Supplemental material

Genetically predicted glucose-dependent insulinotropic polypeptide (GIP) levels and cardiovascular disease risk are driven by distinct causal variants in the *GIPR* region

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Outcome type	Outcome Type 2 diabetes *		Non-cases (for case-control studies) or participants (for continuous trait studies) overall, N	Participating study	PubMed ID for cohort description	
	Type 2 diabetes *	74,124	842,006	DIAMANTE	30297969	
	Type 2 diabetes (BMI adjusted) *	74,124	842,006	DIAMANTE	30297969	
	Coronary artery disease *	34,541	261,984	CARDIoGRAMplusC4D, UK Biobank	29212778	
	Any Stroke *	40,585				
	Any Ischemic Stroke *	34,217				
	Cardioembolic Stroke *	7,193	406,111	MEGASTROKE	29531354	
_	Large Artery Stroke *	4,373				
	Small Vessel Stroke *	5,386				
	Abdominal Aortic Aneurysm *	1,094	366,492			
	Atrial Fibrillation *	16,945	350,641			
	Aortic Valve Stenosis *	2,244	365,342			
Disease outcomes	Coronary Artery Disease *	29,278	338,308			
	Deep Vein Thrombosis *	9,454	358,132			
	Haemorrhagic Stroke (all) *	1,981	365,605			
	Heart Failure *	6,712	360,874			
	Ischaemic Cerebrovascular Disease (all) *	8,084	359,502			
	Pulmonary Embolism *	6,148	361,438	UK Biobank	31756303	
	Peripheral Vascular Disease *	3,415	364,171			
	Thoracic Aortic Aneurysm *	347	367,239			
	Transient Ischaemic Attack *	3,962	363,624			
	Intracerebral Haemorrhage *	1,064	366,522			
	Subarachnoid Haemorrhage *	1,084	366,502			
	Ischaemic Stroke *	4,602	362,984			
	Ischaemic stroke plus haemorrhagic stroke plus unknown stroke (but not TIA) *	9,652	357,934			
	Venous Thromboembolism (all) *	14,097	353,489			
	Fasting glucose (BMI adjusted) *		51,750	MAGIC	22581228	
	Non-fasted plasma glucose †		414,042	UK Biobank; InterAct	25826379	
Glycaemic	2-hr glucose (BMI adjusted) *		41,888	MAGIC	20081857	
outcomes	Fasting insulin (BMI adjusted) *		51,750	MAGIC	22581228	
	Corrected insulin response *		5,318	MAGIC	24699409	
	HbA1C †		453,443	UK Biobank; InterAct	25826379	
	Apolipoprotein A1 †		413,834			
	High-density lipoprotein †		348,236			
Cardiovascular	Apolipoprotein B †		450,487			
and lipid-related	Low-density lipoprotein †		377,025	UK Biobank; InterAct	25826379	
outcomes	Lipoprotein A †		408,307			
	Total cholesterol †		378,287			
-	Triglycerides †		452,256			

Table S1. Summary of the participating studies.

Outcome type	Outcome type Outcome C-reactive protein †		Non-cases (for case-control studies) or participants (for continuous trait studies) overall. N	Participating study	PubMed ID for cohort description	
	C-reactive protein †		451,697			
	BMI †		738,628			
	Hip circumference †		568,765			
Anthropometric	Hip circumference (BMI adjusted) †		633,860			
Anthropometric	Waist circumference †		654,577	GIANT, UK Biobank	25673413;	
outcomes	Waist circumference (BMI adjusted) †		654,253		23820379	
	Waist-to-hip ratio †		636,672			
	Waist-to-hip ratio (BMI adjusted) †		636,282			
	Albumin †		415,862			
	Alkaline phosphatase †		450,882			
	Alanine aminotransferase †		452,402			
Additional	Aspartate transaminase †		450,704			
biomarker	Bilirubin †		450,276	UK Biobank; InterAct	25826379	
outcomes	Calcium †		414,310			
	Creatinine †		452,088			
	Gamma-glutamyl transpeptidase †		452,375			
	Urate †		451,881			
	Android fat mass †					
	Arms fat mass †					
	Gynoid fat mass †					
	Legs fat mass †					
	Peripheral fat mass †					
	Subcutaneous fat mass †					
D · I I · ·/	Total fat mass †					
outcomes	Trunk fat mass †		425.207		2592(270	
(measured by bio-	Visceral fat mass †		435,387	UK Biobank	25826379	
impedance)	Appendicular lean mass †					
	Android lean mass †					
	Arms lean mass †					
	Gynoid lean mass †					
	Legs lean mass †					
	Total lean mass †					
	Trunk lean mass †					
Plasma proteins	4,979 proteins †		10,708	Fenland	27841877	
Metabolites	1,008 metabolites †		11,539	EPIC-Norfolk	10466767	
GIP measures	Fasting and 2hr GIP *		7,828	MDC and PPP-Botnia	29093273	

*Publicly available datasets, the phenotype definitions of which can be found in the original studies (PMID provided) †In-house datasets, the phenotype definitions of which can be found in Table S3

Study	Fenland *	EPIC-Norfolk *	UK Biobank *
Participants, N	10,708	11,539 ‡	452,197
Age at baseline, mean years (SD)	49 (7)	60 (9)	57 (8)
Women, N (%)	5,714 (53)	6,198 (54)	245,277 (54)
Men, N (%)	4,994 (47)	5,341 (46)	206,883 (46)
BMI in kg/m2, mean (SD)	26.9 (4.9)	26.2 (3.7)	27.4 (4.8)
Waist-to-hip ratio, mean (SD)	0.74 (0.08)	0.86 (0.09)	0.87 (0.09)
Systolic blood pressure in mmHg, mean (SD)	123 (15)	136 (18)	138 (19)
Diastolic blood pressure in mmHg, mean (SD)	74 (10)	82 (11)	82 (10)
Fasting glucose in log-pg/mL, median (IQR) †	1.57 (1.50, 1.63)	N/A	N/A
2-hr glucose in log-pg/mL, median (IQR) †	1.63 (1.44, 1.79)	N/A	N/A
Fasting insulin in log-pg/mL, median (IQR) †	3.66 (3.29, 4.06)	N/A	N/A
Study stage	2SMR, colocalisation, conditional analyses	2SMR	2SMR §
Participants with prevalent T2D, N	N/A	N/A ¶	22,610

Table S2. Study participants.

Abbreviations: N/A, not available; N, number of participants; SD, standard deviation; BMI, body mass index; mmHg; Millimetres Mercury; pg; Picograms; mL, Millilitres; IQR, Interquartile range

*The relevant outcomes that make use of data from each study are described in Table S1

†Glycaemic measures from Epic-Norfolk and UK Biobank were not used in this study ‡Participants used in the plasma metabolite GWAS sample

[§]The publicly available GWAS dataset¹ included UK Biobank samples, however, this table only describes samples used for in-house GWAS analyses.

||Participants with prevalent T2D were excluded from the study cohort as part of the exclusion criteria ||Only participants from the quasi-randomly selected samples were used, excluding participants with prevalent T2D

Table S3: Description of the GWAS analyses for in-house datasets and the quality control procedures
applied.

Cohort	Trait	Measurement	Transformations applied	Covariates	Variant-level QC ‡‡
Fenland*	Plasma proteins†	Described in main text	Rank-based inverse normal within each genotyping subset	Age, sex, sample collection site and 10 genetic principal components	MAF < 0.001, Imputation quality < 0.4, HWE P-value < 1x10 ⁻⁷
Fenland	Fasting insulin, fasting glucose, 2hr glucose‡	Fasting glucose and insulin were measured in whole blood after overnight fast. 2hr glucose was measured in plasma two-hours after a 75-gram oral glucose challenge. Glucose levels were quantified using the Dimension RxL Integrated Chemistry System (Siemens, Germany). Insulin levels were quantified using the 1235 AutoDELFIA automatic immunoassay system using a two-step time resolved fluorometric assay (Kit No. B080-101, Perkin Elmer, USA). Individuals were excluded if they had prevalent type 1 or type 2 diabetes (defined by physician diagnosis); reported use of diabetes medication(s); or had fasting glucose levels >=7 mmol/L, 2-hr glucose levels >=11.1mmol/L, or HbA1c >= 6.5%.	Fasting and 2hr glucose: untransformed; fasting insulin: natural log	Age, sex, BMI and the first 10 principal components§	Call rate (< 95%), HWE P<1x10 ⁻⁶ , imputation quality < 0.4, MAF < 1%, tri- allelic, MAC<3, SE<0, SE>10, missing beta or SE or imputation quality estimate ¶
EPIC- Norfolk*	Plasma metabolites	Described in main text	Natural log- transformed and winsorised to 5 SD	Age, sex and measurement batch	Imputation quality < 0.4, MAC < 10, HWE P<1x10 ⁻⁶ , abs(beta) > 10, SE<0, SE>10, MAF < 0.0001 #
UK Biobank and InterAct*	ApoA1, HbA1c, HDL, ApoB, LDL, LpA, Total cholesterol, Triglycerides, CRP, Albumin, ALP, ALT, AST, Bilirubin, Calcium, Creatinine, γ- GGT, Urate	All biomarkers in InterAct, except HbA1c, were measured using a Cobas® (Roche Diagnostics, Mannheim, Germany) assay on a Roche Hitachi Modular P analyser. HbA1c was measured on erythrocyte samples using a Tosoh (HLC-723G8) assay on a Tosoh G8 analyser.	Raw measures regressed on age, age2, sex, centre and 10 genetic principal components to generate residuals which were then rank-based inverse normal transformed within each study **	Age, age2, sex, aliquot, genotyping chip, lipid lowering medication and the top 40 principal components	Imputation quality < 0.4, MAC < 10, HWE P<1x10 ⁻⁶ , abs(beta) > 10, SE<0, SE>10, MAF < 0.0001

UK Biobank and GIANT*	BMI, Hip circumference, Hip circumference adj. BMI, Waist circumference, Waist circumference adj. BMI, WHR, WHRadjBMI	In UK Biobank, weight was measured using a calibrated electronic scale (TANITA model BC-418 MA; Tanita, Tokyo, Japan). Height was measured with a wall-mounted stadiometer (SECA 202; Seca, Birmingham, United Kingdom). BMI (in kg/m2) was calculated as weight divided by height squared. Waist and hip circumferences were measured with a non-stretchable sprung tape measure (Wessex tape, London, United Kingdom). WHR was the ratio between the waist and hip circumferences.	Residuals were generated for each sex independently by regressing each outcome against age, age ² , study- specific covariates and BMI (if applicable) then rank-based inverse normal transformed	Age, sex, genotyping chip, and the top 40 principal components.	Imputation quality < 0.4, MAC < 10, HWE P<1x10 ⁻⁶ , abs(beta) > 10, SE<0, SE>10, MAF < 0.0001 ††
UK Biobank	Bio-impedance	Tanita BC418MA body composition analyser (Amsterdam, The Netherlands)	Natural log- transformed and regressed on age (and total fat mass or height ² – if adjusted) in each sex separately to generate residuals. Residuals were then rank-based inverse normal transformed	Age, sex, genotyping chip, and the top 40 principal components.	Imputation quality < 0.4, MAC < 10, HWE P<1x10 ⁻⁶ , abs(beta) > 10, SE<0, SE>10, MAF < 0.0001

Abbreviations: MAF, Minor allele frequency; MAC, Minor allele count; HWE, Hardy-Weinberg equilibrium; SE, Standard error; BMI, Body mass index; adj., Adjusted for; WHR, Waist-to-hip ratio; ApoA1, Apolipoprotein A1; HbA1c, Glycated haemoglobin; HDL, High density lipoprotein cholesterol; ApoB, Apolipoprotein B; LDL, Low density lipoprotein cholesterol; LpA, Lipoprotein A; CRP, C-reactive protein; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate transaminase; γ-GGT, Gamma-glutamyl transpeptidase

*Studies or genotyping subsets were meta-analysed using inverse variance weighted fixed effect meta-analysis in METAL

†GWAS conducted using BGENIE v1.3

‡GWAS conducted using SNPTEST v2.4.1

§Fasting insulin and fasting glucose were also adjusted for age²

Only variants present in the largest genotyping subset were taken forward

Only samples genotyped using the Affymetrix UK Biobank Axiom Array were included

#If BOLT-LMM failed, related individuals were excluded (IBD > 0.185) and linear regression models were run using SNPTEST v2.4.1, while also adjusting for the top 4 principal components

**Traits measured in UK Biobank were also rank-based inverse normal transformed within each respective aliquot.

††Variant-level QC only applies to UK Biobank, as GIANT data was publicly available

##Variants were excluded if they were outside of the thresholds listed

Table S4: Clusters of colocalised traits identified by the main analysis across the permutations of prior 2 and the regional and alignment thresholds (prior 2: 0.02, 0.01 and 0.001; thresholds: 0.5, 0.6, 0.7, 0.8 and 0.9). A total of 418 variants were included.

Locus	Colocalised traits	PP Coloc	Candidate variant	PP explained	Prior 2	Regional and alignment threshold
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.5
GIPR	Glucose, HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.7248	rs4420638	1	0.02	0.5
GIPR	GIP SOMAmer 16292 288, Fasting GIP, 2hr GIP, BMI, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9782	rs1800437	1	0.02	0.5
GIPR	T2D, T2DadjBMI	0.979	rs8108269	0.9967	0.02	0.5
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.6
GIPR	Glucose, HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.7248	rs4420638	1	0.02	0.6
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9782	rs1800437	1	0.02	0.6
GIPR	T2D, T2DadjBMI	0.979	rs8108269	0.9967	0.02	0.6
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.7
GIPR	Glucose, HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.7248	rs4420638	1	0.02	0.7
GIPR	GIP SOMAmer 16292 288, Fasting GIP, 2hr GIP, BMI, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9782	rs1800437	1	0.02	0.7
GIPR	T2D, T2DadjBMI	0.979	rs8108269	0.9967	0.02	0.7
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.8
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9994	rs4420638	1	0.02	0.8
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI		rs1800437	1	0.02	0.8
GIPR	T2D, T2DadjBMI	0.979	rs8108269	0.9967	0.02	0.8
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.9
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9994	rs4420638	1	0.02	0.9
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9737	rs1800437	1	0.02	0.9
GIPR	T2D, T2DadjBMI	0.979	rs8108269	0.9967	0.02	0.9
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.5
GIPR	Glucose, HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.5725	rs4420638	1	0.01	0.5
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9584	rs1800437	1	0.01	0.5
GIPR	T2D, T2DadjBMI	0.9589	rs8108269	0.9967	0.01	0.5
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.6
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9989	rs4420638	1	0.01	0.6
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9499	rs1800437	1	0.01	0.6
GIPR	T2D, T2DadjBMI	0.9589	rs8108269	0.9967	0.01	0.6
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.7
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9989	rs4420638	1	0.01	0.7

GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adiBMI	0.9499	rs1800437	1	0.01	0.7
GIPR	T2D, T2DadjBMI	0.9589	rs8108269	0.9967	0.01	0.7
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.8
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9989	rs4420638	1	0.01	0.8
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9499	rs1800437	1	0.01	0.8
GIPR	T2D, T2DadjBMI	0.9589	rs8108269	0.9967	0.01	0.8
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.9
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9989	rs4420638	1	0.01	0.9
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.9499	rs1800437	1	0.01	0.9
GIPR	T2D, T2DadjBMI	0.9589	rs8108269	0.9967	0.01	0.9
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.001	0.5
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9889	rs4420638	1	0.001	0.5
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.6398	rs1800437	1	0.001	0.5
GIPR	T2D, T2DadjBMI	0.6999	rs8108269	0.9967	0.001	0.5
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.001	0.6
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9889	rs4420638	1	0.001	0.6
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.6398	rs1800437	1	0.001	0.6
GIPR	T2D, T2DadjBMI	0.6999	rs8108269	0.9967	0.001	0.6
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.001	0.7
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9889	rs4420638	1	0.001	0.7
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference, 2hr Glucose adjBMI	0.6398	rs1800437	1	0.001	0.7
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.001	0.8
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9889	rs4420638	1	0.001	0.8
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BMI, Glucose, Hip circumference, Waist circumference	0.8098	rs1800437	1	0.001	0.8
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.001	0.9
GIPR	HbA1c, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR	0.9889	rs4420638	1	0.001	0.9
GIPR	GIP SOMAmer 16292_288, Fasting GIP, 2hr GIP, BML Hin girgumferance, Waist girgumferance	0.934	rs1800437	1	0.001	0.9

BMI, Hip circumference, Waist circumference Abbreviations: PP, Posterior probability; N, Number; LDL, Low-density lipoprotein; CAD, Coronary artery disease; HDL, High-density lipoprotein; ApoB, Apolipoprotein B; ApoA1, Apolipoprotein A1; HbA1c, Glycated haemoglobin; WHR, Waistto-hip ratio; adjBMI, Adjusted for BMI; BMI, Body mass index; GIP, Gastric inhibitory polypeptide **Table S5:** Clusters of colocalised traits identified by the secondary analysis across the permutations of prior 2 and the regional and alignment thresholds (prior 2: 0.02, 0.01 and 0.001; thresholds: 0.5, 0.6, 0.7, 0.8 and 0.9). A total of 4,996 variants were included.

Locus	Colocalised traits	PP coloc	Candidate variant	PP explained	Prior 2	Regional and alignment threshold
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.5
GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR, T2D	0.8681	rs429358	1	0.02	0.5
GIPR	BMI, Waist circumference	1	rs1800437	1	0.02	0.5
GIPR	Triglycerides, Hip circumference adjBMI	0.983	rs5117	0.9328	0.02	0.5
GIPR	GIP SOMAmer 16292_288, Hip circumference, 2hr Glucose adjBMI	0.908	rs1800437	0.6768	0.02	0.5
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.6
GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR, T2D	0.8681	rs429358	1	0.02	0.6
GIPR	BMI. Waist circumference	1	rs1800437	1	0.02	0.6
GIPR	Triglycerides. Hip circumference adiBMI	0.983	rs5117	0.9328	0.02	0.6
GIPR	GIP SOMAmer 16292_288, Hip circumference, 2hr Glucose adiBMI	0.908	rs1800437	0.6768	0.02	0.6
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.02	0.7
GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR, T2D	0.8681	rs429358	1	0.02	0.7
GIPR	BML Waist circumference	1	rs1800437	1	0.02	0.7
GIPR	Triglycerides. Hip circumference adiBMI	0.983	rs5117	0.9328	0.02	0.7
GIPR	GIP SOMAmer 16292_288, Hip circumference, 2hr Glucose adjBMI	0.908	rs1800437	0.6768	0.02	0.7
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein	1	rs7412	1	0.02	0.8
GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, Waist	0.8681	rs429358	1	0.02	0.8
GIPR	BMI Waist circumference	1	rs1800437	1	0.02	0.8
GIPR	Triglycerides Hin circumference adiBMI	0.983	rs5117	0.0328	0.02	0.8
GIPR	GIP SOMAmer 16292_288, Hip	0.908	rs1800437	0.5528	0.02	0.8
CIDD	circumference, 2hr Glucose adjBMI LDL, CAD, Total Cholesterol, Lipoprotein	0.500	7410	1	0.02	0.0
GIPR	A, ApoB HbA1c HDL ApoA1 WHRadiBMI Waist	I	rs/412	1	0.02	0.9
GIPR	circumference adjBMI, WHR	0.9716	rs429358	1	0.02	0.9
GIPR	BMI, Waist circumference	1	rs1800437	1	0.02	0.9
GIPR	Triglycerides, Hip circumference adjBMI	0.983	rs5117	0.9328	0.02	0.9
GIPR	GIP SOMAmer 16292_288, Hip circumference, 2hr Glucose adjBMI	0.908	rs1800437	0.6768	0.02	0.9
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.5
GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR, T2D	0.7712	rs429358	1	0.01	0.5
GIPR	BMI, Waist circumference	1	rs1800437	1	0.01	0.5
GIPR	Triglycerides, Hip circumference adjBMI	0.9665	rs5117	0.9328	0.01	0.5
GIPR	GIP SOMAmer 16292_288, Hip circumference, 2hr Glucose adjBMI	0.8289	rs1800437	0.6768	0.01	0.5
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.6
GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR, T2D	0.7712	rs429358	1	0.01	0.6
GIPR	BMI, Waist circumference	1	rs1800437	_1	0.01	0.6
GIPR	Triglycerides, Hin circumference adiBMI	0.9665	rs5117	0.9328	0.01	0.6
GIPR	GIP SOMAmer 16292_288, Hip circumference, 2hr Glucose adiBMI	0.8289	rs1800437	0.6768	0.01	0.6
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein A, ApoB	1	rs7412	1	0.01	0.7

GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, Waist circumference adjBMI, WHR, T2D	0.7712	rs429358	1	0.01	0.7
GIPR	BMI. Waist circumference	1	rs1800437	1	0.01	0.7
GIPR	Triglycerides. Hip circumference adjBMI	0.9665	rs5117	0.9328	0.01	0.7
~~~~	GIP SOMAmer 16292 288. Hip					
GIPR	circumference, 2hr Glucose adiBMI	0.8289	rs1800437	0.6768	0.01	0.7
	LDL, CAD, Total Cholesterol, Lipoprotein					
GIPR	A ApoB	1	rs7412	1	0.01	0.8
	HbA1c HDL ApoA1 WHRadiBMI Waist					
GIPR	circumference adiBMI WHR	0.9458	rs429358	1	0.01	0.8
GIPR	BMI Waist circumference	1	rs1800/137	1	0.01	0.8
GIPR	Triglycerides Hin circumference adiBMI	0.9665	rs5117	0.0328	0.01	0.8
OHK	GIB SOMAmor 16202 288 Hin	0.9005	185117	0.9328	0.01	0.8
GIPR	our SOMAINEI 10292_200, HIP	0.8289	rs1800437	0.6768	0.01	0.8
	LDL CAD Tatal Chalasteral Line motion					
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein	1	rs7412	1	0.01	0.9
	A, ApoB					
GIPR	HbAlc, HDL, ApoAl, WHRadjBMI, Waist	0.9458	rs429358	1	0.01	0.9
GUDD	circumference adjBMI, WHR		1000.405		0.04	
GIPR	BMI, Waist circumference	l	rs1800437	l	0.01	0.9
GIPR	Triglycerides, Hip circumference adjBMI	0.9665	rs5117	0.9328	0.01	0.9
GIPR	GIP SOMAmer 16292_288, Hip	0.9614	rs1800437	0.681	0.01	0.9
01111	circumference	019011	151000107	0.001	0.01	0.7
GIPR	LDL, CAD, Total Cholesterol, Lipoprotein	1	rs7/12	1	0.001	0.5
OH K	A, ApoB	1	13/412	1	0.001	0.5
CIDD	HbA1c, HDL, ApoA1, WHRadjBMI, Waist	0.6265	ra120258	1	0.001	0.5
01F K	circumference adjBMI, WHR	0.0303	18429556	1	0.001	0.5
GIPR	BMI, Waist circumference	1	rs1800437	1	0.001	0.5
GIPR	Triglycerides, Hip circumference adjBMI	0.7428	rs5117	0.9328	0.001	0.5
CIDD	GIP SOMAmer 16292 288, Hip	0.000	1000427	0.601	0.001	0.5
GIPK	circumference	0.090	rs1800437	0.081	0.001	0.5
CIDD	LDL, CAD, Total Cholesterol, Lipoprotein	1	7410	1	0.001	0.6
GIPK	A, ApoB	1	rs/412	1	0.001	0.6
CIDD	HbA1c, HDL, ApoA1, WHRadjBMI, Waist	0.000	120250		0.001	0.6
GIPR	circumference adiBMI. WHR	0.6365	rs429358	1	0.001	0.6
GIPR	BMI. Waist circumference	1	rs1800437	1	0.001	0.6
GIPR	Triglycerides. Hip circumference adiBMI	0.7428	rs5117	0.9328	0.001	0.6
	GIP SOMAmer 16292, 288, Hin					
GIPR	circumference	0.696	rs1800437	0.681	0.001	0.6
	I DL CAD Total Cholesterol Lipoprotein					
GIPR	A AnoB	1	rs7412	1	0.001	0.7
GIPR	HhA1c HDI AnoA1 WHRadiBMI WHR	0.9142	rs429358	1	0.001	0.7
GIPR	BMI Waist circumference	1	rs1800437	1	0.001	0.7
GIPR	Triglycerides Hin circumference adiBMI	0 7428	rs5117	0.9328	0.001	0.7
OH K	GIP SOMAmer 16202 288 Hin	0.7420	155117	0.7528	0.001	0.7
GIPR	circumference	0.696	rs1800437	0.681	0.001	0.7
	I DI CAD Total Chalasteral Linoprotein					
GIPR	LDL, CAD, Total Cholesterol, Elpoprotein	1	rs7412	1	0.001	0.8
CIDD	A, APUD	0.0142	ma 120250	1	0.001	0.8
CIPR	DML Waite C	0.9142	18429338	1	0.001	0.8
GIPR	BIVII, Waist circumference	1	rs180043/	1	0.001	0.8
GIPR	GIP SOMAmer 16292_288, Hip	0.696	rs1800437	0.681	0.001	0.8
	circumference					
GIPR	LDL, CAD, Iotal Cholesterol, Lipoprotein	1	rs7412	1	0.001	0.9
GIDD	A, ApoB	0.01.10	1000-00		0.001	0.0
GIPR	HbA1c, HDL, ApoA1, WHRadjBMI, WHR	0.9142	rs429358	1	0.001	0.9
GIPR	BML Hip circumference	0.9806	rs1800437	1	0.001	09

Abbreviations: PP, Posterior probability; N, Number; LDL, Low-density lipoprotein; CAD, Coronary artery disease; HDL, High-density lipoprotein; ApoB, Apolipoprotein B; ApoA1, Apolipoprotein A1; HbA1c, Glycated haemoglobin; WHR, Waistto-hip ratio; adjBMI, Adjusted for BMI; BMI, Body mass index; GIP, Gastric inhibitory polypeptide

Table S6. Association of rs1964272 with CAD after conditioning on E354.

Variant	Chr:pos	EA	EAF	Beta (SE)	P-value	Beta (SE)	P-value	Ν
rs1964272	19:46190268	G	0.5193	0.03 (0.006)	9.65x10 ⁻⁹	0.02 (0.006)	7.18x10 ⁻⁴	299519
	C1 C1					11.1.0	E a 1 1	

Abbreviations: Chr, Chromosome; pos, Position; EA, Effect allele; EAF, Effect allele frequency; SE, Standard error; N, Number of participants

**Table S7.** Association of other previously identified fasting GIP variants with CAD. The association of rs2287019 was not considered due to its high LD with E354.

Variant	Chr:pos	EA	EAF	Beta	SE	P-value	Cases	Controls
rs17681684	17:9792768	Α	0.3082	-0.0074	0.0057	0.1925	34,541	261,984

Abbreviations: Chr, Chromosome; pos, Position; EA, Effect allele; EAF, Effect allele frequency; SE, Standard error

**Fig. S1.** Association of E354 and cardiovascular disease sub-types in UK Biobank. Cardiovascular disease sub-types were defined in UK Biobank and tested for association with E354 using multivariable logistic regression adjusting for age, sex and 10 principal components². Estimates for each disease are expressed per copy of E354. A Bonferroni corrected significance threshold of P<0.0029 was used.

Cardiovascular disease subtype	Cases	Controls	OR (95% CI)		P-value
Ischaemic, haemorrhagic and unknown stroke (but not TIA)	9,652	357,934	1.00 [0.97, 1.04]	⊨∎-1	0.87
Ischaemic Cerebrovascular Disease (all)	8,084	359,502	1.00 [0.96, 1.04]	⊢ <b>∎</b> -I	0.91
Ischaemic Stroke	4,602	362,984	1.00 [0.95, 1.05]	<b>⊢</b>	0.97
Transient Ischaemic Attack	3,962	363,624	1.00 [0.94, 1.05]	<b>⊢</b> ∎→	0.91
Haemorrhagic Stroke (all)	1,981	365,605	0.97 [0.89, 1.05]	<b>⊢</b>	0.43
Intracerebral Haemorrhage	1,064	366,522	0.98 [0.88, 1.09]	<b>——</b>	0.75
Subarachnoid Haemorrhage	1,084	366,502	0.98 [0.88, 1.09]	F	0.73
Abdominal Aortic Aneurysm	1,094	366,492	1.19 [1.07, 1.30]	·	0.003
Thoracic Aortic Aneurysm	347	367,239	0.86 [0.68, 1.04]	<b>⊢−−−</b> −	0.1
Venous Thromboembolism (all)	14,097	353,489	1.03 [1.00, 1.06]		0.03
Deep Vein Thrombosis	9,454	358,132	1.05 [1.01, 1.08]	<b>⊢≡</b> −1	0.02
Pulmonary Embolism	6,148	361,438	1.04 [0.99, 1.08]		0.13
Peripheral Vascular Disease	3,415	364,171	1.05 [0.99, 1.11]	i <b>-∎</b> -i	0.13
Aortic Valve Stenosis	2,244	365,342	0.93 [0.86, 1.00]	<b>⊢</b> ∎	0.05
Atrial Fibrillation	16,945	350,641	1.00 [0.97, 1.03]	Hert	0.89
Heart Failure	6,712	360,874	1.01 [0.97, 1.05]	⊢■→	0.65
			Г		
			0.6 OR (95%	0.8 1 1.2 CI) for cardiovascular disease	1.4 subtype

per copy of E354

Abbreviations: TIA, Transient ischaemic attack; PC, principal component; OR, Odds ratio; CI, Confidence interval

Fig. S2. Associations between E354 and regional adiposity compartments in 435,387 participants measured by bio-impedance. Fat mass in each compartment is shown in orange and lean mass in blue. Estimates for each compartment are in SD per copy of E354 (rs1800437). All estimates are adjusted for age, sex, genotyping chip, and the top 40 principal components. A Bonferroni significance threshold of  $P \le 0.003$  was used to ascertain significance.

Abbreviations: CI, Confidence interval

Bio-impedance compartment	Beta (95% CI)					P-value	
Android fat mass	0.03 (0.03, 0.04	)					
Arms fat mass	0.03 (0.03, 0.04	)	↓ <b>_</b> ↓				
Gynoid fat mass	0.03 (0.02, 0.03	)	<b>⊢−−−−</b>				
Legs fat mass	0.03 (0.02, 0.03	)	<b>⊢−−−−</b>				
Peripheral fat mass	0.03 (0.02, 0.03	)	↓ <b>-</b>				
Subcutaneous fat mass	0.03 (0.03, 0.04	)	► <b>-</b>				
Total fat mass	0.03 (0.03, 0.04	)	► <b>₽</b>				
Trunk fat mass	0.03 (0.03, 0.04	)				6x10 ⁻³⁶	
Visceral fat mass	0.03 (0.02, 0.03	)		H		4x10 ⁻³¹	
Appendicular lean mass	0.02 (0.02, 0.03	)				5x10 ⁻²⁵	
Android lean mass	0.02 (0.02, 0.03	)				1x10 ⁻²³	
Arms lean mass	0.03 (0.02, 0.03	)		H		1x10 ⁻²⁷	
Gynoid lean mass	0.02 (0.02, 0.03	)		-		5x10 ⁻²¹	
Legs lean mass	0.02 (0.02, 0.03	)				1x10 ⁻²²	
Total lean mass	0.02 (0.02, 0.03	)				1x10 ⁻²⁴	
Trunk lean mass	0.02 (0.02, 0.03	)				2x10 ⁻²⁴	
		İ		I	I		
Fat mass	-0.01	0	0.01	0.02	0.03	0.04	
Lean mass	Beta (95%	CI) for	bio-impedance o	compartment pe	r copy of E354		

**Fig. S3.** Associations between E354 and human protein levels. All estimates are adjusted for age, sex, sample collection site and 10 genetic principal components. **Panel A.** Volcano plot showing the associations between E354 and 4,979 human protein levels. The dashed line indicates the Bonferroni significance threshold  $P \le 1x10^{-5}$ . The point size for each protein is proportional to its effect size. Significant protein associations with E354 are shown in blue, non-significant proteins are shown in yellow. Associations with significant proteins and proteins of interest are labelled. Two SOMAmers from the SOMAscan® 4k assay target GIP levels, both are labelled. **Panels B & C.** Regional association plots depicting the E354 (rs1800437) association with both GIP SOMAmers, X16292_288 and X5755_29 respectively.

Abbreviations: QPCTL, Glutaminyl-peptide cyclotransferase like; GIP, Gastric inhibitory polypeptide.



**Fig. S4.** Associations between E354 and human metabolite levels. Volcano plot showing the associations between E354 and the levels of 1,008 human plasma metabolites. All estimates are adjusted for age, sex and measurement batch. The dashed line indicates the Bonferroni significance threshold P  $\leq 5 \times 10^{-5}$ . The point size for each protein is proportional to its effect size. Metabolites are coloured according to their metabolite class. Significant metabolite associations with E354 are labelled in orange.



**Fig. S5.** Gaussian graphical model illustrating the partial correlation network in 11,966 participants between X-12283 and first and second order connections most correlated with X-12283. Positive partial correlation estimates between metabolites are denoted with solid lines whereas negative estimates are shown with dashed lines. Metabolites directly connected with X-12283 represent first order connections, others are second order connections. Metabolites clustered closest to X-12283 are more strongly correlated. Metabolite nodes are coloured by their super pathway. The table outlines the 6 metabolites with a first order connection to X-12283 and shows their partial correlation coefficients and related P-values.



Fig. S6. Stacked regional association plot showing the cluster of cardiovascular-related traits which colocalise near the *GIPR* locus. The purple diamond represents the rs7412 variant, a missense variant in *APOE*. variant markers are coloured by their LD with rs7412, with red indicating LD ( $R^2 > 0.8$ ).



**Fig. S7.** Regional association plot illustrating the cluster of traits which colocalise with the GIP measures at the *GIPR* locus. The purple diamond represents the rs1800437 variant (E354). Variant markers are coloured by their LD with rs1800437, with red indicating LD ( $R^2 > 0.8$ ). Fasting and 2-hour GIP levels are from the MDC cohort of Almgren *et al.* 2017³.



Abbreviations: GIPR, Gastric inhibitory polypeptide receptor; LD, Linkage disequilibrium; adj, Adjusted for; BMI, Body mass index; HbA1c, Glycated haemoglobin

**Fig. S8.** Heatmap matrix depicting the largest pairwise colocalisation estimate between fasting GIP measures from SomaLogic, fasting and 2-hour GIP measures from Almgren *et al.* 2017³, 2hr glucose adjusted for BMI ,BMI, LDL, CAD and T2D. Each colocalisation hypothesis is coloured differently with the colour saturation referring to the evidential strength. Posterior probabilities (PP_{coloc}) were considered significant if they met the following criteria: (H4 + H3  $\ge$  0.9 & H4/H3  $\ge$  3). Trait-pairs with significant posterior probability estimates of colocalisation were outlined in black. To discriminate between H1 and H2 hypotheses, traits along the X-axis were used as "Trait 1" in the analysis and traits listed on the Y-axis were used as "Trait 2".

Abbreviations: H, Hypothesis; BMI, Body mass index; CHD, Coronary heart disease; GIP, Gastric inhibitory polypeptide; 2hr, 2-hour; LDL, Low-density lipoprotein; T2D, Type 2 diabetes



**Fig. S9.** Matrix illustrating the LD between each of the independent CAD variants and rs1800437 (E354) estimated using 5 European populations in LDlink⁴. Pairwise R² values between variants are shown in red in the lower triangle, whereas D' values are shown in blue in the top triangle. Colour saturation represents the strength of the LD estimate between two variants. The LD between rs1800437 and rs1964272 (R² = 0.27) is depicted in light pink, whereas the very low LD between rs1800437 and the other CAD variants are shown as blank spaces.



Fig. S10. Volcano plot showing the associations between rs1964272 and 4,979 human protein levels. All estimates are adjusted for age, sex, sample collection site and 10 genetic principal components. The dashed line indicates the Bonferroni significance threshold  $P \le 1x10^{-5}$ . The point size for each protein is proportional to its effect size. Significant protein associations with rs1964272 are shown in blue, non-significant proteins are shown in yellow.

Abbreviations: QPCTL, Glutaminyl-peptide cyclotransferase like



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