SUPPLEMENTARY DATA

Supplementary Table S1. Number of participants with data on exposures, outcomes and covariates/potential confounders in UCLEB and Fenland studies used in the multivariable and Mendelian randomization analyses

Trait	Variable type*	Available studies	Total N**
ALT (U/L)	Exposure	BRHS, BWHHS, NSHD & Fenland	15371
ALP (U/L)	Exposure	CAPS, NSHD & Fenland	12761
AST (U/L)	Exposure	BRHS, BWHHS, CAPS & NSHD	6624
GGT (U/L)	Exposure	BRHS, BWHHS, CAPS, EAS, NSHD & Fenland	17336
Fasting glucose (mmol/l)	Continuous outcome	BRHS, BWHHS, CAPS, EAS, ELSA, NSHD & WHII	9689
Fasting insulin (µIU/ml)	Continuous outcome	BRHS, BWHHS, CAPS, NSHD & WHII	7024
LDL cholesterol (mmol/L)	Continuous outcome	BRHS, BWHHS, CAPS, EAS, ELSA, WHII, NSHD & Fenland	21296
HDL cholesterol (mmol/L)	Continuous outcome	BRHS, BWHHS, CAPS, EAS, ELSA, WHII, NSHD & Fenland	21464
Total cholesterol (mmol/L)	Continuous outcome	BRHS, BWHHS, CAPS, EAS, ELSA, WHII, NSHD & Fenland	21639
Triglycerides (mmol/l)	Continuous outcome	BRHS, BWHHS CAPS, EAS, ELSA, WHII, NSHD & Fenland	20856
Type 2 diabetes cases	Disease outcome	BRHS, BWHHS, CAPS, EAS, ELSA, WHII, NSHD	1202
Type 2 diabetes controls			10588
Age (years)	Covariate/Potential Confounder	BRHS, BWHHS CAPS, EAS, ELSA, WHII, NSHD & Fenland	21772
BMI (kg/m^2)$^{\$}$	Potential confounder	BRHS, BWHHS CAPS, EAS, ELSA, WHII, NSHD & Fenland	21513
Waist circumference (cm)$^{\$}$	Potential confounder	BRHS, BWHHS, ELSA, WHII, NSHD & Fenland	19595
Sex	Covariate/Potential confounder	BRHS, BWHHS CAPS, EAS, ELSA, WHII, NSHD & Fenland	21772
Smoking$^{\$}$	Potential confounder	BRHS, BWHHS, CAPS, EAS, ELSA, WHII, NSHD & Fenland	21631
Alcohol consumption$^{\$}$	Potential confounder	BRHS, BWHHS, CAPS, EAS, ELSA, WHII, NSHD & Fenland	21501
Social class$^{\$}$	Potential confounder	BRHS, BWHHS, CAPS, EAS, ELSA, NSHD & Fenland	8563

*Variable types as used in the multivariable/Mendelian randomization study.
$^{\$}$Only the multivariable analyses were adjusted for these confounders.
**Number of individuals with non-missing data for each trait in the analysis sample. For each UCLEB study, we included individuals who had complete data for all available genetic variants, age, sex, the liver function markers measured in the study, and were not on lipid lowering medication. For those studies that were only used to estimate the gene-outcome association (i.e.: studies where none of the liver function markers were available), we included individuals who had complete data for all available genetic variants, age and sex only.
ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; BMI: body mass index; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium – BRHS: British Regional Heart Study; BWHHS: British Women's Heart and Health Study; CaPS: Caerphilly Prospective Study; EAS: Edinburgh Artery Study; ELSA: English Longitudinal Study of Ageing; NSHD: MRC National Survey of Health and Development, WHII: Whitehall II study.

SUPPLEMENTARY DATA

Supplementary Table S2a. Distribution of participant characteristics (continuously measured variables) within each UCLEB study and the Fenland study

Variable	BRHS	BWHHS	CAPS	EAS	ELSA	WHII	NSHD	Fenland
N[1]	2090	1733	1221	762	1688	2716	1580	9982
Age (years)	69.01 (5.66)	71.55 (5.31)	56.74 (4.47)	64.51 (5.64)	73.93 (9.60)	60.39 (5.91)	53 (N/A)	48.14 (7.44)
BMI (kg/m2) [2]	26.48 (24.47, 28.83) [2077]	27 (24, 30) [1714]	26.44 (24.40, 28.67) [1202]	25.21 (23.15, 27.40) [762]	26.91 (24.36, 29.96) [1571]	26.00 (23.80, 28.60) [2708]	26.32 (24.15, 29.34) [1574]	26.16 (29.31-23.56) [9905]
Waist circumference (cm)	96.71 (10.22) [2071]	86.35 (12.28) [1707]	Not available	Not available	95.91 (12.78) [1627]	91.29 (12.18) [2713]	90.48 (12.70) [1578]	90.86 (13.43) [9899]
Physical activity (m/s2) [3]	Not available	Not available	Not available	Not available	Not available	Not available	Not available	0.11 (0.09, 0.15)
ALT (U/L) [2]	15 (12, 20)	12 (9, 15)	Not available	Not available	Not available	Not available	26 (21, 34)	25 (19, 34) [9968]
ALP (U/L) [2]	Not available	Not available	89 (75, 105)	Not available	Not available	Not available	79 (67, 94)	83 (69, 98) [9960]
AST (U/L) [2]	23 (19, 27)	22 (19, 25)	19 (16, 23)	Not available	Not available	Not available	24 (21, 29)	Not available
GGT (U/L)[2]	26 (19, 38)	20 (14, 31)	30 (22, 44)	22.50 (16.13, 33.29)	Not available	Not available	29.6 (21.6, 42.3)	26 (20, 38) [9950]
Fasting glucose (mmol/L) [2,4]	5.30 (0.65) [1820]	5.70 (0.50) [1498]	5.10 (0.49) [1055]	5.52 (0.55) [685]	4.90 (0.49) [702]	5.26 (0.49) [2509]	5.48 (0.56) [1420]	Not available
Fasting insulin (µIU/ml) [2,4]	7.70 (5.20, 11.30) [1813]	6.10 (4.40, 9.20) [1498]	4.82 (3.17, 7.10) [535]	Not available	Not available	6.7 (4.6, 10.1) [2438]	42 (28, 60) [740]	Not available
LDL cholesterol (mmol/L)	3.96 (0.98) [2060]	4.25 (1.07) [1687]	3.72 (0.88) [1178]	5.35 (1.24) [759]	3.49 (1.05) [1645]	3.62 (0.87) [2683]	3.53 (0.94) [1374]	3.43 (0.90) [9910]
HDL cholesterol (mmol/L)	1.15 (0.25) [2004]	1.62 (0.45) [1731]	1.02 (0.25) [1214]	1.45 (0.37) [759]	1.50 (0.39) [1677]	1.57 (0.45) [2715]	1.70 (0.51) [1382]	1.53 (0.41)
Total cholesterol (mmol/L)	6.29 (0.99) [2082]	6.73 (1.20) [1733]	5.60 (0.99) [1214]	7.10 (1.33) [762]	5.79 (1.27) [1678]	5.80 (0.95) [2715]	6.10 (1.03) [1473]	5.45 (1.02)
Triglycerides (mmol/L) [2]	1.71 (1.2, 2.48) [1302]	1.62 (1.21, 2.30) [1733]	1.64 (1.18, 2.34) [1214]	1.35 (1.01, 1.78) [762]	1.50 (1.1, 2.2) [1678]	1.10 (0.80, 1.60) [2715]	1.7 (1.2, 2.5) [1470]	1.0 (0.7, 1.4)

[1] Number of individuals in the analysis sample of the Mendelian randomization study. The analysis sample for each UCLEB study included individuals who had complete data for all available SNPs, age, sex, the liver function markers measured in the study, and were not on lipid lowering medication. Note that the analysis sample in UCLEB was not defined based on the availability of complete data for the potential confounders and the outcome variables. Therefore, the number of individuals included in analyses involving the confounders and the outcome variables depends on the number of individuals with non-missing data for each outcome /confounder variable in a given study and is given in brackets if it differed from the N in the analysis sample. Analysis

sample in the Fenland study included individuals who were not on lipid lowering medication and had complete data on age, sex and at least 80% of the SNPs available.

[2] Distributions for these variables are median (interquartile range; IQR) because the distributions were right skewed; all other results are means (standard deviation; SD).

[3] Physical activity was assessed as average acceleration trunk longitudinal axis (m/s2).

[4] For fasting glucose and fasting insulin we removed individuals with type 2 diabetes and/or fasting glucose values ≥ 7.0 mol/L and/or individuals who were taking glucose lowering drugs.

ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase BMI: body mass index; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium – BRHS: British Regional Heart Study; BWHHS: British Women's Heart and Health Study; CaPS: Caerphilly Prospective Study; EAS: Edinburgh Artery Study; ELSA: English Longitudinal Study of Ageing; NSHD: MRC National Survey of Health and Development, WHII: Whitehall II study; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol

SUPPLEMENTARY DATA

Supplementary Table S2b. Distribution of participant characteristics (categorical variables) within each UCLEB study and the Fenland study

Variable		BRHS	BWHHS	CaPS	EAS	ELSA	WHII	NSHD	Fenland
N*		2090	1733	1221	762	1688	2716	1580	9982
Sex	Men	2090	0	1221	369	882	2073	747	4606
	Women	0	1733	0	393	806	643	833	5376
	Missing[a]	0	0	0	0	0	0	0	0
Smoking	Never smokers	585	933	240	292	573	1345	472	5329
	Ever smokers	1503	800	978	456	1115	1368	1033	4609
	Missing[a]	2	0	3	14	0	3	75	44
Alcohol consumption	Never	78	306	70	83	173	67	309	1556
	Ever	1953	1258	1147	679	1515	2623	1271	8413
	Missing	59	169	4	0	0	26	0	13
Social class	Unskilled	62	135	59	25	344		52	
	Semi-skilled	168	171	224	56	325		147	
	Manual skilled	850	432	707	187	350		232	
	Non-manual skilled	192	214	173	139	365	Not available	359	Not available
	Managerial and lower professional	567	282	57	263	290		619	
	Professional	191	124	0	88	0		114	
	Missing	60	375	1	4	14	N/A	57	N/A
Type 2 Diabetes	Yes	251	230	149	76	210	159	127	Not available
	No	1839	1503	1072	686	1478	2557	1453	
	Missing	0	0	0	0	0	0	0	N/A

* Number of individuals in the analysis sample of the Mendelian randomization study. The analysis sample for each study included individuals who had complete data for all available SNPs, age, sex, the liver function markers measured in the study, and were not on lipid lowering medication. N/A: not applicable. UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium – BRHS: British Regional Heart Study; BWHHS: British Women's Heart and Health Study; CaPS: Caerphilly Prospective Study; EAS: Edinburgh Artery Study; ELSA: English Longitudinal Study of Ageing; NSHD: MRC National Survey of Health and Development, WHII: Whitehall II study.

SUPPLEMENTARY DATA

Supplementary Table S3. List of index SNPs associated with ALT, AST, ALP and GGT at genome-wide levels of significance ($P<5 \times 10^{-8}$) selected from published GWAS studies[1]

ıdex SNP om GWAS	Associated liver function marker	Chr	Mapped gene/s[2]	Publication Index SNP selected from	Index SNP in all relevant UCLEB studies	Genotyped/ imputed in UCLEB studies	Index SNP in Fenlan d study	Genotyped/ imputed in Fenland	Proxy SNP used if applicable	R^2 of pro with inde SNP
s6834314	ALT	4	*HSD17B13, MAPK10*	Chambers et al_2011	Yes	imputed	Yes	imputed	N/A	N/A
s2954021	ALP/ALT	8	*TRIB1*	Chambers et al_2011	Yes	imputed	Yes	imputed	N/A	N/A
11597390	ALT	10	*CPN1*	Yuan et al_2008	Yes	genotyped	Yes	genotyped	N/A	N/A
s2143571	ALT	22	*SAMM50*	Yuan et al_2008	Yes	imputed	Yes	genotyped	N/A	N/A
17109512	AST	10	*GOT1*	Shen et al_2011	Yes except in CAPS and EAS [3]	imputed	Yes	genotyped	rs7073497	1.00
rs738407	AST	22	*PNPLA3*	Novel	Yes	imputed	Yes	imputed	N/A	N/A
rs738408	AST	22	*PNPLA3*	Novel	Yes	imputed	Yes	imputed	N/A	N/A
s1780324	ALP	1	*NBPF3-ALPL*	Yuan et al_2008	Yes	genotyped	Yes	genotyped	N/A	N/A
16856332	ALP	2	*ABCB11*	Chambers et al_2011	No	N/A	Yes	genotyped	rs11892966	1.00
s9467160	ALP	6	*GPLD1*	Yuan et al_2008	Yes	imputed	Yes	genotyped	N/A	N/A
s6984305	ALP	8	*PPP1R3B*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
rs514708	ALP	9	*ABO*	Yuan et al_2008	Yes	genotyped	No	N/A	rs8176714	1.00
10819937	ALP	9	*ALDOB, C9orf125*	Chambers et al_2011	No	N/A	Yes	genotyped	No suitable proxy SNP ($R^2 \geq 0.8$) in UCLEB	N/A
rs579459	ALP	9	*ABO*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
s7923609	ALP	10	*JMJD1C, NRBF2*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
rs174601	ALP	11	*C11orf10, FADS1, FADS2*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
s2236653	ALP	11	*ST3GAL4*	Chambers et al_2011	Yes	imputed	Yes	imputed	N/A	N/A
s7186908	ALP	16	*HPR, PMFBP1*	Chambers et al_2011	Yes	imputed	Yes	imputed	N/A	N/A
rs314253	ALP	17	*ASGR1, DLG4*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
rs281377	ALP	19	*FUT2*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
s7267979	ALP	20	*ABHD12, GINS1, PYGB*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
s1497406	GGT	1	*RSG1, EPHA2*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
12145922	GGT	1	*CCBL2, PKN2*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
s1335645	GGT	1	*CEPT1, DENNDD*	Chambers et al_2011	No	N/A	Yes	genotyped	No suitable proxy SNP ($R^2 \geq 0.8$) in UCLEB	N/A
10908458	GGT	1	*DPM3, EFNA1, PKLR*	Chambers et al_2011	Yes	imputed	Yes	imputed	N/A	N/A
s1260326	GGT	2	*C2orf16, GCKR*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
13030978	GGT	2	*MYO1B, STAT4*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
s2140773	GGT	2	*EFHD1, LOC100129166*	Chambers et al_2011	Yes except in the EAS [4]	genotyped	Yes	genotyped	No suitable proxy SNP ($R^2 \geq 0.8$) in EAS	N/A
10513686	GGT	3	*SLC2A2*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
s4547811	GGT	4	*ZNF827*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
s6888304	GGT	5	*CDH6*	Chambers et al_2011	No	N/A	Yes	genotyped	No suitable proxy SNP ($R^2 \geq 0.8$) in UCLEB	N/A
s4074793	GGT	5	*ITGA1*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
s9296736	GGT	6	*MLIP*	Chambers et al_2011	Yes	genotyped	Yes	imputed	N/A	N/A
17145750	GGT	7	*MLXIPL*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A

SUPPLEMENTARY DATA

rs754466	GGT	10	*DLG5*	Chambers et al_2011	No	N/A	Yes	imputed	No suitable proxy SNP ($R^2 \geq 0.8$) in UCLEB	N/A
s7310409	GGT	12	*HNF1A, C12orf7*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
rs944002	GGT	14	*C14orf73*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
rs339969	GGT	15	*RORA*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
s8038465	GGT	15	*CD276*	Chambers et al_2011	No except in the BRHS study [5]	imputed	Yes	genotyped	rs62004612	0.87
s4581712	GGT	16	*DYNLRB2*	Chambers et al_2011	Yes except in BWHHS, EAS and CAPS [6]	imputed	Yes	genotyped	No suitable proxy SNP present in BWHHS, EAS and CAPS stuies	N/A
s9913711	GGT	17	*FLJ37644, SOX9*	Chambers et al_2011	No	N/A	Yes	genotyped	No suitable proxy SNP ($R^2 \geq 0.8$) in UCLEB	N/A
12968116	GGT	18	*ATP8B1*	Chambers et al_2011	No	N/A	Yes	genotyped	No suitable proxy SNP ($R^2 \geq 0.8$) in UCLEB	N/A
s4503880	GGT	18	*NEDD4L*	Chambers et al_2011	No	N/A	Yes	imputed	No suitable proxy SNP ($R^2 \geq 0.8$) in UCLEB	N/A
rs516246	GGT	19	*FUT2*	Chambers et al_2011	Yes	genotyped	Yes	genotyped	N/A	N/A
s4820599	GGT	22	*GGT1*	Yuan et al_2008	Yes	genotyped	Yes	genotyped	N/A	N/A
s1076540	GGT	22	*MICAL3*	Chambers et al_2011	Yes	imputed	Yes	genotyped	N/A	N/A
s2739330	GGT	22	*DDT, DDTL, GSTT1, GSTT 2B, MIF*	Chambers et al_2011	Yes	imputed	Yes	imputed	N/A	N/A

[1] SNPs mapped to the same gene, as reported in the original GWAS publications, were considered as part of the same locus. For loci where the index SNP reported for the same locus was different in independent publications, we selected the SNP that was genotyped in the UCLEB studies. If the different index SNPs reported in independent publications for the same locus were all imputed or genotyped in UCLEB, we selected the one that showed the strongest association in the largest GWAS study. We used a proxy SNP ($R^2 \geq 0.8$) if the index SNP was not present across all or some of relevant the UCLEB studies. If there was more than one eligible proxy, we selected the proxy that was genotyped in the UCLEB studies, and if all eligible proxies were genotyped or imputed we selected a proxy SNP in random. There were seven index SNPs in total (one SNP associated with ALP and six SNPs associated with GGT) that were not genotyped/imputed in any of the UCLEB studies, and did not have a suitable proxy available. These SNPs were therefore not included as genetic instruments in the UCLEB studies. However, all SNPs (or a suitable proxy) associated with a given liver function marker were available in the GWAS and Fenland studies, and were used as genetic instruments in those studies. One further GWAS has been published since we completed our search (July 2017), which found a novel rare variant associated with ALT (rs28929474; MAF=2%). Given that this variant is rare and is not available in T2D GWAS, which is the largest dataset contributing to the MR estimates, we have not included it in our analyses as it would add little information.

[2] Mapped gene for each SNP is given as reported in the original publication.

[3] Index SNP was absent in CAPS and EAS studies therefore we used the SNP rs7073497 in UCLEB studies, which is perfectly correlated with the index SNP and was available across all UCLEB studies.

[4] This SNP was not present in EAS study and there was no suitable proxy SNP present across all studies. Therefore, we did not use the EAS study to estimate the SNP-exposure and SNP-outcome for this locus.

[5] This SNP was used instead of the index SNP as it was present across all the relevant UCLEB studies and is correlated at R^2=0.87 with the

index SNP.

[6] This SNP was absent in BWHHS, EAS and CAPS and there was no suitable proxy that was available across all studies. Therefore, we did not use the BWHHS, EAS and the CAPS study to estimate the SNP-exposure and SNP-outcome for this locus.

ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; SNPs: single nucleotide polymorphisms; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium; GWAS: Genome-wide association study

SUPPLEMENTARY DATA

Supplementary Table S4. Association of novel variants with AST plasma concentration in the replication sample (NFBC1966 and NSHD studies)

SNP	Study	N	Effect size (SD units)	SE	P-value	MAF
rs738407	NFBC1966	3614	0.043	0.022	0.049	0.48
rs738407	NSHD	1580	0.088	0.057	0.120	0.34
	Overall	**5194**	**0.049**	**0.020**	**0.017**	
rs738408	NFBC1966	3614	0.071	0.026	0.006	0.23
rs738408	NSHD	1580	0.087	0.050	0.080	0.16
	Overall	**5194**	**0.075**	**0.023**	**0.001**	

The genome-wide association analyses were carried out in each individual study (BRHS, BWHHS, CaPS, EAS, and ET2DS) using the SnpStats software in R. The individual study estimates were combined using the inverse variance- fixed effect meta-analysis using the METAL software. Monomorphic SNPs, SNPs that were not sufficiently well imputed (Rsq < 0.3), and SNPs with MAF <0.001 were filtered out prior to meta-analyses. Genome-wide significance was inferred at $p< 5 \times 10^{-8}$. Two novel variants (rs738407 and rs738408) near *PNPLA3* gene were associated with AST at genome-wide levels of significance ($P<5 \times 10^{-8}$) in the discovery stage and were replicated in the MRC NHSD study (n = 1,580) (1) and 1966 Northern Finland Cohort (NFBC1966) (n = 3,614) (2). AST: aspartate aminotransferase; BRHS: British Regional Heart Study; BWHHS: British Women's Heart and Health Study; CaPS: Caerphilly Prospective Study; EAS: Edinburgh Artery Study; ET2DS: Edinburgh Type 2 Diabetes Study; MAF: minor allele frequency; NSHD: MRC National Survey of Health and Development; NFBC1966: Northern Finland Birth Cohort 1966; SD: standard deviation; SNP: single nucleotide polymorphism; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium.

SUPPLEMENTARY DATA

Supplementary Table S5. The associations of individual SNPs (used as genetic instruments for type 2 diabetes risk in Mendelian randomization analyses) with type 2 diabetes

SNP	Effect allele	Other allele	Beta	SE	P-value
rs2296173	G	A	0.065	0.009	7.7E-14
rs12088739	G	A	-0.088	0.013	9.8E-12
rs1127655	C	T	0.044	0.008	2.5E-08
rs2493394	G	A	0.073	0.011	1.2E-10
rs340874	T	C	-0.063	0.007	8.4E-18
rs2820426	A	G	-0.052	0.007	1.3E-12
rs348330	G	A	0.049	0.008	1.9E-09
rs2867125	T	C	-0.060	0.010	4.3E-10
rs780094	T	C	-0.069	0.007	5.2E-21
rs17334919	T	C	-0.140	0.013	6.7E-28
rs243019	C	T	0.057	0.007	2.3E-15
rs1009358	C	T	-0.055	0.008	9.8E-12
rs10169613	T	C	-0.043	0.008	3.6E-08
rs12617659	T	C	-0.069	0.010	2.8E-11
rs7572970	A	G	-0.059	0.009	1.4E-11
rs13389219	T	C	-0.072	0.007	2.1E-22
rs2972144	A	G	-0.091	0.008	2.6E-34
rs7561798	G	A	0.040	0.007	2.8E-08
rs1899951	T	C	-0.112	0.011	1.6E-24
rs1496653	G	A	-0.077	0.009	2.6E-18
rs11926707	T	C	-0.046	0.008	1.7E-08
rs2292662	T	C	-0.063	0.011	1.2E-08
rs6795735	T	C	-0.056	0.007	1.6E-14
rs11708067	G	A	-0.097	0.009	5.9E-29
rs9844972	C	G	0.096	0.015	1.0E-10
rs4472028	T	C	0.045	0.007	2.1E-10
rs11925227	A	G	-0.053	0.010	2.3E-08
rs7651090	G	A	0.120	0.008	3.9E-57
rs3887925	C	T	-0.047	0.008	2.5E-09
rs6808574	T	C	-0.055	0.008	4.4E-13

rs1801214	C	T	-0.090	0.007	5.5E-34
rs17086692	T	G	-0.047	0.008	2.5E-08
rs993380	A	G	0.051	0.008	4.6E-10
rs7674212	T	G	-0.047	0.008	6.2E-10
rs11098676	T	C	-0.054	0.010	2.0E-08
rs7685296	T	C	-0.051	0.008	2.3E-10
rs735949	C	T	-0.071	0.011	1.9E-11
rs1061813	G	A	0.043	0.007	3.4E-09
rs4865796	G	A	-0.053	0.008	1.3E-11
rs459193	A	G	-0.071	0.008	8.8E-18
rs3900856	A	G	0.114	0.019	7.4E-10
rs2307111	C	T	-0.041	0.007	3.0E-08
rs7729395	T	C	0.137	0.016	1.1E-17
rs10077431	A	C	-0.049	0.009	4.8E-08
rs1050226	G	A	-0.049	0.007	3.3E-11
rs7756992	G	A	0.130	0.008	6.0E-62
rs2857605	C	T	-0.067	0.009	5.9E-14
rs2071479	T	C	0.147	0.023	6.6E-11
rs9369425	G	A	0.055	0.009	1.1E-10
rs72892910	T	G	0.065	0.010	6.4E-11
rs853974	T	C	0.060	0.009	7.9E-12
rs2246012	C	T	0.053	0.009	2.4E-08
rs622217	C	T	-0.049	0.008	3.1E-10
rs17168486	T	C	0.074	0.009	2.2E-15
rs2191348	G	T	-0.065	0.007	3.4E-19
rs849135	G	A	0.100	0.007	1.0E-43
rs2908282	A	G	0.055	0.009	4.3E-09
rs2299383	T	C	0.041	0.007	1.5E-08
rs13239186	T	C	0.054	0.009	2.7E-10
rs13234269	A	T	-0.058	0.008	7.0E-14
rs7786095	G	A	-0.074	0.013	9.6E-09
rs7841082	T	C	-0.042	0.008	4.9E-08
rs11774915	T	C	0.050	0.009	8.7E-09
rs10100265	A	C	0.049	0.008	6.3E-10
rs17411031	G	C	-0.045	0.008	3.0E-08

rs10087241	G	A	0.048	0.008	2.8E-09
rs12681990	C	T	0.063	0.010	3.6E-11
rs516946	T	C	-0.082	0.009	3.2E-22
rs7845219	C	T	-0.042	0.007	4.5E-09
rs3802177	A	G	-0.122	0.008	2.3E-52
rs2294120	G	A	-0.044	0.008	1.6E-08
rs10974438	C	A	0.059	0.008	3.0E-15
rs1063192	G	A	-0.063	0.007	3.3E-18
rs10811661	C	T	-0.157	0.010	4.1E-58
rs1758632	C	G	-0.049	0.008	1.4E-09
rs17791483	G	A	-0.102	0.015	3.4E-12
rs2796441	A	G	-0.072	0.007	2.0E-22
rs10114341	C	T	-0.041	0.007	1.2E-08
rs687621	G	A	0.043	0.008	1.4E-08
rs11257655	T	C	0.074	0.009	2.0E-17
rs2616132	A	G	0.046	0.008	6.6E-09
rs2633310	T	G	-0.044	0.008	2.4E-08
rs753270	T	C	-0.053	0.008	2.7E-11
rs7923866	T	C	-0.097	0.007	9.3E-40
rs11591741	C	G	-0.048	0.008	1.2E-09
rs7903146	T	C	0.306	0.008	1.0E-200
rs4918796	C	T	0.062	0.009	4.0E-13
rs2421016	T	C	-0.046	0.007	1.5E-10
rs2237892	T	C	-0.096	0.016	8.7E-10
rs5215	C	T	0.068	0.007	2.1E-20
rs7929543	C	A	0.083	0.014	2.2E-09
rs1552224	C	A	-0.103	0.010	8.6E-25
rs10830963	G	C	0.091	0.008	5.8E-30
rs7931302	C	A	0.046	0.008	7.7E-09
rs67232546	T	C	0.060	0.010	4.7E-10
rs11048456	C	T	0.049	0.008	3.0E-09
rs10842994	T	C	-0.076	0.009	1.0E-16
rs2261181	T	C	0.099	0.012	9.2E-17
rs1480474	G	A	0.041	0.007	1.7E-08
rs7138300	C	T	0.044	0.007	5.6E-10

rs11107116	T	G	0.047	0.009	3.8E-08
rs61953351	T	G	-0.070	0.009	2.0E-14
rs940904	G	A	-0.050	0.008	2.1E-09
rs825476	C	T	-0.052	0.007	6.8E-13
rs576674	G	A	0.065	0.010	1.8E-11
rs963740	T	A	-0.048	0.009	2.2E-08
rs1359790	A	G	-0.080	0.008	2.8E-23
rs7144011	T	G	0.048	0.009	1.6E-08
rs4502156	C	T	-0.041	0.007	1.7E-08
rs982077	A	G	0.045	0.007	2.6E-10
rs7177055	G	A	-0.065	0.008	2.7E-16
rs4932143	G	C	0.057	0.009	5.5E-11
rs12910825	G	A	0.052	0.007	2.2E-12
rs9940149	A	G	-0.058	0.010	9.3E-10
rs7185735	G	A	0.106	0.007	1.6E-47
rs244415	A	G	-0.047	0.008	3.9E-09
rs77258096	A	C	-0.117	0.013	1.8E-18
rs2925979	T	C	0.053	0.008	9.1E-12
rs8068804	A	G	0.059	0.008	4.4E-14
rs12945601	T	C	0.048	0.008	1.7E-09
rs17405722	A	G	0.087	0.015	2.3E-09
rs9911983	C	T	-0.040	0.007	4.8E-08
rs9894220	G	A	-0.059	0.008	1.5E-13
rs302864	A	G	0.071	0.013	2.5E-08
rs17631783	T	C	-0.049	0.009	3.9E-08
rs7240767	C	T	0.045	0.008	2.2E-08
rs12970134	A	G	0.056	0.008	5.3E-12
rs10401969	C	T	0.092	0.013	4.1E-12
rs8108269	G	T	0.064	0.008	3.1E-16
rs6515236	C	A	-0.050	0.009	3.3E-08
rs6059662	A	G	-0.045	0.008	1.5E-08
rs4810426	T	C	0.073	0.013	2.1E-08
rs6066138	A	G	-0.049	0.008	1.9E-09
rs16988333	G	A	-0.075	0.013	9.2E-09
rs4823182	G	A	0.048	0.008	3.4E-10

SUPPLEMENTARY DATA

rs6878122	G	A	0.056	0.008	1.2E-12
rs11651755	C	T	0.074	0.008	9.0E-22
rs12299509	G	A	0.047	0.007	2.1E-10
rs1063355	T	G	-0.071	0.008	3.7E-19

SNP: single nucleotide polymorphism; SE: standard deviation. Beta and SE expressed as change in log odds ratio of T2D per effect allele.

SUPPLEMENTARY DATA

Supplementary Table S6. The associations of individual SNPs (used as genetic instruments for fasting insulin in Mendelian randomization analyses) with fasting insulin

SNP	Effect allele	Other allele	Effect allele frequency	Beta	SE	P-value
rs10195252	C	T	0.44	-0.02025	0.003291	4.87E-10
rs1121980	G	A	0.48	-0.02532	0.003165	8.36E-16
rs1167800	A	G	0.45	0.020253	0.003291	2.61E-09
rs1260326	C	T	0.42	0.024051	0.003291	3.84E-14
rs1530559	A	G	0.40	0.017722	0.003291	3.37E-08
rs2745353	T	C	0.45	0.017722	0.003165	5.48E-09
rs2820436	C	A	0.32	0.018987	0.003291	4.36E-09
rs2972143	G	A	0.37	0.017722	0.003291	3.15E-08
rs4865796	A	G	0.29	0.018987	0.003291	2.09E-08
rs731839	A	G	0.34	-0.01772	0.003291	1.72E-08
rs7903146	C	T	0.28	0.022785	0.003544	6.13E-11
rs860598	A	G	0.14	0.022785	0.004051	1.64E-08
rs983309	G	T	0.10	-0.03671	0.00481	3.81E-14
rs9884482	T	C	0.35	-0.02025	0.003038	1.40E-11

SNP: single nucleotide polymorphism; SE: standard deviation. Beta and SE expressed as change in fasting insulin (in SD log pmol/L) per effect allele.

SUPPLEMENTARY DATA

Supplementary Table S7a. Association of liver function markers-related SNPs with continuous potential confounders of the exposure-outcome associations meta-analysed across the relevant UCLEB studies and GIANT consortium data

SNP/ instrument	Potential confounders (Effect size per copy of the liver enzyme raising allele (95% CI))							
	Age (years)	BMI (SD)*	Waist circumference (SD)*	Waist-hip ratio (SD)*	ALT (SD)	AST (SD)	GGT (SD)	ALP (SD)
rs11597390	-0.13 (-0.30, 0.03)	0.00 (-0.01, 0.01)	0.01 (0.00, 0.02)	0.00 (-0.00, 0.01)	N/A	0.06 (0.03, 0.10)	0.03 (-0.00, 0.06)	-0.08 (-0.13, -0.02)
rs2143571	-0.04 (-0.26, 0.17)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	N/A	0.12 (0.07, 0.17)	0.05 (-0.00, 0.09)	0.03 (-0.04, 0.11)
rs2954021	-0.11(0.27, 0.05)	-0.01(-0.02, -0.00)	-0.01 (-0.01, 0.00)	0.00 (-0.01, 0.01)	N/A	-0.00 (-0.03, 0.03)	0.03 (-0.01, 0.06)	0.08 (0.03, 0.13)
rs6834314	0.04(-0.13, 0.22)	-0.01 (-0.02, -0.01)	-0.01 (-0.02, 0.00)	-0.00 (-0.01, 0.01)	N/A	0.04 (0.00, 0.08)	0.03 (-0.00, 0.07)	-0.03 (-0.09, 0.03)
ALT instrument	-0.07 (-0.16, 0.02)	-0.00 (-0.01, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.01)	N/A	0.05 (0.03, 0.07)	0.03 (0.01, 0.05)	-0.00 (-0.03, 0.03)
rs17109512	-0.27 (-0.99, 0.39)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)	-0.00 (-0.03, 0.02)	-0.16 (-0.31, 0.00)	N/A	-0.12 (-0.26, 0.02)	-0.13 (-0.38, 0.13)
rs738407	-0.05 (-0.30, 0.21)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.01)	0.13 (0.07, 0.19)	N/A	0.02 (-0.03, 0.07)	0.03 (-0.05, 0.12)
rs738408	-0.04 (-0.27, 0.19)	-0.01 (-0.01, 0.00)	-0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	0.13 (0.07, 0.18)	N/A	0.01 (-0.03, 0.06)	0.02 (-0.05, 0.10)
AST instrument	-0.06 (-0.22, 0.11)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.01)	0.11 (0.07, 0.15)	N/A	0.01 (-0.03, 0.04)	0.02 (-0.04, 0.07)
rs16856332	0.13 (-0.41, 0.68)	-0.01 (-0.03, 0.00)	-0.02 (-0.04, 0.00)	-0.01 (-0.03, 0.02)	0.04 (-0.09, 0.17)	-0.06 (-0.18, 0.06)	-0.11 (-0.23, -0.00)	N/A
rs174601	-0.04 (-0.20, 0.12)	0.00 (-0.00, 0.01)	0.00 (-0.00, 0.01)	0.00 (-0.00, 0.01)	-0.02 (-0.06, 0.01)	0.00 (-0.03, 0.04)	0.00 (-0.03, 0.04)	N/A
rs1780324	-0.03 (-0.18, 0.13)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.01 (-0.05, 0.02)	-0.01 (-0.04, 0.03)	0.01 (-0.03, 0.04)	N/A
rs2236653	0.16 (-0.02, 0.33)	-0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.01)	-0.00 (-0.04, 0.04)	-0.00 (-0.04, 0.03)	0.02 (-0.01, 0.06)	N/A
rs281377	0.16 (0.00, 0.33)	0.01 (0.00, 0.02)	0.01 (0.00, 0.02)	-0.01 (-0.01, 0.00)	0.00 (-0.04, 0.04)	0.00 (-0.03, 0.04)	-0.05 (-0.08, -0.01)	N/A
rs2954021	-0.11 (-0.27, 0.05)	-0.01 (-0.02, -0.00)	-0.01 (-0.01, 0.00)	0.00 (-0.01, 0.01)	0.03 (-0.00, 0.07)	-0.00 (-0.03, 0.03)	0.03 (-0.01, 0.06)	N/A
rs314253	0.15 (-0.02, 0.31)	-0.000 (-0.01, 0.01)	-0.00 (-0.01, 0.01)	-0.01 (-0.01, 0.00)	0.01 (-0.03, 0.05)	0.00 (-0.03, 0.04)	0.00 (-0.03, 0.04)	N/A
rs514708	-0.13 (-0.31, 0.05)	0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.00)	-0.01 (-0.02, -0.00)	0.02 (-0.03, 0.06)	0.07 (0.03. 0.11)	0.03 (-0.01, 0.06)	N/A
rs579459	-0.12 (-0.32, 0.07)	0.00 (-0.01, 0.01)	0.00 (-0.00, 0.01)	0.00 (-0.00, 0.01)	0.00 (-0.05, 0.05)	0.05 (0.01, 0.10)	-0.05 (-0.09, -0.01)	N/A
rs6984305	-0.00 (-0.25, 0.25)	0.00 (-0.01, 0.01)	0.01 (-0.00, 0.02)	0.01 (0.00, 0.02)	0.10 (0.04, 0.16)	0.07 (0.01, 0.12)	-0.06 (-0.11, -0.01)	N/A
rs7186908	-0.09 (-0.29, 0.12)	-0.00 (-0.01, 0.01)	-0.01 (-0.02, 0.00)	-0.00 (-0.01, 0.01)	-0.01 (-0.06, 0.04)	-0.00 (-0.05, 0.04)	-0.02 (-0.07, 0.02)	N/A
rs7267979	0.11 (-0.05, 0.26)	-0.01 (-0.01, -0.00)	-0.01 (-0.02, -0.01)	-0.01 (-0.02, -0.01)	-0.03 (-0.07, 0.01)	-0.02 (-0.05, 0.02)	0.00 (-0.03, 0.03)	N/A
rs7923609	-0.01 (-0.17, 0.15)	-0.01 (-0.02, -0.00)	-0.01 (-0.02, -0.00)	-0.02 (-0.02, -0.01)	-0.00 (-0.04, 0.03)	-0.02 (-0.05, 0.01)	-0.00 (-0.03, 0.03)	N/A
rs9467160	0.19 (0.01, 0.37)	-0.01 (-0.02, -0.00)	-0.01 (-0.02, -0.00)	-0.00 (-0.01, 0.00)	-0.03 (-0.07, 0.02)	-0.04 (-0.07, 0.00)	-0.00 (-0.05, 0.02)	N/A
ALP instrument	0.02 (-0.02, 0.07)	-0.00 (-0.00, -0.00)	-0.00 (-0.00, -0.00)	-0.00 (-0.01, -0.00)	-0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.00)	N/A
rs10513686	-0.02 (-0.26, 0.22)	0.01 (0.00, 0.02)	0.01 (-0.00, 0.02)	0.01 (-0.00, 0.02)	0.03 (-0.03, 0.08)	-0.01 (-0.06, 0.04)	N/A	-0.01 (-0.09, 0.07)
rs1076540	0.02 (-0.17, 0.22)	0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.01)	0.01 (-0.00, 0.02)	0.03 (-0.01, 0.08)	0.02 (-0.02, 0.06)	N/A	0.01 (-0.06, 0.07)
rs10908458	0.01 (-0.16, 0.17)	0.01 (-0.00, 0.01)	-0.00 (-0.01, 0.01)	-0.01 (-0.01, 0.00)	0.01 (-0.02, 0.05)	0.01 (-0.02, 0.05)	N/A	-0.01 (-0.06, 0.04)
rs12145922	-0.04 (-0.20, 0.12)	-0.01 (-0.02, -0.00)	0.00 (-0.01, 0.01)	0.01 (-0.00, 0.01)	-0.02 (-0.06, 0.01)	-0.01 (-0.04, 0.02)	N/A	-0.01 (-0.06, 0.05)
rs1260326	-0.21 (-0.37, -0.05)	-0.01 (-0.02, -0.01)	-0.01 (-0.01, -0.00)	0.00 (-0.00, 0.01)	0.03 (-0.01, 0.07)	0.03 (-0.00, 0.07)	N/A	0.04 (-0.01, 0.10)
rs12968116	SNP not in UCLEB	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)	SNP not in UCLEB	SNP not in UCLEB	N/A	SNP not in UCLEB
rs13030978	-0.07 (-0.33, 0.19)	-0.00 (-0.01, 0.01)	-0.01 (-0.01, 0.00)	-0.00 (-0.01, 0.01)	0.02 (-0.04, 0.08)	0.04 (-0.02, 0.09)	N/A	-0.09 (-0.17, -0.00)
rs1335645	SNP not in UCLEB	0.01 (-0.00, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)	SNP not in UCLEB	SNP not in UCLEB	N/A	SNP not in UCLEB
rs1497406	0.08 (-0.12, 0.27)	-0.01 (-0.01, 0.00)	-0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	0.01 (-0.03, 0.06)	0.02 (-0.02, 0.06)	N/A	-0.01 (-0.08, 0.05)
rs17145750	0.04 (-0.17, 0.25)	-0.01 (-0.02, -0.00)	-0.00 (-0.01, 0.01)	0.01 (0.00, 0.02)	-0.06 (-0.11, -0.01)	-0.04 (-0.09, 0.00)	N/A	0.01 (-0.06, 0.08)
rs2140773	-0.08 (-0.25, 0.09)	0.00 (-0.00, 0.01)	0.00 (-0.01, 0.01)	0.01 (-0.00, 0.01)	-0.00 (-0.04, 0.04)	-0.02 (-0.05, 0.02)	N/A	-0.03 (-0.08, 0.02)
rs2739330	0.09 (-0.10, 0.28)	-0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.00)	0.00 (-0.01, 0.01)	-0.02 (-0.06, 0.03)	-0.00 (-0.04, 0.04)	N/A	0.04 (-0.02, 0.10)
rs339969	-0.13 (-0.31, 0.06)	0.01 (0.01, 0.02)	0.01 (-0.002, 0.02)	-0.00 (-0.01, 0.01)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)	N/A	-0.01 (-0.07, 0.05)

SUPPLEMENTARY DATA

SNP/ instrument	Potential confounders (Effect size per copy of the liver enzyme raising allele (95% CI))							
	Age (years)	BMI (SD)*	Waist circumference (SD)*	Waist-hip ratio (SD)*	ALT (SD)	AST (SD)	GGT (SD)	ALP (SD)
SNP/ instrument	Age (years)	BMI (SD)	Waist circumference (SD)	Waist-hip ratio (SD)	ALT (SD)	AST (SD)	GGT (SD)	ALP (SD)
rs4074793	-0.04 (-0.34, 0.26)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.00 (-0.01, 0.02)	0.07 (-0.00, 0.14)	0.04 (-0.03, 0.10)	N/A	0.11 (0.01, 0.21)
rs4503880	SNP not in UCLEB	-0.00 (-0.01, 0.01)	-0.00 (-0.02, 0.01)	-0.00 (-0.02, 0.01)	SNP not in UCLEB	SNP not in UCLEB	N/A	SNP not in UCLEB
rs4547811	0.12 (-0.13, 0.37)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.01)	0.06 (0.00, 0.12)	0.04 (-0.01, 0.09)	N/A	0.04 (-0.04, 0.13)
rs4581712	-0.12 (-0.57, 0.32)	0.00 (-0.00, 0.01)	0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.01)	0.02 (-0.07, 0.11)	-0.00 (-0.10, 0.09)	N/A	0.03 (-0.11, 0.18)
rs4820599	-0.09 (-0.27, 0.08)	-0.003 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.03 (-0.07, 0.01)	-0.02 (-0.06, 0.02)	N/A	-0.00 (-0.06, 0.06)
rs516246	-0.16 (-0.31, -0.00)	-0.01 (-0.01, -0.00)	-0.01 (-0.01, 0.00)	0.01 (-0.02, 0.01)	-0.00 (-0.04, 0.04)	0.00 (-0.03, 0.04)	N/A	-0.06 (-0.11, -0.01)
rs6888304	SNP not in UCLEB	-0.01 (-0.01, 0.00)	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)	SNP not in UCLEB	SNP not in UCLEB	N/A	SNP not in UCLEB
rs7310409	0.00 (-0.16, 0.17)	0.00 (-0.00, 0.01)	0.00 (-0.00, 0.01)	0.01 (0.00, 0.01)	-0.01 (-0.04, 0.03)	-0.00 (-0.03, 0.03)	N/A	-0.07 (-0.13, -0.02)
rs754466	SNP not in UCLEB	-0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.05)	0.00 (-0.01, 0.01)	SNP not in UCLEB	SNP not in UCLEB	N/A	SNP not in UCLEB
rs8038465	0.11 (-0.12, 0.34)	-0.00 (-0.01, 0.01)	-0.01 (-0.01, 0.00)	-0.00 (-0.01, 0.01)	0.06 (0.00, 0.11)	0.03 (-0.02, 0.08)	N/A	-0.03 (-0.11, 0.04)
rs9296736	0.09 (-0.08, 0.26)	0.01 (0.00, 0.01)	0.01 (-0.00, 0.01)	0.00 (-0.01, 0.01)	0.03 (-0.01, 0.07)	-0.01 (-0.04, 0.03)	N/A	-0.00 (-0.06, 0.05)
rs944002	-0.24 (-0.42, -0.06)	-0.00 (-0.01, 0.01)	-0.00 (-0.02, 0.01)	-0.00 (-0.01, 0.01)	-0.01 (-0.05, 0.04)	-0.01 (-0.05, 0.03)	N/A	-0.01 (-0.07, 0.05)
rs9913711	SNP not in UCLEB	-0.00 (-0.01, 0.01)	-0.01 (-0.01, 0.00)	-0.01 (-0.02, 0.00)	SNP not in UCLEB	SNP not in UCLEB	N/A	SNP not in UCLEB
GGT instrument	-0.04 (-0.08, 0.00)	-0.00 (-0.00, 0.00)	-0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)	0.00 (-0.00, 0.02)	0.00 (-0.00, 0.01)	N/A	-0.01 (-0.02, 0.00)

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; BMI: body mass index; N/A: not applicable; SD: standard deviation; SNPs: single nucleotide polymorphisms. GIANT: The Genetic Investigation of Anthropometric Traits. *Summary-level data publicly available from the GIANT consortium was used for these traits in addition to the data from the relevant UCLEB studies.

SUPPLEMENTARY DATA

Supplementary Table S7b. Association of liver function markers-related SNPs with potentially confounding dichotomous traits meta-analysed across the relevant UCLEB studies.

	Potential confounders (Odds ratio per copy of the liver function marker raising allele (95% CI))			
SNP/ instrument	Sex	Smoking	Alcohol consumption	Social class
rs11597390	0.98 (0.91, 1.06)	0.97 (0.92, 1.02)	1.08 (0.98, 1.18)	1.06 (1.00, 1.14)
rs2143571	0.99 (0.89, 1.09)	1.01 (0.93, 1.09)	1.09 (0.96, 1.25)	1.08 (0.99, 1.18)
rs2954021	0.98 (0.91, 1.05)	1.03 (0.98, 1.09)	1.00 (0.92, 1.10)	1.00 (0.94, 1.06)
rs6834314	0.99 (0.92, 1.07)	0.99 (0.93, 1.05)	0.95 (0.86, 1.06)	1.01 (0.94, 1.08)
ALT instrument	0.98 (0.95, 1.02)	1.00 (0.97, 1.03)	1.02 (0.97, 1.08)	1.03 (1.00, 1.07)
rs17109512	1.09 (0.79, 1.52)	0.87 (0.68, 1.11)	1.37 (0.94, 1.99)	0.83 (0.63, 1.10)
rs738407	1.07 (0.95, 1.20)	1.00 (0.92, 1.10)	1.01 (0.87, 1.17)	1.02 (0.92, 1.13)
rs738408	1.01 (0.92, 1.12)	0.99 (0.91, 1.07)	1.03 (0.90, 1.17)	1.06 (0.97, 1.16)
AST instrument	1.04 (0.97, 1.12)	0.99 (0.93, 1.05)	1.04 (0.95, 1.14)	1.03 (0.96, 1.10)
rs10819937	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB
rs16856332	0.99 (0.76, 1.29)	0.95 (0.78, 1.15)	1.07 (0.78, 1.47)	1.07 (0.85, 1.33)
rs174601	1.03 (0.96, 1.11)	0.98 (0.93, 1.04)	0.95 (0.86, 1.04)	1.00 (0.94, 1.07)
rs1780324	0.97 (0.90, 1.04)	0.93 (0.88, 0.99)	0.97 (0.89, 1.07)	1.04 (0.98, 1.11)
rs2236653	0.90 (0.84, 0.98)	0.98 (0.92, 1.04)	0.95 (0.86, 1.04)	0.98 (0.91, 1.05)
rs281377	1.06 (0.99, 1.14)	0.95 (0.90, 1.00)	0.96 (0.87, 1.05)	1.04 (0.98, 1.11)
rs2954021	0.98 (0.91, 1.05)	1.03 (0.98, 1.09)	1.00 (0.92, 1.10)	1.00 (0.94, 1.06)
rs314253	0.96 (0.90, 1.04)	0.99 (0.93, 1.04)	1.04 (0.95, 1.15)	1.01 (0.94, 1.07)
rs514708	0.98 (0.90, 1.06)	0.96 (0.91, 1.02)	1.09 (0.98, 1.21)	1.03 (0.95, 1.10)
rs579459	1.01 (0.93, 1.11)	0.99 (0.92, 1.06)	1.03 (0.92, 1.15)	1.05 (0.97, 1.13)
rs6984305	1.03 (0.92, 1.16)	0.97 (0.89, 1.05)	1.04 (0.90, 1.21)	1.03 (0.93, 1.14)
rs7186908	1.05 (0.95, 1.15)	1.05 (0.98, 1.12)	1.02 (0.91, 1.15)	1.06 (0.98, 1.15)
rs7267979	1.05 (0.97, 1.12)	1.01 (0.96, 1.07)	1.01 (0.92, 1.10)	1.03 (0.96, 1.09)
rs7923609	1.00 (0.93, 1.08)	1.05 (0.99, 1.11)	1.01 (0.92, 1.11)	1.04 (0.97, 1.11)
rs9467160	0.99 (0.91, 1.07)	0.98 (0.92, 1.04)	1.01 (0.91, 1.12)	1.05 (0.98, 1.13)
ALP instrument	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)	1.00 (0.98, 1.03)	1.03 (1.01, 1.05)
rs10513686	0.93 (0.84, 1.04)	0.98 (0.90, 1.06)	0.99 (0.86, 1.14)	0.99 (0.90, 1.09)
rs1076540	0.93 (0.86, 1.02)	1.02 (0.96, 1.09)	1.08 (0.97, 1.20)	0.96 (0.88, 1.03)
rs10908458	0.96 (0.89, 1.04)	0.99 (0.94, 1.05)	1.01 (0.92, 1.02)	1.02 (0.96, 1.09)
rs12145922	1.04 (0.97, 1.12)	0.95 (0.90, 1.01)	0.97 (0.89, 1.07)	1.00 (0.93, 1.06)
rs1260326	0.98 (0.91, 1.05)	0.98 (0.93, 1.04)	0.91(0.83, 1,00)	0.98 (0.92, 1.04)
rs12968116	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB
rs13030978	0.92 (0.82, 1.04)	1.08 (0.99, 1.19)	0.87 (0.75, 1.01)	0.94 (0.84, 1.04)
rs1335645	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB
rs1497406	1.04 (0.95, 1.14)	1.01 (0.94, 1.08)	0.96 (0.85, 1.07)	1.01 (0.94, 1.10)
rs17145750	1.00 (0.91, 1.10)	0.97 (0.90, 1.04)	0.89 (0.78, 1.01)	0.98 (0.90, 1.06)

rs2140773	1.05 (0.97, 1.13)	0.96 (0.91, 1.02)	1.01 (0.92, 1.11)	1.05 (0.98, 1.12)
rs2739330	1.08 (0.99, 1.18)	1.01 (0.94, 1.07)	0.88 (0.78, 0.98)	0.98 (0.91, 1.06)
rs339969	0.97 (0.89, 1.05)	1.03 (0.96, 1.09)	0.96 (0.86, 1.07)	1.01 (0.94, 1.09)
rs4074793	0.94 (0.82, 1.09)	1.02 (0.92, 1.13)	1.02 (0.86, 1.22)	0.90 (0.80, 1.02)
rs4503880	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB
rs4547811	1.06 (0.94, 1.19)	0.96 (0.88, 1.05)	0.97 (0.84, 1.12)	1.03 (0.93, 1.14)
rs4581712	0.91 (0.78, 1.07)	1.02 (0.89, 1.17)	1.12 (0.88, 1.44)	0.89 (0.76, 1.05)
rs4820599	0.97 (0.89, 1.05)	1.03 (0.97, 1.09)	1.00 (0.91, 1.11)	1.01 (0.94, 1.08)
rs516246	0.95 (0.88, 1.02)	1.05 (0.99, 1.11)	1.06 (0.97, 1.16)	0.96 (0.90, 1.02)
rs6888304	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB
rs7310409	0.97 (0.90, 1.04)	0.97 (0.92, 1.03)	1.04 (0.95, 1.14)	1.05 (0.98, 1.12)
rs754466	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB
rs8038465	0.97 (0.88, 1.08)	1.02 (0.94, 1.10)	1.08 (0.95, 1.24)	1.03 (0.93, 1.13)
rs9296736	1.04 (0.96, 1.13)	0.98 (0.92, 1.04)	0.95 (0.86, 1.04)	1.05 (0.98, 1.12)
rs944002	0.98 (0.90, 1.07)	1.05 (0.99, 1.12)	1.04 (0.94, 1.16)	1.00 (0.93, 1.08)
rs9913711	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB	SNP not in UCLEB
GGT instrument	0.99 (0.97, 1.01)	1.00 (0.99, 1.02)	0.99 (0.96, 1.01)	1.00 (0.98, 1.02)

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; SNPs: single nucleotide polymorphisms; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium

SUPPLEMENTARY DATA

Supplementary Table S8. Fully adjusted multivariable regression and Mendelian Randomization associations / effects of liver function markers with continuous outcomes meta-analysed across UCLEB, Fenland* and GWAS studies

	Mean difference (in S.D units) for each continuous outcome per one S.D increase in each liver function marker (95% CI)					
	Glucose (mmol/L)	**Insulin (μIU/ml)**	**HDL-C (mmol/L)**	**LDL-C (mmol/L)**	**Total cholesterol (mmol/L)**	**Triglycerides (mmol/L)**
ALT						
Multivariable	0.08 (-0.03, 0.19)	0.19 (0.11, 0.28)	-0.01 (-0.04, 0.02)	0.03 (-0.03, 0.08)	0.06 (0, 0.11)	0.1 (0.05, 0.15)
MR-IVW	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.06)	-0.09 (-0.35, 0.16)	0.08 (-0.33, 0.48)	0.05 (-0.39, 0.48)	0.07 (-0.45, 0.59)
MR-Egger	0.12 (-0.11, 0.34)	0.08 (-0.13, 0.29)	0.62 (0.16, 1.09)	-0.75 (-1.54, 0.04)	-0.8 (-1.7, 0.11)	-1.07 (-2.16, 0.02)
MR-Weighted median	-0.02 (-0.17, 0.12)	0 (-0.08, 0.08)	-0.09 (-0.25, 0.07)	-0.1 (-0.2, 0.01)	-0.11 (-0.21, -0.01)	-0.06 (-0.16, 0.04)
AST						
Multivariable	0 (-0.04, 0.04)	0.05 (0.01, 0.09)	0.06 (0.04, 0.09)	-0.02 (-0.05, 0.01)	0.01 (-0.02, 0.03)	0.02 (-0.04, 0.07)
MR-IVW	-0.01 (-0.07, 0.04)	0.01 (-0.04, 0.06)	-0.09 (-0.15, -0.04)	-0.07 (-0.13, -0.01)	-0.11 (-0.17, -0.04)	0.03 (-0.03, 0.08)
MR-Egger	0.01 (-0.18, 0.2)	0.08 (-0.03, 0.18)	-0.06 (-0.19, 0.07)	-0.17 (-0.31, -0.02)	-0.21 (-0.34, -0.07)	-0.03 (-0.16, 0.09)
MR-Weighted median	-0.01 (-0.06, 0.04)	0.01 (-0.04, 0.06)	-0.09 (-0.15, -0.03)	-0.07 (-0.13, -0.01)	-0.11 (-0.17, -0.04)	0.02 (-0.03, 0.08)
ALP						
Multivariable	0.01 (-0.04, 0.06)	0.02 (-0.03, 0.08)	-0.04 (-0.08, -0.01)	0.02 (-0.04, 0.07)	0.02 (-0.04, 0.07)	0.05 (0, 0.1)
MR-IVW	-0.03 (-0.08, 0.03)	-0.01 (-0.04, 0.01)	-0.06 (-0.13, 0.02)	-0.17 (-0.28, -0.06)	-0.16 (-0.28, -0.04)	0.08 (-0.07, 0.24)
MR-Egger	-0.06 (-0.22, 0.1)	0 (-0.05, 0.04)	-0.07 (-0.35, 0.21)	-0.27 (-0.46, -0.07)	-0.25 (-0.45, -0.05)	0.03 (-0.28, 0.34)
MR-Weighted median	-0.03 (-0.06, 0)	-0.01 (-0.04, 0.02)	-0.03 (-0.12, 0.06)	-0.2 (-0.34, -0.06)	-0.19 (-0.31, -0.08)	0.03 (-0.05, 0.12)
GGT						
Multivariable	0.07 (0.02, 0.11)	0.1 (0.04, 0.16)	0.04 (0.01, 0.07)	0.05 (0, 0.1)	0.11 (0.06, 0.16)	0.15 (0.1, 0.2)
MR-IVW	-0.05 (-0.12, 0.03)	-0.02 (-0.07, 0.02)	-0.04 (-0.08, 0)	-0.03 (-0.1, 0.03)	0.02 (-0.07, 0.11)	0.16 (0.02, 0.3)
MR-Egger	0.07 (-0.11, 0.24)	0.1 (-0.01, 0.22)	-0.07 (-0.17, 0.03)	-0.11 (-0.38, 0.16)	-0.17 (-0.37, 0.02)	-0.14 (-0.44, 0.17)
MR-Weighted median	0 (-0.11, 0.11)	-0.01 (-0.05, 0.03)	-0.03 (-0.07, 0.01)	-0.06 (-0.15, 0.03)	-0.04 (-0.11, 0.04)	0 (-0.04, 0.04)

*Fenland study was only included in the instrumental variables analyses of the associations between the exposures ALT, ALP, GGT and lipid outcomes. IVW: inverse-variance weighted method. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium; GWAS: Genome-wide association study; MR: Mendelian randomization; IVW: Inverse variance weighted estimator; S.D: standard deviation; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol

SUPPLEMENTARY DATA

Supplementary Table S9. MR-Egger intercept values (pooled across UCLEB, Fenland and GWAS studies)

Liver function marker	Mean difference (S.D) of each continuous outcome per one S.D increase in the liver function marker (95% CI)					
	Glucose (mmol/L)	Insulin (μIU/ml)	HDL-C (mmol/L)	LDL-C (mmol/L)	Total cholesterol (mmol/L)	Triglycerides (mmol/L)
ALT						
MR-Egger intercept	-0.01 (-0.02, 0.01)	0 (-0.01, 0.01)	-0.04 (-0.06, -0.01)	0.05 (0.02, 0.09)	0.06 (0.02, 0.1)	0.06 (0.01, 0.12)
AST						
MR-Egger intercept	0.03 (-0.01, 0.07)	0.01 (-0.02, 0.04)	0 (-0.02, 0.03)	0.01 (-0.05, 0.07)	0.01 (-0.06, 0.08)	0.01 (-0.02, 0.03)
ALP						
MR-Egger intercept	0.01 (-0.01, 0.02)	0 (-0.01, 0.01)	0 (-0.03, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)
GGT						
MR-Egger intercept	-0.01 (-0.03, 0)	-0.01 (-0.02, 0)	0 (-0.01, 0.01)	0.01 (-0.02, 0.03)	0.01 (0, 0.03)	0.02 (0, 0.04)

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium; GWAS: Genome-wide association study; MR: Mendelian randomization; IVW: Inverse variance weighted estimator; S.D: standard deviation

SUPPLEMENTARY DATA

References

1. Wadsworth M, Kuh D, Richards M, Hardy R. Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development). Int J Epidemiol. 2006;35(1):49-54.
2. Rantakallio P. The longitudinal study of the northern Finland birth cohort of 1966. Paediatr Perinat Epidemiol. 1988;2(1):59-88.