eAppendix 1. Genome-wide association study for blood glucose using UK Biobank data.

Secondary release data of UK Biobank (UKB) were used in the current study to generate blood glucose genetic summary statistics. UKB is a large-scale multi-center cohort with over 500,000 participants aged 38–73 years old. Blood glucose levels and genotypes were measured through blood samples, and other information, such as demographic characteristics and medical history, were collected from the National Health Service registries and self-reported questionnaires [e1]. In UKB, genotyping was performed using two Affymetrix genotyping arrays, the UK BiLEVE Axiom array or UK Biobank Axiom array. Quality control (QC) was performed for samples and variants. Sample QC excluded the participants with low DNA concentration, call rate<95%, excess heterozygosity, sex chromosome abnormality, or sample duplication. Variant QC excluded variants that exhibits poor clustering of allele calls, batch, plate, array, or sex effects, departures from Hardy–Weinberg equilibrium (HWE), or demonstrates discordance between technical replicate samples. After quality control, the samples were imputed to approximately 92 million SNPs using both the reference panel of the Haplotype Reference Consortium (HRC) as well as a combined reference panel of the 1000 Genomes Project10 and UK10K [e2]. In the present GWAS, a subsample of participants of European ancestry was used, and individuals with diagnosis of diabetes in the inpatient registry (defined as E10-14 in ICD 10 and 2500-2529 in ICD 9) or with self-reported diabetes in questionnaires were excluded. SNPs with minor allele frequency<0.1%, HWE p-value<1×10^{-10}, and INFO score<0.8 were dropped. A mixed linear model-based method was used in association testing to control for population stratification and relatedness between individuals by principal components and a genetic relationship matrix. Finally, 326,885 participants were analyzed. Fasting time, year of blood sample collection, age, inferred sex, batch and plate, genotyping array, and principal components 1-10 were included as covariates. Manhattan plot and Q-Q plot of the GWAS were presented in **eFigure 8 and 9 in the Supplement**. The genomic inflation factor of the GWAS is 1.19.

eAppendix 2. Associations between genetic variation in anti-diabetic drug targets and cardiovascular diseases / hippocampal volume.

The cardiovascular effects of many anti-diabetic drugs are still debated. We have summarized the trial evidence from recent reviews in **eTable 6 in the Supplement**. Considering the conflicting trials evidence, cardiovascular endpoints might serve as 'golden standard' for the validation of our IVs. Nevertheless, we have explored the relationship of genetic variation in anti-diabetic drug targets with coronary heart disease (CHD), heart failure (HF), and stroke (**eFigure 2**). All the estimates yielded extremely wide confidence intervals, indicating high instability.

One GWAS had been conducted for hippocampal volume consisting of 33,536 participants and found that genetic variants associated with increased hippocampal volume were also associated with a lower risk for Alzheimer's disease (genetic correlation=−0.155) [e3]. Herein, we further explored the association between genetic variation in anti-diabetic drug targets and hippocampal volume. We observed indications showing that genetic variation in sulfonylurea and GLP-1 analogue targets were associated with an increased hippocampal volume (**eFigure 11 in the Supplement**), which corresponded to their protective effects on AD observed in our primary analysis.

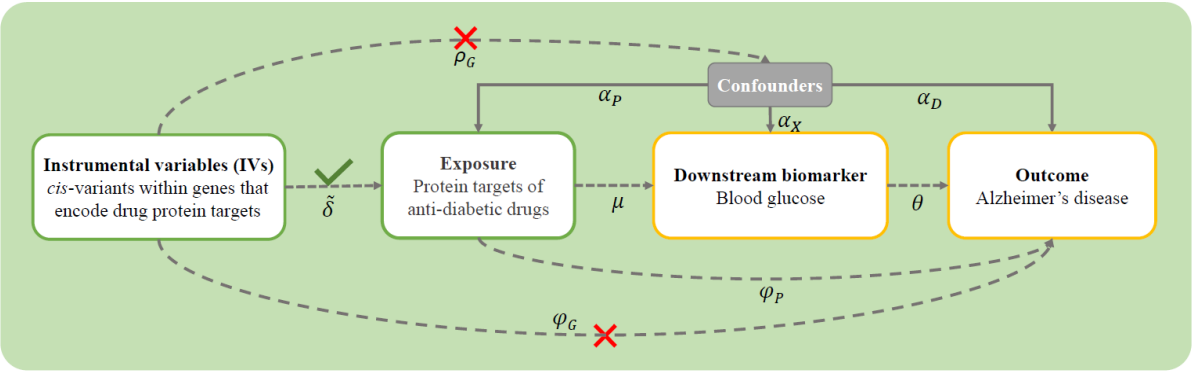
eAppendix 3. Colocalization analysis for sulfonylureas and GLP-1 analogues.

Colocalization analysis for blood glucose and AD was performed within the genes that encode the protein targets of sulfonylureas and GLP-1 analogues. The colocalization results are shown in **eTable 5 in the Supplement**. Generally, we did not observe a high probability of shared casual variants for blood glucose and AD within the encoding genes for sulfonylureas (2-3%); however, when looking at the regional association plots for the variants within *KCNJ11* and *ABCC8* (**eFigure 3 in the Supplement**), it shows a trend of colocalization between blood glucose and AD. Meanwhile, the plot also indicates that the negative colocalization results might be due to the weak association with AD in the region (smallest p for AD is 0.015). For GLP-1 analogues, we did not find any evidence of either sharing a common variant or a distinct trend of colocalization within *GLP1R* (**eTable 5 and eFigure 4 in the Supplement**).

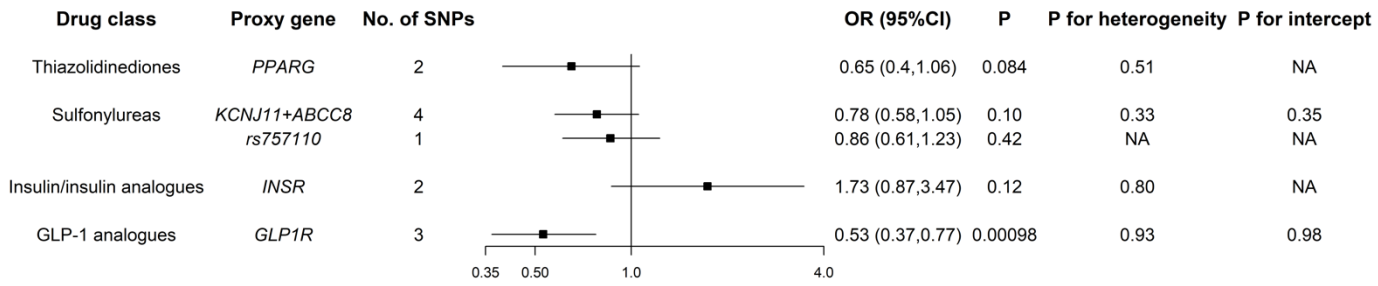
On the other hand, colocalization and MR analysis may focus on difference questions. Colocalization analysis is designed to explore whether two traits share one common causal variant (**eFigure 5, panel a and c, in the Supplement**), while MR analysis is designed to explore the association between two traits (**eFigure 5, dashed line in panel c, in the Supplement**) using genetic variants as IVs. Thus, colocalization might have a relatively stricter requirement for variant-trait 1 and variant-trait 2 association, while MR analysis only requires the IV to be robustly associated with the exposure.

Another concern is that the observed MR association could be driven by the IVs in LD with nearby gene, which could lead to heterogeneity within IVs and cause bias through pleiotropic effects. However, we did not detect any substantial heterogeneity (P=0.69 for sulfonylureas and P=0.87 for GLP-1 analogues) or pleiotropy (P=0.93 for sulfonylureas and P=0.92 for GLP-1 analogues) in our MR analysis. To be more conservative, we curated the LD for the IV-AD association. For sulfonylureas, the IV, *rs3758953,* might be in mild LD with a peak variant associated with AD in the *USH1C* gene (**eFigure 6 in the Supplement**). Therefore, we performed a sensitivity analysis excluding *rs3758953* for sulfonylureas, and the results remained unchanged (OR=0.42, 95%CI=0.21-0.86, P=0.017, P for heterogeneity=0.62, P for pleiotropy=0.52). Meanwhile**,** the three IVs for GLP-1 analogues were not shown to be in strong LD with variation from nearby genes (**eFigure 7 in the Supplement**).

eFigure 1. Framework for the MR study design of repurposing anti-diabetic drugs for Alzheimer's disease. Three assumptions are essential for our MR design, which are 1) a robust association between IVs and the drug protein target (*relevance*, $\tilde{\delta}\neq 0$), 2) independence of IVs on confounders (*exchangeability*, $\rho_G=0$), which is often secure because of random allocation of genetics variants at conception, and 3) no direct effects of IVs on outcome other than through the drug protein target (*exclusion restriction*, $\varphi_G=0$). When these three assumptions are valid, the estimation for the effects of anti-diabetic drug on AD (ω), via the modification of the drug protein target, would be the IV-AD association ($\tilde{\delta}\varphi_P + \tilde{\delta}\mu\theta$) divided by the IV-protein target association ($\tilde{\delta}$), that is, $\omega = \frac{\tilde{\delta}(\varphi_P+\mu\theta)}{\tilde{\delta}} = \varphi_P + \mu\theta$. Unfortunately, genetic association data on the proteins of our interest, that is, target proteins of anti-diabetic drugs, are unavailable, but GWAS data of blood glucose, a major, established physiological response to the use of anti-diabetic drugs, are available. We alternatively replaced the IV- protein target association ($\tilde{\delta}$) by IV-blood glucose association ($\mu\tilde{\delta}$), resulting in $\omega_{bw} = \frac{\tilde{\delta}(\varphi_P+\mu\theta)}{\tilde{\delta}\mu} = \frac{\varphi_P+\mu\theta}{\mu} = \frac{1}{\mu}\times\omega$, where ω_{bw} is ω weighted by blood glucose. Noteworthily, although ω_{bw} does not equal to ω, it may still provide a valid null-hypothesis test of $\omega = 0$, because $\omega_{bw} \neq 0$ implies $\omega \neq 0$. Green tick means the association that is allowed in our MR model, while red cross means these should be avoided. SNP, single nucleotide polymorphism [e4].

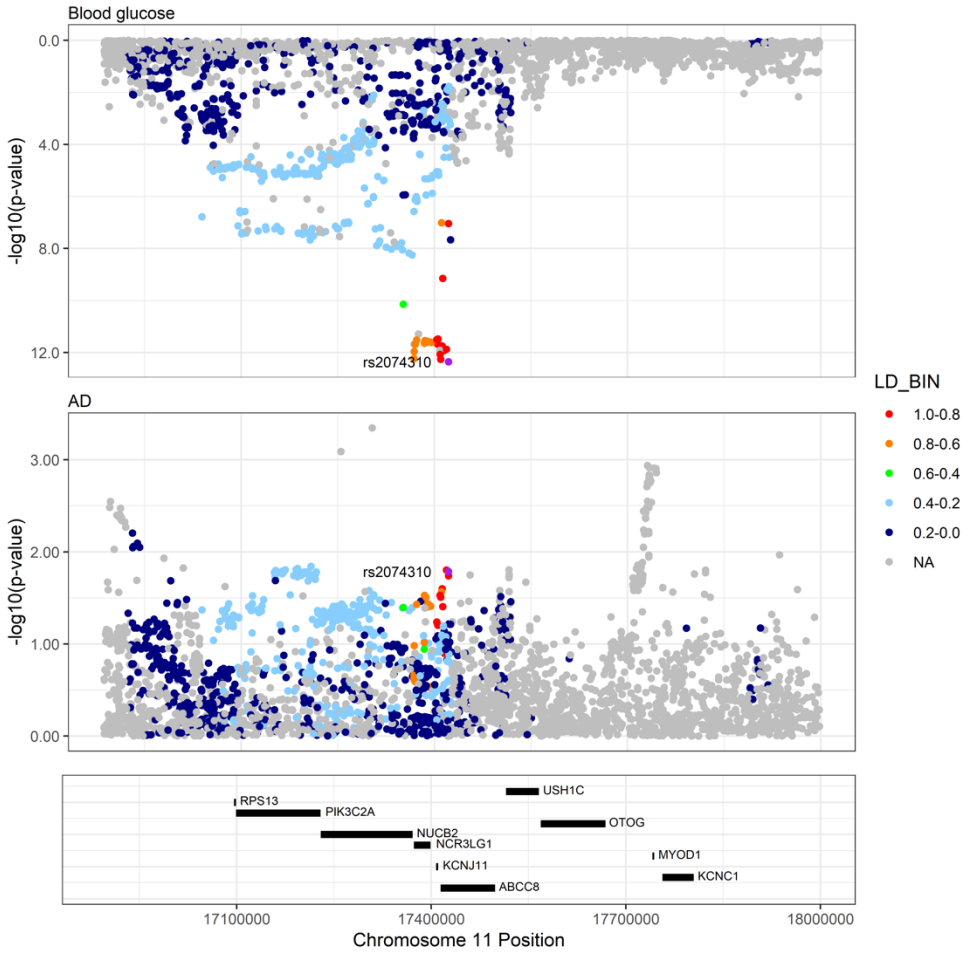


eFigure 2. Estimated effects of genetic variation in anti-diabetic drug targets on Alzheimer's disease, results from the sensitivity analysis using a GWAS dataset comprising 71,880 AD / AD-by-proxy cases. Proxy gene is the gene that encodes the drug target protein, and *rs757110* is the variant that has been validated to modulate the protein target of sulfonylureas. P for heterogeneity<0.05 indicates possible pleiotropy, while P for intercept<0.05 indicates substantial bias from pleiotropy. All the ORs were scaled to per 1 mmol/L decrement in blood glucose. NA indicates that the Cochran's Q test (heterogeneity test) or the MR-Egger regression (intercept test) is not available because of limited number of IVs. IV, instrumental variables; TZD, thiazolidinediones; GLP-1 analogues, glucagon-like peptide-1 analogues; GWAS, genome-wide association study.

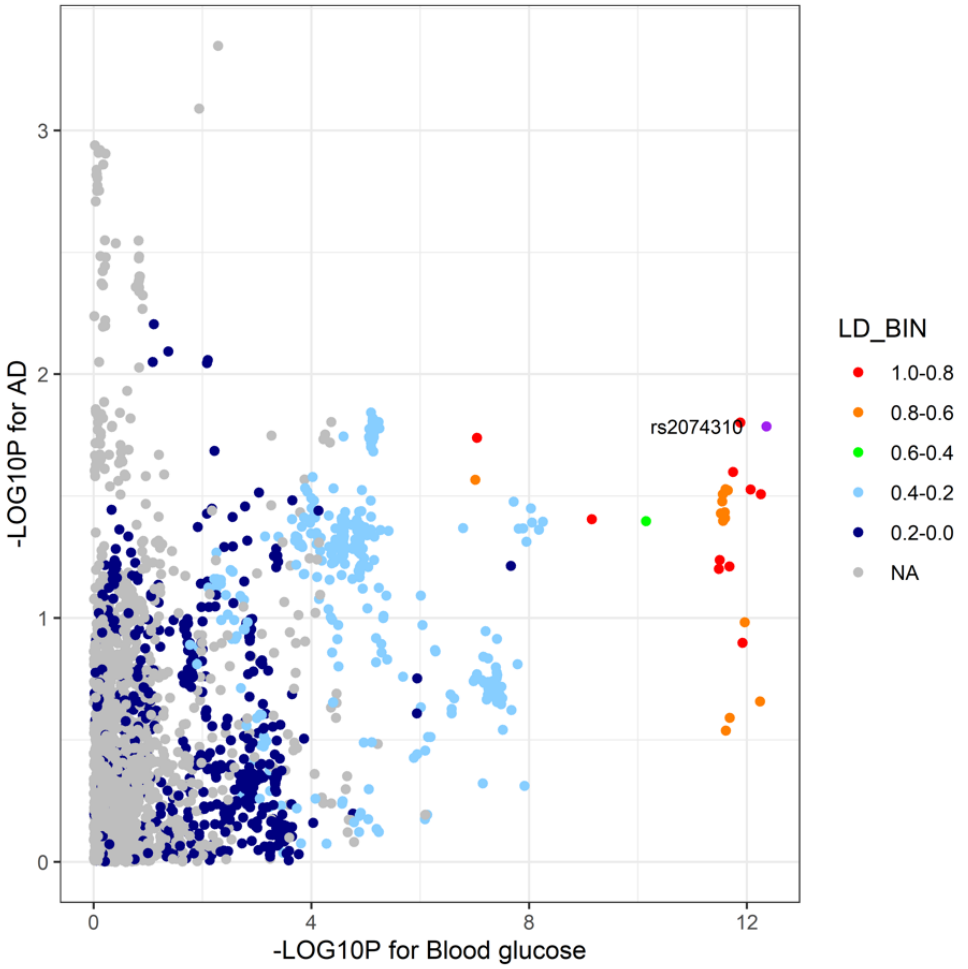


eFigure 3. Regional plots for the associations of blood glucose and AD within ±50KB of *KCNJ11* and *ABCC8*. a) regional association plot. b) regional Q-Q plot. *rs2074310* is the leading SNP identified to be associated with blood glucose within the region and colored as purple in the plot.

a)

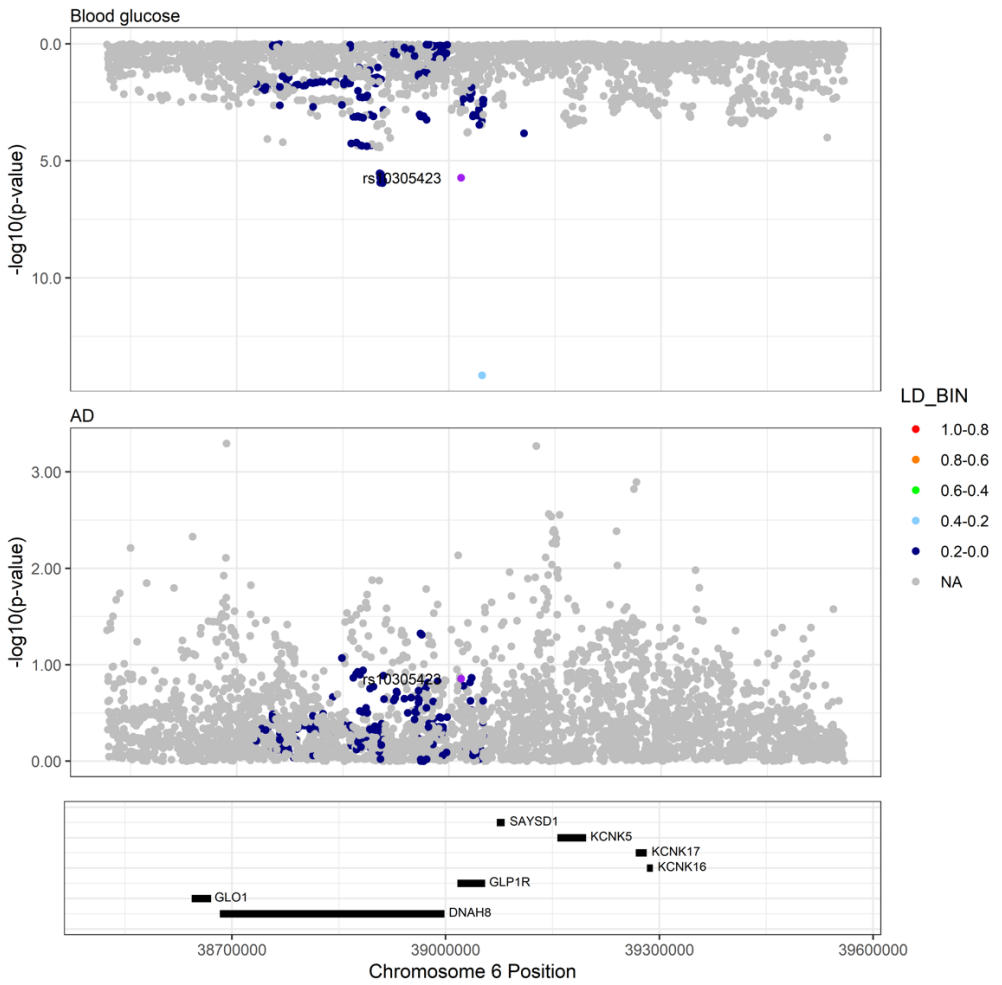


b)

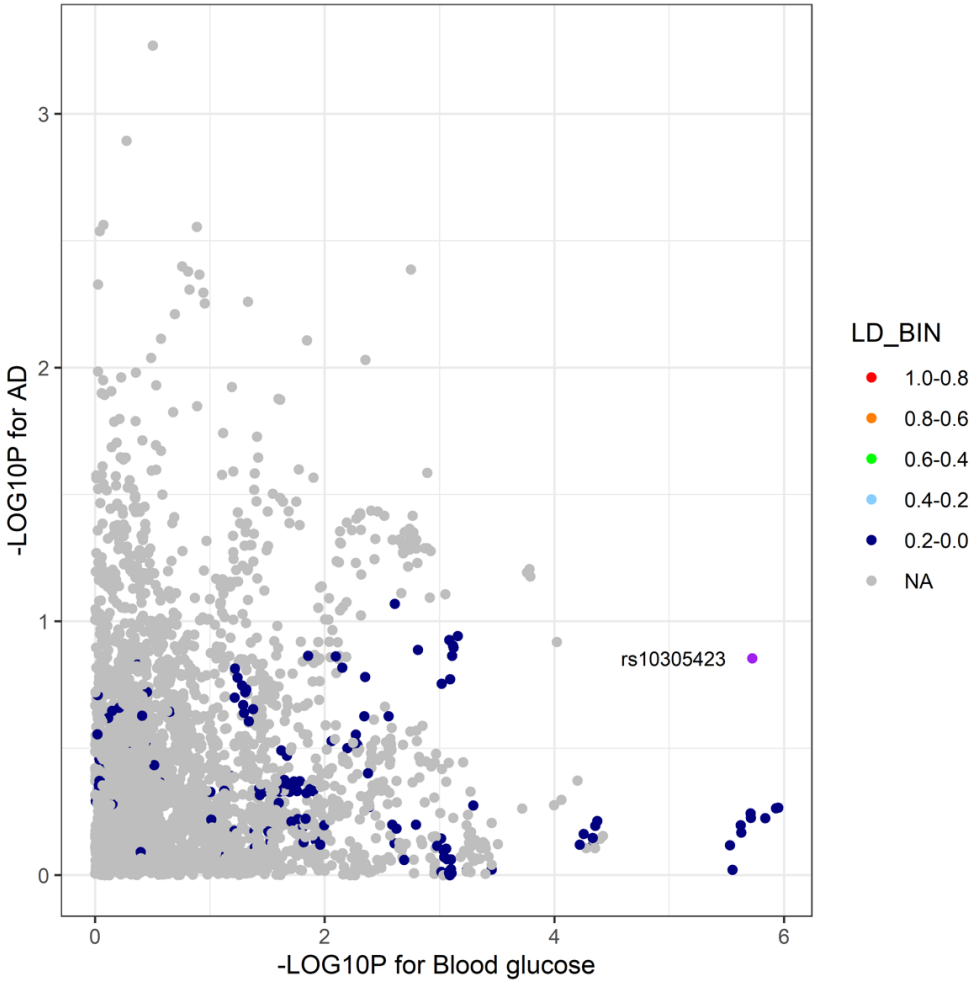


eFigure 4. Regional plots for the associations of blood glucose and AD within ±50KB of *GLP1R*. a) regional association plot. b) regional Q-Q plot. *rs10305423* is the leading SNP identified to be associated with blood glucose within the region and colored as purple in the plot.

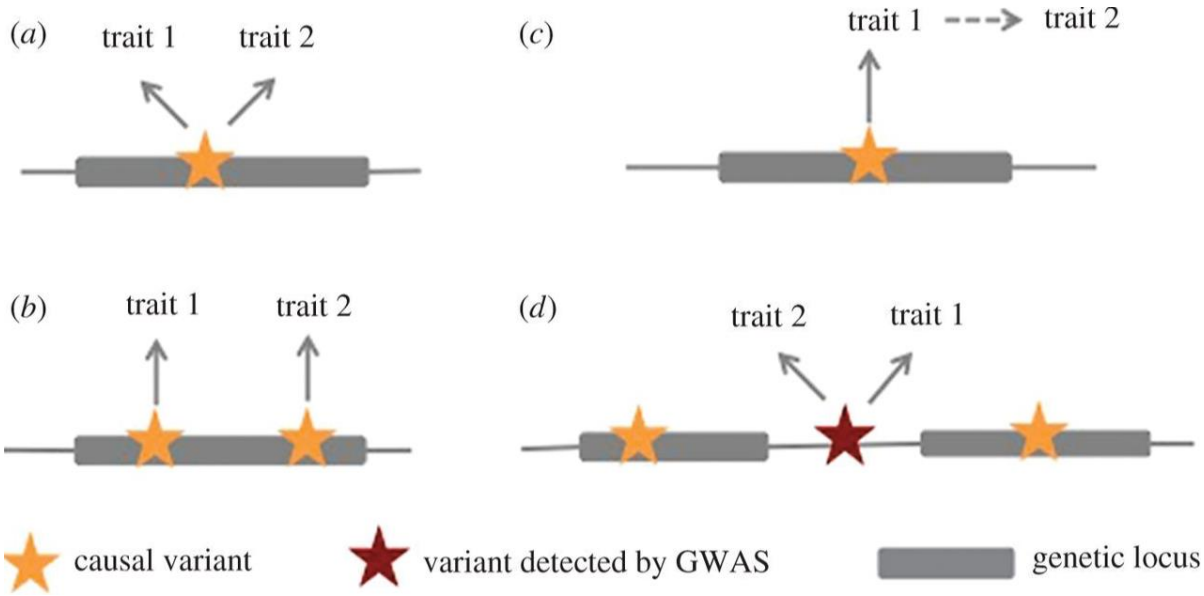
a)



b)



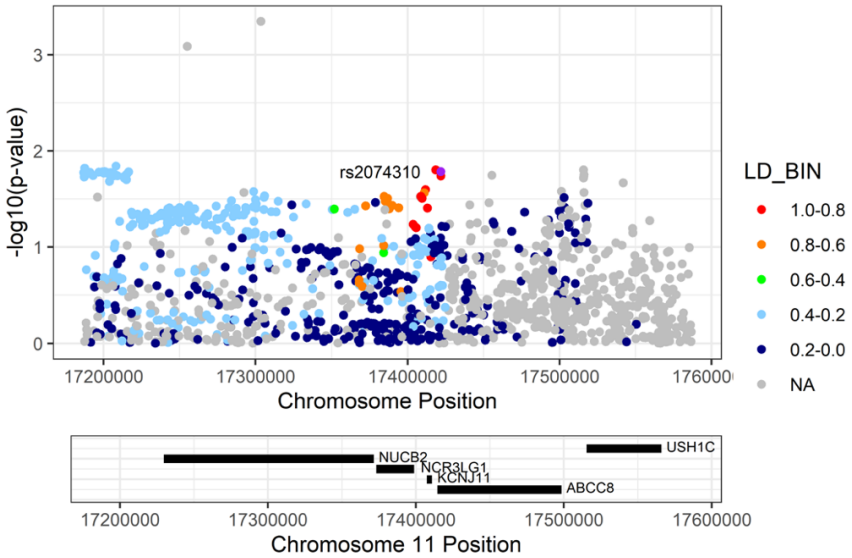
eFigure 5. Schematic representation of different scenarios for cross-phenotype associations.



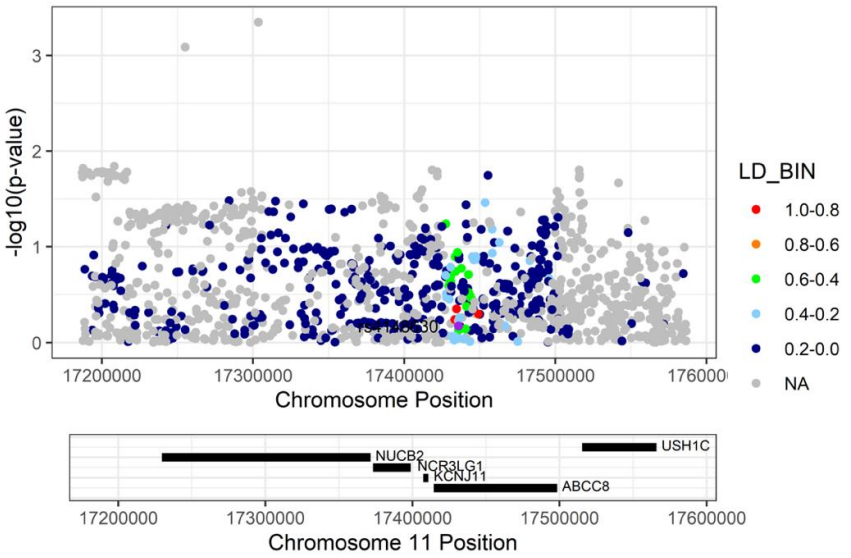
Ref. Hackinger S, et al. Open Biol. 2017

eFigure 6. Regional plots for the association with AD within ±20KB of *KCNJ11* and *ABCC8* showing LD patterns. The variants used as IVs in MR analysis was labeled and colored purple.

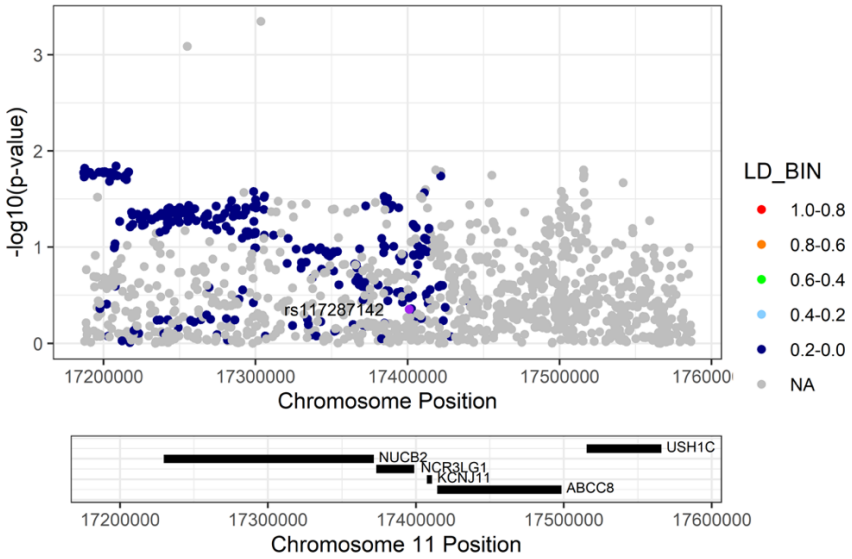
rs2074310



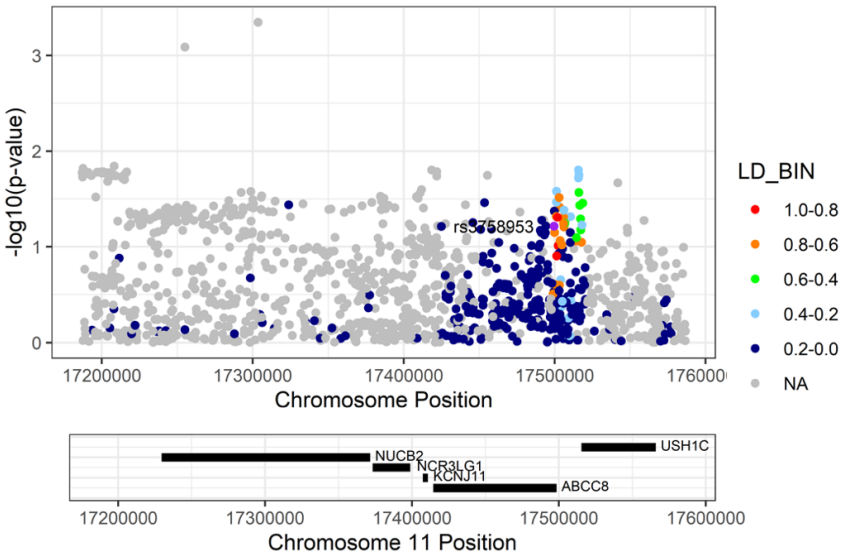
rs4148630



rs117287142

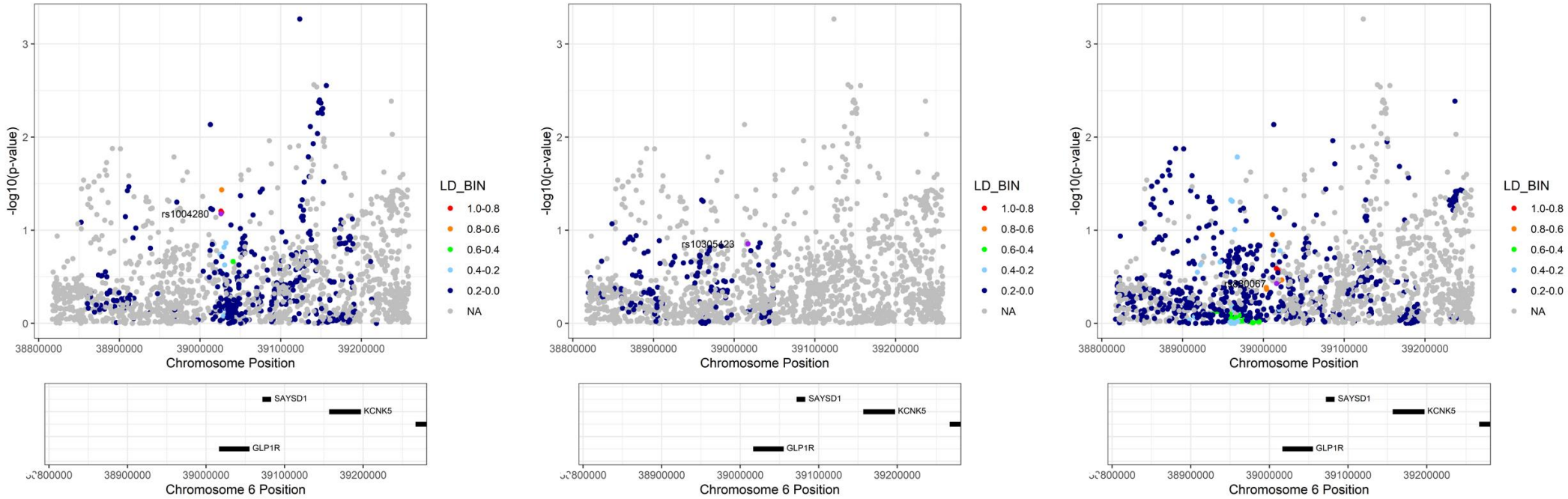


rs3758953

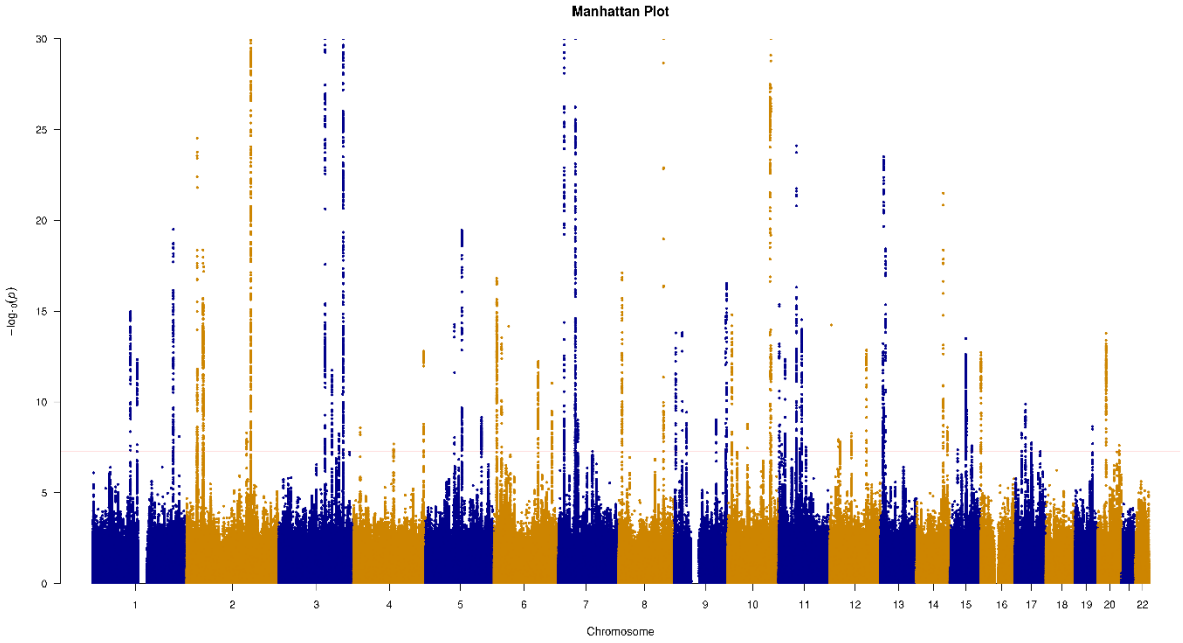


eFigure 7. Regional plots for the association with AD within ±20KB of *GLP1R* showing LD patterns. The variants used as IVs in MR analysis was labeled and colored purple.

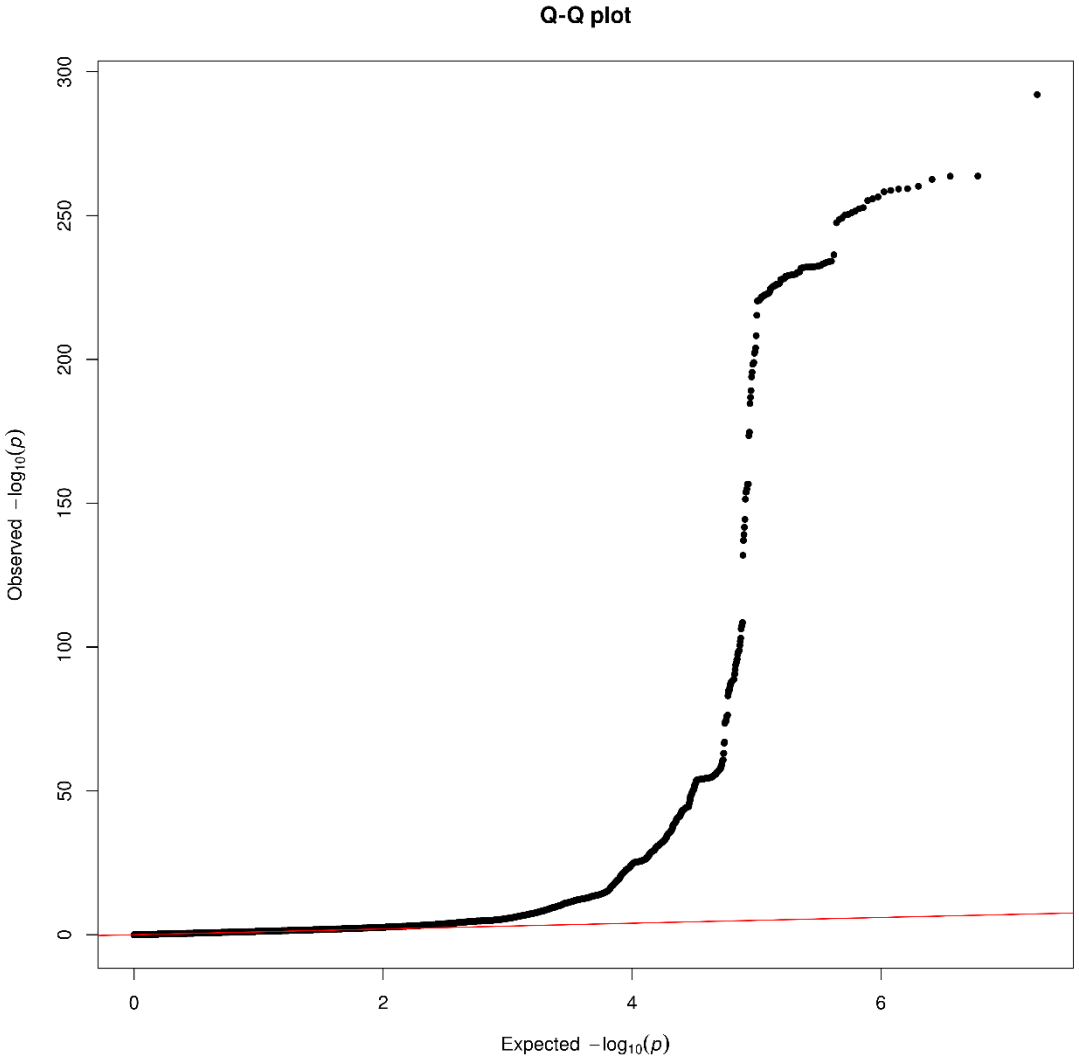
rs1004280 ***rs10305423*** ***rs880067***



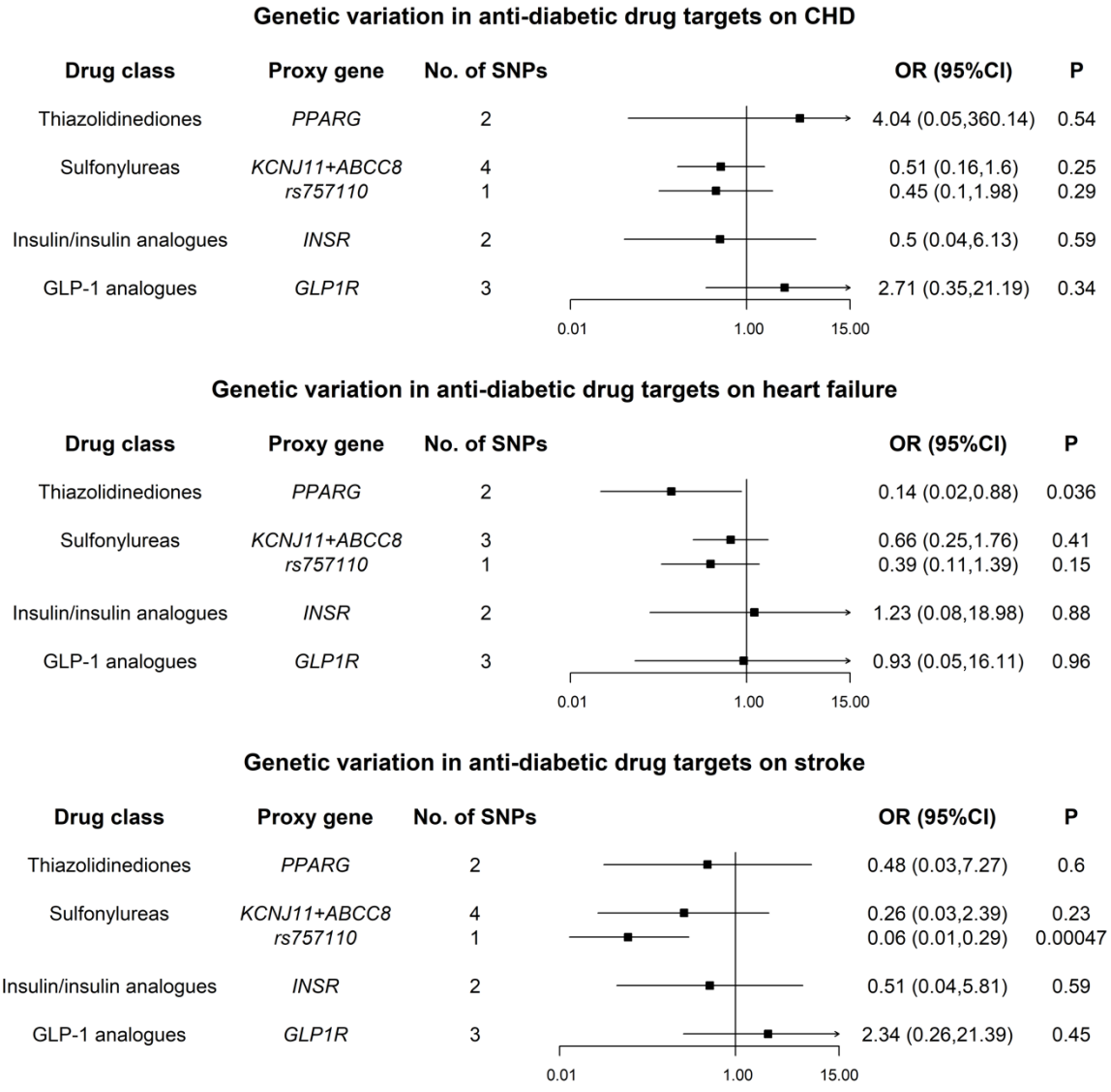
eFigure 8. Manhattan plot of the UKB blood glucose GWAS (n=326,885). The P value smaller than 1×10^{-30} (below 0.0001 quantile) were transferred to 1×10^{-30} to avoid the extreme values stretching the plot.



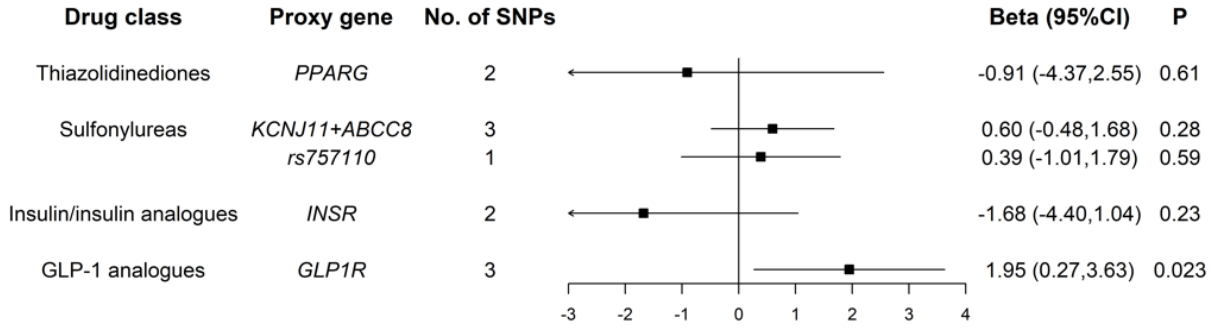
eFigure 9. Q-Q plot of the P values of the UKB blood glucose GWAS.



eFigure 10. Estimated effects of genetic variation in anti-diabetic drug targets on cardiovascular diseases. CHD, coronary heart disease; HF, heart failure. All the estimates were scaled to per 1 mmol/L decrement in blood glucose.



eFigure 11. Estimated effects of genetic variation in anti-diabetic drug targets on hippocampal volume. All the estimates were scaled to per 1 mmol/L decrement in blood glucose.



eTable 1. Summary information of the GWAS data used in the present study. NA indicates not applicable.

Traits	Data source	Participants	GWAS PMID	Web source	Annotations
Blood glucose	UK Biobank	326,885 participants of European ancestry	NA	Available upon application	Covariates include fasting time, year of blood sample collection, age, inferred sex, and PCs 1-10
AD	PGC-ALZ, IGAP, ADSP, and UKB	24,087 clinically-diagnosed AD cases and 55,058 controls of European ancestry in phase 1 71,880 AD / AD-by-proxy cases and 383,378 controls of European ancestry in phase 3	30617256	https://ctg.cncr.nl/software/summary_statistics	Adjusted for sex, batch (if applicable), and the first four ancestry principal components
Type 2 diabetes	BioME, deCODE, DGDG, DGI, EGCUT_ExomeCore, EGCUT_Human370CNV, EGCUT_OmniExpress, FHS, FUSION, GCKD, GENOA, GERA, GoDARTS, GOMAP, TEENAGE, HPFS, INTERACT_coreexome, INTERACT_GWAS, KORA, MESA, METSIM, MGI, NHS, NUGENE, PIVUS, PROSPER, RS1, RS2, RS3, UK BioBank, ULSAM, UPCH, WTCCC	74,124 T2D cases and 824,006 controls of European ancestry	30297969	https://diagram-consortium.org/downloads.html	We used the summary statistics unadjusted for BMI.
Insulin secretion	DGI, Amish Family Diabetes Study, Sorbs, HBCS, French obese adults, RISC	5,318 non-diabetic participants of European ancestry	24699409	https://magicinvestigators.org/downloads/	Insulin secretion was measured as corrected insulin response (CIR) to glucose at 30 min during an oral glucose tolerance test.
Insulin resistance (HOMA-IR)	CHS, FHS, DGI, BLSA , FUSION, CoLaus, InCHIANTI, NFBC1966, NTR / NESDA, Rotterdam Study, PROCARDIS, Sorbs, ERF, CROAS (Vis Study), ORCADES (Orkney), MICROS (Tyrol), AGES, ARIC, BSN, FamHS, Fenland, French Adult Control, GENOA, GenomEUtwin, HABC, Health2000, Korcula, Split, SUVIMAX, DESIR, PIVUS, ULSAM, Swedish Twin Registry, Fenland, Ely, Whitehall, SEGOVIA STUDY, AMISH, GLACIER, NTR2, SCARFSHEEP, BSN, FUSION stage 2, METSIM, DRsEXTRA HBCS, QFS, PROSPER, THISEAS, DPS, D2D2007, DIAGEN	Up to 51,750 non-diabetic participants of European ancestry	22581228	https://magicinvestigators.org/downloads/	HOMA-IR were derived from fasting glucose and fasting insulin measures.

Body mass index	GIANT consortium and UK Biobank	694,649 individuals of European ancestry	30239722	https://zenodo.org/record/1251813#.Yew8tBOZP0o	NA
Waist circumference Hip circumference	BLSA, COROGENE, DESIR (GWAS), EGCUT-370, EGCUT-OMNI, ERF, FamHS, GOOD, HBCS, Health ABC, HERITAGE, HYPERGENES, InCHIANTI, LifeLines, LLS, LOLIPOP_EW610, LOLIPOP_EWA, LOLIPOP_EWP, PREVEND, PROCARDIS, QFS, RISC, RS-II, RSIII, SHIP-TREND, Sorbs, TRAILS, TWINGENE, TwinsUK, WGHS, YFS,, Previous GWAS Data, AGES Reykjavik~, Amish, ARIC, B58C (T1DGC), B58C (WTCCC), BRIGHT, CHS, CoLaus, deCODE, DGI, EGCUT, EPIC-Obesity Study, Fenland, FRAM, FTC, FUSION, GENMETS, KORA3, KORA4, NFBC-1966, NHS, NTR & NESDA, ORCADES, PROCARDIS, RS-I, SHIP, T2D_WTCCC, VIS, MICROS, Metabochip Data, ADVANCE-CAD controls, ARIC Metabochip, B1958C, BHS, CLHNS, D2D 2007, DESIR (Metabochip), DIAGEN, DILGOM, DPS, DR'S EXTRA, DUNDEE cases, DUNDEE controls, EGCUT, Ely Study, EMIL, EPIC-Norfolk Cohort, EPIC-Norfolk T2D cases, FBPP, Fenland, FUSION stage 2, GLACIER, GXE, HNR, HUNT 2, IMPROVE, KORA S3, KORA S4, Leipzig Adults, LURIC , METSIM, MORGAM, NSHD, PIVUS, PROMIS, SardiNIA, SCARFSHEEP, SPT, STR, TANDEM, THISEAS, Tromsø, ULSAM, WHI, Metabochipm, Whitehall , WTCCC-T2D	Up to 224,459 individuals of European ancestry	25673412	https://portals.broadinstitute.org/collaboration/giant/index.php/Main_Page	Adjusted for age, age-squared, and study-specific covariates if necessary
Hippocampal volume	The ENIGMA Consortium and the CHARGE Consortium	26,814 individuals of European ancestry	28098162	http://enigma.ini.usc.edu/protocols/genetics-protocols/	Hippocampal volume was assessed through high-resolution MRI brain scans.

Coronary artery disease	CARDIoGRAMplusC4D Consortium	60,801 cases and 123,504 controls. The majority (77%) of the participants were of European ancestry; 13% and 6% were of South Asian (India and Pakistan) and East Asian (China and Korea) ancestry, respectively, with smaller samples of Hispanic and African Americans.	26343387	http://www.cardiogramplusc4d.org/	We used the dataset from the additive model where the log(genotype risk ratio) (log(GRR)) for a genotype was proportional to the number of risk alleles.
Heart failure	ARIC, BIOSTAT, CHS, COGEN, DECODE, DiscoverEHR, EPHESUS, EPIC-Norfolk, Estonia 370, Estonia exome, Estonia Omni, FHS, FINRISK, GoDARTS Affy, GoDARTS Illumina, GRADE, LURIC, MDCS, PHFS, PIVUS, PREVEND, PROSPER, Rotterdam 1, SHIP, SOLID, TwinGene, UKB, ULSAM, and WGHS	47,309 cases and 930,014 controls of European ancestry	31919418	https://www.ebi.ac.uk/gwas/publications/31919418	Cases included participants with a clinical diagnosis of HF of any aetiology with no inclusion criteria based on LV ejection fraction; controls were participants without HF.
Stroke	CHARGE, METASTROKE, SIGN, DECODE, EPIC-CVD, Young Lacunar DNA, SIFAP, INTERSTROKE EUR, HVH1, Glasgow, CADISP, Barcelna, FINLAND, SAHLSIS, MDC, HVH2, and ICH	40,585 cases; 406,111 controls of European ancestry	29531354	https://www.megastroke.org/index.html	See details in the GWAS paper

eTable 2. Characteristics of instrumental variables for each drug class in the blood glucose and Alzheimer's disease datasets. Chr, chromosome; Pos, position; Efal, effect allele; Otheral, other allele.

							Exposure (Blood glucose)		Outcome (AD)		Outcome (AD / AD-by-proxy)			
Drug class	***Proxy gene/variant***	**SNP**	**Chr**	**Pos**	**Efal**	**Otheral**	**Beta**	**SE**	**Beta**	**SE**	**Beta**	**SE**	**R^2**	**F statistics**
Sulfonylureas	*rs757110*	rs757110	11	17418477	C	A	0.0126	0.0018	0.0131	0.0054	0.0018	0.0022	0.0002	50.3
	KCNJ11 and ABCC8	rs117287142	11	17401050	A	G	0.0225	0.0076	0.0481	0.0625	0.0106	0.0130	0.0003	23.5
		rs2074310	11	17421886	T	C	0.0129	0.0018	0.0132	0.0055	0.0015	0.0022		
		rs3758953	11	17499547	A	G	-0.0064	0.0017	-0.0099	0.0053	-0.0099	0.0053		
		rs4148630	11	17435966	G	A	-0.0084	0.0020	-0.0026	0.0061	-0.0034	0.0025		
Thiazolidinediones	*PPARG*	rs138779828	3	12414770	G	A	-0.0186	0.0059	0.0241	0.0333	-0.0045	0.0072	0.0001	12.3
		rs2067819	3	12359049	G	A	0.0079	0.0021	0.0084	0.0064	0.0046	0.0026		
Insulin analogues	*INSR*	rs2894553	19	7182145	C	T	0.0102	0.0029	-0.0013	0.0094	-0.0053	0.0038	0.0001	10.8
		rs74569625	19	7252613	G	A	-0.0105	0.0036	0.0085	0.0111	0.0085	0.0111		
GLP-1 analogues	*GLP1R*	rs1004280	6	39025882	A	G	0.0076	0.0020	0.0112	0.0061	0.0054	0.0025	0.0001	16.0
		rs10305423	6	39017062	C	T	0.0244	0.0051	0.0252	0.0171	0.0152	0.0070		
		rs880067	6	39016357	C	T	-0.0063	0.0020	-0.0055	0.0062	-0.0033	0.0026		

eTable 3. Characteristics of instrumental variables for each drug class in the positive control analyses. Chr, chromosome; Pos, position; Efal, effect allele; Otheral, other allele.

								Exposure (Blood glucose)		Outcome	
Outcome GWAS	**Drug class**	**Proxy gene/variant**	**SNP**	**Chr**	**Pos**	**Efal**	**Otheral**	**Beta**	**SE**	**Beta**	**SE**
Type 2 diabetes	Sulfonylureas	*rs757110*	rs757110	11	17418477	C	A	0.0126	0.0018	0.0680	0.0065
		KCNJ11 and ABCC8	rs117287142	11	17401050	A	G	0.0225	0.0076	0.0330	0.0340
			rs2074310	11	17421886	T	C	0.0129	0.0018	0.0680	0.0066
			rs3758953	11	17499547	A	G	-0.0064	0.0017	-0.0050	0.0064
			rs4148630	11	17435966	G	A	-0.0084	0.0020	-0.0150	0.0073
	Thiazolidinediones	*PPARG*	rs138779828	3	12414770	G	A	-0.0186	0.0059	0.0360	0.0220
			rs2067819	3	12359049	G	A	0.0079	0.0021	0.0600	0.0077
	Insulin analogues	*INSR*	rs2894553	19	7182145	C	T	0.0102	0.0029	0.0360	0.0110
			rs74569625	19	7252613	G	A	-0.0105	0.0036	-0.0250	0.0130
	GLP-1 analogues	*GLP1R*	rs1004280	6	39025882	A	G	0.0076	0.0020	0.0042	0.0075
			rs10305423	6	39017062	C	T	0.0244	0.0051	0.0260	0.0190
			rs880067	6	39016357	C	T	-0.0063	0.0020	-0.0160	0.0073
Insulin secretion	Sulfonylureas	*rs757110*	rs757110	11	17418477	C	A	0.0126	0.0018	-0.0420	0.0210
		KCNJ11 and ABCC8	rs2355017	11	17434603	C	T	-0.0083	0.0020	0.0580	0.0230
			rs3758953	11	17499547	A	G	-0.0064	0.0017	0.0270	0.0210
			rs5215	11	17408630	C	T	0.0127	0.0018	-0.0460	0.0200
	GLP-1 analogues	*GLP1R*	rs1076733	6	39045908	G	A	0.0061	0.0017	-0.0130	0.0250
			rs13202369	6	39022698	A	G	-0.0061	0.0019	0.0150	0.0230
Insulin resistance	Thiazolidinediones	*PPARG*	rs2067819	3	12359049	G	A	0.0079	0.0021	0.0110	0.0039
	Insulin analogues	*INSR*	rs4608435	19	7235137	G	T	0.0068	0.0019	0.0083	0.0039
Body mass index	Sulfonylureas	*rs757110*	rs757110	11	17418477	C	A	0.0126	0.0018	-0.0104	0.0017
		KCNJ11 and ABCC8	rs117287142	11	17401050	A	G	0.0225	0.0076	0.0058	0.0087
			rs2074310	11	17421886	T	C	0.0129	0.0018	-0.0089	0.0020
			rs3758953	11	17499547	A	G	-0.0064	0.0017	0.0016	0.0017

	Thiazolidinediones	*PPARG*	rs4148630	11	17435966	G	A	-0.0084	0.0020	-0.0001	0.0022
			rs138779828	3	12414770	G	A	-0.0186	0.0059	-0.0007	0.0064
			rs2067819	3	12359049	G	A	0.0079	0.0021	-0.0030	0.0020
	Insulin analogues	*INSR*	rs2894553	19	7182145	C	T	0.0102	0.0029	-0.0070	0.0033
			rs74569625	19	7252613	G	A	-0.0105	0.0036	0.0021	0.0038
	GLP-1 analogues	*GLP1R*	rs1004280	6	39025882	A	G	0.0076	0.0020	-0.0040	0.0022
			rs10305423	6	39017062	C	T	0.0244	0.0051	0.0073	0.0056
			rs880067	6	39016357	C	T	-0.0063	0.0020	-0.0004	0.0022
Waist circumference	Sulfonylureas	*rs757110*	rs757110	11	17418477	C	A	0.0126	0.0018	-0.0098	0.0036
		KCNJ11 and ABCC8	rs2074310	11	17421886	T	C	0.0129	0.0018	-0.0140	0.0054
			rs2355017	11	17434603	C	T	-0.0083	0.0020	-0.0086	0.0048
			rs3758953	11	17499547	A	G	-0.0064	0.0017	0.0012	0.0043
	Thiazolidinediones	*PPARG*	rs2067819	3	12359049	G	A	0.0079	0.0021	-0.0110	0.0040
	Insulin analogues	*INSR*	rs4608435	19	7235137	G	T	0.0068	0.0019	-0.0003	0.0051
	GLP-1 analogues	*GLP1R*	rs1076733	6	39045908	G	A	0.0061	0.0017	-0.0014	0.0050
			rs13202369	6	39022698	A	G	-0.0061	0.0019	-0.0041	0.0052
Hip circumference	Sulfonylureas	*rs757110*	rs757110	11	17418477	C	A	0.0126	0.0018	-0.0120	0.0037
		KCNJ11 and ABCC8	rs2074310	11	17421886	T	C	0.0129	0.0018	-0.0190	0.0057
			rs2355017	11	17434603	C	T	-0.0083	0.0020	-0.0056	0.0049
			rs3758953	11	17499547	A	G	-0.0064	0.0017	0.0037	0.0045
	Thiazolidinediones	*PPARG*	rs2067819	3	12359049	G	A	0.0079	0.0021	-0.0093	0.0042
	Insulin analogues	*INSR*	rs4608435	19	7235137	G	T	0.0068	0.0019	-0.0100	0.0052
	GLP-1 analogues	*GLP1R*	rs1076733	6	39045908	G	A	0.0061	0.0017	-0.0046	0.0051
			rs13202369	6	39022698	A	G	-0.0061	0.0019	0.0002	0.0054

eTable 4. Sensitivity analyses for the effects of genetic variation in anti-diabetic drug targets on Alzheimer's disease. Results from weighted median method and MR-Egger regression in the analysis using a dataset of 24,087 clinically diagnosed late-onset AD cases. NA indicates that MR-Egger regression or MR-PRESSO was not available because of limited number of IVs. P for intercept<0.05 indicates substantial bias from pleiotropy. All the ORs were scaled to per 1 mmol/L decrement in blood glucose.

Exposure	No. of IVs	Methods	OR (95%CI)	P	Pleiotropy (P)
Sulfonylureas	4	Weighted median	0.38 (0.17,0.84)	0.016	
		MR Egger	0.42 (0.05,3.79)	0.52	0.0010(0.93)
Glucagon-like peptide-1 (GLP-1) analogues	3	Weighted median	0.34 (0.11,1.07)	0.066	
		MR Egger	0.35 (0.05,2.52)	0.49	0.0011 (0.92)

eTable 5. Colocalization results in the target gene region of sulfonylureas and GLP-1 analogues for blood glucose and Alzheimer' disease. The region was defined as ±2500 base pairs of gene region.

Drug class	Drug target encoding gene	PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
Sulfonylureas	*KCNJ11*	0.00%	0.00%	97.00%	0.14%	2.50%
	ABCC8	0.00%	0.00%	96.00%	0.35%	3.90%
GLP-1 analogues	*GLP1R*	80.0%	0.18%	19.0%	0.04%	0.48%

PP indicates posterior probability.

H0: neither trait has a genetic association in the region

H1: only AD has a genetic association in the region

H2: only blood glucose has a genetic association in the region

H3: both traits are associated, but with different causal variants

H4: both traits are associated and share a single causal variant

eTable 6. Evidence for the effects of anti-diabetic drugs on cardiovascular diseases from clinical trials .

Drug class	Cardiovascular impact	Ref.
Thiazolidinedione (TZD)	Possible increase in the risk for heart failure but undetermined for other cardiovascular diseases.	Savarese G et al. *Cardiovasc Res*. 2021
Sulfonylureas	Unclear. Some trials suggested cardiovascular toxicity, while others suggested null association or even protective effects.	
GLP-1 analogues	Cardioprotective effects.	
Insulin / insulin analogues	Unclear. Some trials suggested null association, but a few suggested cardioprotective effects.*	Younk L M, et al. *Expert opinion on drug safety*. 2014.

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