beta	P	N	Beta	P	N	Beta	SE	P	N
14 SNPs	BF %	0.014	7E-4	5714	0.015	0.002	6792	0.012	2E-6	19431	0.034	3E-5	2483	NA	NA	NA	0.02	0.002	1E-13	34420
	BMI	0.012	0.04	5744	0.007	0.2	7330	0.001	0.8	19270	0.04	7E-6	2604	0.02	0.001	2705	0.01	0.002	4E-4	37653
	ALT	-0.01	0.12	5731	-0.011	0.05	5800	NA	NA	NA	-0.02	0.09	1755	NA	NA	NA	-0.01	0.003	0.003	13286
	TG	-0.03	8E-8	5727	-0.03	3E-5	4803	NA	NA	NA	-0.02	0.05	2526	NA	NA	NA	-0.03	0.004	5E-12	13056
	HDL	0.03	5E-8	5727	0.023	2E-5	5792	0.022	4E-17	18770	0.015	7E-2	2509	NA	NA	NA	0.02	0.002	6E-28	32798
	Adipo	0.03	1E-10	5718	NA	NA	NA	NA	NA	NA	0.008	0.5	1240	NA	NA	NA	0.03	0.005	5E-10	6958
	Fasting insulin	-0.01	0.01	5731	NA	NA	NA	NA	NA	NA	-0.01	0.08	2590	NA	NA	NA	-0.01	0.004	0.003	8321
7 "additional" SNPs	BF %	0.01	0.16	5714	0.007	0.3	6792	0.008	0.1	19431	0.02	0.08	2513	NA	NA	NA	0.01	0.003	0.005	34450
	BMI	0.01	0.13	5744	0.001	0.9	7330	-0.004	0.4	19270	0.04	0.002	2639	0.02	0.041	2705	0.01	0.003	0.1	37688
	ALT	-0.001	0.87	5731	-0.02	0.02	5800	NA	NA	NA	-0.01	0.6	1784	NA	NA	NA	-0.01	0.005	0.06	13315
	TG	-0.04	4E-6	5727	-0.04	1E-6	4803	NA	NA	NA	-0.03	0.008	2561	NA	NA	NA	-0.04	0.005	9E-13	13091
	HDL	0.03	2E-4	5727	0.028	2E-4	5792	0.027	2E-8	18770	0.02	0.06	2544	NA	NA	NA	0.03	0.003	2E-15	32833
	Adipo	0.02	8E-3	5718	NA	NA	NA	NA	NA	NA	0.004	0.8	1253	NA	NA	NA	0.02	0.007	0.01	6971
	Fasting insulin	0.001	0.9	5731	NA	NA	NA	NA	NA	NA	-0.01	0.5	2625	NA	NA	NA	-0.003	0.007	0.6	8356

SUPPLEMENTARY DATA

Supplementary Table 6. The association of "favourable adiposity" polygenic score and individual variants with body fat % and disease outcomes from published GWAS studies. SE: standard error; P: p-value.

Outcome	Analysis	Exposure	Effect	SE	P	Reference
Body fat %	All	14 SNPs	0.16 %	0.001	1x10 ⁻⁴³	Lu et al, Nature communication, 2011
Type 2 diabetes	All	14 SNPs	0.96 OR	0.004	7x10 ⁻²¹	Mahajan et al, Nature genetics, 2014
Heart disease	All	14 SNPs	0.98 OR	0.003	2x10 ⁻¹⁵	Nikpey et al, Nature genetics, 2015
Systolic blood pressure	All	14 SNPs	-0.15 mmHg	0.02	3x10 ⁻¹⁵	Wain et al, Hypertension, 2017
Diastolic blood	All	14 SNPs	-0.08 mmHg	0.01	3x10 ⁻¹²	Wain et al, Hypertension, 2017
Body fat %	All	7 "additional" SNPs	0.14%	0.002	5x10 ⁻¹⁶	Lu et al, Nature communication, 2011
Type 2 diabetes	All	7 "additional" SNPs	0.98 OR	0.006	2x10 ⁻⁴	Mahajan et al, Nature genetics, 2014
Heart disease	All	7 "additional" SNPs	0.98 OR	0.004	3x10 ⁻⁸	Nikpey et al, Nature genetics, 2015
Systolic blood pressure	All	7 "additional" SNPs	-0.14 mmHg	0.02	2x10 ⁻⁷	Wain et al, Hypertension, 2017
Diastolic blood	All	7 "additional" SNPs	-0.08 mmHg	0.02	1.5x10 ⁻⁶	Wain et al, Hypertension, 2017
Type 2 diabetes	All	AEBP2---[]--PDE3A	0.97 OR	0.02	0.2	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	LYPLAL1---[]---SLC30A10	0.97 OR	0.02	0.033	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	GRB14---[]--COBLL1	0.93 OR	0.01	8E-7	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	[PPARG]	0.88 OR	0.02	5.7E-10	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	[MAFF]	1 OR	0.01	0.76	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	[FAM13A]	0.98 OR	0.01	0.095	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	NYAP2---[]---IRS1	0.92 OR	0.02	0.000000024	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	TRIB1---[]	1.01 OR	0.02	0.62	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	ANKRD55---[]---MAP3K1	0.95 OR	0.02	0.00052	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	CITED2---[]	0.99 OR	0.01	0.42	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	[DNAH10]	0.95 OR	0.02	0.0073	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	[PEPD]	0.96 OR	0.02	0.0057	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	KLF14---[]---MKLN1	0.95 OR	0.02	0.00045	Mahajan et al, Nature genetics, 2014
Type 2 diabetes	All	VEGFA---[]---C6orf223	0.97 OR	0.02	0.1	Mahajan et al, Nature genetics, 2014
Heart disease	All	AEBP2---[]--PDE3A	1 OR	0.01	0.9766445	Nikpey et al, Nature genetics, 2015
Heart disease	All	LYPLAL1---[]---SLC30A10	0.99 OR	0.01	0.306953	Nikpey et al, Nature genetics, 2015
Heart disease	All	GRB14---[]--COBLL1	0.97 OR	0.01	0.0187829	Nikpey et al, Nature genetics, 2015
Heart disease	All	[PPARG]	0.998 OR	0.01	0.9364154	Nikpey et al, Nature genetics, 2015
Heart disease	All	[MAFF]	0.998 OR	0.01	0.85394	Nikpey et al, Nature genetics, 2015
Heart disease	All	[FAM13A]	0.98 OR	0.01	0.0500724	Nikpey et al, Nature genetics, 2015
Heart disease	All	NYAP2---[]---IRS1	0.96 OR	0.01	0.000053	Nikpey et al, Nature genetics, 2015
Heart disease	All	TRIB1---[]	0.96 OR	0.01	0.0000666	Nikpey et al, Nature genetics, 2015
Heart disease	All	ANKRD55---[]---MAP3K1	0.98 OR	0.01	0.0745602	Nikpey et al, Nature genetics, 2015
Heart disease	All	CITED2---[]	0.99 OR	0.01	0.1972927	Nikpey et al, Nature genetics, 2015
Heart disease	All	[DNAH10]	0.97 OR	0.01	0.0059085	Nikpey et al, Nature genetics, 2015
Heart disease	All	[PEPD]	0.97 OR	0.01	0.0011167	Nikpey et al, Nature genetics, 2015
Heart disease	All	KLF14---[]---MKLN1	0.98 OR	0.01	0.0282587	Nikpey et al, Nature genetics, 2015

SUPPLEMENTARY DATA

Heart disease	All	VEGFA-[]---C6orf223	0.96 OR	0.01	0.0000221	Nikpey et al, Nature genetics, 2015
Systolic blood pressure	All	AEBP2---[]--PDE3A	-0.007 mmHg	0.08	0.92708814	Wain et al, Hypertension, 2017
Systolic blood pressure	All	LYPLAL1---[]---SLC30A10	-0.193 mmHg	0.07	0.003606794	Wain et al, Hypertension, 2017
Systolic blood pressure	All	GRB14---[]---COBLL1	-0.171 mmHg	0.07	0.008912066	Wain et al, Hypertension, 2017
Systolic blood pressure	All	[PPARG]	0.017 mmHg	0.09	0.854389408	Wain et al, Hypertension, 2017
Systolic blood pressure	All	[MAFF]	0.049 mmHg	0.07	0.454212446	Wain et al, Hypertension, 2017
Systolic blood pressure	All	[FAM13A]	-0.132 mmHg	0.06	0.040574444	Wain et al, Hypertension, 2017
Systolic blood pressure	All	NYAP2---[]---IRS1	-0.312 mmHg	0.07	3.96244E-06	Wain et al, Hypertension, 2017
Systolic blood pressure	All	TRIB1---[]	-0.111 mmHg	0.07	0.129211778	Wain et al, Hypertension, 2017
Systolic blood pressure	All	ANKRD55---[]---MAP3K1	-0.12 mmHg	0.07	0.103187472	Wain et al, Hypertension, 2017
Systolic blood pressure	All	CITED2---[]	-0.22 mmHg	0.07	0.000981594	Wain et al, Hypertension, 2017
Systolic blood pressure	All	[DNAH10]	-0.19 mmHg	0.07	0.007897604	Wain et al, Hypertension, 2017
Systolic blood pressure	All	[PEPD]	-0.099 mmHg	0.06	0.118136956	Wain et al, Hypertension, 2017
Systolic blood pressure	All	KLF14---[]---MKLN1	-0.253 mmHg	0.07	0.000108203	Wain et al, Hypertension, 2017
Systolic blood pressure	All	VEGFA-[]---C6orf223	-0.201 mmHg	0.07	0.005721477	Wain et al, Hypertension, 2017
Diastolic blood	All	AEBP2---[]--PDE3A	-0.053 mmHg	0.05	0.278393597	Wain et al, Hypertension, 2017
Diastolic blood	All	LYPLAL1---[]---SLC30A10	-0.056 mmHg	0.04	0.173513933	Wain et al, Hypertension, 2017
Diastolic blood	All	GRB14---[]---COBLL1	-0.096 mmHg	0.04	0.017430699	Wain et al, Hypertension, 2017
Diastolic blood	All	[PPARG]	0.066 mmHg	0.06	0.257194407	Wain et al, Hypertension, 2017
Diastolic blood	All	[MAFF]	0.025 mmHg	0.04	0.543799397	Wain et al, Hypertension, 2017
Diastolic blood	All	[FAM13A]	-0.116 mmHg	0.04	0.003577279	Wain et al, Hypertension, 2017
Diastolic blood	All	NYAP2---[]---IRS1	-0.148 mmHg	0.04	0.000360846	Wain et al, Hypertension, 2017
Diastolic blood	All	TRIB1---[]	-0.061 mmHg	0.04	0.171755508	Wain et al, Hypertension, 2017
Diastolic blood	All	ANKRD55---[]---MAP3K1	-0.046 mmHg	0.05	0.309485295	Wain et al, Hypertension, 2017
Diastolic blood	All	CITED2---[]	-0.122 mmHg	0.04	0.002630972	Wain et al, Hypertension, 2017
Diastolic blood	All	[DNAH10]	-0.096 mmHg	0.04	0.02527869	Wain et al, Hypertension, 2017
Diastolic blood	All	[PEPD]	-0.091 mmHg	0.04	0.019628177	Wain et al, Hypertension, 2017
Diastolic blood	All	KLF14---[]---MKLN1	-0.083 mmHg	0.04	0.039865517	Wain et al, Hypertension, 2017
Diastolic blood	All	VEGFA-[]---C6orf223	-0.164 mmHg	0.04	0.000264132	Wain et al, Hypertension, 2017

SUPPLEMENTARY DATA

Supplementary Table 7. The association of "favourable adiposity" polygenic score with measures fat distribution.

Cohort	Trait/disease	Analysis	14 SNPs			7 “additional” SNPs			N
			Beta (SD)	Se	p-value	Beta (SD)	Se	p-value	
UKB	WHR-BMIadj	ALL	-0.0180	0.0006	8.44E-191	-0.0238	0.0009	2.68E-170	449216
		Women	-0.0020	0.0000	<E-300	-0.0023	0.0001	2.36E-272	243742
		Men	0.0001	0.0009	0.9	-0.0051	0.0012	2.88E-05	205474
	Hip circumference-BMIadj	ALL	0.0152	0.0006	1.59E-161	0.0164	0.0008	9.45E-96	450276
		Women	0.0171	0.0008	3.52E-109	0.0180	0.0011	8.07E-62	244400
		Men	0.0130	0.0008	1.80E-53	0.0145	0.0012	2.00E-34	205876
	Waist circumference-	ALL	0.0029	0.0005	5.93E-09	0.0011	0.0007	1.03E-01	450323
		Women	-0.0032	0.0008	3.70E-05	-0.0056	0.0011	2.41E-07	244415
		Men	0.0113	0.0008	1.67E-40	0.0098	0.0012	8.32E-17	205908
Published	WHR-BMIadj	All	-0.0128	0.0010	3.03E-34	-0.0174	0.0015	1.05E-31	230000
		Women	-0.0234	0.0014	8.86E-66	-0.0266	0.0019	1.15E-42	230000
		Men	0.0012	0.0015	0.4	-0.0046	0.0022	0.03	230000
	Hip circumference-BMIadj	All	0.0125	0.0011	1.56E-30	0.0122	0.0015	2.56E-15	230000
		Women	0.0158	0.0014	7.48E-30	0.0155	0.0020	4.25E-15	230000
		Men	0.0086	0.0016	6.21E-08	0.0078	0.0022	0.00046	230000
	Waist circumference-	All	-0.0032	0.0010	0.002	-0.0076	0.0015	2.99E-07	230000
		Women	-0.0131	0.0013	4.54E-23	-0.0161	0.0019	1.68E-17	230000
		Men	0.0091	0.0015	9.22E-10	0.0030	0.0021	0.15	230000

SUPPLEMENTARY DATA

Supplementary Table 8. The association of "favourable adiposity" genetic variants with measures of abdominal fat distribution from MRI/CT scans. SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; LCI: lower confidence interval; UCI: upper confidence interval; P: p-value.

Locus	Analysis	SAT				VAT				VATSAT ratio				Liver fat			
		BETA (SD)	LCI	UCI	P	BETA (SD)	LCI	UCI	P	BETA (SD)	LCI	UCI	P	BETA (SD)	LCI	UCI	P
AEBP2---[]--PDE3A	All	0.016	-0.001	0.033	0.06	0.007	-0.01	0.024	0.4	-0.013	-0.028	0.002	0.098	0.013	-0.023	0.049	0.47
ANKRD55---[]--MAP3K	All	0.005	-0.012	0.021	0.6	0.027	0.011	0.043	0.001	0.026	0.011	0.041	0.001	0.001	-0.031	0.034	0.94
CITED2---[]	All	0.005	-0.011	0.021	0.5	-0.013	-0.029	0.002	0.098	-0.025	-0.039	-0.011	0.001	-0.027	-0.057	0.002	0.065
[DNAH10]	All	0.017	0	0.034	0.05	-0.012	-0.028	0.005	0.2	-0.031	-0.046	-0.016	5E-5	-0.027	-0.061	0.007	0.13
[FAM13A]	All	0.023	0.007	0.039	0.004	-0.004	-0.019	0.012	0.65	-0.028	-0.042	-0.014	9E-5	-0.009	-0.037	0.02	0.55
GRB14---[]--COBLL1	All	0.022	0.007	0.038	0.006	0.008	-0.007	0.024	0.3	-0.014	-0.028	0	0.05	-0.052	-0.081	-0.022	0.001
KLF14---[]---MKLN1	All	0.024	0.007	0.04	0.005	0.004	-0.012	0.02	0.64	-0.02	-0.035	-0.005	0.007	-0.021	-0.053	0.012	0.2
LYPLAL1---[]--SLC30	All	0.021	0.005	0.037	0.01	-0.007	-0.023	0.008	0.36	-0.027	-0.041	-0.013	0.0002	0.008	-0.021	0.037	0.6
[MAFF]	All	0.019	0.003	0.035	0.02	0.022	0.006	0.037	0.007	0.003	-0.011	0.017	0.64	-0.012	-0.043	0.018	0.44
NYAP2---[]---IRS1	All	0.021	0.005	0.037	0.01	-0.004	-0.02	0.012	0.6	-0.029	-0.043	-0.014	8E-5	-0.034	-0.064	-0.004	0.026
[PEPD]	All	0.007	-0.009	0.023	0.4	0.019	0.004	0.034	0.015	0.016	0.002	0.03	0.02	-0.011	-0.04	0.017	0.43
[PPARG]	All	0.026	0.009	0.044	0.004	-0.003	-0.021	0.014	0.7	-0.028	-0.045	-0.012	0.001	-0.064	-0.106	-0.022	0.003
TRIB1---[]	All	0.013	-0.003	0.029	0.12	-0.012	-0.028	0.004	0.14	-0.023	-0.038	-0.009	0.002	-0.072	-0.103	-0.04	8E-6
VEGFA---[]---C6orf223	All	0.013	-0.003	0.029	0.1	-0.004	-0.02	0.011	0.6	-0.021	-0.035	-0.007	0.003	-0.012	-0.033	0.008	0.24
AEBP2---[]--PDE3A	Men	0.013	-0.005	0.031	0.145	0.01	-0.008	0.028	0.278	-0.004	-0.021	0.013	0.638	0.011	-0.036	0.058	0.648
ANKRD55---[]--MAP3K	Men	0.002	-0.015	0.02	0.8	0.018	0.001	0.036	0.042	0.021	0.005	0.038	0.012	0.036	-0.007	0.079	0.102
CITED2---[]	Men	0.002	-0.016	0.019	0.845	-0.006	-0.023	0.011	0.489	-0.011	-0.028	0.005	0.162	-0.005	-0.044	0.033	0.789
[DNAH10]	Men	0.007	-0.011	0.025	0.44	-0.016	-0.034	0.002	0.074	-0.024	-0.041	-0.008	0.004	-0.01	-0.056	0.035	0.651

SUPPLEMENTARY DATA

[FAM13A]	Men	0.008	-0.009	0.025	0.348	-0.01	-0.027	0.008	0.274	-0.015	-0.031	0.001	0.062	0.007	-0.03	0.045	0.703
GRB14--[]---COBLL1	Men	0.029	0.012	0.046	0.001	0.012	-0.005	0.03	0.161	-0.014	-0.03	0.002	0.088	-0.033	-0.071	0.005	0.09
KLF14--[]---MKLN1	Men	0.019	0.002	0.037	0.031	0.011	-0.007	0.029	0.227	-0.011	-0.027	0.006	0.204	-0.009	-0.052	0.033	0.669
LYPLAL1--[]---SLC30	Men	0.026	0.009	0.043	0.003	0.008	-0.009	0.025	0.376	-0.02	-0.036	-0.004	0.014	0.026	-0.012	0.064	0.184
[MAFF]	Men	0.02	0.003	0.037	0.022	0.023	0.006	0.04	0.009	0.005	-0.011	0.021	0.544	-0.006	-0.044	0.032	0.74
NYAP2--[]---IRS1	Men	0.025	0.008	0.042	0.005	-0.004	-0.021	0.013	0.658	-0.036	-0.052	-0.02	1E-5	-0.002	-0.042	0.037	0.916
[PEPD]	Men	0.001	-0.016	0.018	0.897	0.018	0.001	0.035	0.04	0.02	0.004	0.036	0.015	0.004	-0.033	0.041	0.844
[PPARG]	Men	0.032	0.014	0.051	0.001	0.009	-0.009	0.028	0.311	-0.023	-0.041	-0.006	0.01	-0.054	-0.109	0	0.051
TRIB1--[]	Men	0.018	0.001	0.036	0.04	-0.005	-0.023	0.012	0.558	-0.019	-0.035	-0.002	0.024	-0.091	-0.132	-0.05	2E-5
VEGFA--[]---C6orf223	Men	0.019	0.002	0.036	0.031	-0.003	-0.02	0.014	0.708	-0.03	-0.045	-0.014	0.0003	-0.001	-0.038	0.036	0.958
AEBP2--[]---PDE3A	Women	0.011	-0.008	0.029	0.256	-0.001	-0.019	0.017	0.907	-0.019	-0.036	-0.002	0.029	0.015	-0.039	0.069	0.584
ANKRD55--[]---MAP3K	Women	0	-0.018	0.018	0.99	0.018	0	0.035	0.05	0.019	0.002	0.036	0.025	-0.033	-0.083	0.016	0.186
CITED2--[]	Women	0.007	-0.01	0.025	0.423	-0.015	-0.032	0.002	0.089	-0.029	-0.045	-0.013	0.0004	-0.05	-0.094	-0.006	0.026
[DNAH10]	Women	0.021	0.003	0.04	0.021	-0.002	-0.02	0.015	0.782	-0.029	-0.045	-0.012	0.001	-0.054	-0.105	-0.003	0.037
[FAM13A]	Women	0.026	0.008	0.044	0.004	-0.001	-0.018	0.016	0.921	-0.034	-0.05	-0.018	3E-5	-0.031	-0.074	0.012	0.153
GRB14--[]---COBLL1	Women	0.008	-0.009	0.026	0.351	0	-0.017	0.018	0.967	-0.011	-0.027	0.005	0.177	-0.07	-0.114	-0.025	0.002
KLF14--[]---MKLN1	Women	0.017	-0.001	0.035	0.068	-0.007	-0.024	0.011	0.446	-0.024	-0.041	-0.008	0.004	-0.017	-0.065	0.031	0.483
LYPLAL1--[]---SLC30	Women	0.007	-0.011	0.024	0.459	-0.022	-0.039	-0.005	0.011	-0.026	-0.042	-0.01	0.001	-0.01	-0.054	0.034	0.649
[MAFF]	Women	0.007	-0.011	0.024	0.465	0.01	-0.007	0.027	0.264	0	-0.016	0.016	0.98	-0.014	-0.058	0.03	0.546
NYAP2--[]---IRS1	Women	0.011	-0.007	0.029	0.238	-0.002	-0.019	0.015	0.81	-0.012	-0.028	0.004	0.145	-0.068	-0.114	-0.023	0.003
[PEPD]	Women	0.01	-0.008	0.027	0.277	0.011	-0.006	0.028	0.192	0.005	-0.01	0.021	0.507	-0.026	-0.068	0.016	0.233
[PPARG]	Women	0.004	-0.014	0.023	0.644	-0.013	-0.031	0.005	0.163	-0.019	-0.037	-0.001	0.034	-0.074	-0.138	-0.009	0.026
TRIB1--[]	Women	0.003	-0.015	0.021	0.711	-0.012	-0.029	0.006	0.183	-0.017	-0.033	0	0.047	-0.051	-0.099	-0.004	0.033
VEGFA--[]---C6orf223	Women	0.002	-0.016	0.02	0.831	-0.001	-0.018	0.016	0.921	-0.003	-0.019	0.013	0.743	-0.034	-0.077	0.009	0.119

SUPPLEMENTARY DATA

Supplementary Table 9. The sensitivity analysis of the association of "favourable adiposity" polygenic score with liver fat in pre and post menopausal women.

		UK Biobank				TUF				Meta-analysis				
Group	Genetic score	Beta (SD)	Se	p-value	N	Beta (SD)	Se	p-value	N	Beta %	Se	p-value	N	Pdifference
Pre	14 SNPs	-0.054	0.026	0.04	245	-0.059	0.025	0.018	188	-0.258	0.018	0.002	433	0.144
Post		-0.030	0.010	0.0018	1998	-0.010	0.022	0.6	358	-0.124	0.009	0.002	2356	
Pre	7 "additional" SNPs	-0.048	0.039	0.22	245	-0.076	0.035	0.03	188	-0.294	0.026	0.015	433	0.152
Post		-0.028	0.013	0.029	1998	0.013	0.033	0.7	358	-0.106	0.012	0.06	2356	

Supplementary Table 10. The sensitivity analysis of the association of "favourable adiposity" polygenic score with liver fat excluding people with type 2 diabetes (T2D) from the analysis.

			Including people with T2D				Excluding people with T2D				
Genetic score	Analysis	Unit	Beta	Se	p-value	N	Beta	Se	p-value	N	Pdifference
14 SNPs	All	SD	-0.09936	0.0056	0.0002	5045	-0.08832	0.0057	0.0007	4823	0.764
	Women	SD	-0.18492	0.0082	0.000001	2648	-0.16422	0.0082	0.00002	2559	0.698
	Men	SD	0.00506	0.0076	0.88	2397	0.00276	0.0077	0.94	2264	0.963
7 "additional" SNPs	All	SD	-0.10258	0.0078	0.004	5045	-0.11362	0.0079	0.0017	4823	0.829
	Women	SD	-0.1633	0.0113	0.0012	2648	-0.15916	0.0113	0.002	2559	0.955
	Men	SD	-0.02898	0.0107	0.55	2397	-0.05106	0.0109	0.3	2264	0.753

SUPPLEMENTARY DATA

Supplementary Table 11. The sensitivity analysis of the association of "favourable adiposity" polygenic score with liver fat in non-drinkers, moderate drinkers and heavy drinkers. LCI: lower confidence interval; UCI: upper confidence interval; P: pvalue.

Group	MEN					WOMEN				
	Beta	LCI	UCI	P	N	Beta	LCI	UCI	P	N
Heavy drinkers	-0.0035	-0.0222	0.0152	0.7	1,198	-0.0497	-0.0827	-0.0166	0.003	579
Moderate drinkers	-0.0048	-0.0192	0.0095	0.5	2,658	-0.0406	-0.0548	-0.0265	2E-8	3,205
Non-drinkers	0.0448	-0.0237	0.1133	0.2	146	-0.0084	-0.0649	0.0480	0.769	253

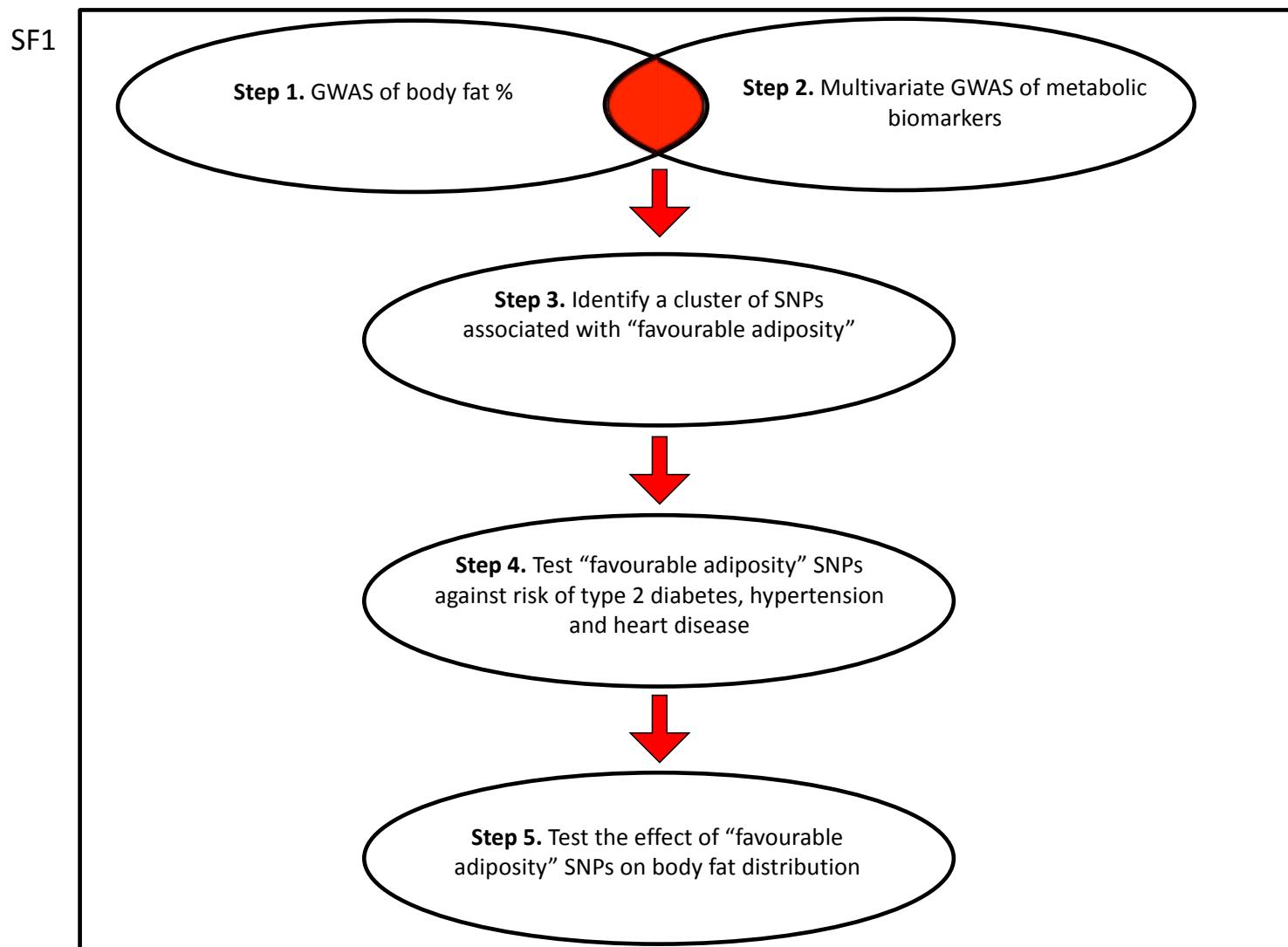
SUPPLEMENTARY DATA

Supplementary Table 12. Inclusion of adiponectin, SHBG and ALT in the multivariate analysis increases the power of metaCCA to detect "favourable adiposity" variants.

RSID	Gene context	Metacca p-value (7 traits)	MetaCCA p-value (excluding adiponectin, SHBG and ALT)	MetaCCA p-value (excluding adiponectin and SHBG)
rs2943653	NYAP2---[]---IRS1	2E-43	7E-22	3E-32
rs13389219	GRB14--[]--COBLL1	5E-41	4E-21	3E-26
rs2980888	TRIB1--[]	1E-35	2E-33	6E-21
rs11118306	LYPLAL1---[]---SLC30A10	3E-21	9E-13	3E-13
rs2276936	[FAM13A]	3E-20	9E-9	5E-14
rs972283	KLF14--[]---MKLN1	1E-19	9E-13	1E-26
rs7133378	[DNAH10]	2E-17	1E-6	4E-13
rs2267373	[MAFF]	8E-14	1E-11	3E-8
rs40271	ANKRD55---[]---MAP3K1	1E-12	1E-9	1E-8
rs7258937	[PEPD]	5E-12	0.0002	4E-7
rs998584	VEGFA---[]---C6orf223	5E-11	0.0002	2E-6
rs1801282	[PPARG]	2E-10	3E-5	3E-7
rs632057	CITED2---[]	3E-10	1E-5	8E-9
rs11045172	AEBP2---[]---PDE3A	4E-9	4E-6	0.008

SUPPLEMENTARY DATA

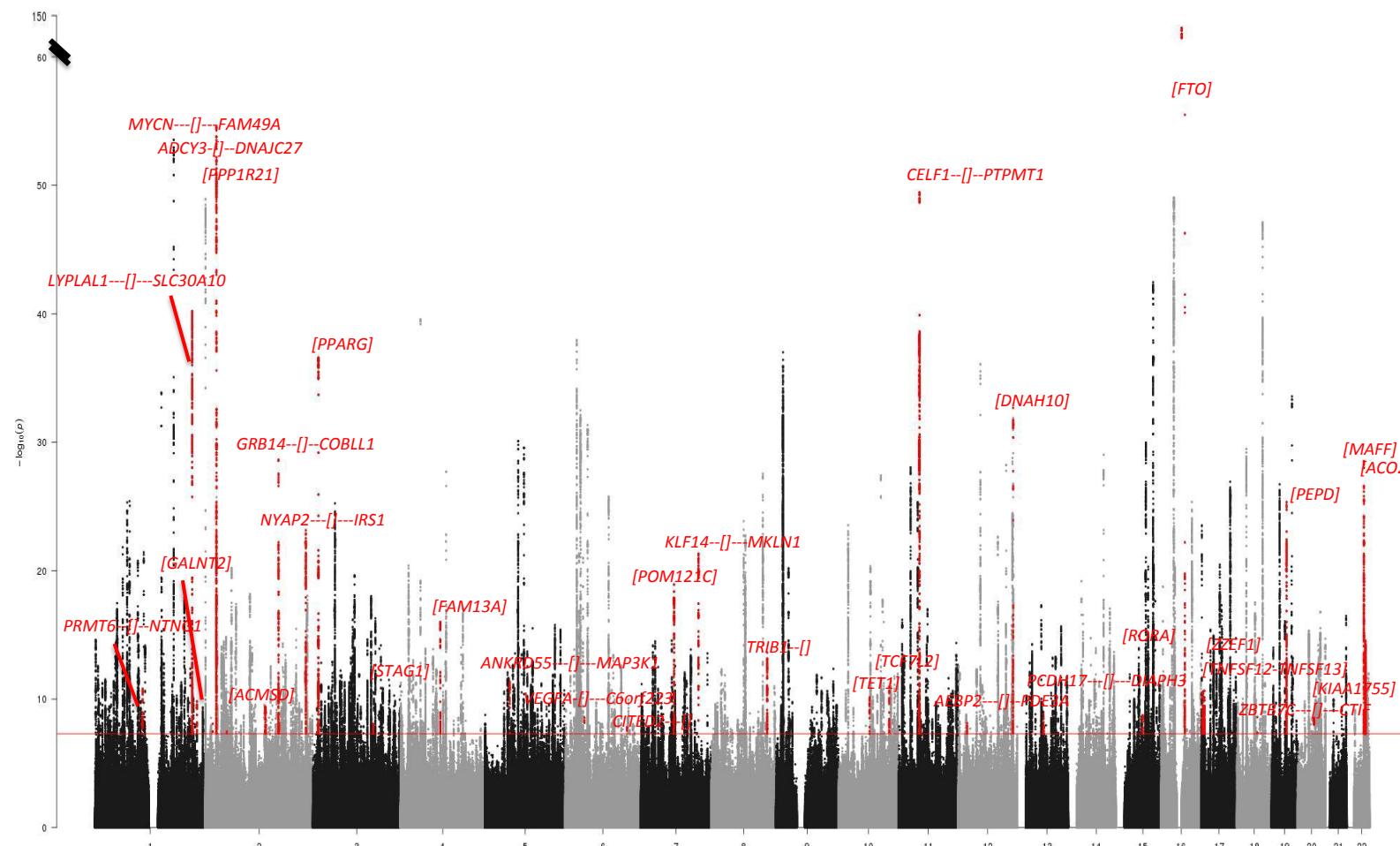
Supplementary Figure 1. Study design.



SUPPLEMENTARY DATA

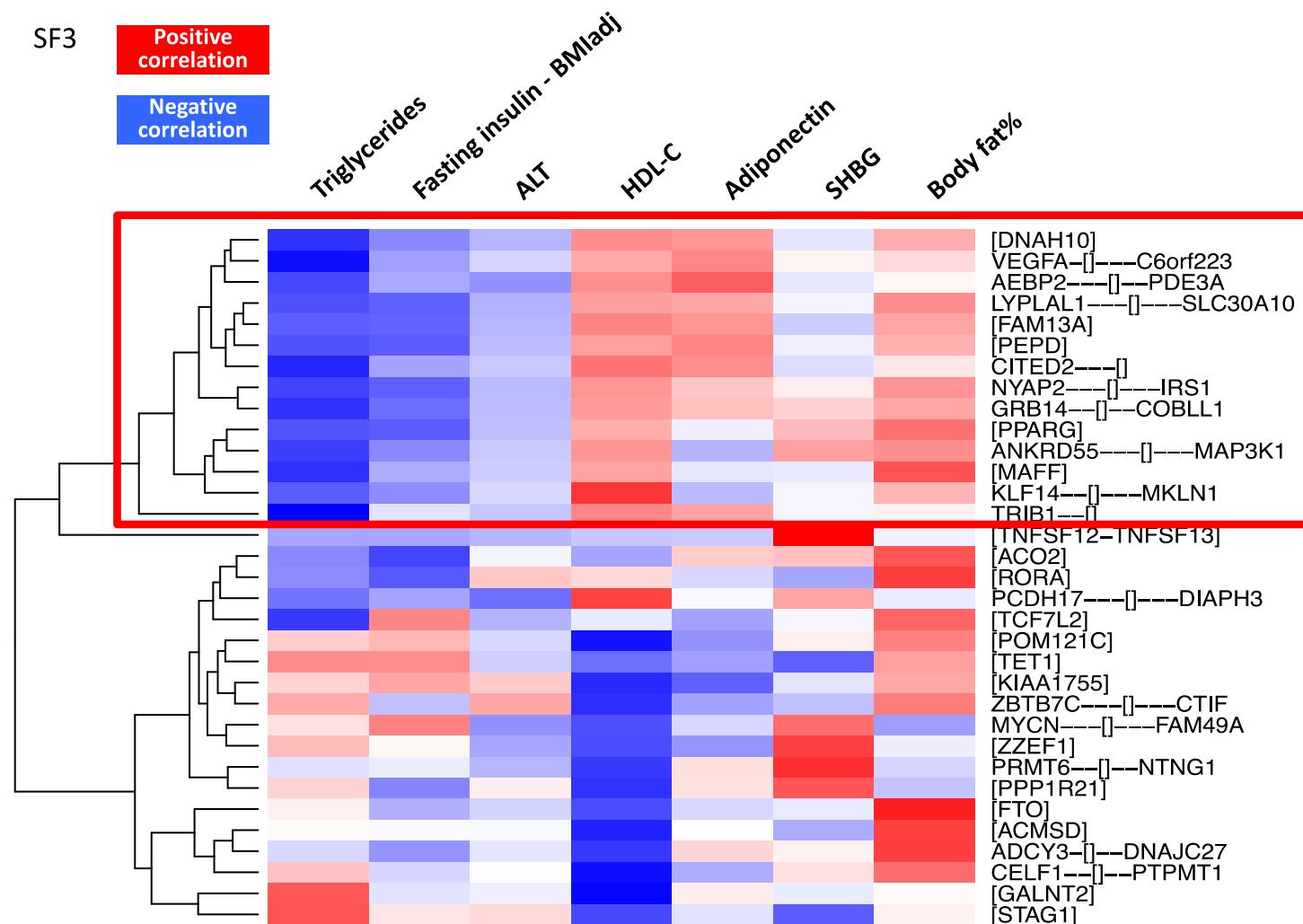
Supplementary Figure 2. Manhattan plot of variants associated with a Bio-impedance measures of body fat % in UK Biobank study.

SF2



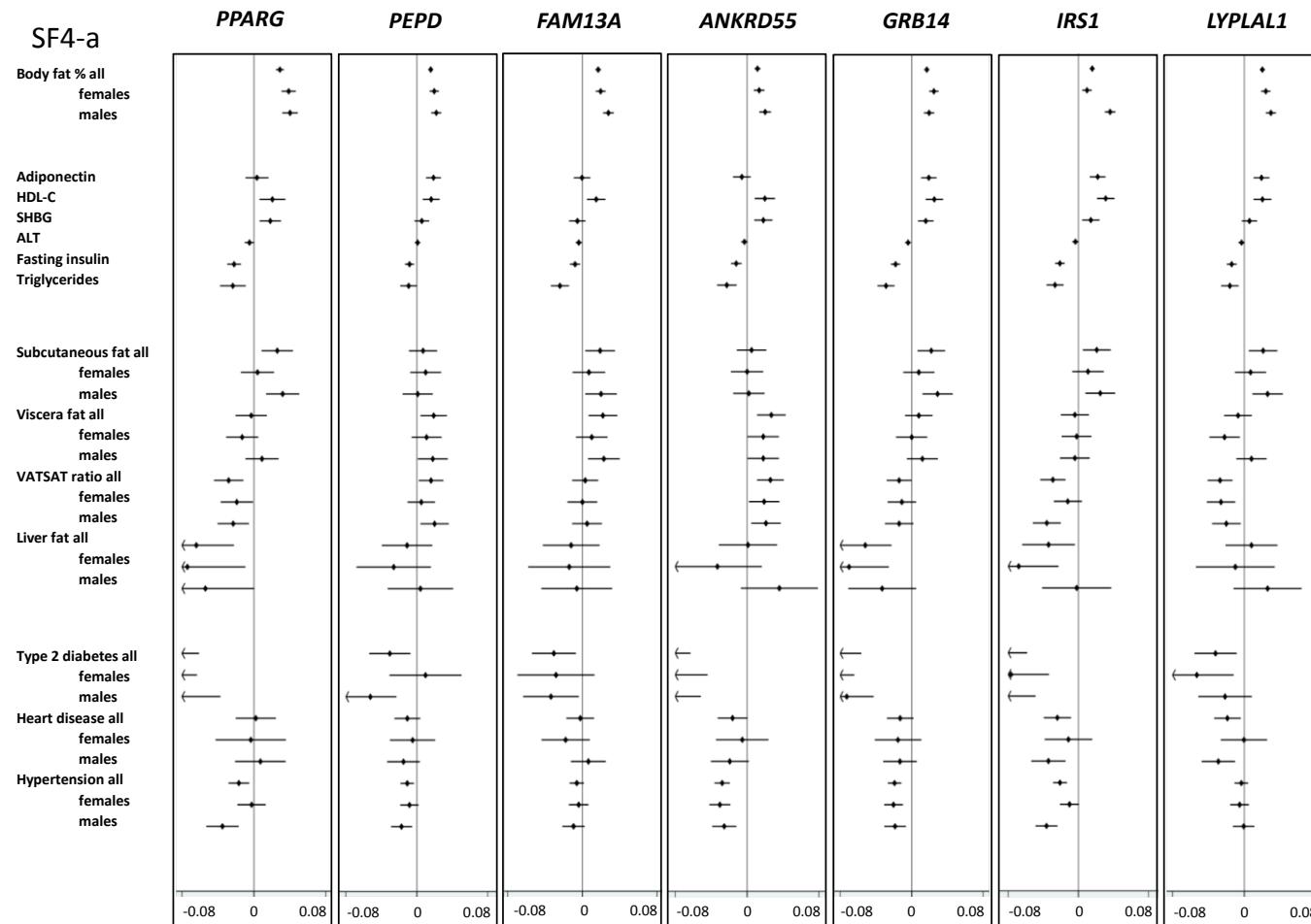
SUPPLEMENTARY DATA

Supplementary Figure 3. We use hierarchical clustering approach to narrow down the list to ones showing a pattern of “favourable adiposity”: alleles associated with higher body fat % being generally correlated with higher HDL-C, higher SHBG, higher adiponectin, lower fasting insulin, lower triglycerides and lower alanine transaminase. The red box illustrates the “favourable adiposity” variants which cluster together 94% of the time.



SUPPLEMENTARY DATA

Supplementary Figure 4. The effect of 7 previously known “favourable adiposity” variants (a) and 7 “additional” variants (b) on body fat % (data from UK Biobank), metabolic biomarkers (data from published GWASs), measures of abdominal adipose tissue (data from meta-analysis of 5 studies) and cardiometabolic disease outcome (data from UK Biobank). The x-axis is the effect size for “favourable adiposity” allele. The effect sizes are in SD for body fat % and measures of abdominal fat, log transformed for adiponectin, HDL, Triglycerides, alanine transaminase (ALT) and fasting insulin, nmol/L for sex hormone binding globulin (SHBG) and log(OR) for disease outcomes.



SUPPLEMENTARY DATA

