Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Weights of normalized transcript per million values for meta-analysis of single nucleotide polymorphism effect estimates across all tissues.

Tissue	**TPM**
Adipose Subcutaneous	0.005347
Adipose Visceral Omentum	0.004417
Adrenal Gland	0.00238
Artery Aorta	0
Artery Coronary	0.004562
Artery Tibial	0.010602
Brain Amygdala	0.001507
Brain Anterior cingulate cortex BA24	0.004436
Brain Caudate basal ganglia	0.038985
Brain Cerebellar Hemisphere	0.003724
Brain Cerebellum	0.00421
Brain Cortex	0.00981
Brain Frontal Cortex BA9	0.00401
Brain Hippocampus	0.003104
Brain Hypothalamus	0.029825
Brain Nucleus accumbens basal ganglia	0.021023
Brain Putamen basal ganglia	0.018393
Brain Spinal cord cervical c1	0.002074
Brain Substantia nigra	0
Breast Mammary Tissue	0.010591
Cells Cultured fibroblasts	0
Cells EBV transformed lymphocytes	0
Colon Sigmoid	0.001191
Colon Transverse	0.002594
Esophagus Gastroesophageal Junction	0.000986
Esophagus Mucosa	0.002147
Esophagus Muscularis	0
Heart Atrial Appendage	0.132596

Heart Left Ventricle	0.044741
Kidney Cortex	0.003166
Liver	0
Lung	0.024889
Minor Salivary Gland	0.019252
Muscle Skeletal	0
Nerve Tibial	0.06929
Ovary	0
Pancreas	0.355041
Pituitary	0.002163
Prostate	0.007568
Skin Not Sun Exposed Suprapubic	0.01113
Skin Sun Exposed Lower leg	0.016588
Small Intestine Terminal Ileum	0.005497
Spleen	0.002499
Stomach	0.03184
Testis	0.058527
Thyroid	0.024682
Uterus	0.001873
Vagina	0.001368
Whole Blood	0.001372

Normalized TPM values were calculated by dividing the median TPM of each tissue by the sum of the median TPMs across all tissues, thus representing each tissue's proportional contribution to the total systemic effect (i.e., the sum across all tissues = 1.0).

Abbreviations: TPM—transcript per million.

eTable 2. Genetic variants associated with systemic *GLP1R* expression used to create the genetic risk score.

Chr	**Pos**	**NEA**	**EA**	**TSS**	**Beta**	**SE**	***p*-value**
6	39048860	C	T	62	0.152523	0.036477	2.90E-05
6	39073305	A	G	24507	-0.29631	0.090058	0.001001
6	39011665	G	C	-37133	-0.18453	0.040686	5.75E-06
6	39264926	G	A	216128	0.284428	0.090481	0.001669
6	39128276	G	C	79478	-0.25225	0.077073	0.001065
6	39051177	G	A	2379	-0.28656	0.065503	1.22E-05
6	39808404	A	G	759606	-0.08121	0.022217	0.000257
6	38237522	C	T	-811276	0.226757	0.073015	0.001899
6	38363354	T	A	-685444	-0.3703	0.094072	8.27E-05
6	39615359	T	C	566561	0.1659	0.049471	0.000798
6	39327729	G	T	278931	-0.12515	0.041186	0.002376
6	38927373	G	C	-121425	0.083492	0.026902	0.001912
6	39381589	G	A	332791	0.119934	0.03203	0.000181
6	39591175	A	C	542377	0.085053	0.022002	0.000111
6	39397525	T	C	348727	0.172934	0.055966	0.002002

Abbreviations: Chr—chromosome; Pos—position; NEA—non-effect allele; EA—effect allele; TSS—transcription start site distance; Beta—effect size; SE—standard error.

eTable 3. Definition of end-stage kidney disease.

Outcome	**Definition**
eGFR < 15 ml/min/1.73m2	An outpatient laboratory measurement of eGFR < 15 mL/min/1.73 m^2 with confirmatory eGFR < 15 at least 3 months apart.
Dialysis	Either 2 outpatient codes for dialysis or 1 outpatient and 1 inpatient diagnosis code dialysis in the primary position at least 3 months apart.
Transplant	Either an outpatient code for renal transplant or an inpatient code for renal transplant positioned as the primary diagnosis. In the outpatient setting two codes are required on two different dates.

Abbreviations: eGFR—estimated glomerular filtration rate.

eTable 4. Diagnosis codes for covariates.

Dialysis	
ICD-9	V45.1, V45.11, V56.0, V56.1, V56.2, V56.8, 585.6, V45.12, V56.31, V56.32, 792.5, 39.95, 39.952, 54.982, 39.953, 54.98, 54.983, 99.78
ICD-10	N18.6 R88.0 Z49.31, Z49.32, Z91.15,3E1M39Z Z49.01, Z49.02, Z99.2
ICD9P C	39.951, 54.981
CPT	90941, 90942, 90943, 90944, G0491, G0492, M0916, M0920, M0931, M0932, 90996, A4690, A4750, A4755, 90935, 90937, 90947, 90999, 90988, 90997, 4054F, 4055F, E1590, G8715, G8727, M0936, 36516, 36901, 36902, 36903, 36904, 36905, 36906, 36516, 36901, 36902, 36903, 36904, 36905, 36906, 36907, 36908, 36909, 4052F, 4053F, 90939, 90940, 90963, 90964, 90965 ,90966, 90967, 90968, 90969, 90970, 90976, 90977, 90978, 90979, 90982, 90983, 90984, 90985, 90991, 90994, 99512, 99559, G0257, G0320, G0321, G0322, G0323, G0327, G8075, G8076, G8714, G8956, G9264, G9265, G9266, M0923, M0928, M0937, M0940, M0944, M0945, M0948, M0952, M0956, S9335, S9339, G9240, G9241, 0505F, 0507F, 9092, 90921, 90924, 90925,90951, 90952, 90953, 90954, 90955, 90956, 90957, 90958, 90959, 90960, 90961, 90962, 90989, 90990, 90992, 90993, 90995, 90998, 4054F, 4055F
Diabetes	
ICD-9	250.1, 250.12, 250.21, 250.4, 250.41, 250.43, 250.5, 250.51, 250.6, 250.63, 250.72, 250.83, 250.93, 357.2, 362.03, 250, 250.22, 250.23, 250.3, 250.31, 250.53, 250.91, 362.01, 362.04, 362.06, 362.07, V53.91, 250.01, 250.03, 250.13, 250.2, 250.42, 250.52, 250.73, 250.82, 250.9, 250.92, 362.02, 362.05, 366.41, 250.11, 250.32, 250.33, 250.61, 250.62, 250.7, 250.71, 250.8, 250.81, V45.85 250.02
ICD-10	E11.311, E10.42, E11.319, E11.628, E11.69, E10.618, E10.9, E10.37X3, E10.37X2, E10.11, E10.638, E11.3493, E11.8, E10.319, E11.3592, E11.3391, E10.69, E11.10, E10.29, E10.37X9, E11.9, E10.621, E11.3492, E09.36, E11.3399, E11.11, E11.3591, E11.3299, E10.620, E11.638, E09.42, E10.10, E10.65, E11.3499, E11.01, E11.630, E10.630, E08.36, E10.51, E11.649, E11.621, E11.620, E11.39, E10.21, E10.8, E11.65, E11.51, E10.40, Z46.81, E11.3393, E10.39, E13.42, E11.3593, E10.641, E10.311, E11.36, E11.3292, E10.649, E11.3491, E11.622, E11.3291, E11.618, E11.3599, E10.36, E11.00, E08.42, E13.36, Z96.41, E11.29, E11.3293, E10.628, E11.40, E13.10, E10.622, E11.641, E10.37X1, E11.42, E11.3392, E11.21

Abbreviations: ICD—International Classification of Diseases; CPT—Current Procedural Terminology.

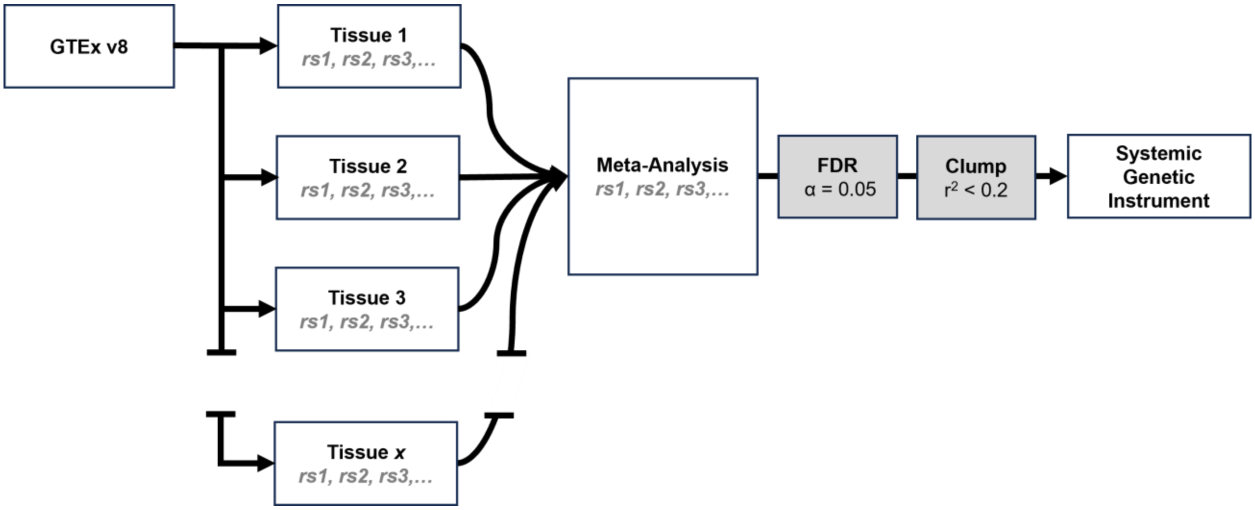
eTable 5. Survival analysis of the *GLP1R* genetic risk score effect on kidney disease progression, including stepwise adjustments for covariates and subgroup analyses.

Overall				
	N	HR	95% CI	*p*-value
Model 1	353153	0.956	0.921 – 0.993	**0.022**
Model 2	315815	0.958	0.922 – 0.995	**0.028**
Model 3	315509	0.961	0.925 – 0.999	**0.042**
Diabetes				
	N	HR	95% CI	*p*-value
Model 1	90728	0.951	0.905 – 1.000	0.051
Model 2	86216	0.949	0.902 – 0.998	**0.041**
No diabetes				
	N	HR	95% CI	*p*-value
Model 1	262425	0.969	0.914 – 1.028	0.295
Model 2	229599	0.975	0.919 – 1.035	0.404
Overweight/obese				
	N	HR	95% CI	*p*-value
Model 1	284713	0.952	0.914 – 0.992	**0.019**
Model 2	258729	0.957	0.918 – 0.997	**0.037**
Normal weight				
	N	HR	95% CI	*p*-value
Model 1	63482	0.985	0.887 – 1.094	0.777
Model 2	56780	0.969	0.871 – 1.078	0.560
Diabetes & overweight/obese				
	N	HR	95% CI	*p*-value
Model 1	82831	0.949	0.901 – 0.999	**0.047**
Model 2	78914	0.947	0.899 – 0.998	**0.044**
Diabetes & normal weight				
	N	HR	95% CI	*p*-value
Model 1	7709	0.988	0.822 – 1.186	0.893
Model 2	7267	0.973	0.808 – 1.172	0.771

No diabetes & overweight/obese				
	N	HR	95% CI	*p*-value
Model 1	201882	0.963	0.901 – 1.028	0.258
Model 2	179815	0.974	0.911 – 1.041	0.440
No diabetes & normal weight				
	N	HR	95% CI	*p*-value
Model 1	55773	0.987	0.869 – 1.122	0.845
Model 2	49513	0.975	0.856 – 1.110	0.698

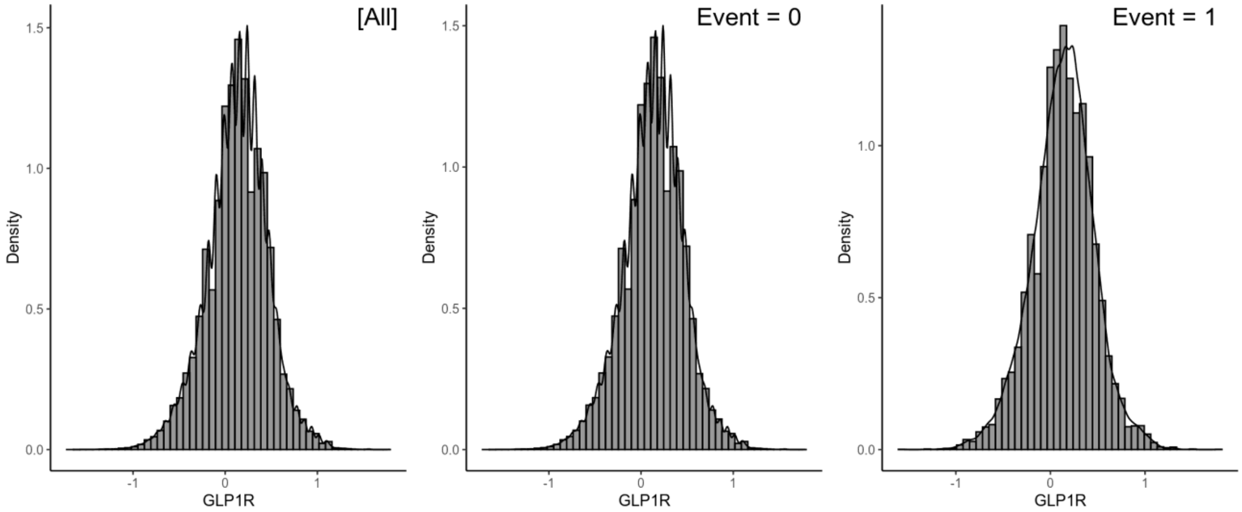
The hazard ratio for kidney disease progression represents the top tertile versus the bottom tertile of the genetic risk score for systemic *GLP1R* expression. Model 1 is unadjusted. Model 2 is adjusted for age, sex, the first 10 principal components, systolic blood pressure, and the use of an ACE or ARB. Model 3 is Model 2 plus adjustments for body mass index and the presence or absence of diabetes.

eFigure 1. Flowchart detailing the generation of a systemic genetic instrument for GLP1R expression from the Genotype-Tissue Expression Project.



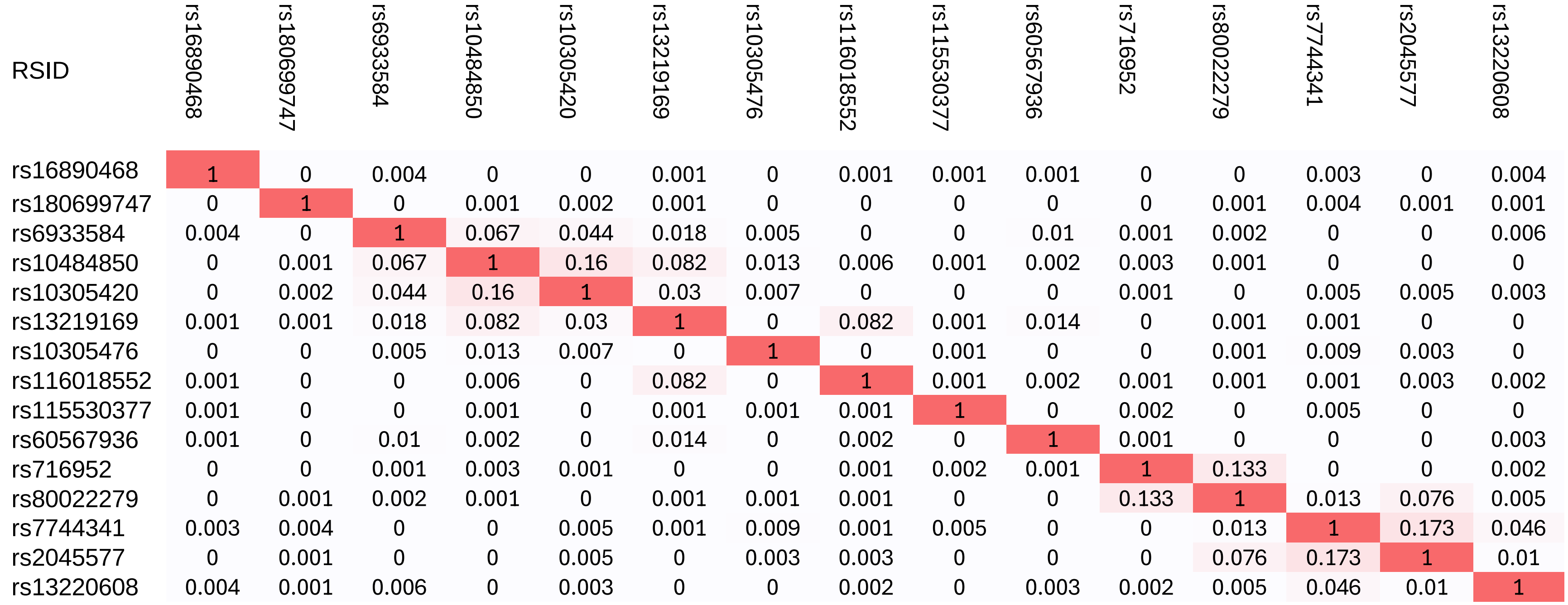
Abbreviations: GTEx v8—The Genotype-Tissue Expression project version 8; FDR—false discovery rate.

eFigure 2. Distribution of genetic risk scores for systemic *GLP1R* expression among study participants.



Event corresponds to kidney disease progression, defined as the incident decline in eGFR of 40% or end-stage kidney disease during the follow-up period.

eFigure 3. Linkage disequilibrium matrix for the genetic variants associated with systemic *GLP1R* expression used to create the genetic risk score.



RSID	rs16890468	rs180699747	rs6933584	rs10484850	rs10305420	rs13219169	rs10305476	rs116018552	rs115530377	rs60567936	rs716952	rs80022279	rs7744341	rs2045577	rs13220608
rs16890468	1	0	0.004	0	0	0.001	0	0.001	0.001	0.001	0	0	0.003	0	0.004
rs180699747	0	1	0	0.001	0.002	0.001	0	0	0	0	0	0.001	0.004	0.001	0.001
rs6933584	0.004	0	1	0.067	0.044	0.018	0.005	0	0	0.01	0.001	0.002	0	0	0.006
rs10484850	0	0.001	0.067	1	0.16	0.082	0.013	0.006	0.001	0.002	0.003	0.001	0	0	0
rs10305420	0	0.002	0.044	0.16	1	0.03	0.007	0	0	0	0.001	0	0.005	0.005	0.003
rs13219169	0.001	0.001	0.018	0.082	0.03	1	0	0.082	0.001	0.014	0	0.001	0.001	0	0
rs10305476	0	0	0.005	0.013	0.007	0	1	0	0.001	0	0	0.001	0.009	0.003	0
rs116018552	0.001	0	0	0.006	0	0.082	0	1	0.001	0.002	0.001	0.001	0.001	0.003	0.002
rs115530377	0.001	0	0	0.001	0	0.001	0.001	0.001	1	0	0.002	0	0.005	0	0
rs60567936	0.001	0	0.01	0.002	0	0.014	0	0.002	0	1	0.001	0	0	0	0.003
rs716952	0	0	0.001	0.003	0.001	0	0	0.001	0.002	0.001	1	0.133	0	0	0.002
rs80022279	0	0.001	0.002	0.001	0	0.001	0.001	0.001	0	0	0.133	1	0.013	0.076	0.005
rs7744341	0.003	0.004	0	0	0.005	0.001	0.009	0.001	0.005	0	0	0.013	1	0.173	0.046
rs2045577	0	0.001	0	0	0.005	0	0.003	0.003	0	0	0	0.076	0.173	1	0.01
rs13220608	0.004	0.001	0.006	0	0.003	0	0	0.002	0	0.003	0.002	0.005	0.046	0.01	1

The plot illustrates pairwise linkage disequilibrium between the genetic variants associated with systemic GLP1R expression based on the European reference population. These were generated using the National Institutes of Health LDlink. The colors correspond to R^2 values, where white indicates no correlation and red indicates absolute correlation.

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