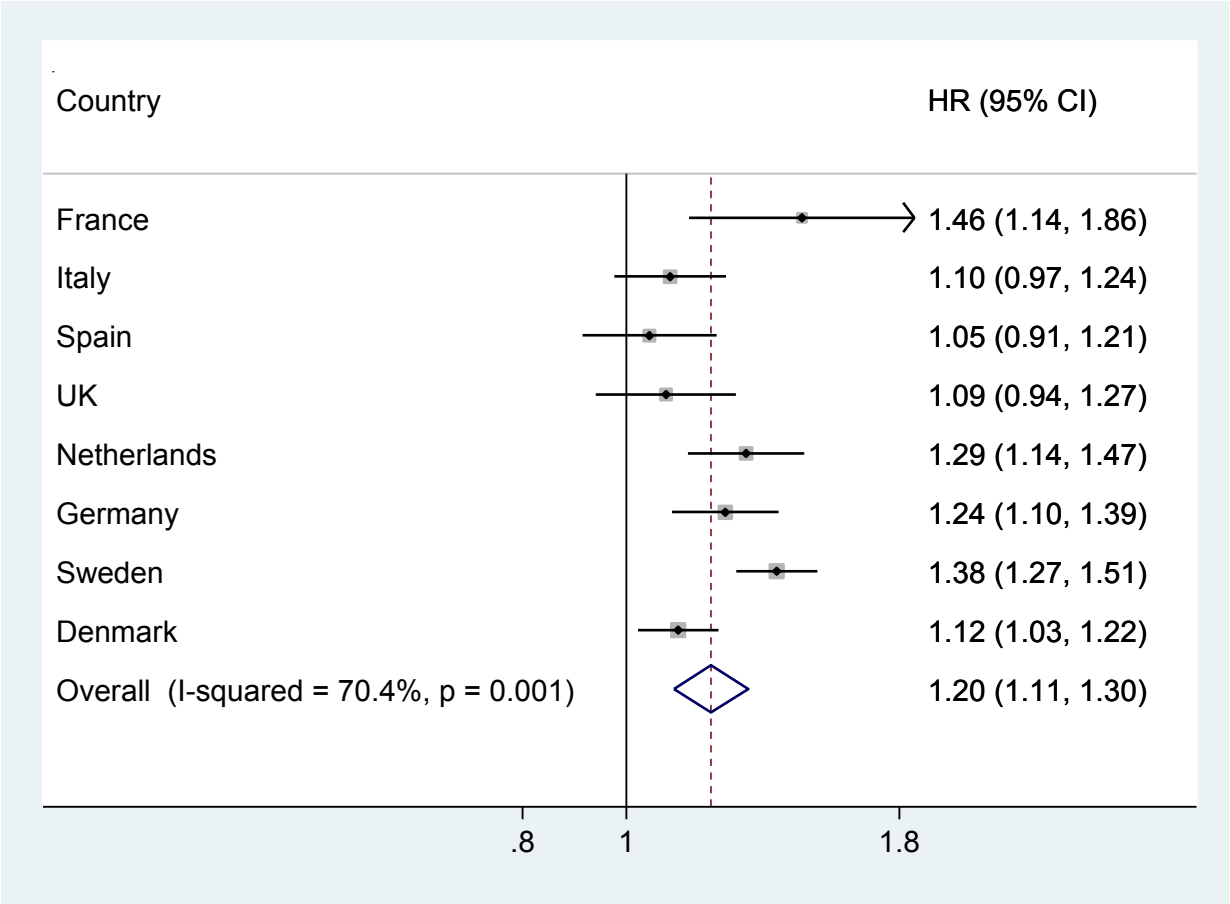
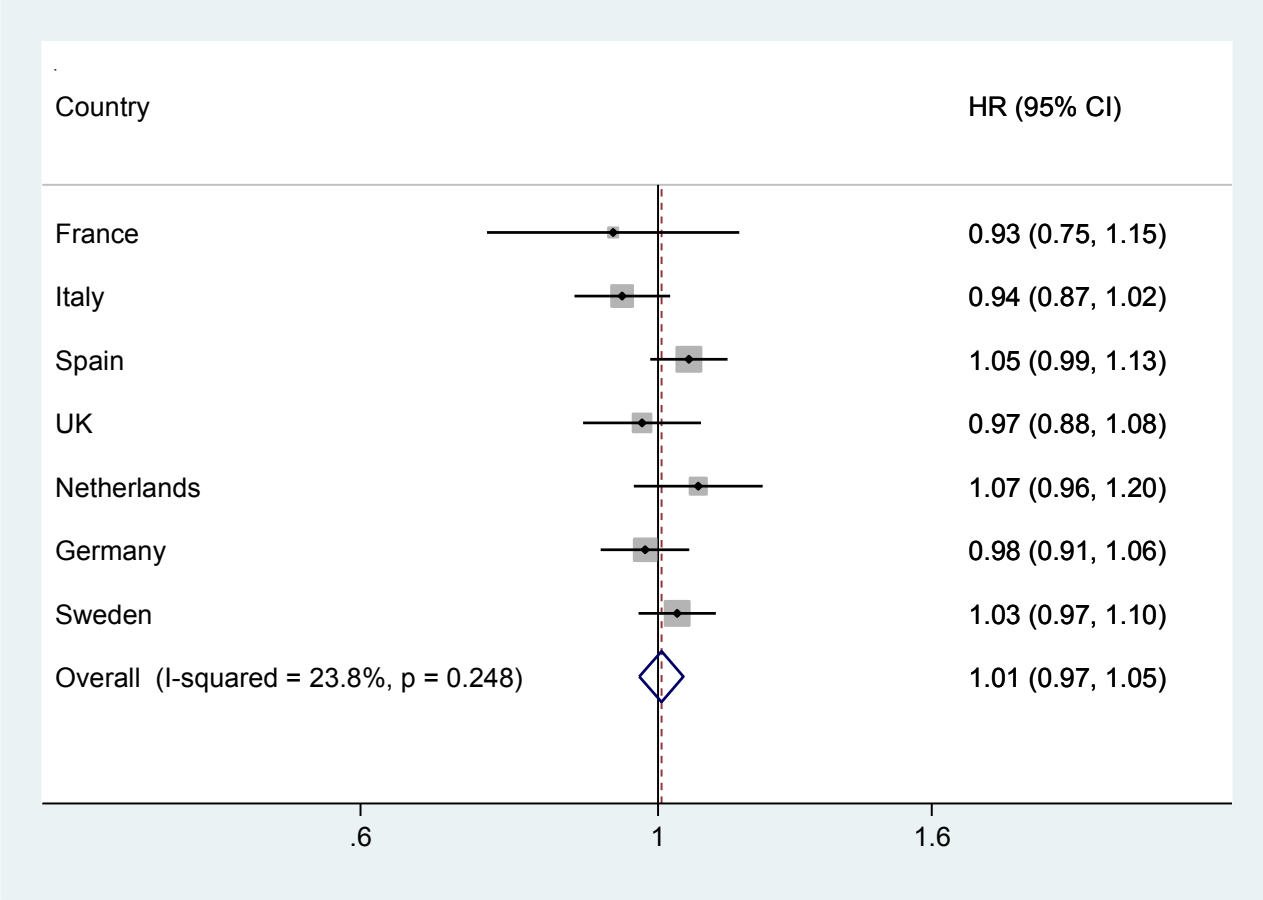
SUPPLEMENTARY DATA

Supplementary Figure 1. Observational association of circulating uric acid with incident type 2 diabetes per EPIC-InterAct country, and I^2 for the proportion of heterogeneity between countries. The pooled estimate is based on random effects meta-analysis. Values are HR (95% CI) per 59.48 µmol/L (1 mg/dL) increase in uric acid, and estimates were adjusted for study center, sex, age (as underlying time scale), BMI, systolic blood pressure, prevalent hypertension, non-HDL cholesterol (=total – HDL cholesterol), triglycerides, eGFR, alcohol consumption, smoking status, highest educational level, and level of physical activity. N = 24,265 with 10,576 incident type 2 diabetes cases.



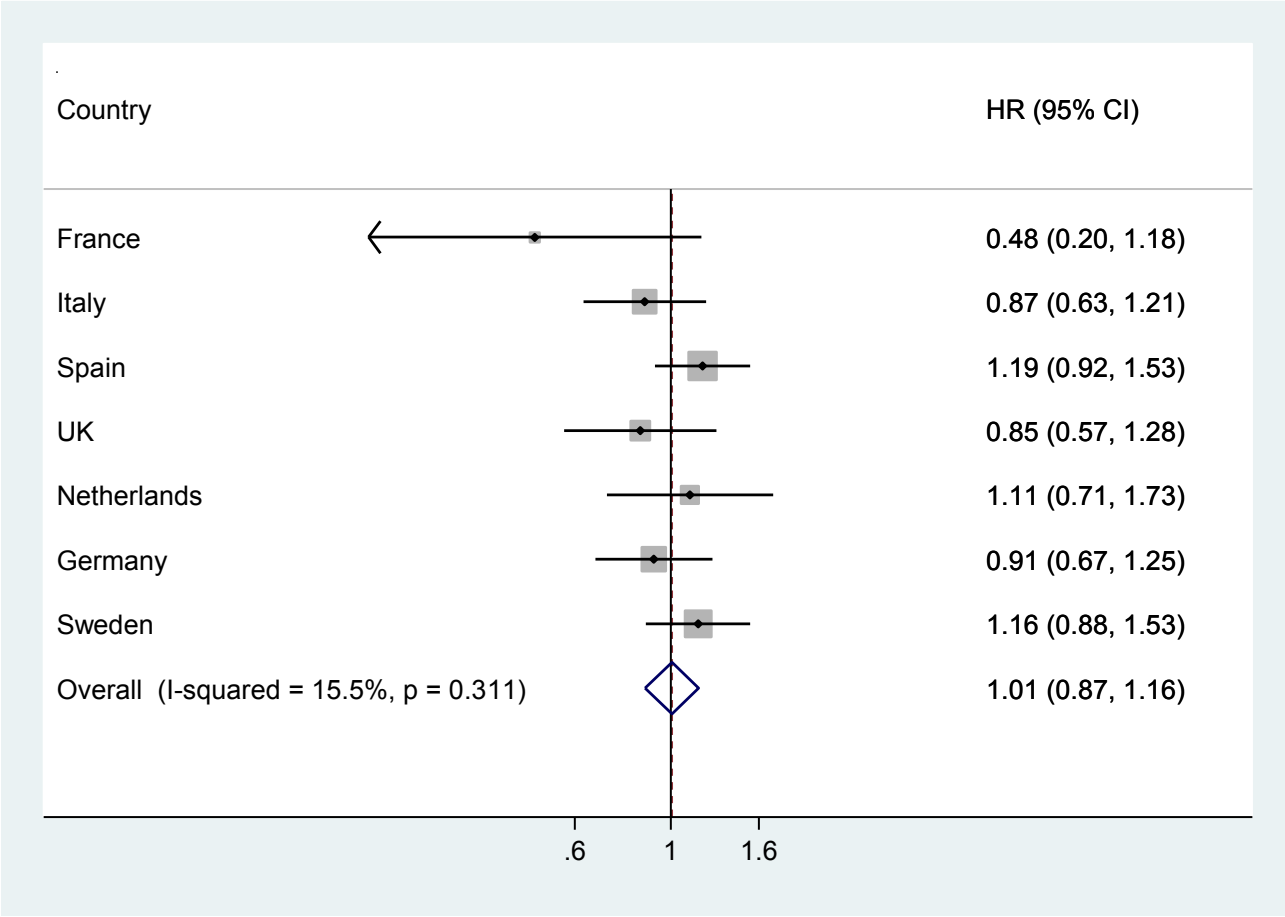
SUPPLEMENTARY DATA

Supplementary Figure 2. Association of genetic score with incident type 2 diabetes per EPIC-InterAct country, and I^2 for the proportion of heterogeneity between countries. The pooled estimate is based on random effects meta-analysis. Values are HR (95% CI) per SD increase in the genetic score, and estimates were adjusted for study center. N = 17,118 with 7,319 incident type 2 diabetes cases.



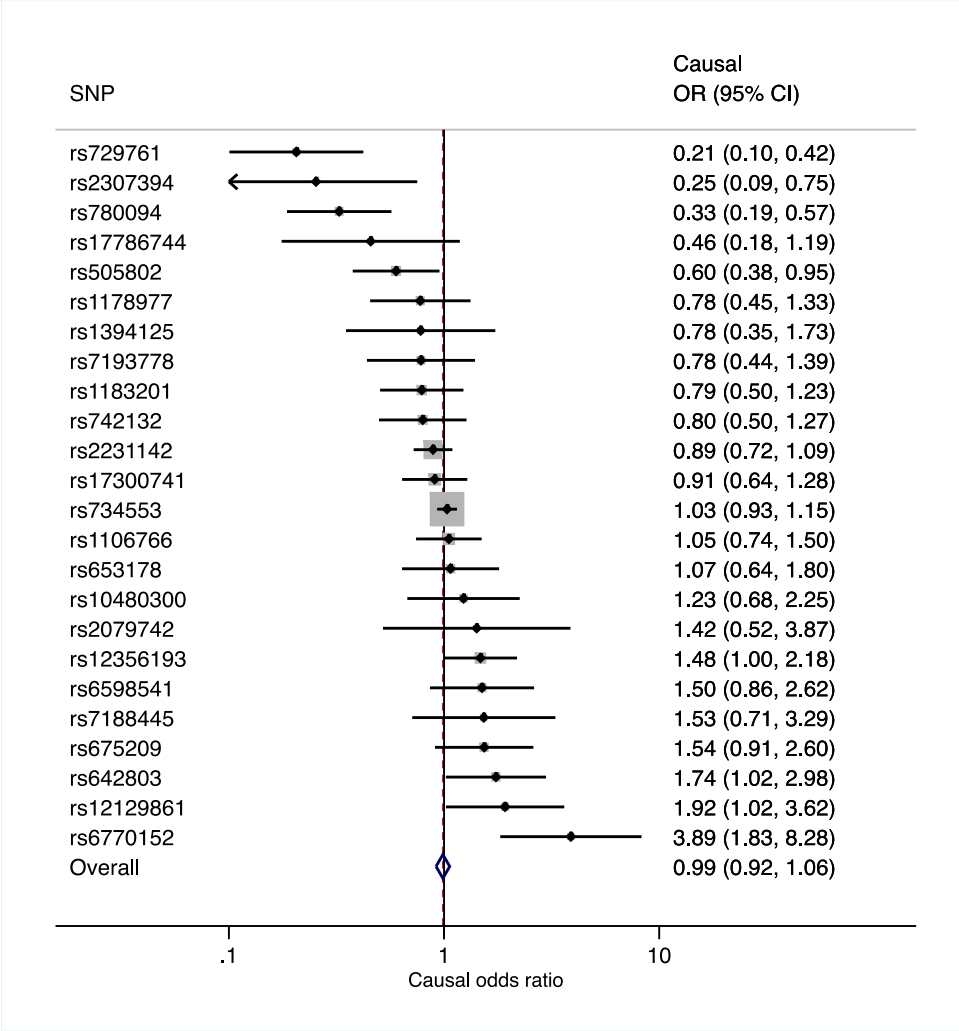
SUPPLEMENTARY DATA

Supplementary Figure 3. Instrumental variable estimates of the effect of circulating uric acid on diabetes risk per EPIC-InterAct country, and I^2 for the proportion of heterogeneity between countries. Estimates were derived from two stage control function estimator approach analysis. The pooled estimate is based on random effects meta-analysis. Values are HR (95% CI) per 59.48 µmol/L (1 mg/dL) increase in uric acid, and estimates were adjusted for study center. N = 17,118 with 7,319 incident type 2 diabetes cases.



SUPPLEMENTARY DATA

Supplementary Figure 4. Forrest plot of the causal estimates of circulating uric acid and diabetes derived for each SNP, incorporating data from InterAct and DIAGRAM with a total 41,508 cases.



SUPPLEMENTARY DATA

Supplementary Table 1. SNPs included in the genetic scores and weights assigned to each SNP

					Sensitivity analyses		
Uric acid associated SNP	Weight used for deriving externally weighted genetic score	Available for Illumina 660W chip study sample (n=8,582)	Available for Cardiometabochip + study sample (n=8,536)	Proxy r^2	Included in score that excluded SNPs not associated with uric acid in our study	Included in score that excluded SNPs with proxy $r^2 <$ 0.80	Included in score that excluded rs734553 and 2231142
rs780094	0.05	Yes	Yes		Yes	Yes	Yes
rs734553	0.32	Yes: imputed	Yes		Yes	Yes	No
rs2231142	0.17	yes	Yes		Yes	Yes	No
rs742132	0.05	Yes: imputed	Yes		Yes	Yes	Yes
rs675209	0.06	Yes	Yes		Yes	Yes	Yes
rs12356193	0.08	Yes	Yes		Yes	Yes	Yes
rs17300741	0.06	Yes: imputed	Yes		Yes	Yes	Yes
rs12129861	0.06	Yes: imputed	Yes		Yes	Yes	Yes
rs1183201	0.06	Yes: imputed	Yes		Yes	Yes	Yes
rs505802	0.06	Yes	Yes		Yes	Yes	Yes
rs1106766	0.07	Yes: imputed	Yes		Yes	Yes	Yes
rs2307394	0.03	Yes	Proxy: rs1449959	0.7	No	No	Yes
rs6770152	0.04	Yes: imputed	Proxy: rs2581806	0.73	Yes	No	Yes
rs729761	0.05	Yes: imputed	Proxy: rs881858	0.83	Yes	Yes	Yes
rs1178977	0.05	Yes: imputed	Yes		Yes	Yes	Yes
rs10480300	0.04	Yes: imputed	Proxy: rs7805747	1	Yes	Yes	Yes
rs17786744	0.03	Yes: imputed	Proxy: rs10109414	0.94	Yes	Yes	Yes
rs642803	0.04	Yes: imputed	Yes		No	Yes	Yes
rs653178	0.04	Yes	Yes		No	Yes	Yes
rs1394125	0.04	Yes	Yes		No	Yes	Yes
rs6598541	0.04	Yes: imputed	Yes		Yes	Yes	Yes
rs7193778	0.05	Yes: imputed	Proxy: rs7200764	0.94	Yes	Yes	Yes
rs7188445	0.03	Yes: imputed	Proxy: rs17767383	0.93	No	Yes	Yes
rs2079742	0.04	Yes	Proxy: rs9895661	0.88	No	Yes	Yes

SUPPLEMENTARY DATA

Supplementary Table 2. Associations of genetic score with circulating uric acid per InterAct country*

Country	n	Beta (95%CI) mg/dL
France	320	21 (15, 28)
Italy	1,466	13 (9, 16)
Spain	2,443	16 (13, 19)
UK	1,071	18 (13, 22)
Netherlands	1,172	20 (16, 24)
Germany	1,634	17 (13, 21)
Sweden	2,129	17 (14, 20)
Total	10,235	17 (15, 18)

* Beta obtained from linear regression with uric acid modeled in μmol/L; estimates are per 1 SD increase in genetic score; adjusted for study center.

SUPPLEMENTARY DATA

Supplementary Table 3. Associations of genetic score with potential confounders and glycemic traits *

Continuous Traits	Beta (95%CI)	P-value
Age, years	-0.07 (-0.23, 0.10)	0.43
Alcohol consumption, g/d	-3.92 (-7.69, 1.01)	0.13
Red meat intake, g/d	0.08 (-0.51, 0.67)	0.79
Dietary vitamin C intake, mg/d	1.308 (0.003, 2.614)	0.05
BMI, kg/m^2	0.02 (-0.06, 0.10)	0.58
Systolic blood pressure, mmHg	-0.16 (-0.58, 0.26)	0.46
Triglycerides, mmol/L	0.01 (0.001, 0.02)	0.03
eGFR, $mL/min/1.73m^2$	0.04 (-0.34, 0.41)	0.85
Non-HDL cholesterol, mmol/L	0.02 (-0.004, 0.04)	0.10
Non-fasting glucose, mmol/L	0.01 (-0.02, 0.03)	0.53
HbA1c, %, (mmol/mol)	<-0.01 [<-0.01, 0.01] (-0.02 [-0.12, 0.08])	0.70
Binary Traits	**Odd ratio (95%CI)**	
Sex, male	1.00 (0.95, 1.04)	0.83
Physically active	0.96 (0.92, 1.00)	0.05
Current smoking	1.04 (0.99, 1.10)	0.10
Prevalent hypertension	1.04 (0.99, 1.10)	0.10

* Beta obtained from linear regression (age, alcohol consumption, red meat intake, vitamin C intake, BMI, systolic blood pressure, triglycerides, eGFR, non-HDL cholesterol, glucose, HbA1c); OR obtained from logistic regression (sex, current smoking, physical activity, prevalent hypertension); estimates are per 1 SD increase in genetic score; adjusted for study center, among 10,235 subcohort participants (for intakes of vitamin C, red meat and alcohol, N=10,019); Triglycerides and alcohol consumption were logarithmically transformed before the analysis and back transformed after the analysis; non-HDL cholesterol = total – HDL cholesterol.

SUPPLEMENTARY DATA

Supplementary Table 4. Instrumental variable estimates of the effect of circulating uric acid on diabetes risk in strata of sex, age, BMI and duration of follow-up *

	HR (95%CI) per 59.48 µmol/L (1 mg/dL) increase in uric acid
Men	0.97 (0.80, 1.17)
Women	1.03 (0.84, 1.27)
Age ≤53 years	1.01 (0.84, 1.21)
Age >53 years	0.98 (0.79, 1.20)
BMI ≤ 25 kg/m2	1.07 (0.74, 1.57)
BMI > 25 kg/m2	1.00 (0.87, 1.16)
Follow-up ≤ 5 years	0.98 (0.81, 1.18)
Follow-up 5-10 years	0.96 (0.77, 1.21)
Follow-up >10 years	1.05 (0.83, 1.33)

* N = 17,118 with 7,319 incident type 2 diabetes cases, estimates were derived from two stage control function estimator approach analysis, and were pooled with random effects meta-analysis.

Supplementary Table 5. Instrumental variable estimates of the effect of circulating uric acid on glycemic traits

Source	**Trait**	**Number of individuals**	**Beta (95%CI) per 59.48 µmol/L (1 mg/dL) increase in circulating uric acid**
EPIC-Interact *	Non-fasting glucose, mmol/L	9,414	0.03 (-0.06, 0.12)
	HbA1c, %, (mmol/mol)	10,125	< -0.01 [-0.04, 0.03] (-0.08 [-0.43, 0.28])
MAGIC consortium	Fasting glucose, mmol/L	58,074	0.00 [-0.02, 0.02] (0.00 [-0.02, 0.02]) §
	HOMA-IR, log units	37,073	0.01 (-0.02, 0.03)

* Beta obtained from linear regression, and estimates were adjusted for study center.
§ fasting glucose adjusted for BMI

SUPPLEMENTARY DATA

Supplementary Table 6. Sensitivity analysis of instrumental variable association of circulating uric acid with diabetes, after exclusion of SNPs most strongly associated with uric acid

Sensitivity analysis	**Causal OR of diabetes per 59.48 µmol/L (1 mg/dL) increase in circulating uric acid derived from DIAGRAM and InterAct**
Including all 28 SNPs	**0.99 (0.92, 1.06)**
Excluding rs734553 in SLC2A9	**0.95 (0.86, 1.05)**
Excluding rs2231142 in ABCG2	**1.00 (0.93, 1.08)**
Excluding both rs734553 in SLC2A9 and rs2231142 in ABCG2	**0.97 (0.86, 1.09)**

Supplementary Table 7. Power estimates for various relative risks and excluding the SNP with the largest effect (two-sided alpha of 0.05).

	Data Source			
Relative risk	**InterAct**: (7,319 cases (42.8%) in 17,118 individuals)		**DIAGRAM:** 34,840 cases (23.3%) and 114,981 controls (DIAGRAM)	
	All SNPs (R^2=4.1%)	Minus rs734553 (R^2=1.5%)	Minus rs734553 (R^2=1.5%)	Minus rs734553 and rs2231142 (R^2=1.2%)
1.51	100%	92%	100%	100%
1.25	85%	44%	100%	99%
1.20	68%	31%	97%	93%

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Supplementary Table 8. Overview of previously performed Mendelian randomization studies of circulating uric acid, type 2 diabetes and metabolic and cardiovascular traits

Study	Participants	Uric acid associated loci	Main outcome(s)	Causal estimate	Conclusion
Rotterdam study Sedaghat, 2014(1)	N= 5,791, European ancestry	Genetic score of 30 variants in loci listed in Köttgen et al.	Systolic blood pressure Diastolic blood pressure	Systolic blood pressure: β -0.75 (95%CI: -1.31, -0.19) mmHg Diastolic blood pressure: β -0.92 (95%CI: -1.62, -0.23) mmHg Per SD increase in genetic score.	Uric acid causally decreases systolic blood pressure and diastolic blood pressure
Atherosis Risk in Communities and Framingham Heart Rasheed, 2014 (2)	N= 8,208, European ancestry	Genetic score of SLC2A9, ABCG2, SLC17A1, SLC22A11, SLC22A12	Triglycerides	β -1.01 (SE: 0.80) mmol/L Per unit change in uric acid.	Uric acid has no causal effect on triglycerides
Mallamaci, 2007 (3)	N = 459, European ancestry	SLC2A9	Systolic blood pressure Diastolic blood pressure	Higher mean clinic systolic blood pressure among TT individuals. No difference in mean diastolic blood pressure.	Uric acid causally increases clinic systolic blood pressure, but not diastolic blood pressure
Copenhagen General Population Study and Copenhagen City Heart Study Palmer, 2013 (4)	N=68,674, of which 7172 ischemic heart disease events, European ancestry	SLC2A9	Ischemic heart disease Systolic blood pressure Diastolic blood pressure	Ischemic heart disease: Hazard Ratio: 0.93 (95%CI: 0.79, 1.09) Systolic blood pressure: β 0.65 mm Hg (95%CI: −0.54, 1.85) Diastolic blood pressure : β 0.63 mm Hg (95%CI: −0.04, 1.29) Per SD increase in uric acid.	Uric acid has no causal effect on ischemic heart disease, systolic blood pressure and diastolic blood pressure
Dongfeng-Tongji Cohort study Dai, 2013 (5)	N= 23,345, Asian ancestry	Genetic score of SLC2A9, ABCG2	Metabolic syndrome	Odds Ratio 1.03 (95 % CI 0.98–1.09) Per uric acid increasing allele in the risk score.	Uric acid is not causally related to metabolic syndrome
CoLaus study Lyngdoh, 2012 (6)	N= 6,184, European ancestry	SLC2A9	Weight Fat mass Body mass index Waist circumference	Weight: β 0.01 (95%CI:-0.12, 0.14) kg Fat mass: β 0.05 (95%CI:-0.10, 0.19) kg Body mass index: β 0.01 (95%CI: -0.16, 0.14) kg/m^2 Waist circumference β 0.08 (95%CI: -0.05, 0.21) cm Per SD increase in uric acid.	Uric acid is not causally related to measures of adiposity

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Cardiovascular risk in Young Finns study Oikonen, 2012 (7)	N=1,985, European ancestry	SLC2A9	Body mass index Carotid intima media thickness	Carotid intima media thickness: β <0.0001 mm, P-value 0.99 among men. Body mass index: β 0.04 kg/m^2, P-value 0.82 among men and β 0.07 kg/m^2, P-value 0.57 among women Per SD increase in uric acid.	Uric acid has no causal effect on BMI or atherosclerosis
Hereditary and Phenotype Intervention Heart Study Parsa, 2012 (8)	N=516, European ancestry	SLC2A9	Systolic blood pressure Diastolic blood pressure	Systolic blood pressure: β 2.2 (SE: 0.79) mmHg Diastolic blood pressure: β 0.42 (0.5) mmHg Per 1 mg/dl change in uric acid.	Uric acid causally decreases systolic blood pressure, but not diastolic blood pressure
Cambridgeshire, ADDITION-Ely and Norfolk Diabetes Pfister, 2011 (9)	N=16,064, of which 7,504 type 2 diabetes cases	Genetic score of PDZK1, LRRC16A, SLC22A12, SLC16A9, SLC22A11, SLC17A1, ABCG2, SLC2A9	Type 2 diabetes	Odds ratio 0.99 (95% CI: 0.94,1.04) Per genetic score tertile.	Uric acid has no causal effect on type 2 diabetes
CHARGE Cohorts Yang, 2010 (10)	N=28,283, European ancestry	Genetic score of SLC22A11, GCKR, INHBC, RREB1, PDZK1, SLC2A9, ABCG2, SLC17A1	Fasting glucose	β -0.06 (95%CI: -0.13, 0,02) mmol/L Per 100 µmol/L urate.	Uric acid has no causal effect on fasting glucose
ORCADES study McKeigue, 2010 (11)	N=706, European ancestry	SLC2A9	Metabolic syndrome	Causal effect parameter β_x: -1.25 (95%CI: -2.91, 0.05)	Uric acid has no causal effect on metabolic syndrome

SUPPLEMENTARY DATA

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