Online-only supplementary material

Table of contents

Supplement to:

Genetic variation in sodium-glucose cotransporter 2 and heart failure

Julius L. Katzmann, Amy M. Mason, Winfried März, Marcus E. Kleber, Alexander Niessner, Matthias Blüher, Thimoteus Speer, Ulrich Laufs

Appendix: Genotyping, laboratory procedures, ethical approval, outcome selection, and outcome definitions

Genotyping and laboratory procedures

In UK Biobank, genotyping was performed using the Affymetrix UK BiLEVE Axiom array and the Affymetrix UK Biobank Axiom array. Genotype data were imputed with IMPUTE4 using the Haplotype Reference Consortium (HRC) and UK10K + 1000 Genomes panel 26[1]. The laboratory analyses were conducted as documented by the UK Biobank[2].

In the LURIC study, genotyping was performed using Affymetrix Human SNP Array 6.0. Genotypes were imputed with IMPUTE2 using the 1000G reference panel (March 2012). The routine laboratory analyses have been described previously[3]. NT-proBNP was measured by electrochemiluminescence on an Elecsys 2010 analyser (Roche Diagnostics).

Ethical approval

This research was conducted under UK Biobank application number 61650. UK Biobank is approved by the Northwest Multi-Center Research Ethics Committee. All participants provided written informed consent. The LURIC study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz. All participants provided written informed consent.

The study complies with the declaration of Helsinki.

Outcome selection

Outcomes and potential mediators of the reduced risk of heart failure observed under pharmacologic SGLT2 inhibition were selected according to the results of the randomized clinical trials of SGLT2 inhibitors or mechanistic plausibility[4–9].

The following outcomes were included in the analyses: Type 2 diabetes (T2DM), heart failure and in the LURIC study, the phenotypes of heart failure with reduced and preserved ejection fraction (HFrEF, HFpEF)[10], ASCVD events, thrombotic events, chronic kidney disease, cardiovascular, heart failure, and all-cause death. Biomarkers and anthropometric traits considered to be potential mediators of the effect of SGLT2 inhibitors on heart failure included parameters of glucose metabolism, cardiovascular risk factors (lipoproteins, blood pressure, C-reactive protein [CRP]), parameters of kidney function, parameter reflecting volume status, uric acid, and physiological parameters (weight, waist circumference, body impedance measurements).

Outcome definitions

The definitions of disease outcomes in the LURIC study have been described previously[3]. In brief, T2DM was defined according to the American Diabetes Association 2010 guidelines or

history of T2DM. Coronary artery disease (CAD) was defined as luminal narrowing of >20% in at least one of 15 segments according to the American Heart Association. Heart failure was defined as the presence of symptoms (dyspnea) and impaired left ventricular function defined by imaging techniques such as echocardiography, and graded semiquantitatively. All participants underwent echocardiography. Information on vital status was obtained from local registries. Death certificates, autopsy data, and medical data from local hospitals were independently reviewed by two experienced clinicians blinded to patient characteristics who classified the cause of death.

For definitions of disease outcomes in the UK Biobank, see **supplementary Table S1**.

Both prevalent and incident diagnoses were considered as incident as to the lifelong exposure to the genetic polymorphisms. In the subgroup analyses in UK Biobank of the association of *SLC5A2* polymorphisms with heart failure stratified by the presence of CAD and T2DM, there were no information on the order of occurrence of CAD, T2DM, and heart failure, which has to be taken into account when interpreting the results. Importantly, this does not affect the subgroups without CAD or T2DM.

Table S1: Outcome definitions in the UK Biobank

Outcome	Outcome definition/diagnostic code
Heart failure	ICD-9: 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.X; ICD-10: I11.0, I13.0, I13.2, I50.X, I42.0; self-report 20002: 1076
Type 2 diabetes mellitus (T2DM)	The definition is based on a previously published algorithm[11]. All incident and prevalent cases with possible or probable T2DM were included, and cases with ICD-10 codes E11.X (but not for E10.X) from hospital episode statistics (HES) and death certificates were added. This results in a liberal estimate of whether participants have T2DM, and in a conservative estimate of whether participants do not have T2DM.
Coronary artery disease	Composite of myocardial infarction, coronary revascularization, and coronary death
Myocardial infarction	ICD-9: 410.X, 411.0.X, 412.X, 429.79; ICD-10: I21.X, I22.X, I23.X, I24.1, I25.2; self-report 20002: 1075
Coronary revascularization	Self-report 20004: 1070, 1095, 1523; procedures (OPCS): K50.1, K40.X, K41.X, K42.X, K43.X, K44.X
Coronary death	Death ICD-10: I21.X, I22.X, I23.X, I24.X, I25.1, I25.2, I25.3, I25.5, I25.6, I25.8, I25.9
Stroke	ICD-9: 430.X, 431.X, 434.X, 436.X; ICD-10: I60.X, I61.X, I63.X, I64.X; self-report 20002: 1081, 1086, 1491, 1583
Peripheral artery disease	ICD-9: 440.X, 443.8, 443.9, 444.X; ICD-10: I70.X, I73.8, I73.9, I74.X; self-report 20002: 1067; self-report 20004: 1102, 1108
Chronic kidney disease	ICD-9: 403.X, 585.X, 586.X; ICD-10: N18.X, N19.X, I12.X, I13.X; self-report 20002: 1192, 1193, 1194; self-report 20004: 1580, 1581, 1582
Deep vein thrombosis	ICD-9: 451.1.X; ICD-10: I80.2; self-report 20002: 1094
Pulmonary embolism	ICD-9: 415.1.X; ICD-10: I26.X; self-report 20002: 1093
Cardiovascular death	Composite of coronary death and ischemic stroke death (death 40001, 40002: I63.X, I64.X)

Table S2: Baseline metabolic characteristics

	UK Biobank	LURIC
Glucose (mg/dL)	92.1±21.5	113.9±35.7
HbA1c (%, median [interquartile range])	5.4 (5.1−5.6)	6.0 (5.6−6.6)
Creatinine (mg/dL)	0.82±0.20	0.98±0.38
Cystatin C (mg/L)	0.91±0.17	1.00±0.40
Urea (mg/dL)	32.6±8.3	39.5±15.6
Total cholesterol (mg/dL)	221.1±44.1	208.5±44.0
LDL cholesterol (mg/dL)	138.2±33.6	116.5±34.3
HDL cholesterol (mg/dL)	56.2±14.8	38.7±10.8
Triglycerides (mg/dL, median [interquartile range])	131.9 (93.0–190.7)	145 (107–200)
Apolipoprotein B (mg/dL)	103.5±23.8	104.5±24.6
Lipoprotein(a) (median [interquartile range])	20.2 (9.4–60.1) nmol/L	16.0 (7–38) mg/dL
Hemoglobin (g/dL)	14.2±1.2	13.8±1.5
Hematocrit (%)	41.1±3.5	40.5±4.2
Uric acid (mg/dL)	5.2±1.3	5.1±1.7
NT-proBNP (pg/mL, median [interquartile range])	–	293 (106–868)

Notes: Plus-minus values are means±SD, or as indicated.

Table S3: Association of SNPs in *SLC5A2* with NT-proBNP in all LURIC study participants

SNP	Coefficient NT-proBNP (95% CI)*	*p* value NT-proBNP
rs11646054	-0.04 (-0.11–0.03)	0.305
rs144413428	0.20 (-0.12–0.52)	0.226
rs3116149	0.01 (-0.17–0.18)	0.939
rs3116150	-0.04 (-0.14–0.06)	0.446
rs3813007	-0.14 (-0.40–0.13)	0.326
rs3813008	-0.04 (-0.15–0.06)	0.405
rs9934336	0.00 (-0.08–0.08)	0.995

Notes: SNPs in *SLC5A2* with minor allele frequency >0.01 in UK Biobank are shown.
* Given as natural logarithm.
SNP: single nucleotide polymorphism.

Table S4: Associations of the genetic SGLT2 score with continuous traits

	UK Biobank		LURIC	
	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value
Glucose metabolism				
Glucose (mg/dL)	-0.034 (-0.101–0.033)	0.316	-1.28 (-2.77–0.22)	0.095
HbA1c (%)*	-0.00064 (-0.0009– -0.00037)	<0.001	-0.0073 (-0.0142– -0.0004)	0.038
Glucose 1 h post OGTT (mg/dL)	–	–	-2.80 (-5.86–0.27)	0.074
Glucose 2 h post OGTT (mg/dL)	–	–	-4.00 (-7.45– -0.55)	0.023
Insulin fasting	–	–	-0.38 (-0.82–0.05)	0.083
Proinsulin fasting (U/L)	–	–	-0.49 (-0.88– -0.09)	0.017
C-peptide fasting (mg/dL)	–	–	0.031 (-0.046–0.109)	0.428
HOMA index	–	–	-0.19 (-0.35– -0.04)	0.016
Renal function				
Creatinine (mg/dL)	-0.00023 (-0.00075–0.00030)	0.402	-0.0030 (-0.0171–0.0110)	0.674
Cystatin C (mg/L)	-0.00034 (-0.00081–0.00013)	0.154	-0.0046 (-0.0211–0.0110)	0.588
Urea (mg/dL)	-0.019 (-0.043–0.005)	0.130	0.097 (-0.501–0.696)	0.750
Lipids				
Total cholesterol (mg/dL)	0.039 (-0.093–0.171)	0.562	-0.59 (-2.40–1.21)	0.518
LDL cholesterol (mg/dL)	-0.0069 (-0.1086–0.0949)	0.895	-0.047 (-1.458–1.364)	0.948
HDL cholesterol (mg/dL)	0.051 (0.011–0.091)	0.013	-0.15 (-0.58–0.28)	0.498
Triglycerides (mg/dL)*	-0.0013 (-0.0027–0.0002)	0.086	-0.0048 (-0.0249–0.0154)	0.638
Apolipoprotein B (mg/dL)	-0.013 (-0.085–0.059)	0.726	-0.091 (-1.102–0.920)	0.860
Lipoprotein(a) (nmol/L [UK Biobank]/mg/dL [LURIC])*	0.00078 (-0.00306–0.00463)	0.690	-0.079 (-0.151– -0.006)	0.034
Volume status				
Hemoglobin (g/dL)	-0.00022 (-0.00316–0.00272)	0.883	-0.022 (-0.079–0.034)	0.443
Hematocrit (%)	-0.0016 (-0.0103–0.0071)	0.712	-0.051 (-0.215–0.112)	0.540
Total protein (g/dL)	-0.00081 (-0.00209–0.00047)	0.214	-0.013 (-0.035–0.008)	0.220
Albumin (g/dL)	-0.000046 (-0.000852–0.000759)	0.910	-0.021 (-0.046–0.004)	0.096
Others				
Uric acid (mg/dL)	-0.0039 (-0.0071– -0.0007)	0.017	-0.023 (-0.09–0.044)	0.506
CRP (mg/dL)*	0.00095 (-0.00193–0.00383)	0.519	0.043 (-0.036–0.122)	0.284

Physiological measures					
	Weight (kg)	0.022 (-0.017–0.062)	0.265	-0.17 (-0.65–0.30)	0.481
	Waist circumference (cm)	-0.025 (-0.042– -0.008)	0.003	-0.097 (-0.396–0.203)	0.528
	Systolic blood pressure (mmHg)	0.095 (0.044–0.146)	<0.001	-0.54 (-1.46–0.38)	0.247
	Diastolic blood pressure (mmHg)	0.0092 (-0.0194–0.0377)	0.529	-0.43 (-0.91–0.04)	0.071
	Heart rate (min^{-1})	-0.022 (-0.055–0.011)	0.184	-0.21 (-0.71–0.28)	0.394
	Body fat percentage (%)	-0.021 (-0.031– -0.011)	<0.001	0.68 (-0.50–1.85)	0.260
	Body impedance (ohm)	-0.40 (-0.55– -0.25)	<0.001	0.72 (-3.91–5.35)	0.760
	Left ventricular ejection fraction (echocardiography)	–	–	0.013 (-0.343–0.368)	0.945

Notes: The Bonferroni-corrected threshold for statistical significance is 0.05/24=0.0021 in UK Biobank and 0.05/31=0.0016 in the LURIC study.

* Given as natural logarithm.

OGTT: oral glucose tolerance test, HOMA: homeostasis model assessment.

Table S5: Mediation analyses

	OR (95% CI) for heart failure per allele of the genetic SGLT2 score in UK Biobank	Mediation (95% CI) in %
Unadjusted	0.973 (0.951–0.995)	–
Adjusted for		
Glucose metabolism		
HbA1c (%)*	0.976 (0.954–0.998)	11.9 (3.7–47.1)
Lipids		
HDL cholesterol (mg/dL)	0.975 (0.952–0.999)	10.3 (1.2–30.8)
Triglycerides (mg/dL)*	0.975 (0.953–0.998)	8.7 (6.2–11.2)
Others		
Uric acid (mg/dL)	0.975 (0.953–0.998)	10.0 (-2.5–15.4)
Anthropometric measures		
Waist circumference (cm)	0.974 (0.952–0.996)	4.5 (-0.1–16.5)
Circulatory parameters		
Systolic blood pressure (mmHg)	0.974 (0.952–0.996)	4.7 (0.6–13.2)
Impedance measurements		
Body fat percentage (%)	0.973 (0.951–0.995)	0.8 (0.0–3.6)
Body impedance (ohm)	0.973 (0.951–0.995)	2.0 (0.5–7.1)
HbA1c + HDL cholesterol	0.978 (0.955–1.002)	20.1 (4.9–98.9)
+ uric acid	0.980 (0.956–1.004)	25.8 (5.5–117.3)
+ systolic blood pressure	0.981 (0.957–1.005)	30.3 (7.5–136.5)
+ waist circumference	0.982 (0.958–1.006)	33.5 (8.0–146.0)
+ body impedance	0.982 (0.958–1.007)	35.0 (7.9–155.8)

Notes: All parameters from supplementary Table S4 associated with the genetic SGLT2 score in UK Biobank at $p<0.10$ were included in this analysis.
* Analysed as natural logarithm.

Table S6: Association of SNPs in *SLC5A2* with HbA1c in UK Biobank

SNP	EAF	Coefficient HbA1c (95% CI)*	*p* value HbA1c
rs11646054	0.59	-0.00018 (-0.00054–0.00018)	0.329
rs144413428	0.02	0.00258 (0.00113–0.00402)	<0.001
rs3116149	0.05	0.00130 (0.00052–0.00208)	0.001
rs3116150	0.76	-0.00076 (-0.00117– -0.00035)	<0.001
rs3813007	0.99	0.00107 (-0.00067–0.00281)	0.228
rs3813008	0.15	0.00064 (0.00014–0.00113)	0.012
rs9934336	0.28	-0.00086 (-0.00125– -0.00046)	<0.001

Notes: The effect allele was defined as in Table 2 according to the association of the respective SNP with heart failure in UK Biobank, also if this association was not statistically significant. In the genetic SGLT2 scores that were used in the sensitivity analyses, rs144413428, rs3116149, rs3116150, and rs9934336 were included with the exposure allele defined as the allele associated with lower HbA1c. Rs3813008 was not included as it was in linkage disequilibrium with rs3116149 (r^2=0.332).
* Given as natural logarithm.

Table S7: Associations of the unweighted alternative genetic SGLT2 score with continuous traits

	UK Biobank		LURIC	
	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value
Glucose metabolism				
Glucose (mg/dL)	-0.032 (-0.097–0.033)	0.334	-1.07 (-2.51–0.37)	0.145
HbA1c (%)*	-0.00080 (-0.00105– -0.00054)	<0.001	-0.0059 (-0.0126–0.0009)	0.089
Glucose 1 h post OGTT (mg/dL)	–	–	-2.44 (-5.43–0.55)	0.109
Glucose 2 h post OGTT (mg/dL)	–	–	-3.61 (-7.02– -0.19)	0.038
Insulin fasting			-0.30 (-0.74–0.13)	0.170
Proinsulin fasting (U/L)	–	–	-0.35 (-0.74–0.03)	0.073
C-peptide fasting (mg/dL)	–	–	0.032 (-0.045–0.109)	0.411
HOMA index	–	–	-0.16 (-0.31–0.00)	0.046
Renal function				
Creatinine (mg/dL)	-0.00021 (-0.00072–0.00030)	0.409	-0.0035 (-0.0173–0.0104)	0.625
Cystatin C (mg/L)	-0.00025 (-0.00071–0.00020)	0.269	-0.0075 (-0.0239–0.0088)	0.365
Urea (mg/dL)	-0.018 (-0.041–0.005)	0.128	0.11 (-0.48–0.70)	0.718
Lipids				
Total cholesterol (mg/dL)	0.037 (-0.090–0.164)	0.567	-0.73 (-2.50–1.03)	0.416
LDL cholesterol (mg/dL)	-0.0096 (-0.1078–0.0886)	0.848	-0.36 (-1.74–1.02)	0.610
HDL cholesterol (mg/dL)	0.050 (0.011–0.088)	0.012	-0.069 (-0.491–0.352)	0.747
Triglycerides (mg/dL)*	-0.0013 (-0.0027–0.0001)	0.072	-0.0035 (-0.0234–0.0163)	0.727
Apolipoprotein B (mg/dL)	-0.0039 (-0.0735–0.0658)	0.914	-0.12 (-1.12–0.87)	0.807
Lipoprotein(a) (nmol/L [UK Biobank]/mg/dL [LURIC])*	-0.00060 (-0.00431–0.00311)	0.750	-0.075 (-0.146– -0.005)	0.036
Volume status				
Hemoglobin (g/dL)	0.0010 (-0.0018–0.0038)	0.484	0.005 (-0.051–0.061)	0.860
Hematocrit (%)	0.0015 (-0.0069–0.0099)	0.722	0.010 (-0.150–0.171)	0.899
Total protein (g/dL)	-0.0011 (-0.0024–0.0001)	0.076	-0.011 (-0.032–0.011)	0.326
Albumin (g/dL)	-0.00016 (-0.00094–0.00062)	0.684	-0.015 (-0.040–0.009)	0.212
Others				
Uric acid (mg/dL)	-0.0033 (-0.0064– -0.0002)	0.037	-0.012 (-0.079–0.054)	0.715
CRP (mg/dL)*	0.00098 (-0.00180–0.00376)	0.491	0.032 (-0.045–0.109)	0.416

Physiological measures					
	Weight (kg)	0.021 (-0.017–0.059)	0.283	-0.26 (-0.73–0.21)	0.278
	Waist circumference (cm)	-0.024 (-0.040– -0.008)	0.004	-0.05 (-0.34–0.24)	0.737
	Systolic blood pressure (mmHg)	0.084 (0.035–0.133)	0.001	-0.59 (-1.49–0.31)	0.199
	Diastolic blood pressure (mmHg)	0.010 (-0.017–0.038)	0.470	-0.43 (-0.89–0.03)	0.069
	Heart rate (min^{-1})	-0.015 (-0.047–0.017)	0.357	-0.30 (-0.78–0.19)	0.227
	Body fat percentage (%)	-0.019 (-0.029– -0.010)	<0.001	0.68 (-0.51–1.86)	0.261
	Body impedance (ohm)	-0.37 (-0.51– -0.22)	<0.001	-0.28 (-4.89–4.34)	0.907
	Left ventricular ejection fraction (echocardiography)	–	–	-0.025 (-0.369–0.319)	0.887

Notes: The Bonferroni-corrected threshold for statistical significance is 0.05/24=0.0021 in UK Biobank and 0.05/31=0.0016 in the LURIC study.
* Given as natural logarithm.
OGTT: oral glucose tolerance test, HOMA: homeostasis model assessment.

Table S8: Associations of the weighted alternative genetic SGLT2 score with continuous traits

	UK Biobank		LURIC	
	Coefficient (95% CI)	*p* value	Coefficient (95% CI)	*p* value
Glucose metabolism				
Glucose (mg/dL)	-0.052 (-0.199–0.096)	0.490	-1.44 (-4.71–1.83)	0.389
HbA1c (%)*	-0.0022 (-0.0028– -0.0016)	<0.001	-0.0077 (-0.0230–0.0077)	0.326
Glucose 1 h post OGTT (mg/dL)	–	–	-4.13 (-10.82–2.56)	0.226
Glucose 2 h post OGTT (mg/dL)	–	–	-5.39 (-13.04–2.26)	0.167
Insulin fasting			-0.65 (-1.63–0.33)	0.194
Proinsulin fasting (U/L)	–	–	-0.25 (-1.13–0.63)	0.574
C-peptide fasting (mg/dL)	–	–	0.061 (-0.113–0.234)	0.491
HOMA index	–	–	-0.32 (-0.67–0.04)	0.079
Renal function				
Creatinine (mg/dL)	-0.00027 (-0.00144–0.00089)	0.643	-0.0160 (-0.0474–0.0155)	0.321
Cystatin C (mg/L)	-0.00034 (-0.00137–0.00069)	0.514	-0.038 (-0.075– -0.001)	0.046
Urea (mg/dL)	-0.017 (-0.070–0.036)	0.519	0.23 (-1.10–1.57)	0.733
Lipids				
Total cholesterol (mg/dL)	0.045 (-0.245–0.335)	0.761	-1.62 (-5.63–2.40)	0.430
LDL cholesterol (mg/dL)	-0.037 (-0.261–0.187)	0.744	-1.61 (-4.75–1.53)	0.314
HDL cholesterol (mg/dL)	0.088 (0.000–0.176)	0.051	0.030 (-0.927–0.986)	0.952
Triglycerides (mg/dL)*	-0.0029 (-0.0060–0.0003)	0.076	0.0026 (-0.0425–0.0477)	0.911
Apolipoprotein B (mg/dL)	-0.0094 (-0.1682–0.1494)	0.908	-0.44 (-2.69–1.82)	0.704
Lipoprotein(a) (nmol/L [UK Biobank]/mg/dL [LURIC])*	-0.0024 (-0.0109–0.0061)	0.578	-0.20 (-0.36– -0.04)	0.012
Volume status				
Hemoglobin (g/dL)	0.0053 (-0.0011–0.0118)	0.106	0.13 (0.00–0.26)	0.044
Hematocrit (%)	0.012 (-0.007–0.031)	0.228	0.322 (-0.043–0.687)	0.084
Total protein (g/dL)	-0.0026 (-0.0054–0.0002)	0.073	-0.011 (-0.059–0.037)	0.643
Albumin (g/dL)	-0.00059 (-0.00236–0.00118)	0.512	0.00030 (-0.05466–0.05527)	0.991
Others				
Uric acid (mg/dL)	-0.0044 (-0.0115–0.0027)	0.225	-0.022 (-0.172–0.129)	0.778
CRP (mg/dL)*	0.0020 (-0.0044–0.0083)	0.540	-0.023 (-0.198–0.151)	0.795

Physiological measures					
	Weight (kg)	0.023 (-0.063–0.109)	0.602	-0.55 (-1.61–0.51)	0.313
	Waist circumference (cm)	-0.043 (-0.080– -0.005)	0.025	-0.0051 (-0.6729–0.6628)	0.988
	Systolic blood pressure (mmHg)	0.14 (0.03–0.26)	0.013	-0.87 (-2.91–1.17)	0.403
	Diastolic blood pressure (mmHg)	0.024 (-0.039–0.086)	0.459	-0.43 (-1.47–0.62)	0.425
	Heart rate (min^{-1})	-0.022 (-0.094–0.051)	0.556	-0.85 (-1.94–0.25)	0.131
	Body fat percentage (%)	-0.038 (-0.060– -0.015)	0.001	1.25 (-1.57–4.07)	0.384
	Body impedance (ohm)	-0.63 (-0.97– -0.30)	<0.001	-3.41 (-14.38–7.57)	0.543
	Left ventricular ejection fraction (echocardiography)	–	–	-0.031 (-0.816–0.754)	0.938

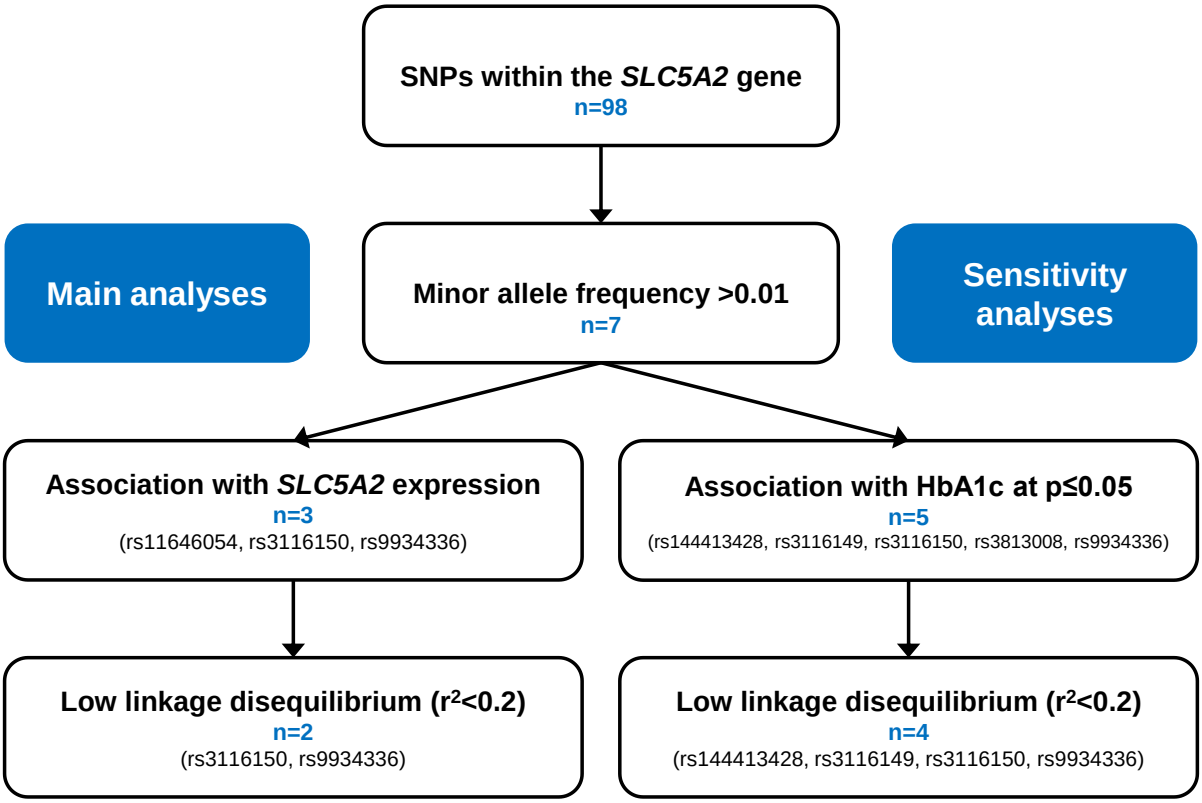
Notes: The Bonferroni-corrected threshold for statistical significance is 0.05/24=0.0021 in UK Biobank and 0.05/31=0.0016 in the LURIC study.
* Given as natural logarithm.
OGTT: oral glucose tolerance test, HOMA: homeostasis model assessment.

Table S9: Mediation analyses using the unweighted alternative genetic SGLT2 score

	OR (95% CI) for heart failure per allele of the unweighted alternative genetic SGLT2 score in UK Biobank	Mediation (%)
Unadjusted	0.981 (0.960–1.003)	–
Adjusted for		
Glucose metabolism		
HbA1c (%)*	0.985 (0.964–1.007)	20.0
Lipids		
HDL cholesterol (mg/dL)	0.985 (0.962–1.008)	17.5
Triglycerides (mg/dL)*	0.984 (0.963–1.007)	16.0
Volume status		
Total protein	0.983 (0.961–1.007)	10.4
Others		
Uric acid (mg/dL)	0.985 (0.963–1.007)	17.8
Anthropometric measures		
Waist circumference (cm)	0.982 (0.961–1.004)	6.1
Circulatory parameters		
Systolic blood pressure (mmHg)	0.983 (0.961–1.004)	6.5
Impedance measurements		
Body fat percentage (%)	0.982 (0.960–1.003)	1.0
Body impedance (ohm)	0.982 (0.961–1.004)	2.6
HbA1c + uric acid	0.988 (0.966–1.011)	38.4
+ HDL cholesterol	0.989 (0.966–1.012)	40.5
+ total protein	0.989 (0.966–1.013)	41.2
+ systolic blood pressure	0.990 (0.967–1.014)	47.3
+ waist	0.991 (0.968–1.015)	51.3
+ body impedance	0.991 (0.968–1.015)	53.5

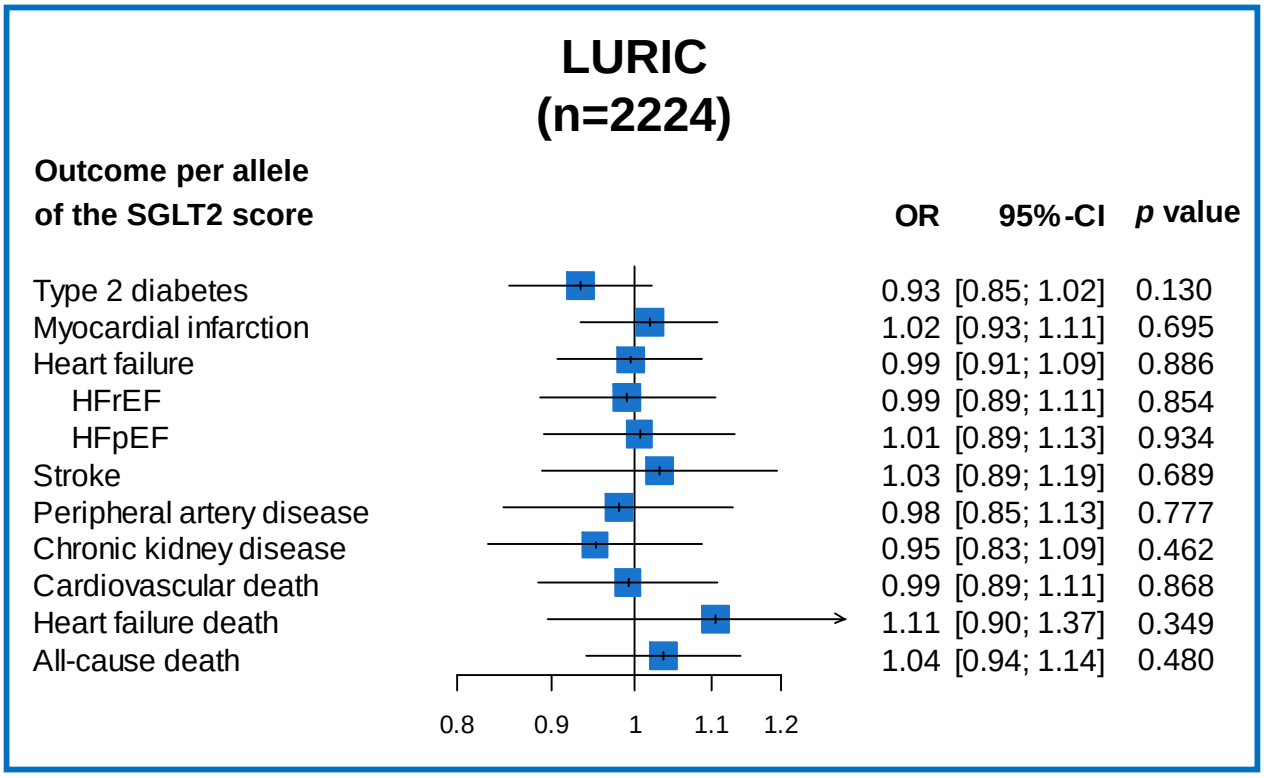
Notes: All parameters from supplementary Table S7associated with the unweighted alternative genetic SGLT2 score in UK Biobank at $p<0.10$ were included in this analysis. As the unadjusted effect was not statistically significant, the analysis has to be considered exploratory, and no CI for the mediation effect is provided. As the association between heart failure and the weighted alternative SGLT2 score was weak (OR [95% CI], 0.996 [0.947–1.046], $p=0.860$), no reasonable mediation analyses could be conducted with the weighted alternative SGLT2 score.
* Analysed as natural logarithm.

Figure S1: Selection of genetic variants for the main and sensitivity analyses



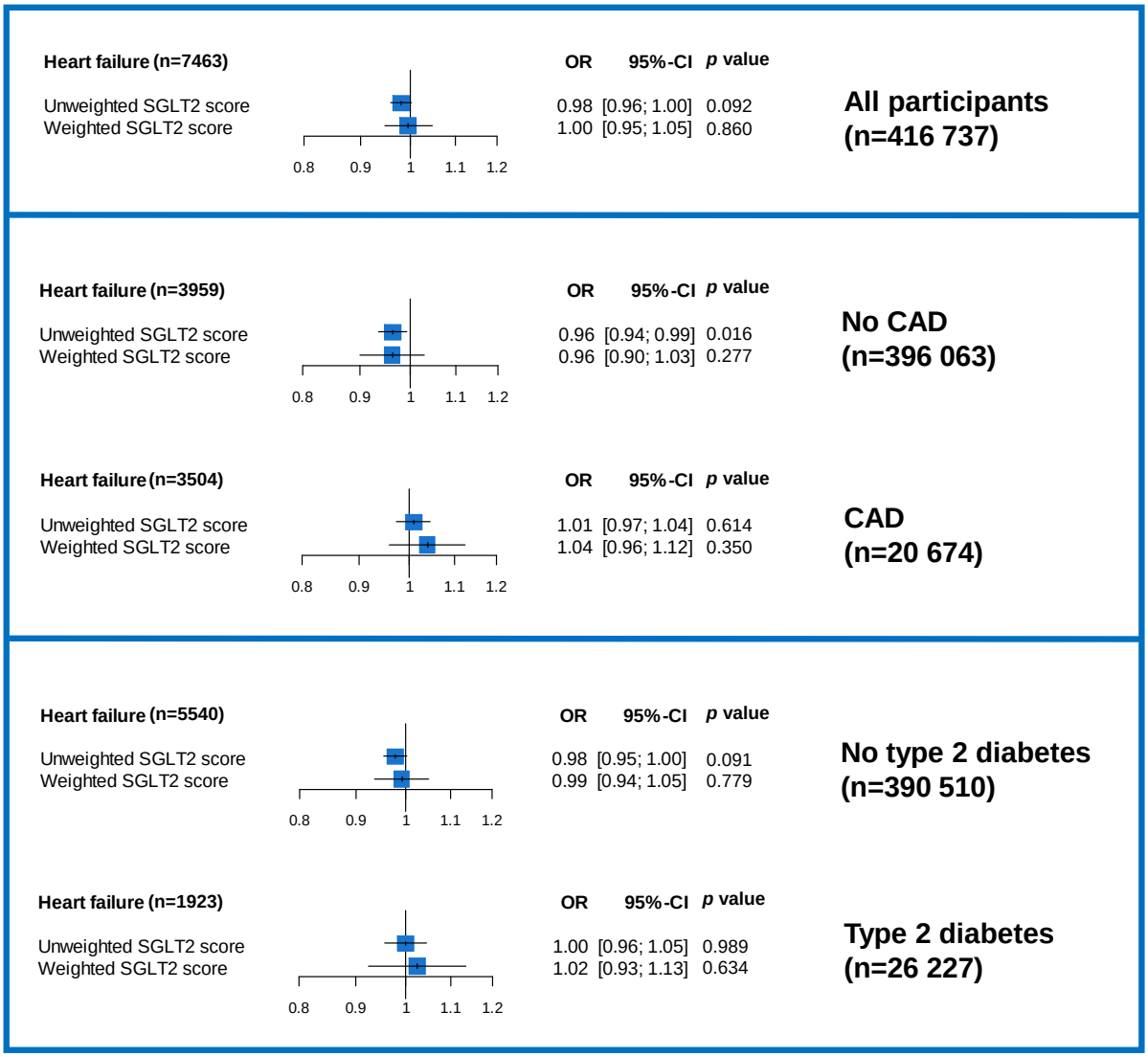
All SNPs with a minor allele frequency >0.01 in UK Biobank were considered. The association with *SLC5A2* expression was assessed using data from the GTEx project[12], linkage disequilibrium was tested with the online tool LDlink[13].

Figure S2: Associations of the genetic SGLT2 score with outcomes in the LURIC study



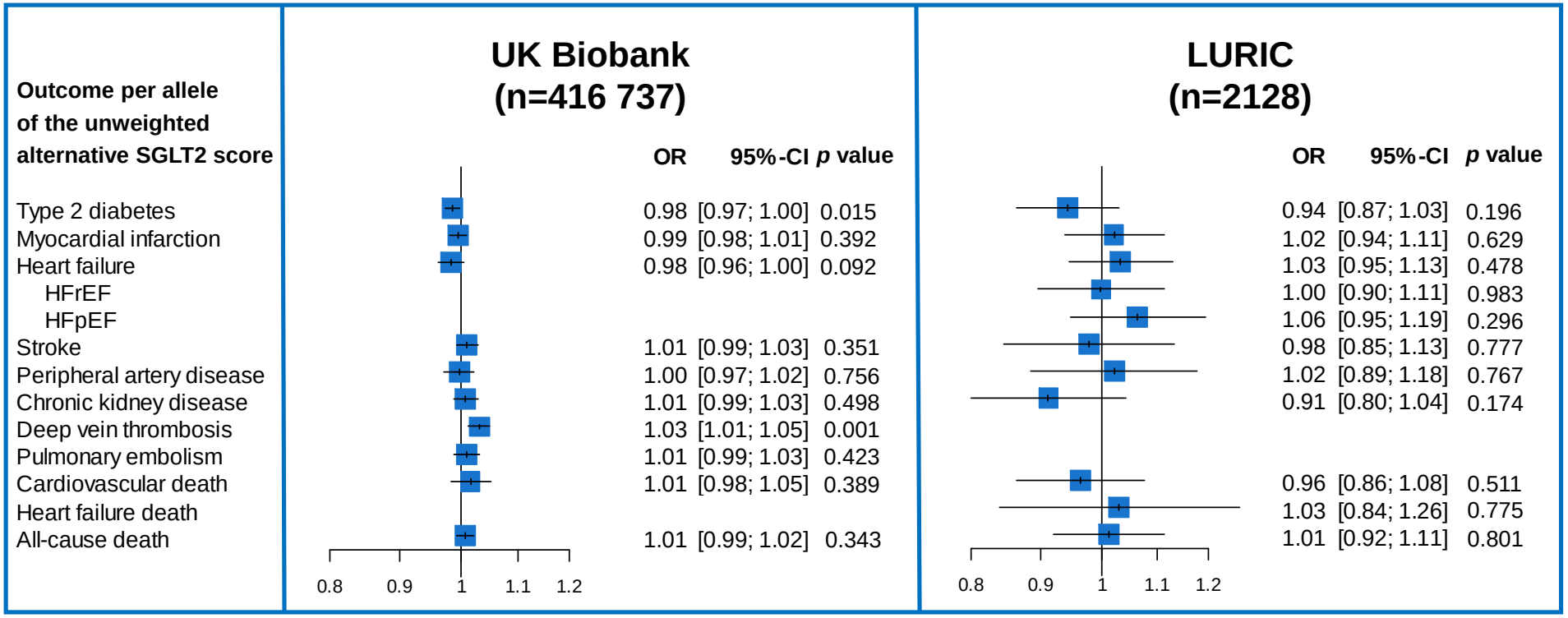
Notes: The Bonferroni-corrected threshold for statistical significance is 0.05/11=0.0045.
HFrEF/HFpEF: Heart failure with reduced/preserved ejection fraction.

Figure S3: Associations of the alternative genetic SGLT2 scores with heart failure in all UK Biobank participants and stratified by CAD and type 2 diabetes



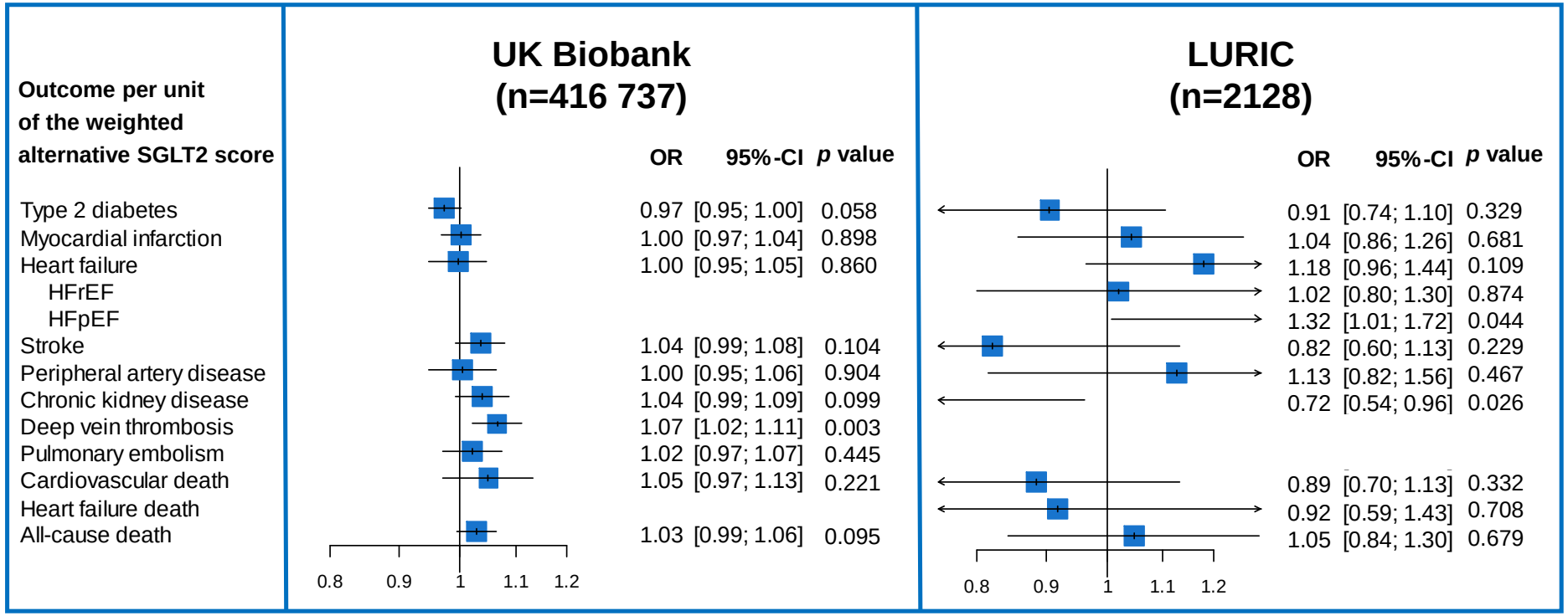
Associations of the unweighted and weighted alternative genetic SGLT2 scores with heart failure in UK Biobank for all participants and stratified by coronary artery disease (CAD) and type 2 diabetes.
Comparison of subgroups: CAD vs no CAD: unweighted score: *z* test: *p*=0.051, interaction term: *p*=0.033; weighted score: *z* test: *p*=0.157, interaction term: *p*=0.106; type 2 diabetes vs no type 2 diabetes: unweighted score: *z* test: *p*=0.397, interaction term: *p*=0.373; weighted score: *z* test: *p*=0.581, interaction term: *p*=0.555.

Figure S4: Associations of the unweighted alternative genetic SGLT2 score with outcomes in UK Biobank and the LURIC study



Associations of the unweighted alternative genetic SGLT2 score with outcomes in UK Biobank and LURIC.
Notes: The Bonferroni-corrected threshold for statistical significance is 0.05/10=0.005 in UK Biobank and 0.05/11=0.0045 in the LURIC study.
HFrEF/HFpEF: Heart failure with reduced/preserved ejection fraction.

Figure S5: Associations of the weighted alternative genetic SGLT2 score with outcomes in UK Biobank and the LURIC study



Associations of the weighted alternative genetic SGLT2 score with outcomes in UK Biobank and LURIC.
Notes: The Bonferroni-corrected threshold for statistical significance is 0.05/10=0.005 in UK Biobank and 0.05/11=0.0045 in the LURIC study.
HFrEF/HFpEF: Heart failure with reduced/preserved ejection fraction.

References

1. Bycroft, C. *et al. Genome-wide genetic data on ~500,000 UK Biobank participants* vol. **12** (2017).
2. UK Biobank. Biomarkers. http://www.ukbiobank.ac.uk/wp-content/uploads/2018/11/BCM023_ukb_biomarker_panel_website_v1.0-Aug-2015-edit-2018.pdf (13 January 2020).
3. Winkelmann, B. R. *et al.* Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. *Pharmacogenomics* **2**, S1-73 (2001).
4. Zinman, B. *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N. Engl. J. Med.* **373**, 2117–2128 (2015).
5. Neal, B. *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N. Engl. J. Med.* **377**, 644–657 (2017).
6. Wiviott, S. D. *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **380**, 347–357 (2019).
7. McMurray, J. J. *et al.* Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **381**, 1995–2008 (2019).
8. Lytvyn, Y., Bjornstad, P., Udell, J. A., Lovshin, J. A. & Cherney, D. Z. I. Sodium Glucose Cotransporter-2 Inhibition in Heart Failure: Potential Mechanisms, Clinical Applications, and Summary of Clinical Trials. *Circulation* **136**, 1643–1658 (2017).
9. Marx, N. & McGuire, D. K. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. *Eur. Heart J.* **37**, 3192–3200 (2016).
10. Koller, L. *et al.* C-reactive protein predicts mortality in patients referred for coronary angiography and symptoms of heart failure with preserved ejection fraction. *Eur. J. Heart Fail.* **16**, 758–766 (2014).

11. Eastwood, S. V. *et al.* Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. *PloS one* **11**, e0162388 (2016).
12. GTEx consortium. Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017) https://www.nature.com/articles/nature24277.pdf.
13. Machiela, M. J. & Chanock, S. J. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics* **31**, 3555–3557 (2015).