Supplementary Material

Supplementary Table 1. SNPs associated with hepatic TG in the GOLD GWAS, and their associations with HTGC in the Dallas Heart Study.

Gene	SNP	Gold P-value	DHS P-value
PNPLA3	rs738409	4.30E-34	1.73E-18
TM6SF2 *	rs58542926	1.22E-11	3.11E-07
GCKR	rs780094	2.56E-04	0.0032
PPP1R3B	rs4240624	3.68E-18	0.7886
LYPLAL1	rs12137855	1.06E-04	0.9627

* The SNP rs22286030, which is in high linkage disequilibrium with TM6SF2 rs58542926, was reported in the GOLD GWAS.

Supplementary Table 2. Baseline characteristics of cirrhosis cases and controls in the Copenhagen Cohort.

Trait	Cirrhosis cases	Controls	P
N, (%)	384 (0.4)	93,335 (99.6)	-
Male, (%)	251 (65)	41,724 (45)	<0.001
Age, y	62 (55-69)	58 (48-67)	<0.001
Body mass index (kg/m^2), (IQR)	27 (24-30)	26 (23-28)	<0.001
Heavy alcohol consumption	134 (35)	15,562 (17)	<0.001

Values are number and (percentage) or median (interquartile range). Heavy alcohol consumption was defined as self-reported consumption of >21/14 units alcohol per week in males/females.

Supplementary Table 3. Associations of 30 known adiposity-associated SNPs with BMI and HTGC in the Dallas Heart Study.

SNP	Weight	Beta (BMI)	P (BMI)	Beta(HTGC^0.3)	P (HTGC)
rs1558902	0.0851	0.448	0.12	-0.008	0.78
rs2867125	0.0681	0.264	0.47	0.029	0.40
rs571312	0.0557	0.610	0.08	0.061	0.06
rs11847697	0.0554	0.736	0.25	0.053	0.37
rs13107325	0.0512	-0.377	0.51	-0.110	0.04
rs543874	0.0470	-0.455	0.19	-0.051	0.12
rs10767664	0.0445	0.564	0.11	0.069	0.04
rs12444979	0.0435	0.092	0.82	0.036	0.34
rs10938397	0.0423	0.098	0.73	0.035	0.19
rs987237	0.0418	0.887	0.02	0.071	0.04
rs9816226	0.0405	0.270	0.49	0.015	0.68
rs2287019	0.0370	0.256	0.49	0.030	0.38
rs2815752	0.0351	-0.134	0.65	0.026	0.35
rs2241423	0.0347	-0.088	0.79	-0.038	0.22
rs7359397	0.0325	0.558	0.05	0.017	0.52
rs713586	0.0309	0.584	0.04	0.018	0.50
rs7138803	0.0303	0.165	0.56	0.061	0.02
rs13078807	0.0260	0.443	0.21	-0.011	0.75
rs4771122	0.0258	-0.478	0.15	-0.050	0.11
rs10968576	0.0257	-0.592	0.05	-0.009	0.76
rs3817334	0.0256	-0.007	0.98	0.031	0.25
rs3810291	0.0249	0.103	0.74	-0.017	0.55
rs887912	0.0242	0.887	0.01	0.012	0.70
rs2112347	0.0241	0.022	0.94	0.031	0.26
rs1514175	0.0240	0.454	0.11	0.065	0.01
rs29941	0.0224	0.248	0.40	-0.023	0.40
rs206936	0.0208	0.668	0.05	-0.009	0.78
rs1555543	0.0198	0.025	0.93	0.029	0.29
rs4929949	0.0183	-0.042	0.88	-0.008	0.77
rs2206734	0.0172	-0.176	0.64	-0.011	0.74

Weight: Effect size reported in previous GWAS [1,2] used to weigh the SNP in the allele score. Beta (BMI): per-allele increase in BMI (kg/m^2) in the Dallas Heart Study. P(BMI): SNP-association with BMI. Beta(HTGC^0.3): per-allele increase in power-transformed HTGC in the Dallas Heart Study. P(HTGC): SNP-association with HTGC.

Supplementary Table 4. Metabolic traits associated with body mass index in the Dallas Heart Study.

Category	Phenotype	N	Spearman's rho	Partial r*	Partial r^2	P-value	Genes
Liver fat	HTGC	2676	0.43	0.41	0.17	2.69E-109	*PNPLA3, TM6SF2, GCKR*
Plasma lipids	HDL	4462	-0.24	-0.29	0.08	1.15E-87	*CETP*
	TG	4462	0.21	0.22	0.05	1.32E-51	*APOA5, GCKR, LPL*
Glycemic (non-DM)**	Fasting glucose	3904	0.24	0.25	0.06	7.57E-56	*GCK, G6PC2*
	Fasting insulin	3611	0.59	0.54	0.29	2.15E-268	
	HOMA-IR	3563	0.59	0.54	0.29	2.15E-270	
	HbA1c	2604	0.25	0.23	0.05	2.11E-33	
BP	Systolic BP	4459	0.28	0.27	0.07	6.63E-74	
	Diastolic BP	4459	0.28	0.25	0.06	2.81E-63	
Biomarkers	Leptin	2929	0.67	0.74	0.55	<1E-300	*LEP*
	Adiponectin	3354	-0.30	-0.29	0.08	2.26E-66	*ADIPOQ*
	CRP	3349	0.47	0.44	0.19	6.53E-159	*CRP*
	Uric Acid	4450	0.26	0.37	0.14	3.32E-143	*SLC2A9, SLC22A12*
Sterols	Campesterol	3088	-0.22	-0.24	0.06	6.58E-41	*ABCG5/ABCG8*
	Sitosterol	3090	-0.24	-0.26	0.07	1.67E-47	*ABCG5/ABCG8*
	Stigmasterol	3090	-0.23	-0.26	0.07	2.66E-48	*ABCG5/ABCG8*
	14-desmethyl Lanosterol	3091	-0.27	-0.28	0.08	3.97E-57	*ABCG5/ABCG8*
	Vit D3	3092	-0.26	-0.21	0.05	3.95E-33	*GC*

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* Partial correlation (r) was obtained from linear regression models treating phenotype as a dependent variable (response), BMI as an independent variable (predictor), and adjusted for age, gender and self-reported ethnicity. Phenotype values (except for HTGC) were transformed using an inverse normal transformation to approximate a normal distribution of residuals. For HTGC, a power transformation (^0.3) was used as elsewhere in the manuscript. Individuals with missing phenotype or genotype data were excluded.

** Diabetics were excluded from analysis. The results obtained in the full cohort, including diabetic individuals, were not materially different.

Supplementary Table 5. Gene × adiposity interaction on adiposity-related traits in the Dallas Heart Study.

Phenotype	Gene/locus	SNP	N	Partial r (BMI)	Partial r (SNP)	Beta (BMI)	Beta (SNP)	P (Main effect)	P (Interaction)	MAF AA	MAF EA	MAF HA
Leptin	*LEP*	rs17151919	2928	0.74	-0.12	0.08	-0.22	2.28E-11	0.6020	8.3%	0.1%	0.7%
CRP	*CRP*	rs876537	3350	0.44	-0.14	0.06	-0.18	7.99E-16	0.3042	21.6%	40.0%	39.2%
HTGC	*PPP1R3B*	rs4240624	2308	0.42	-0.01	0.06	-0.01	0.7886	0.3824	19.9%	11.6%	25.4%
HTGC	*LYPLAL1*	rs12137855	2326	0.42	0.00	0.06	0.00	0.9627	0.3591	17.6%	18.8%	14.4%
HTGC	*PNPLA3*	rs738409	2674	0.41	0.17	0.06	0.26	1.73E-18	3.74E-05	14.1%	23.2%	48.2%
HTGC	*TM6SF2*	rs58542926	2675	0.41	0.10	0.06	0.29	3.11E-07	0.0058	3.3%	7.7%	4.2%
HTGC	*GCKR*	rs780094	2675	0.40	0.06	0.06	0.08	0.0032	4.33E-05	16.0%	41.2%	35.1%
HTGC	*GCKR*	rs1260326	2673	0.40	0.06	0.06	0.08	0.0038	5.47E-05	13.4%	41.9%	34.5%
HTGC	*MBOAT7*	rs641738	2675	0.40	0.04	0.06	0.05	0.0296	0.3467	32.2%	42.1%	33.7%
Uric Acid	*SLC2A9*	rs3775948	4449	0.38	-0.18	0.04	-0.23	1.31E-33	0.6249	32.4%	23.6%	33.2%
Uric Acid	*SLC22A12*	rs505802	4449	0.37	-0.07	0.04	-0.09	8.38E-07	0.9598	29.6%	69.8%	43.6%
HbA1c	*FN3KRP*	rs1046896	3109	0.28	0.11	0.04	0.16	5.35E-10	0.2235	22.6%	32.1%	40.0%
FG	*G6PC2*	rs560887	3901	0.25	-0.07	0.03	-0.14	1.58E-05	0.0870	4.3%	30.5%	12.5%
FG	*GCK*	rs730497	3903	0.25	0.06	0.03	0.09	4.86E-04	0.9983	17.5%	18.6%	24.1%
HbA1c	*FN3KRP*	rs1046896	2603	0.24	0.14	0.03	0.21	5.66E-13	0.2930	22.1%	31.3%	41.0%
TG	*LPL*	rs326	4458	0.23	-0.08	0.03	-0.11	1.50E-07	0.0376	56.4%	29.9%	26.5%
TG	*APOA5*	rs3135506	4460	0.22	0.13	0.03	0.31	4.17E-17	0.0293	6.8%	6.1%	14.2%
TG	*GCKR*	rs780094	4461	0.22	0.09	0.03	0.13	7.24E-09	0.1682	16.2%	39.3%	33.8%
TG	*GCKR*	rs1260326	4459	0.22	0.08	0.03	0.13	9.52E-08	0.0254	13.2%	40.1%	33.2%
Vit D3	*GC*	rs4588	3091	-0.22	-0.14	-0.03	-0.22	3.08E-14	0.9041	11.2%	29.1%	20.6%
Campesterol	*ABCG8*	rs4245791	3087	-0.24	0.23	-0.03	0.39	7.10E-37	0.9889	12.8%	32.6%	17.3%
Sitosterol	*ABCG8*	rs4245791	3089	-0.26	0.25	-0.03	0.43	2.25E-44	0.6523	12.8%	32.7%	17.3%
Stigmasterol	*ABCG8*	rs4245791	3089	-0.26	0.21	-0.03	0.36	1.43E-33	0.8823	12.8%	32.7%	17.3%
14-desmethyl Lanosterol	*ABCG8*	rs4245791	3090	-0.28	0.23	-0.04	0.40	6.39E-40	0.4465	12.8%	32.7%	17.3%
HDL	*CETP*	rs247616	4460	-0.29	0.12	-0.04	0.18	1.98E-16	0.1265	24.8%	33.4%	31.9%
Adiponectin	*ADIPOQ*	rs1648707	3353	-0.29	0.10	-0.04	0.13	1.64E-08	0.4425	45.7%	65.1%	52.4%

Partial r (BMI): Partial correlation between the trait and body mass index, obtained from linear regression models adjusted for age, gender and self-reported ethnicity. The traits associated with BMI are provided in descending order based of partial r (BMI). Partial r (SNP): Partial correlation between the SNP and the trait. Beta (BMI): change in standardized BMI per one unit increase in standardized trait. Beta (SNP): per-allele change in standardized trait. P(Main effect): Association of SNP with trait. P(Interaction): SNP × BMI interaction on trait. MAF: Minor allele frequencies in African Americans(AA), European Americans(EA), and Hispanic Americans(HA) in the Dallas Heart Study.
Phenotype values (except for HTGC) were transformed using an inverse normal transformation to approximate a normal distribution of residuals. For HTGC, a power transformation (^0.3) was used as elsewhere in the manuscript. The values were further standardized to have mean 0 and standard deviation of 1. Individuals with missing phenotype or genotype data are excluded. Beta coefficients are in sd units.

Supplementary Table 6. Replication of gene × adiposity interactions on plasma triglyceride levels in the Dallas Biobank and Copenhagen Cohort.

Cohort	**Phenotype**	**Gene/Locus**	**SNP**	**N**	**P (Main effect)**	**P (Interaction, BMI × SNP)**
Dallas Biobank	Plasma TG	*GCKR*	rs1260326	4958	1.25E-06	0.78
	Plasma TG	*LPL*	rs326	4958	6.92E-05	0.12
	Plasma TG	*APOA5*	rs3135506	4958	8.03E-14	0.52
Copenhagen Cohort	Plasma TG	*GCKR*	rs1260326	70096	1.83E-65	0.02
	Plasma TG	*LPL*	rs326	57549	1.75E-72	0.71
	Plasma TG	*APOA5*	rs3135506	64483	1.06E-117	0.18

Supplementary References.

1. Speliotes, E.K. *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* **42**, 937-48 (2010).

2. Monda, K.L. *et al*. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nat Genet* **45**, 690-6 (2013).

3. Voorman, A., Lumley, T., McKnight, B. & Rice, K. Behavior of QQ-plots and genomic control in studies of gene-environment interaction. *PLoS One* **6**, e19416 (2011).