

## **Supplementary materials**

### **Supplementary Method**

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- (2) Measurement of body fat percentage (BFP)*
- (3) Formulas for body-shape indices: a body-shape index (ABSI), hip index (HI) and waist hip index (WHI)*
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**Supplementary Table 1.** Association between *KLF14* rs4731702 genotypes and body-shape indices and metabolic traits in Taiwan Biobank participants

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**Supplementary Figure 1.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for HDL-cholesterol levels.

**Supplementary Figure 2.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for triglyceride levels.

**Supplementary Figure 3.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for mean blood pressure.

**Supplementary Figure 4.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for metabolic syndrome.

**Supplementary Figure 5.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for body mass index.

**Supplementary Figure 6.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for waist circumference.

**Supplementary Figure 7.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for a body-shape index.

**Supplementary Figure 8.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for hip circumference.

**Supplementary Figure 9.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for hip index.

**Supplementary Figure 10.** Regional association studies for genetic variants at positions between 130.3 to 130.5 mega-base on chromosome 7q32.2 for body fat percentage.

**Supplementary Figure 11.** Linkage disequilibrium map of the *KLF14* gene upstream region for lead single-nucleotide polymorphisms of the study phenotypes

## Supplementary Methods

### *(1) Definitions of hypertension, diabetes mellitus, obesity, current smoking and metabolic syndrome*

Hypertension was defined as systolic blood pressure (BP) of  $\geq 140$  mmHg, diastolic BP of  $\geq 90$  mmHg or a self-reported history of hypertension. Diabetes mellitus (DM) was defined as a fasting plasma glucose level of  $\geq 126$  mg/dL, a glycohemoglobin value of  $\geq 6.5\%$ , or a self-reported history of DM. Obesity was defined as a BMI of  $\geq 25$  kg/m<sup>2</sup>. Current smoking was defined as regular cigarette smoking at the time of survey.

Because medication histories were unavailable, metabolic syndrome characteristics were based on the recent update of the third report of the National Cholesterol Education Program's Adult Treatment Panel III criteria (Grundy et al., 2005) with modifications. Participants with three or more of the following attributes are typically defined as having metabolic syndrome: (1) BP of  $\geq 130/85$  mmHg or a history of hypertension; (2) triglyceride level of  $\geq 150$  mg/dL; (3) high-density lipoprotein cholesterol level of  $< 40$  mg/dL for men or  $< 50$  mg/dL for women; (4) fasting plasma glucose of  $\geq 100$  mg/dL or a history of DM; and (5) waist circumference of  $> 90$  cm for men or  $> 80$  cm for women.

### **Reference:**

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-52.

### *(2) Measurement of body fat percentage (BFP)*

BFP was measured by "Body Composition Analyzer BC-420MA" TANITA, a device that sends a weak electric current through the body to measure the impedance (electrical resistance) of the body. After switched on the analyzer, we enter the weight of the clothes (it can be entered in the range of 0.0–10.0 kg) and then the participants stand on the electrode, barefoot, with both legs parallel to the electrodes facing the weighing scale without bending the legs. Then input the ID number, select the body type, gender, age and height of the participants. The results are printed automatically.

### *(3) Formulas for body shape indices: a body shape index (ABSI), hip index (HI) and waist hip index (WHI)*

The anthropometric measurements were converted to allometric body shape indices. The published formulas for ABSI and HI have previously been derived for participants in the National Health and Nutrition Examination Survey (NHANES) and the formula for WHI was previously reported. (Christakoudi et al., 2021)

$$\text{ABSI} = \text{WC} * \text{Weight}^{-2/3} * \text{Height}^{5/6}.$$

$$\text{HI} = \text{HC} * \text{Weight}^{-0.482} * \text{Height}^{0.310}.$$

$$\text{WHI} = \text{WHR} * [\text{Weight (kg)/Height}^2 \text{ (cm)}]^{-1/4}.$$

## Reference:

Christakoudi S, Evangelou E, Riboli E, Tsilidis KK. GWAS of allometric body-shape indices in UK Biobank identifies loci suggesting associations with morphogenesis, organogenesis, adrenal cell renewal and cancer. *Scientific reports*. 2021;11:10688.

*(4) Formulas for the product of triglyceride and fasting plasma glucose (the TyG index), TyG with adiposity status (TyG-body mass index [BMI] and TyG waist circumference)*

TyG index has been revealed to be an efficient marker for early identification of insulin resistance (Guerrero-Romero et al., 2010, Du et al., 2014). BMI and waist circumference are simple, inexpensive and noninvasive anthropometric parameters and are commonly adopted as useful indicators of obesity and other metabolic risk. A combination of obesity and TyG can potentially identify IR more strongly than other surrogate markers. Thus, we use TyG and TyG related parameters (TyG BMI and TyG WC) as surrogate markers of IR. TyG related parameters were calculated as follows: TyG index:  $\text{Ln} [\text{TG (mg/dL)} * \text{FPG (mg/dL)} / 2]$ , TyG-BMI: TyG index  $\times \text{BM}$ , TyG-WC: TyG index  $\times \text{WC}$  (Er et al., 2016).

## References:

Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic hyperinsulinemic clamp. *The Journal of clinical endocrinology and metabolism*. 2010; 95:3347–3351.

Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovascular Diabetology*. 2014;13:146.

Er LK, Wu S, Chou HH, Hsu LA, Teng MS, Sun YC, et al. Triglyceride Glucose-Body Mass Index Is a Simple and Clinically Useful Surrogate Marker for Insulin Resistance in Nondiabetic Individuals. PLoS One. 2016;11:e0149731.

**Supplementary Table 1.** Association between *KLF14* rs4731702 genotypes and body-shape indices and metabolic traits in Taiwan Biobank participants

	beta	SE	P value
Age (years)	0.0186	0.0580	0.7479
Body-shape indices			
Body height (cm)	-0.0612	0.0298	0.0402
Body weight (kg)	-0.0438	0.0244	0.0732
Hip circumference (cm)	0.1014	0.0205	$7.43 \times 10^{-7}$
Waist circumference (cm)	0.1193	0.0276	$1.5 \times 10^{-5}$
Waist hip ratio	0.0002	0.0003	0.4331
Body fat percentage (%)	0.0511	0.0137	0.0002
Body mass index (kg/m <sup>2</sup> )	0.0898	0.0197	$5.2 \times 10^{-6}$
ABSI	0.0117	0.0025	$2.15 \times 10^{-6}$
WHI	0.0009	0.0013	0.4763
HI	0.0201	0.0027	$1.26 \times 10^{-13}$
Blood pressure and heart rate			
Mean heart rate <sup>†</sup> (/min)	-0.0279	0.0523	0.5937
Systolic BP <sup>†</sup> (mmHg)	-0.3788	0.0833	$5.00 \times 10^{-6}$
Diastolic BP <sup>†</sup> (mmHg)	-0.2894	0.0543	$9.70 \times 10^{-8}$
Mean BP <sup>†</sup> (mmHg)	-0.3192	0.0597	$8.75 \times 10^{-8}$
Lipid profiles			
Total cholesterol <sup>§</sup> (mmol/L)	0.0003	0.0004	0.5122
HDL cholesterol <sup>§</sup> (mmol/L)	0.0038	0.0005	$6.69 \times 10^{-14}$
LDL cholesterol <sup>§</sup> (mmol/L)	-0.0003	0.0006	0.6471
Triglyceride <sup>§</sup> (mmol/L)	-0.0093	0.0012	$1.18 \times 10^{-14}$
Glucose metabolism			
Fasting plasma glucose <sup>‡</sup> (mmol/L)	-0.2390	0.0824	0.0037
HbA1c <sup>‡</sup> (%)	-0.0106	0.0033	0.0013
Insulin resistance surrogate markers			
TyG index <sup>§, ‡</sup>	-275.84	54.41	$3.99 \times 10^{-7}$
TyG-BMI <sup>§, ‡</sup> ( $\times 10^3$ )	-6932	1428	$1.00 \times 10^{-6}$
TyG-WC <sup>§, ‡</sup> ( $\times 10^3$ )	-21873	4940	$1.00 \times 10^{-5}$
Atherosclerotic risk factors			
Diabetes mellitus (%)	-0.0706	0.0199	0.0004
Hypertension (%)	-0.0581	0.0146	$7.20 \times 10^{-5}$
Metabolic syndrome (%)	-0.1089	0.0153	$9.92 \times 10^{-13}$

Abbreviations, adjusted condition and subjects recruited for analysis as in Figure 1 and Table 2.

P: adjusted for age, sex, BMI, and current smoking; Age: adjusted for sex, BMI and current smoking; and BMI: adjusted for age, sex and smoking. <sup>†</sup> hypertension, <sup>‡</sup> diabetes mellitus, and <sup>§</sup> hyperlipidemia.

Significance was defined as a P value of  $< 0.05/(131+27) = 3.16 \times 10^{-4}$

**Supplementary Table 2.** Association between *KLF14* rs4731702 genotypes and body-shape indices and metabolic traits according to obesity status

Clinical and laboratory parameters	Non - obesity (n = 49,943)			Obesity (n = 28,799)		
	beta	SE	P value	beta	SE	P value
Age (years)	0.0176	0.0727	0.8083	0.0432	0.0935	0.6439
Body-shape indices						
Body height (cm)	-0.1079	0.0372	0.0037	0.0148	0.0497	0.7661
Body weight (kg)	-0.0785	0.0268	0.0033	0.0088	0.0466	0.8497
Hip circumference (cm)	0.0530	0.0243	0.0288	0.1826	0.0368	$7.15 \times 10^{-7*}$
Waist circumference (cm)	0.0160	0.0336	0.6342	0.2941	0.0474	$5.62 \times 10^{-10**}$
Waist hip ratio	-0.0003	0.0004	0.4056	0.0012	0.0005	0.0125
Body fat percentage (%)	0.0468	0.0159	0.0033	0.0707	0.0223	0.0016
Body mass index (kg/m <sup>2</sup> )	0.0151	0.0129	0.2412	0.0693	0.0249	0.0054
ABSI	0.0041	0.0032	0.2088	0.0245	0.0038	$1.1 \times 10^{-10**}$
WHI	-0.0014	0.0017	0.3905	0.0050	0.0020	0.0136
HI	0.0155	0.0033	$2.26 \times 10^{-6}$	0.0269	0.0046	$6.36 \times 10^{-9}$
Blood pressure and heart rate						
Mean heart rate <sup>†</sup> (/min)	0.0998	0.0635	0.1161	-0.2897	0.0916	0.0016**
Systolic BP <sup>†</sup> (mmHg)	-0.3109	0.1005	0.0020	-0.5082	0.1481	$6.02 \times 10^{-4}$
Diastolic BP <sup>†</sup> (mmHg)	-0.2287	0.0651	$4.42 \times 10^{-4}$	-0.4123	0.0976	$2.40 \times 10^{-5}$
Mean BP <sup>†</sup> (mmHg)	-0.2561	0.0717	$3.57 \times 10^{-4}$	-0.4443	0.1068	$3.20 \times 10^{-5}$
Lipid profiles						
Total cholesterol <sup>§</sup> (mmol/L)	0.0005	0.0005	0.3761	-0.0001	0.0007	0.9367
HDL cholesterol <sup>§</sup> (mmol/L)	0.0033	0.0006	$3.25 \times 10^{-7}$	0.0048	0.0008	$1.01 \times 10^{-8}$
LDL cholesterol <sup>§</sup> (mmol/L)	-0.0002	0.0008	0.7853	-0.0004	0.0011	0.7096
Triglyceride <sup>§</sup> (mmol/L)	-0.0078	0.0014	$5.23 \times 10^{-8}$	-0.0119	0.0021	$2.22 \times 10^{-8}$
Glucose metabolism						
Fasting plasma glucose <sup>‡</sup> (mmol/L)	-0.1275	0.0870	0.1429	-0.4367	0.1695	0.0100
HbA1c <sup>‡</sup> (%)	-0.0069	0.0035	0.0505	-0.0172	0.0066	0.0092
Insulin resistance surrogate markers						
TyG <sup>§, †</sup>	-218.40	55.05	$7.30 \times 10^{-5}$	-385.54	116.95	0.0010
TyG-BMI <sup>§, †</sup> ( $\times 10^3$ )	-4907	1266	$1.06 \times 10^{-4}$	-10842	3331	0.0011
TyG-WC <sup>§, †</sup> ( $\times 10^3$ )	-17,044	4663	$2.57 \times 10^{-4}$	-31,323	11133	0.0049
Atherosclerotic risk factors						
Diabetes mellitus (%)	-0.0759	0.0306	0.0133	-0.0650	0.0260	0.0123
Hypertension (%)	-0.0606	0.0208	0.0036	-0.0538	0.0205	0.0086
Metabolic syndrome (%)	-0.0952	0.0250	$1.41 \times 10^{-4}$	-0.1140	0.0192	$2.80 \times 10^{-9}$

Abbreviations, adjusted condition and subjects recruited for analysis as in Figure 1 and Table 2.

P: adjusted for age, sex, BMI and current smoking and age: adjusted for sex, BMI and current smoking. <sup>†</sup> hypertension, <sup>‡</sup> diabetes mellitus, and <sup>§</sup> hyperlipidemia.

Significance was defined as a P value of  $< 0.05/(131+27) = 3.16 \times 10^{-4}$

t-test : \*\* P < 0.001, \* P < 0.01

**Supplementary Table 3.** Association between *KLF14* rs4731702 genotypes and body-shape indices and metabolic traits according to obesity in male

Clinical and laboratory parameters	Male, Non-obese (n = 14,266)			Male, Obese (n = 14,217)		
	beta	SE	P value*	beta	SE	P value*
Age (years)	0.0536	0.1453	0.7121	-0.0547	0.1366	0.6886
Body-shape indices						
Body height (cm)	-0.0769	0.0747	0.3036	0.0804	0.0735	0.2740
Body weight (kg)	-0.0636	0.0575	0.2687	0.0792	0.0707	0.2626
Hip circumference (cm)	-0.0241	0.0439	0.5834	0.0573	0.0486	0.2384
Waist circumference (cm)	-0.0659	0.0545	0.2264	0.1229	0.0572	0.0319
Waist hip ratio	-0.0005	0.0005	0.3765	0.0006	0.0005	0.2421
Body fat percentage (%)	0.0564	0.0355	0.1120	0.0325	0.0345	0.3473
Body mass index (kg/m <sup>2</sup> )	-0.0027	0.0223	0.9051	0.0259	0.0338	0.4435
ABSI	-0.0047	0.0048	0.3265	0.0074	0.0043	0.0852
WHI	-0.0023	0.0025	0.3602	0.0026	0.0024	0.2686
HI	0.0008	0.0056	0.8839	0.0033	0.0058	0.5730
Blood pressure and heart rate						
Mean heart rate <sup>†</sup> (/min)	0.0610	0.1307	0.6409	-0.2846	0.1383	0.0396
Systolic BP <sup>†</sup> (mmHg)	-0.3446	0.1912	0.0715	-0.4900	0.2091	0.0191
Diastolic BP <sup>†</sup> (mmHg)	-0.2766	0.1266	0.0289	-0.4147	0.1437	0.0039
Mean BP <sup>†</sup> (mmHg)	-0.2993	0.1372	0.0291	-0.4398	0.1545	0.0044
Lipid profiles						
Total cholesterol <sup>§</sup> (mmol/L)	0.0001	0.0010	0.9380	-0.0002	0.0010	0.8117
HDL cholesterol <sup>§</sup> (mmol/L)	-0.0017	0.0012	0.1600	0.0024	0.0012	0.0410
LDL cholesterol <sup>§</sup> (mmol/L)	0.0014	0.0015	0.3691	-0.0007	0.0015	0.6417
Triglyceride <sup>§</sup> (mmol/L)	0.0006	0.0029	0.8313	-0.0072	0.0031	0.0211
Glucose metabolism						
Fasting plasma glucose <sup>‡</sup> (mmol/L)	0.0240	0.1913	0.9001	-0.2691	0.2518	0.2852
HbA1c <sup>‡</sup> (%)	0.0014	0.0080	0.8641	-0.0137	0.0097	0.1578
Insulin resistance surrogate markers						
TyG <sup>§, ‡</sup>	-106.08	135.62	0.4341	-237.72	195.68	0.2244
TyG-BMI <sup>§, ‡</sup> ( $\times 10^3$ )	-2575	3120	0.4093	-6915	5561	0.2137
TyG-WC <sup>§, ‡</sup> ( $\times 10^3$ )	-10,104	11508	0.3800	-20479	18,886	0.2782
Atherosclerotic risk factors						
Diabetes mellitus (%)	-0.0302	0.0483	0.5310	-0.0402	0.0368	0.2750
Hypertension (%)	-0.0534	0.0336	0.1124	-0.0757	0.0282	0.0073
Metabolic syndrome (%)	-0.0148	0.0470	0.7535	-0.0819	0.0276	0.0030

Abbreviations, adjusted condition and subjects recruited for analysis as in Figure 1 and Table 2.

P\*: adjusted for age, BMI, and current smoking; Age: adjusted for BMI and current smoking; and BMI: adjusted for age and smoking. <sup>†</sup> hypertension, <sup>‡</sup> diabetes mellitus, and <sup>§</sup> hyperlipidemia.

Significance was defined as a P value of  $< 0.05/(131+27) = 3.16 \times 10^{-4}$



**Supplementary Table 4.** Association between *KLF14* DNA methylation levels and *KLF14* variants and age

IlmnID	Base position	UCSC_RefGene_Name	UCSC_RefGene_Group	Relation_to_UCS C_CpG_Island	$\beta$ values of DNA methylation levels#	P values						
						rs3996352 genotypes	rs1364422 genotypes	rs4731702 genotypes	rs972283 genotypes	Age*	Age**	Age***
cg14788130	130380731	<i>KLF14</i>			0.8857 (0.8774 - 0.8949)	0.261	0.8339	0.1262	0.5212	0.0462	0.0169	0.5952
cg15769180	130391882	<i>KLF14</i>			0.8254 (0.8068 - 0.8441)	0.5455	0.4525	0.5219	0.2336	$1.29 \times 10^{-42}$	$5.59 \times 10^{-15}$	$1.17 \times 10^{-30}$
cg16271549	130406947	<i>KLF14</i>			0.2351 (0.2114 - 0.2604)	0.2294	0.3614	0.3184	0.5106	0.6924	0.622	0.9289
cg19027884	130414263	<i>KLF14</i>		N-Shelf	0.6517 (0.6276 - 0.6756)	0.2402	0.9017	0.3096	0.2383	$3.60 \times 10^{-8}$	0.0007	$1.11 \times 10^{-5}$
cg03578375	130417085	<i>KLF14</i>		N-Shore	0.8960 (0.8838 - 0.9076)	0.9435	0.2751	0.91	0.7339	0.0274	0.0458	0.2576
cg23399222	130417715	<i>KLF14</i>	1 <sup>st</sup> Exon;3'UTR	N-Shore	0.8099 (0.7900 - 0.8289)	0.2847	0.9051	0.3426	0.7956	0.1301	0.2178	0.3626
cg04528819	130418315	<i>KLF14</i>	1 <sup>st</sup> Exon	Island	0.1764 (0.1571 - 0.1954)	0.4777	0.8799	0.5894	0.7377	$8.47 \times 10^{-119}$	$5.07 \times 10^{-63}$	$1.78 \times 10^{-59}$
cg20426994	130418324	<i>KLF14</i>	1 <sup>st</sup> Exon	Island	0.1140 (0.0959 - 0.1341)	0.1787	0.6853	0.1912	0.1406	$2.08 \times 10^{-111}$	$3.33 \times 10^{-59}$	$3.14 \times 10^{-55}$
cg00094518	130418549	<i>KLF14</i>	1 <sup>st</sup> Exon	Island	0.1936 (0.1624 - 0.2283)	0.7445	0.406	0.7645	0.663	$4.15 \times 10^{-141}$	$4.19 \times 10^{-77}$	$5.20 \times 10^{-70}$
cg09823095	130419042	<i>KLF14</i>	TSS200	Island	0.0197 (0.0150 - 0.0249)	0.3876	0.1777	0.4113	0.6812	$2.26 \times 10^{-17}$	$1.25 \times 10^{-10}$	$1.44 \times 10^{-8}$
cg25109431	130419057	<i>KLF14</i>	TSS200	Island	0.0186 (0.0146 - 0.0226)	0.8381	0.4882	0.8799	0.4485	$8.09 \times 10^{-7}$	0.0061	$2.68 \times 10^{-5}$
cg21449170	130419062	<i>KLF14</i>	TSS200	Island	0.0567 (0.0485 - 0.0661)	0.4869	0.7431	0.4766	0.4567	$3.69 \times 10^{-30}$	$1.87 \times 10^{-16}$	$8.18 \times 10^{-16}$
cg05651960	130419064	<i>KLF14</i>	TSS200	Island	0.0533 (0.0461 - 0.0617)	0.1841	0.0326	0.3231	0.1074	$7.98 \times 10^{-12}$	$4.87 \times 10^{-8}$	$1.96 \times 10^{-5}$
cg18751682	130419066	<i>KLF14</i>	TSS200	Island	0.0471 (0.0397 - 0.0558)	0.7911	0.7577	0.8534	0.9897	$9.20 \times 10^{-25}$	$1.11 \times 10^{-16}$	$4.32 \times 10^{-10}$
cg08097417	130419133	<i>KLF14</i>	TSS1500	Island	0.1741(0.1492 - 0.1998)	0.5339	0.2318	0.6571	0.416	$3.83 \times 10^{-253}$	$9.28 \times 10^{-135}$	$2.97 \times 10^{-127}$

cg0795599 5	130419159	<i>KLF14</i>	TSS1500	Island	0.0573 (0.0434 - 0.0749)	0.9929	0.0835	0.967	0.6541	$4.20 \times 10^{-153}$	$9.22 \times 10^{-78}$	$6.92 \times 10^{-79}$
cg2228587 8	130419173	<i>KLF14</i>	TSS1500	Island	0.0655 (0.0533 - 0.0793)	0.6426	0.197	0.7456	0.6767	$8.16 \times 10^{-59}$	$3.62 \times 10^{-38}$	$9.58 \times 10^{-24}$
cg2152093 3	130419340	<i>KLF14</i>	TSS1500	Island	0.1203 (0.0903 - 0.1630)	0.4646	0.0512	0.3312	0.2751	0.0853	0.1357	0.3602
cg0653362 9	130419370	<i>KLF14</i>	TSS1500	Island	0.1239 (0.1039 - 0.1449)	0.0469	0.4193	0.0325	0.3854	$3.77 \times 10^{-8}$	$8.07 \times 10^{-6}$	0.0009
cg0871971 2	130419485	<i>KLF14</i>	TSS1500	S-Shore	0.1294 (0.1129 - 0.1481)	0.0745	0.1835	0.0501	0.1083	$5.64 \times 10^{-38}$	$7.58 \times 10^{-18}$	$2.66 \times 10^{-22}$
cg0277824 5	130419514	<i>KLF14</i>	TSS1500	S-Shore	0.0917 (0.0790 - 0.1050)	0.7298	0.6379	0.7621	0.3155	$3.21 \times 10^{-10}$	$1.26 \times 10^{-5}$	$5.89 \times 10^{-6}$
cg1864529 7	130419594	<i>KLF14</i>	TSS1500	S-Shore	0.0840 (0.0663 - 0.1049)	0.4737	0.6493	0.4825	0.2474	0.1704	0.1351	0.6828
cg1731702 3	130419614	<i>KLF14</i>	TSS1500	S-Shore	0.0907 (0.0766 - 0.1058)	0.1595	0.1022	0.265	0.443	$1.07 \times 10^{-16}$	$4.87 \times 10^{-9}$	$4.61 \times 10^{-9}$
cg0603865 5	130419675	<i>KLF14</i>	TSS1500	S-Shore	0.2058 (0.1725 - 0.2428)	0.715	0.1339	0.6919	0.8807	$3.21 \times 10^{-7}$	$1.82 \times 10^{-5}$	0.0035
cg0391491 3	130419754	<i>KLF14</i>	TSS1500	S-Shore	0.0834 (0.0676 - 0.1024)	0.6374	0.7033	0.5772	0.5944	0.319	0.3018	0.6847
cg0952913 8	130419792	<i>KLF14</i>	TSS1500	S-Shore	0.1487 (0.1258 - 0.1742)	0.1558	0.3704	0.1097	0.4827	0.2065	0.4608	0.2943
cg0242304 4	130419932	<i>KLF14</i>	TSS1500	S-Shore	0.2096 (0.1785 - 0.2467)	0.9079	0.1863	0.9502	0.6601	0.371	0.3216	0.7843
cg0238511 0	130421878	<i>KLF14</i>		S-Shelf	0.7276 (0.7001 - 0.7568)	0.2608	0.372	0.2758	0.2378	0.127	0.1431	0.4641
cg2404277 2	130478741	<i>KLF14</i>			0.8602 (0.8468 - 0.8719)	0.4067	0.9123	0.4398	0.1147	$8.09 \times 10^{-12}$	$2.48 \times 10^{-5}$	$4.49 \times 10^{-8}$
cg0886792 3	130499719	<i>KLF14</i>			0.5786 (0.5495 - 0.6069)	0.2891	0.5253	0.2776	0.6012	$4.40 \times 10^{-8}$	$4.49 \times 10^{-5}$	$7.94 \times 10^{-5}$
cg2063172 0	130507724	<i>KLF14</i>			0.2264 (0.1892 - 0.2658)	0.838	0.3898	0.8495	0.5819	$5.78 \times 10^{-19}$	$7.88 \times 10^{-5}$	$3.40 \times 10^{-19}$
cg2078981 9	130516373	<i>KLF14</i>			0.1511 (0.1283 - 0.1732)	0.4298	0.3613	0.4675	0.3296	$1.07 \times 10^{-104}$	$2.40 \times 10^{-46}$	$1.10 \times 10^{-60}$

The UCSC\_RefGene\_Name, UCSC\_RefGene\_Group, Relation\_to\_UCSC\_CpG\_Island, and Regulatory\_Feature\_Group are derived from the UCSC (University of California Santa Cruz) database.  
<https://genome.ucsc.edu/>

\* *P* value for age using total population for analysis

\*\* *P* value for age using female participants for analysis  
\*\*\* *P* value for age using female participants for analysis  
# Median (interquartile range)

**Supplementary Table 5.** Association of the cg08097417 methylation status with body-shape indices and metabolic traits according to sex

Clinical and laboratory parameters	Male (n = 762)				Female (n = 874)			
	beta	SE	<i>P</i> value**	<i>P</i> value*	beta	SE	<i>P</i> value**	<i>P</i> value*
Age (years)	0.0154	0.0005	$6.84 \times 10^{-124}$	-	0.0153	0.0006	$3.15 \times 10^{-119}$	-
Body-shape indices								
Body height (cm)	-0.0083	0.0014	$1.47 \times 10^{-9}$	0.7015	-0.0088	0.0014	$1.04 \times 10^{-9}$	0.6823
Body weight (kg)	-0.0094	0.0016	$3.96 \times 10^{-9}$	0.6703	-0.0112	0.0019	$5.40 \times 10^{-9}$	0.7139
Hip circumference (cm)	-0.0107	0.0022	$2.00 \times 10^{-6}$	0.1958	-0.0102	0.0021	$2.00 \times 10^{-6}$	0.3230
Waist circumference (cm)	0.0064	0.0018	$3.82 \times 10^{-4}$	0.678	0.0075	0.0015	$3.48 \times 10^{-7}$	0.6819
Waist hip ratio	1.3487	0.1783	$1.12 \times 10^{-13}$	0.1667	1.0214	0.1315	$2.30 \times 10^{-14}$	0.3481
Body fat percentage (%)	0.002	0.0028	0.4861	0.0487	0.0002	0.0036	0.9569	0.0761
Body mass index (kg/m <sup>2</sup> )	-0.0062	0.0027	0.0198	0.2756	0.0045	0.0022	0.0413	0.5934
ABSI	0.1145	0.0206	$4.02 \times 10^{-8}$	0.716	0.0987	0.0152	$1.26 \times 10^{-10}$	0.6763
WHI	0.2926	0.0399	$5.50 \times 10^{-13}$	0.1841	0.2187	0.0292	$1.56 \times 10^{-13}$	0.3986
HI	-0.0314	0.0185	0.0891	0.1123	-0.034	0.0164	0.0382	0.3566
Blood pressure and heart rate								
Mean heart rate <sup>†</sup> (/min)	-0.0008	0.0019	0.6855	0.1633	-0.0047	0.0019	0.0147	0.5480
Systolic BP <sup>†</sup> (mmHg)	0.0031	0.0006	$3.15 \times 10^{-7}$	0.8515	0.0053	0.0006	$1.45 \times 10^{-20}$	0.0013
Diastolic BP <sup>†</sup> (mmHg)	0.003	0.0009	$6.05 \times 10^{-4}$	0.3545	0.0036	0.0009	$9.10 \times 10^{-5}$	0.0886
Mean BP <sup>†</sup> (mmHg)	0.0037	0.0008	$9.00 \times 10^{-6}$	0.5046	0.0055	0.0008	$1.28 \times 10^{-11}$	0.0111
Lipid profiles								
Total cholesterol <sup>§</sup> (mmol/L)	0.1489	0.1131	0.1883	0.1123	0.6792	0.1015	$4.02 \times 10^{-11}$	0.7140
HDL cholesterol <sup>§</sup> (mmol/L)	0.0492	0.0969	0.6119	0.8618	0.1364	0.0906	0.1325	0.8499
LDL cholesterol <sup>§</sup> (mmol/L)	0.0056	0.0741	0.9394	0.2975	0.3235	0.0676	$2.00 \times 10^{-6}$	0.4901
Triglyceride <sup>§</sup> (mmol/L)	0.0746	0.0395	0.0589	0.2516	0.1627	0.0382	$2.30 \times 10^{-5}$	0.5189
Glucose metabolism								
Fasting plasma glucose <sup>‡</sup> (mmol/L)	0.0008	0.0006	0.156	0.2471	0.0014	0.0005	0.0058	0.5417
HbA1c <sup>‡</sup> (%)	0.0189	0.0133	0.1544	0.1028	0.073	0.0146	$6.47 \times 10^{-7}$	0.7476
Insulin resistance surrogate markers								
TyG <sup>§, †</sup>	$8.52 \times 10^{-7}$	$7.31 \times 10^{-7}$	0.2443	0.7013	$3.00 \times 10^{-6}$	$1.00 \times 10^{-6}$	0.0015	0.4966
TyG-BMI <sup>§, †</sup> ( $\times 10^3$ )	$2.54 \times 10^{-8}$	$2.66 \times 10^{-8}$	0.3398	0.8221	$1.16 \times 10^{-7}$	$4.09 \times 10^{-8}$	0.0045	0.4196
TyG-WC <sup>§, †</sup> ( $\times 10^3$ )	$9.44 \times 10^{-9}$	$7.72 \times 10^{-9}$	0.222	0.7286	$4.05 \times 10^{-8}$	$1.23 \times 10^{-8}$	0.001	0.3929
Atherosclerotic risk factors								
Diabetes mellitus (%)	1.962	0.6539	0.0027	0.7132	2.6383	0.8606	0.0022	0.7792
Hypertension (%)	2.9381	0.42	$2.64 \times 10^{-12}$	0.016	3.2286	0.4906	$4.67 \times 10^{-11}$	0.1135
Metabolic syndrome (%)	1.2252	0.4326	0.0046	0.9084	1.5966	0.4468	$3.53 \times 10^{-4}$	0.8181

Abbreviations, adjusted condition and subjects recruited for analysis as in Figure 1 and Table 2

<sup>†</sup> hypertension, <sup>‡</sup> diabetes mellitus, and <sup>§</sup> hyperlipidemia.

*P*\*\*<sub>1</sub>: adjusted for BMI, and current smoking and BMI: adjusted for smoking.

*P*\*<sub>1</sub>: adjusted for age, BMI, and current smoking; Age: adjusted for BMI and current smoking; and BMI: adjusted for age and smoking

Significance between cg08097417 and studied phenotypes was defined as a *P* value of  $< 0.05/(24+27) = 9.80 \times 10^{-4}$ . *t*-test: \*\* *p* < 0.001, \* *p* < 0.01.

**Supplementary Table 6.** Association of the cg08097417 methylation status with body-shape indices and metabolic traits according to obesity

Clinical and laboratory parameters	Non-obese (n = 1,018)				Obese (n = 618)			
	beta	SE	P value#	P value	beta	SE	P value#	P value
Age (years)	0.0151	0.0005	$1.39 \times 10^{-140}$	-	0.0155	0.0006	$7.36 \times 10^{-99}$	-
Body-shape indices								
Body height (cm)	-0.0096	0.0013	$7.34 \times 10^{-14}$	0.5070	-0.0067	0.0015	$1.00 \times 10^{-5}$	0.9647
Body weight (kg)	-0.0130	0.0017	$1.34 \times 10^{-13}$	0.5870	-0.0070	0.0016	$1.50 \times 10^{-5}$	0.8432
Hip circumference (cm)	-0.0113	0.0020	$4.41 \times 10^{-8}$	0.2763	-0.0093	0.0023	$6.10 \times 10^{-5}$	0.2145
Waist circumference (cm)	0.0051	0.0015	$7.19 \times 10^{-4}$	0.6079	0.0091	0.0017	$1.06 \times 10^{-7}$	0.1031
Waist hip ratio	0.9151	0.1348	$1.92 \times 10^{-11}$	0.8669	1.4414	0.1710	$2.50 \times 10^{-16}$	0.0150
Body fat percentage (%)	-0.0002	0.0030	0.9389	0.6812	-0.0008	0.0033	0.8165	0.7403
Body mass index (kg/m <sup>2</sup> )	0.0133	0.0040	0.0010	0.5338	-0.0125	0.0036	$5.45 \times 10^{-4**}$	0.2283
ABSI	0.0822	0.0150	$5.72 \times 10^{-8}$	0.7272	0.1535	0.0207	$4.17 \times 10^{-13*}$	0.0934
WHI	0.1956	0.0293	$3.77 \times 10^{-11}$	0.8869	0.3321	0.0393	$2.29 \times 10^{-16*}$	0.0136
HI	-0.0227	0.0157	0.1466	0.3989	-0.0310	0.0200	0.1213	0.1153
Blood Pressure								
Mean heart rate <sup>†</sup> (/min)	-0.0006	0.0009	0.5217	0.7655	-0.0017	0.0011	0.1295	0.7169
Systolic BP <sup>†</sup> (mmHg)	0.0045	0.0005	$3.28 \times 10^{-16}$	0.0244	0.0036	0.0006	$4.30 \times 10^{-9}$	0.3210
Diastolic BP <sup>†</sup> (mmHg)	0.0031	0.0009	$2.82 \times 10^{-4}$	0.2730	0.0035	0.0009	$1.67 \times 10^{-4}$	0.1010
Mean BP <sup>†</sup> (mmHg)	0.0047	0.0008	$1.62 \times 10^{-9}$	0.0868	0.0043	0.0008	$5.40 \times 10^{-7}$	0.1398
Lipid profiles								
Total cholesterol <sup>§</sup> (mmol/L)	0.4552	0.0975	$3.00 \times 10^{-6}$	0.9026	0.3092	0.1207	0.0107	0.0257
HDL cholesterol <sup>§</sup> (mmol/L)	0.1224	0.0861	0.1554	0.9235	0.0822	0.1017	0.4195	0.7305
LDL cholesterol <sup>§</sup> (mmol/L)	0.1944	0.0650	0.0029	0.8831	0.0908	0.0781	0.2455	0.0609
Triglyceride <sup>§</sup> (mmol/L)	0.1360	0.0371	$2.61 \times 10^{-4}$	0.8972	0.0772	0.0403	0.0563	0.4835
Glucose metabolism								
Fasting plasma glucose <sup>‡</sup> (mmol/L)	0.0013	0.0006	0.0255	0.4838	0.0009	0.0005	0.0625	0.8094
HbA1c <sup>‡</sup> (%)	0.0328	0.0136	0.0161	0.0459	0.0509	0.0139	$2.65 \times 10^{-4}$	0.4458
Insulin resistance surrogate markers								
TyG <sup>§, ‡</sup>	$3.00 \times 10^{-6}$	$1.00 \times 10^{-6}$	0.0095	0.7942	$1.00 \times 10^{-6}$	$7.12 \times 10^{-7}$	0.1377	0.4039
TyG-BMI <sup>§, ‡</sup> ( $\times 10^3$ )	$1.09 \times 10^{-7}$	$4.41 \times 10^{-8}$	0.0135	0.7642	$3.58 \times 10^{-8}$	$2.49 \times 10^{-8}$	0.1516	0.4281
TyG-WC <sup>§, ‡</sup> ( $\times 10^3$ )	$3.66 \times 10^{-8}$	$1.29 \times 10^{-8}$	0.0046	0.7411	$1.21 \times 10^{-8}$	$7.32 \times 10^{-9}$	0.1004	0.3715
Atherosclerotic risk factors								
Diabetes mellitus (%)	2.0546	0.7376	0.0053	0.5157	2.3726	0.7453	0.0015	0.5319
Hypertension (%)	2.9773	0.4576	$7.69 \times 10^{-11}$	0.0250	3.0894	0.4513	$7.63 \times 10^{-12}$	0.1102
Metabolic syndrome (%)	1.7148	0.5420	0.0016	0.9195	1.0864	0.3829	0.0045	0.8752

Abbreviations, adjusted condition and subjects recruited for analysis as in Figure 1 and Table 2. *P*: adjusted for age, sex, BMI and current smoking and age: adjusted for sex, BMI and current smoking. <sup>†</sup> hypertension, <sup>‡</sup> diabetes mellitus, and <sup>§</sup> hyperlipidemia.  
*P*#: adjusted for sex, BMI, and current smoking; Age: adjusted for BMI and current smoking; and BMI: adjusted for age and smoking.  
Significance between cg08097417 and studied phenotypes was defined as a *P* value of  $< 0.05/(24+27) =$

9.80 × 10<sup>-4</sup>  
*t-test* : \*\* P < 0.001, \* P < 0.01

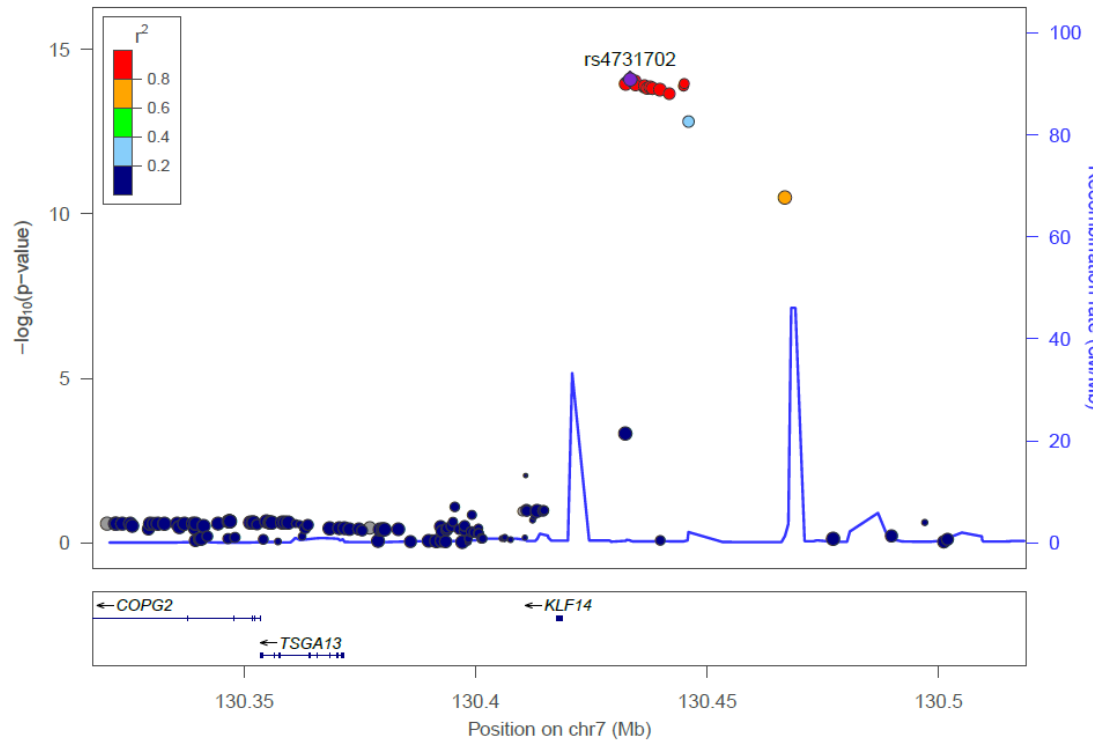
**Supplementary Table 7.** Association of *KLF14* rs4731702 genotypes and cg08097417 methylation status with metabolically healthy and unhealthy phenotypes in obese Taiwan

Biobank participants

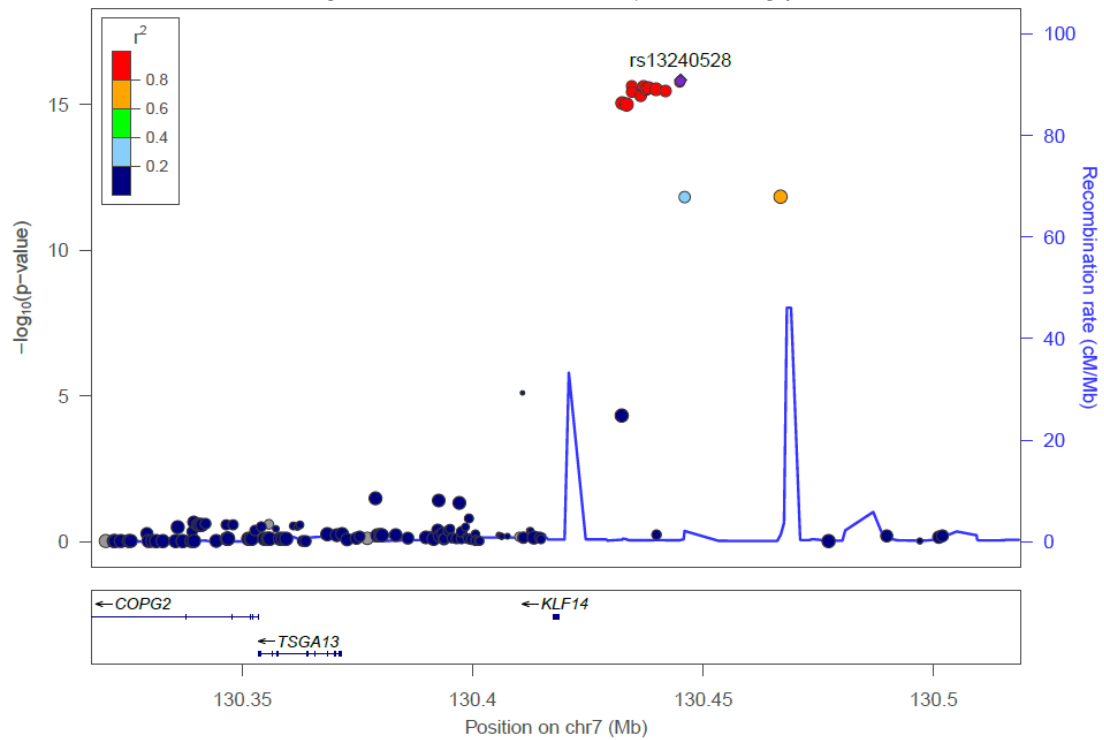
MHO vs. MUO		N	OR	95%CI	Beta	SE	P value
rs4731702 genotypes	Total	29,891	0.88	0.85 - 0.92	-0.12	0.02	1.92 × 10 <sup>-11</sup>
cg08097417 methylation status	Total	633	4.04	1.95 - 8.41	1.40	0.37	1.81 × 10 <sup>-4</sup>

MHO: metabolically healthy obese, MUO: metabolically unhealthy obese, N: number, OR odds ratio, 95% CI: 95% confidence interval, SE standard error.  
P: adjusted for age, sex, BMI and current smoking

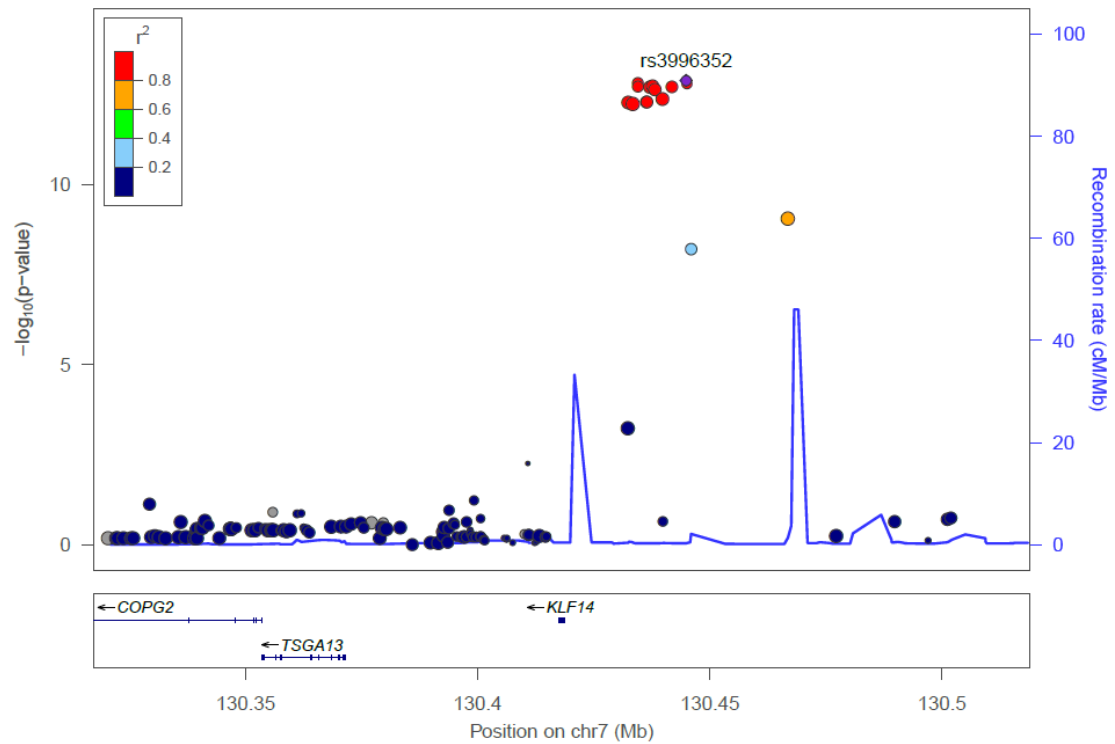
**Supplementary Figure 1.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for the high-density lipoprotein cholesterol level.



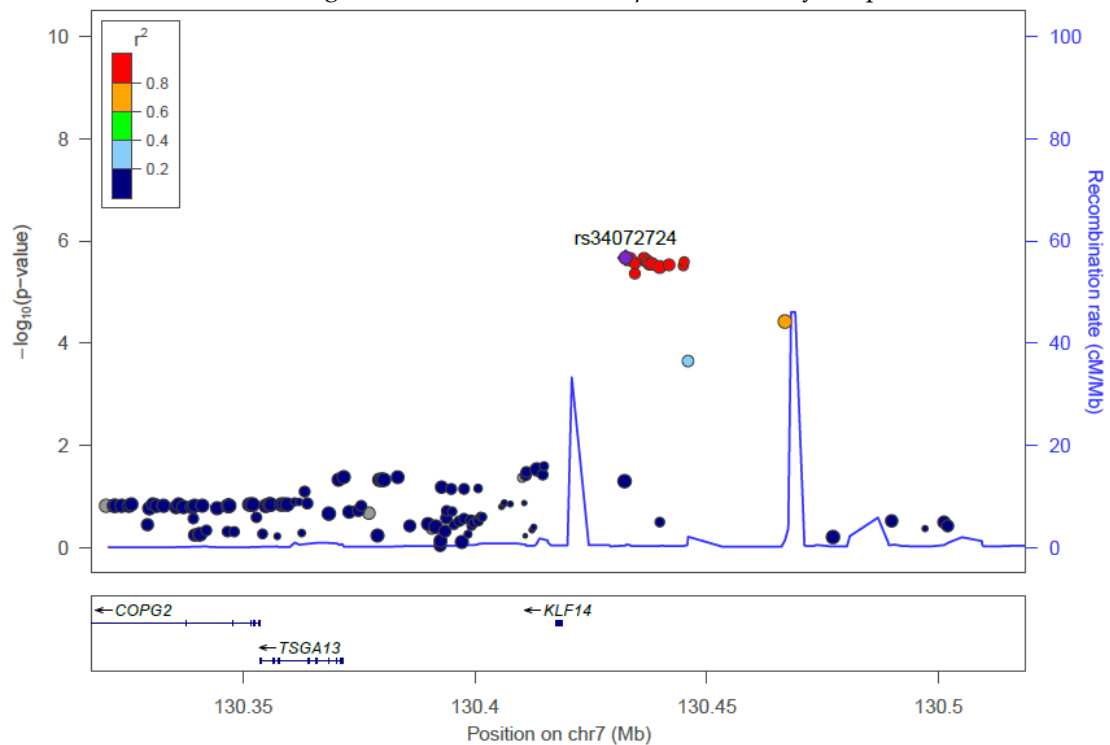
**Supplementary Figure 2.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for triglyceride level.



**Supplementary Figure 3.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for the risk of metabolic syndrome.

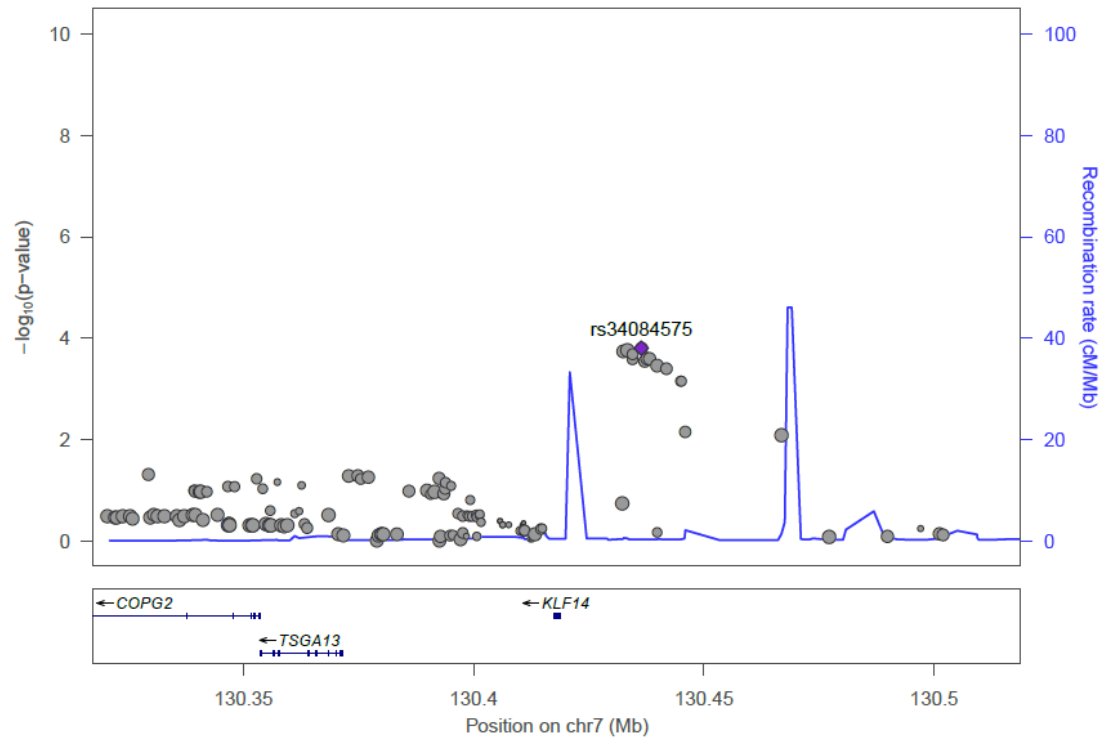


**Supplementary Figure 4.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for a body-shape index.

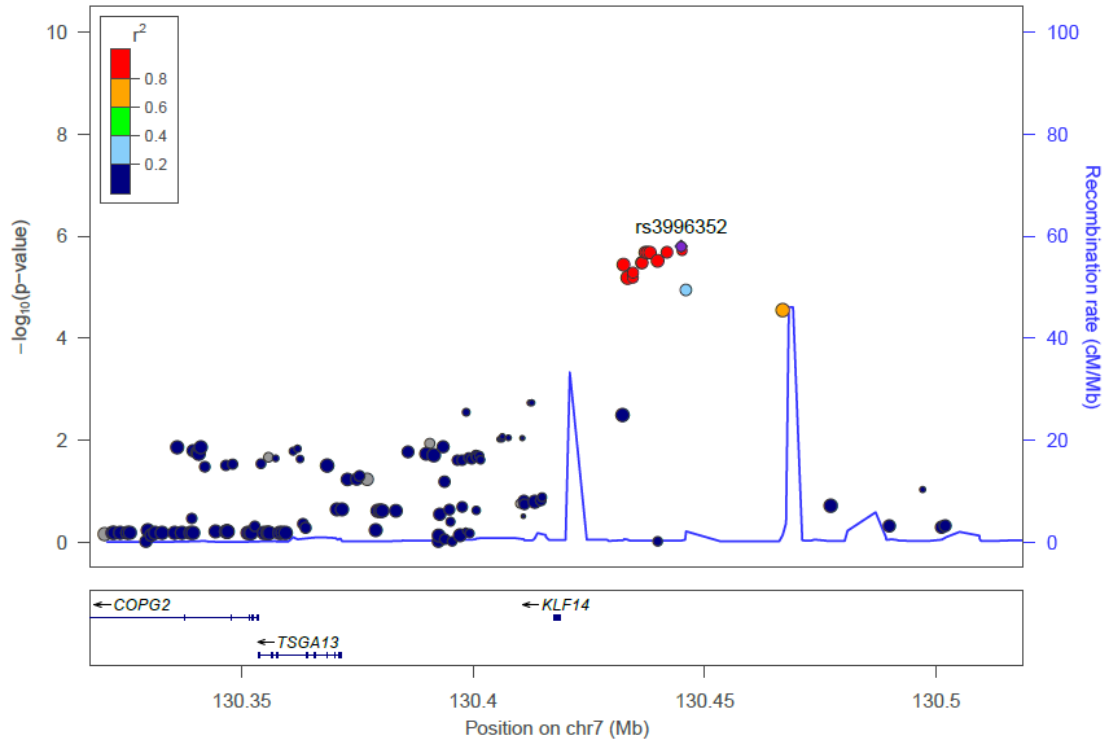




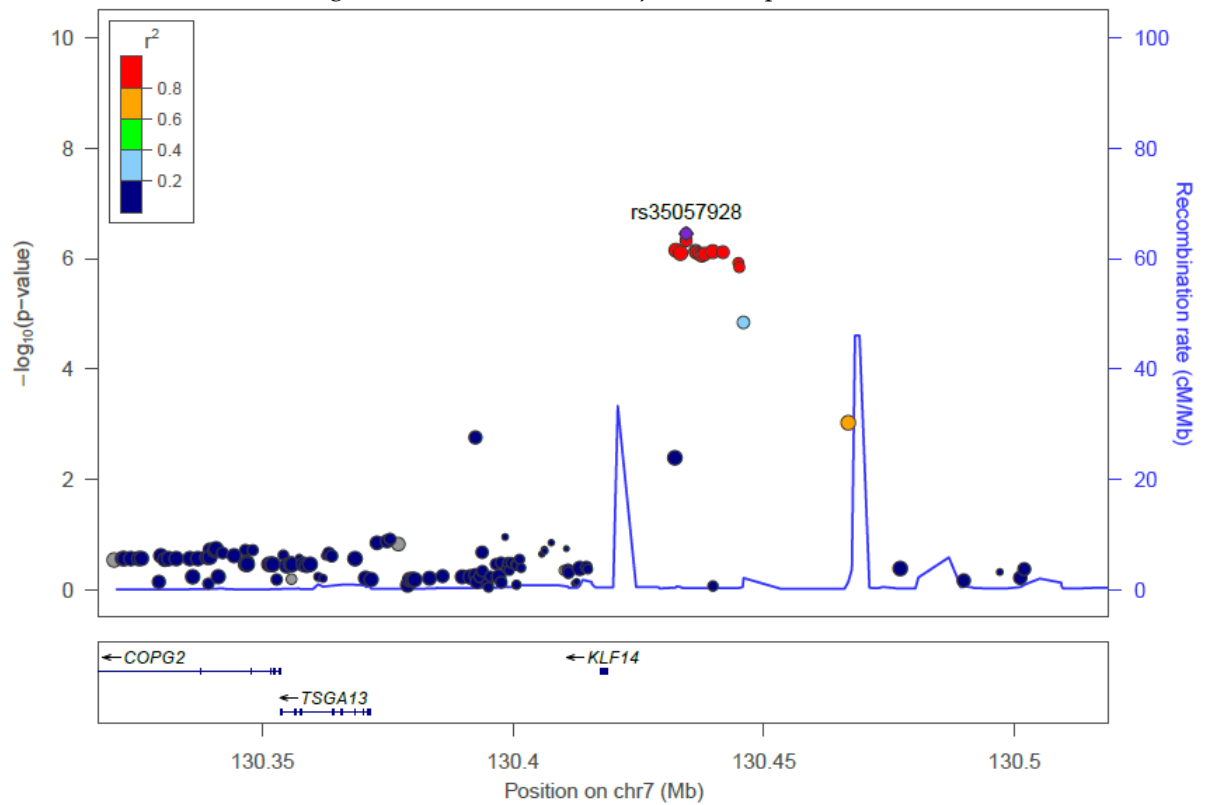
**Supplementary Figure 5.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for body fat percentage.



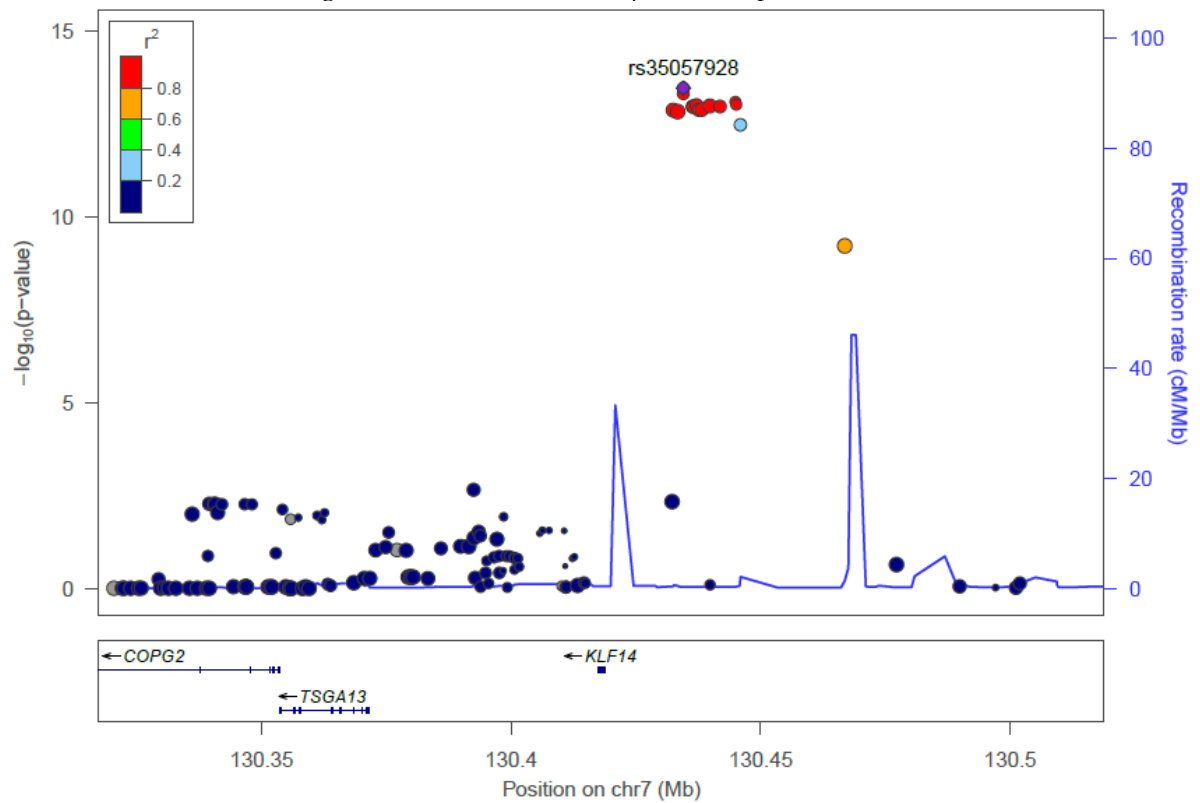
**Supplementary Figure 6.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for body mass index.



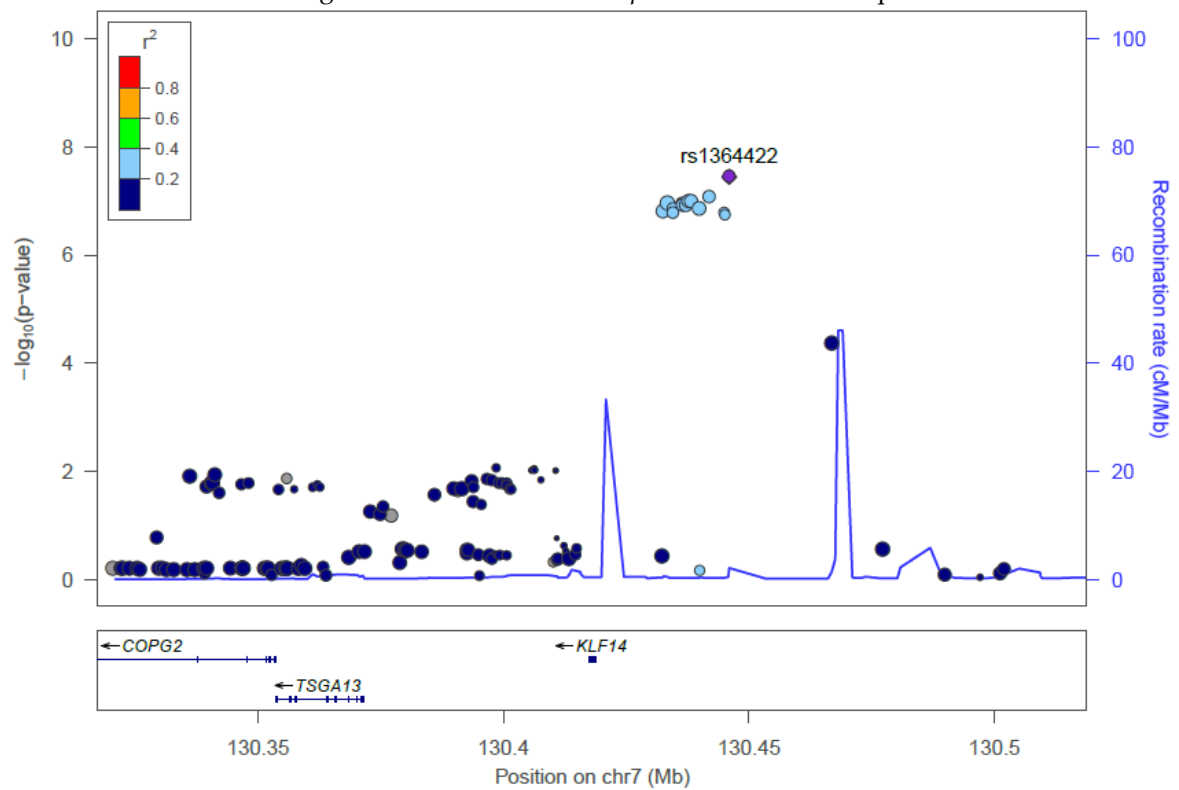
**Supplementary Figure 7.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for hip circumference.



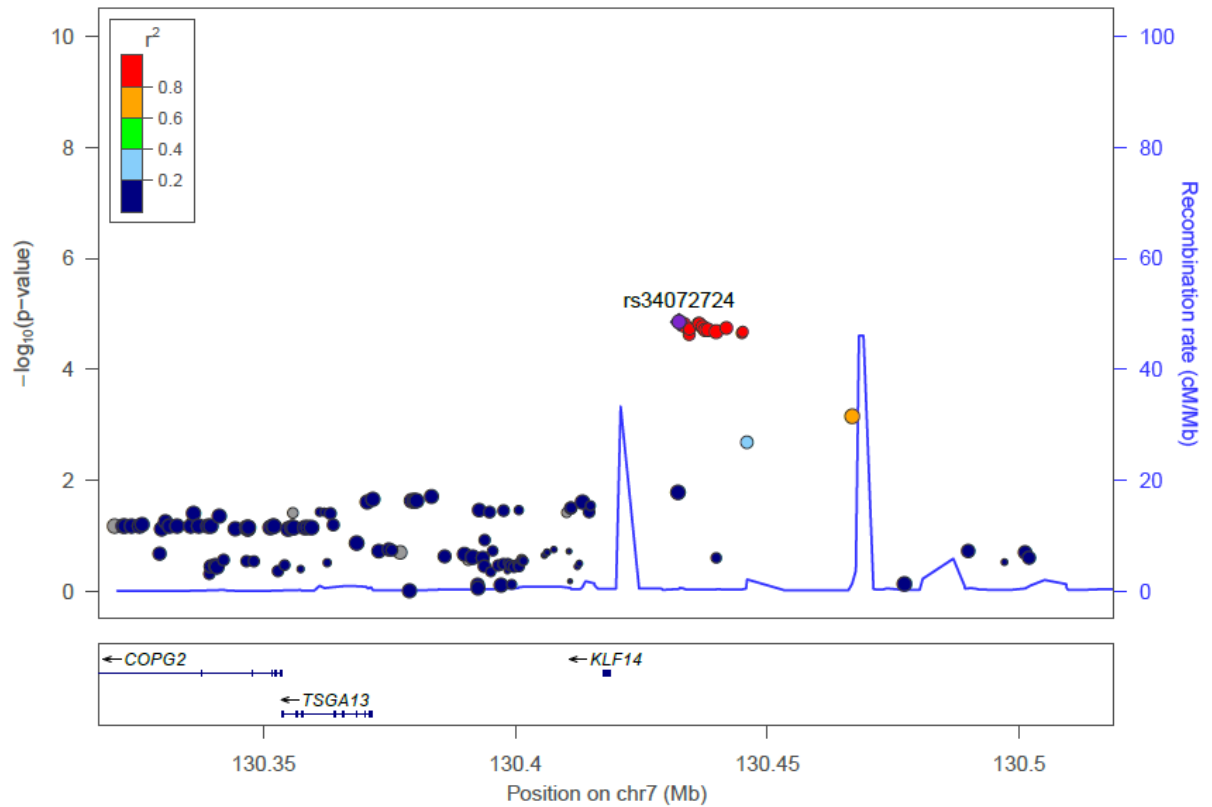
**Supplementary Figure 8.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for hip index.



**Supplementary Figure 9.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for mean blood pressure.



**Supplementary Figure 10.** Regional association studies for genetic variants at positions between 130.3 and 130.5 mega-base on chromosome 7q32.2 for waist circumference.



**Supplementary Figure 11.** Linkage disequilibrium map of the *KLF14* gene upstream region for lead single-nucleotide polymorphisms of the study phenotypes.

