SUPPLEMENTARY DATA

Supplementary Table 1. Nineteen independent genetic variants associated with fasting insulin as reported in the most recent Meta-Analysis of Glucose and Insulin Consortium (MAGIC) genome wide association study (1).

variant	Chr	Position	Gene	Alleles (effect/other)	EAF
rs10195252	2	165221337	*GRB14*	T/C	0.6
rs1167800	7	75014132	*HIP1*	A/G	0.54
rs1421085	16	52358455	*FTO*	C/T	0.42
rs1530559	2	135472099	*YSK4*	A/G	0.52
rs17036328	3	12365484	*PPARG*	T/C	0.86
rs2126259	8	9222556	*PPP1R3B*	T/C	0.11
rs2745353	6	127494628	*RSPO3*	T/C	0.51
rs2943645	2	226807424	*IRS1*	T/C	0.63
rs3822072	4	89960292	*FAM13A*	A/G	0.48
rs459193	5	55842508	*ANKRD55-MAP3K1*	G/A	0.73
rs4846565	1	217788727	*LYPLAL1*	G/A	0.67
rs4865796	5	53308421	*ARL15*	A/G	0.67
rs6822892	4	157954125	*PDGFC*	A/G	0.68
rs6912327	6	34872900	*UHRF1BP1*	T/C	0.8
rs731839	19	38590905	*PEPD*	G/A	0.34
rs7903146	10	114748339	*TCF7L2*	C/T	0.72
rs974801	4	106290513	*TET2*	G/A	0.38
rs780094	2	27594741	*GCKR*	C/T	0.61
rs35767	12	101399699	*IGF1*	G/A	0.82

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Supplementary Table 2. 32 variants associated with BMI from the Genetic Investigation of ANthropometric Traits (GIANT) consortium (2).

variant	Chr	Position	Gene	Alleles (effect/other)	EAF
rs2867125	2	612,827	*TMEM18*	C/T	0.83
rs571312	18	55,990,749	*MC4R*	A/C	0.24
rs10938397	4	44,877,284	*GNPDA2*	G/A	0.43
rs10767664	11	27,682,562	*BDNF*	A/T	0.78
rs2815752	1	72,585,028	*NEGR1*	A/G	0.61
rs7359397	16	28,793,160	*SH2B1*	T/C	0.4
rs9816226	3	187,317,193	*ETV5*	T/A	0.82
rs3817334	11	47,607,569	*MTCH2*	T/C	0.41
rs29941	19	39,001,372	*KCTD15*	G/A	0.67
rs543874	1	176,156,103	*SEC16B*	G/A	0.19
rs987237	6	50,911,009	*TFAP2B*	G/A	0.18
rs7138803	12	48,533,735	*FAIM2*	A/G	0.38
rs10150332	14	79,006,717	*NRXN3*	C/T	0.21
rs713586	2	25,011,512	*RBJ*	C/T	0.47
rs12444979	16	19,841,101	*GPRC5B*	C/T	0.87
rs2241423	15	65,873,892	*MAP2K5*	G/A	0.78
rs2287019	19	50,894,012	*QPCTL*	C/T	0.8
rs1514175	1	74,764,232	*TNNI3K*	A/G	0.43
rs13107325	4	103,407,732	*SLC39A8*	T/C	0.07
rs2112347	5	75,050,998	*FLJ35779*	T/G	0.63
rs10968576	9	28,404,339	*LRRN6C*	G/A	0.31
rs3810291	19	52,260,843	*TMEM160*	A/G	0.67
rs887912	2	59,156,381	*FANCL*	T/C	0.29
rs13078807	3	85,966,840	*CADM2*	G/A	0.2
rs11847697	14	29,584,863	*PRKD1*	T/C	0.04
rs2890652	2	142,676,401	*LRP1B*	C/T	0.18
rs1555543	1	96,717,385	*PTBP2*	C/A	0.59
rs4771122	13	26,918,180	*MTIF3*	G/A	0.24
rs4836133	5	124,360,002	*ZNF608*	A/C	0.48
rs4929949	11	8,561,169	*RPL27A*	C/T	0.52
rs206936	6	34,410,847	*NUDT3*	G/A	0.21

SUPPLEMENTARY DATA

Supplementary Table 3. Details of metabolic disease outcomes.

Metabolic disease outcomes	N studies	N individuals per study	Ethnicity	Covariates	Trait definition/measurement	Range of age mean across studies	Range of BMI mean across studies	REF (PMCID)
Type 2 diabetes	12	269-1,924 cases	European descent	Study-specific covariates, including indicators of population structure	Doctor diagnosed diabetes without insulin treatment in the first year and for most studies includes exclusion of individuals with GAD antibodies and monogenic forms of diabetes based on clinical criteria	44-68	26-31	PMC3442244
Coronary artery disease	14	278- 6640 cases	European descent	sex and age	1 artery with >50% stenosis in angiography, MI based on ECG and enzymes, PTCA or CABG	42-75	27-32	PMC3679547
Systolic and diastolic blood pressure	29	562-8096	European descent	age, age2, sex, BMI and other appropriate covariates (e.g. pc)	Blood pressure was measured using either an automated machine or a mercury column sphygmomanometer on upper arm with the subject in the sitting position after sitting quietly for 5 minutes, and the average of 2 measures was used for the analyses.	31-72	24-28	PMC3340926
cIMT	9	1,054-7,767	European descent	age, sex and other appropriate covariates (e.g. pc)	Summarized as the mean of the maximum of several measurements. For most studies, this was an average of multiple measurements from both the left and right arteries using high-resolution B-mode ultrasonography	43-76	25-29	PMC3257519
Carotid plaque	7	1,054-7,767	European descent	age, sex and other appropriate covariates (e.g. pc)	Either the presence of plaque or the proxy measure of stenosis >25% in carotid artery using high-resolution B-mode ultrasonography	43-76	25-29	PMC3257519

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Supplementary Table 4. Results of genotype risk score analysis.

			FI (18 variants)*		FI cluster 1		FI cluster 2		*PPP1R3B*		*FTO*		*GCKR*		BMI (32 variants)	
Category	**Trait**	**Unit**	**beta**	**p**	**beta**	**p**	**beta**	**p**	**beta**	**p**	**beta**	**p**	**beta**	**P**	**beta**	**p**
Non-disease metabolic traits of monogenic insulin resistance	**SHBG (BMI adjusted)**	natural log	-0.004	**$5x10^{-5}$**	-0.010	**$9x10^{-13}$**	0.003	0.2	-0.024	**$4x10^{-4}$**	0.008	0.08	0.032	**$3x10^{-12}$**	NA	NA
	HDL-C	SD	-0.015	**$3x10^{-32}$**	-0.020	**$7x10^{-37}$**	-0.003	0.2	-0.073	**$1x10^{-22}$**	-0.021	**$3x10^{-5}$**	0.011	0.03	-0.010	**$4x10^{-23}$**
	Adiponectin (BMI adjusted)	log	-0.011	**$2x10^{-19}$**	-0.015	**$2x10^{-26}$**	-0.005	0.03	-0.014	0.07	0.003	0.4	0.016	**$5x10^{-4}$**	NA	NA
	BMI	SD	-0.002	0.1	-0.008	**$7x10^{-8}$**	0.012	**$3x10^{-6}$**	0.004	0.6	0.080	**$1x10^{-62}$**	0.008	0.09	0.036	**$7x10^{-299}$**
	VATSAT ratio	z-score	0.010	**$9x10^{-6}$**	0.015	**$6x10^{-7}$**	0.006	0.2	0.010	0.3	-0.014	0.2	-0.016	0.1	-0.009	**$1x10^{-6}$**
	CT measured hepatic steatosis	SD	0.000	0.9	0.021	**$3x10^{-4}$**	-0.015	0.1	-0.251	**$6x10^{-16}$**	0.026	0.1	-0.065	**$2x10^{-4}$**	-0.007	0.04
	ALT	log10	0.002	**$3x10^{-6}$**	0.002	**$3x10^{-5}$**	0.001	0.2	0.008	0.006	0.002	0.3	0.001	0.7	0.002	**$2x10^{-6}$**
	Triglyceride	SD	0.004	**$3x10^{-4}$**	0.018	**$4x10^{-29}$**	0.002	0.4	0.013	0.09	0.011	0.05	-0.112	**$7x10^{-125}$**	0.007	**$2x10^{-12}$**
Metabolic disease and disease related outcomes	**Type 2 diabetes**	OR	1.013	0.006	1.043	**$5x10^{-13}$**	0.925	**$1x10^{-15}$**	1.050	0.07	1.110	**$1x10^{-9}$**	1.040	0.02	1.021	**$1x10^{-12}$**
	Coronary artery disease	OR	1.014	**$7x10^{-9}$**	1.013	**$1x10^{-5}$**	1.016	**$4x10^{-4}$**	1.005	0.6	1.014	0.1	1.017	0.09	1.010	**$1x10^{-7}$**
	Systolic blood pressure (BMI adjusted)	mmHg	0.097	**$1x10^{-4}$**	0.135	**$2x10^{-5}$**	0.046	0.4	0.146	0.4	-0.120	0.2	-0.099	0.3	NA	NA
	Diastolic blood pressure (BMI adjusted)	mmHg	0.053	**$9x10^{-4}$**	0.075	**$2x10^{-4}$**	0.017	0.6	0.103	0.3	-0.142	0.02	-0.038	0.5	NA	NA
	cIMT	log	0.000	0.9	0.000	0.7	0.000	1	-0.001	0.6	0.002	0.1	0.001	0.3	0.001	0.06
	Carotid plaques	OR	1.005	0.4	1.005	0.5	1.004	0.7	1.012	0.7	1.003	0.9	0.997	0.9	1.000	0.9

Beta is the effect size per fasting insulin increasing allele on each trait.
Statistically significant P values (< 0.001) are shown in bold.
FI cluster 1 and 2 refer to the clusters of 11 and 5 fasting insulin variants respectively, from the hierarchical cluster analysis.
SD: Standard deviation; OR: odds ratio; VATSAT ratio: visceral-to-subcutaneous adipose tissue ratio.
NA in the table indicates that data uncorrected for BMI was not available.
* The genetic risk score excludes the genetic variant at *FTO* as it has a primary effect on BMI.

SUPPLEMENTARY DATA

Supplementary Table 5. Sensitivity analysis.

Trait	Unit	beta	p	W1-beta	W1-p	W2-beta	W2-p	W3-beta	W3-p
Non-disease metabolic traits of monogenic insulin resistance									
SHBG (BMI adjusted)	natural log	-0.010	$9x10^{-13}$	-0.007	$1x10^{-7}$	-0.007	$1x10^{-14}$	-0.006	$4x10^{-6}$
HDL-C	SD	-0.020	$7x10^{-37}$	-0.019	$1x10^{-36}$	-0.014	$1x10^{-37}$	-0.017	$1 x10^{-34}$
Adiponectin (BMI adjusted)	log	-0.015	$2x10^{-26}$	-0.011	$3x10^{-16}$	-0.010	$3x10^{-26}$	-0.011	$4 x10^{-17}$
BMI	SD	-0.008	$7x10^{-8}$	-0.003	0.02	-0.006	$4x10^{-09}$	-0.004	0.005
VATSAT ratio	z-score	0.015	$6x10^{-7}$	0.011	$8x10^{-6}$	0.010	$5x10^{-07}$	0.011	$2x10^{-5}$
CT measured hepatic steatosis	SD	0.021	$3x10^{-4}$	0.017	0.002	0.014	$3x10^{-4}$	0.011	0.03
ALT	log10	0.002	$3x10^{-5}$	0.003	$3x10^{-7}$	0.002	$1x10^{-05}$	0.002	$8x10^{-7}$
Triglyceride	SD	0.018	$4x10^{-29}$	0.005	$2x10^{-4}$	0.012	$1x10^{-30}$	0.002	0.1
Metabolic disease and disease related outcomes									
Type 2 diabetes	OR	1.043	$5x10^{-13}$	1.027	$1x10^{-6}$	1.031	$1x10^{-15}$	1.032	$5x10^{-9}$
Coronary artery disease	OR	1.013	$1x10^{-5}$	1.013	$2x10^{-7}$	1.008	$3x10^{-05}$	0.013	$2x10^{-7}$
Systolic blood pressure (BMI adjusted)	mmHg	0.135	$2x10^{-5}$	0.109	$3x10^{-4}$	0.096	$4x10^{-06}$	0.108	$3x10^{-4}$
Diastolic blood pressure (BMI adjusted)	mmHg	0.075	$2x10^{-4}$	0.059	$1x10^{-3}$	0.052	$9x10^{-05}$	0.060	$9x10^{-4}$
cIMT	log	0.000	0.70	-0.000	0.7	0.000	0.7	-0.000	0.8
Carotid plaques	OR	1.005	0.50	1.006	0.3	1.004	0.4	1.007	0.3

SUPPLEMENTARY DATA

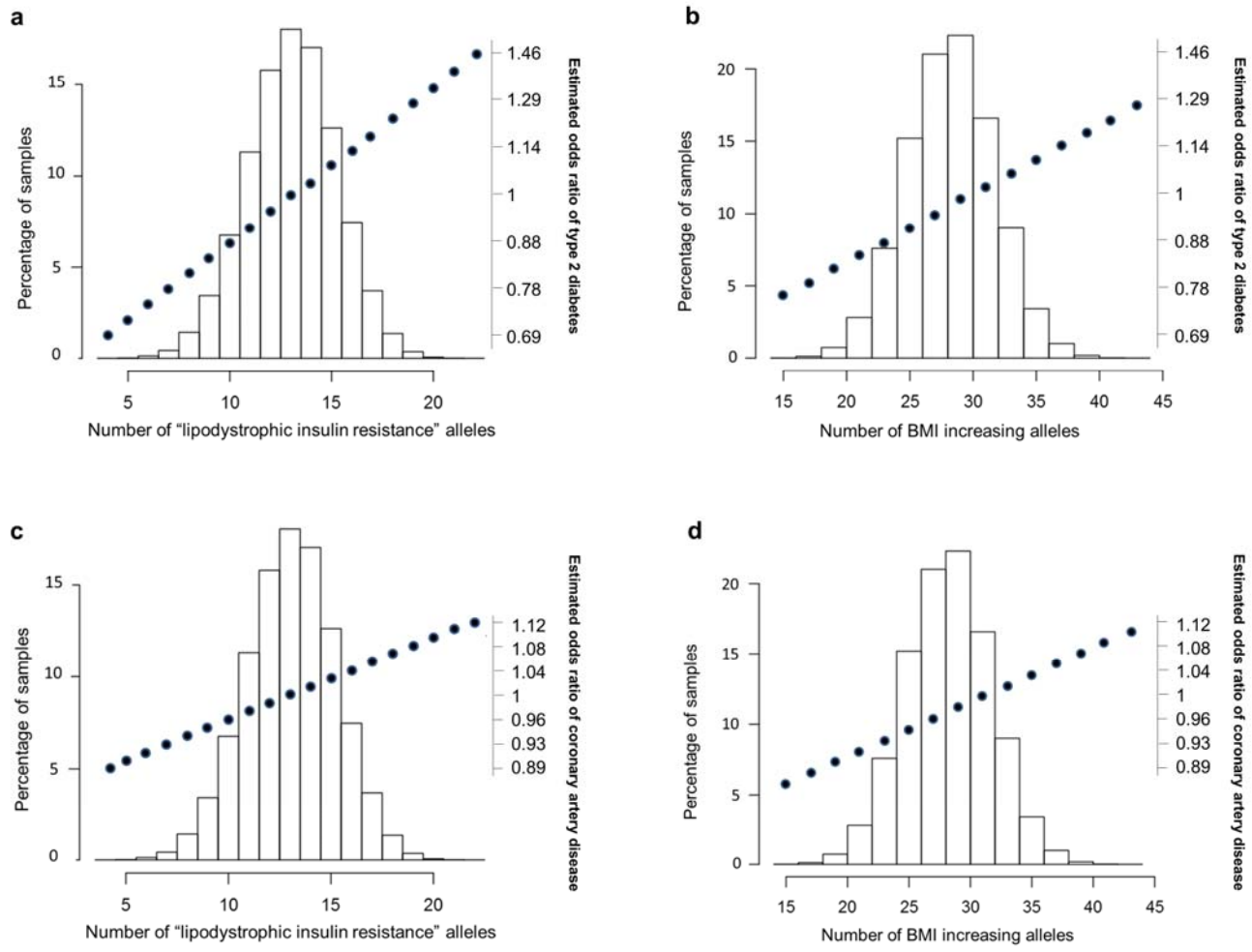
Supplementary Table 6. Results of genotype risk score analysis.

			FI cluster 1		FI cluster 1 excluding *IRS1*	
Category	**Trait**	**Unit**	**beta**	**p**	**beta**	**p**
Non-disease metabolic traits of monogenic insulin resistance	**SHBG (BMI adjusted)**	natural log	-0.010	**$9x10^{-13}$**	-0.009	**$4x10^{-10}$**
	HDL-C	SD	-0.020	**$7x10^{-37}$**	-0.019	**$5x10^{-30}$**
	Adiponectin (BMI adjusted)	log	-0.015	**$2x10^{-26}$**	-0.014	**$5x10^{-22}$**
	BMI	SD	-0.008	**$7x10^{-8}$**	-0.008	**$2x10^{-6}$**
	VATSAT ratio	z-score	0.015	**$6x10^{-7}$**	0.013	**$3x10^{-5}$**
	CT measured hepatic steatosis	SD	0.021	**$3x10^{-4}$**	0.021	**$6x10^{-4}$**
	ALT	log10	0.002	**$3x10^{-5}$**	0.002	**$7x10^{-5}$**
	Triglyceride	SD	0.018	**$4x10^{-29}$**	0.017	**$9x10^{-24}$**
Metabolic disease and disease related outcomes	**Type 2 diabetes**	OR	1.043	**$5x10^{-13}$**	1.039	**$3x10^{-10}$**
	Coronary artery disease	OR	1.013	**$1x10^{-5}$**	1.013	**$4x10^{-5}$**
	Systolic blood pressure (BMI adjusted)	mmHg	0.135	**$2x10^{-5}$**	0.129	**$1x10^{-4}$**
	Diastolic blood pressure (BMI adjusted)	mmHg	0.075	**$2x10^{-4}$**	0.072	**$6x10^{-4}$**
	cIMT	log	0.000	0.7	0.000	0.8
	Carotid plaques	OR	1.005	0.5	1.003	0.7

Beta is the effect size per fasting insulin increasing allele on each trait.
Statistically significant P values (< 0.001) are shown in bold.
FI cluster 1 refers to the clusters of 11 fasting insulin variants from the hierarchical cluster analysis.
SD: Standard deviation; OR: odds ratio; VATSAT ratio: visceral-to-subcutaneous adipose tissue ratio.

SUPPLEMENTARY DATA

Supplementary Figure 1. The estimated cumulative effect of the 11 "lipodystrophic insulin resistance" and 32 BMI variants on risk of type 2 diabetes and coronary artery disease. We used package "PredictABEL" in R (3) to simulate 2 separate genotype dataset for 50,000 individuals based on allele frequencies of 11 "lipodystrophic insulin resistance" and 32 BMI variants. We assumed (i) the genetic variants are independent (no linkage disequilibrium), (ii) there is no interaction between genetic variants, (iii) all genotypes are in Hardy-Weinberg equilibrium and (iv) the combined effect of genetic variants on disease risk follows "log additive" risk model. Individuals were grouped based on the number of "lipodystrophic insulin resistance" alleles (**a** and **c**) and BMI increasing alleles (**b** and **d**). The odds ratio of type 2 diabetes and coronary artery disease for each group is plotted (black circles). The superimposed histogram represents the proportion of samples with number of "lipodystrophic insulin resistance" or BMI increasing variants.



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