Supplementary table S1 Keywords and search strategy used in the umbrella review

MEDLINE (OvidSP) 1. Uric acid.mp. or Uric Acid/ 2. Uric Acid/ or urate*.mp. 3. Acid uric.mp. or Uric Acid/ 4. Hyperuricemia.mp. or Uric Acid/ or Hyperuricemia/ 5. Uric Acid/ or hypouricemia.mp. 6. Uric Acid/ or hyperuricosuria.mp. 7. Uric Acid/ or hypouricosuria.mp. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. "Review Literature as Topic"/ or "Review"/ or review*.mp. 10. Meta-Analysis as Topic/ or meta-analys*.mp. 11. Mendelian Randomization Analysis/ or Mendelian randomi*.mp. 12. 9 or 10 or 11 13. 8 and 12
EMBASE (OvidSP) 1. Uric acid.mp. or uric acid/ 2. Urate*.mp. or urate/ 3. Uric acid/ or acid uric.mp. 4. Hyperuricemia.mp. or hyperuricemia/ 5. Hypouricemia.mp. or hypouricemia/ 6. Hyperuricosuria.mp. or hyperuricosuria/ 7. Uric acid/ or hypouricosuria.mp. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. Systematic review.mp. or "systematic review"/

10. "Systematic review"/ or meta-analys*.mp. 11. Mendelian randomization analysis/ or Mendelian randomi*.mp. or Mendelian randomization/ 12. 9 or 10 or 11 13. 8 and 12
Cochrane library (uric acid OR acid uric OR urate* OR hyperuricemia OR hypouricemia OR hyperuricosuria OR hypouricosuria) AND (systematic review* OR meta-analys*)

Supplementary table S2 General characteristics and main findings of the systematic reviews of observational studies

Author	Year	Population	Study design	Comparison	Outcome	N studies	Authors' interpretation
Cardiovascular Outcomes							
Baker[1]	2005	Healthy subjects	Cohort	SUA level	CVD	10	The excess risk associated with SUA in healthy patients is likely to be small. High SUA is likely an independent risk factor in patients at high CVD risk.
Baker[1]	2005	Patients at high CVD risk	Cohort	SUA level	CVD	11	
Strazzullo[2]	2007	General	Cohort	SUA level	CVD	16	SUA is a very weak predictor of CVD in healthy population, but a significant independent predictor among subjects at high or very high risk.
Strazzullo[2]	2007	Patients with arterial hypertension	Cohort	SUA level	CVD	8	
Strazzullo[2]	2007	Patients at high CVD risk	Cohort	SUA level	CVD	5	
Barron[3]	2015	General	Cohort	SUA level	CVD	3	Greater risk of CVD/all-cause mortality in those with the highest than with the lowest quartiles of SUA.
Dimitroula[4]	2008	General	Cohort	SUA level	Stroke	13	It remains controversial whether elevated serum uric acid is neuroprotective or injurious at the onset of acute stroke.
Hwu[5]	2010	General	Cross-sectional	SUA level	Hypertension	6	All except one study have documented a direct association with either incident hypertension or increase in blood pressure.
Hwu[5]	2010	General	Cohort/case-control	Hyper vs normal	Hypertension	17	
Kidney disease							
Avram[6]	2008	General	Cohort	SUA level	Kidney dysfunction	9	Nearly all published prospective studies support the role of hyperuricemia as an independent risk factor for renal dysfunction.
Feig[7]	2009	General	Observational	SUA level	Chronic kidney disease (CKD)	11	The preponderance of epidemiological evidence suggests a direct link between uric acid and CKD.
Cognitive diseases							
Alonso[8]	2010	General	Cohort/case-control	SUA level	Parkinson's disease (PD)	10	PD patients have lower SUA levels than controls; SUA is strongly and linearly associated with reduced risk of PD.
Alonso[8]	2010	PD patients	Cohort/case-control	SUA level	Clinical disability and worse cognitive performance	3	
Chang[9]	2014	AD patients vs control	Case-control	SUA level	Alzheimer's disease (AD)	6	Three studies elaborate that plasma or serum uric acid level is significantly lower in AD, while three other studies do not observe this difference.
Other Outcomes							
Cnossen[10]	2006	Women	Cohort	SUA level	Pre-eclampsia	5	There is currently insufficient evidence to draw firm conclusions about the accuracy of serum uric acid determination in predicting pre-eclampsia.

Supplementary table S3 General characteristics and main findings of the 144 meta-analyses of observational studies

Author	Year	Outcome	Population	Comparison	N Studies	N Participants	N Cases	Type of metric	Effect model reported	Reported summary effect (95% CI)	Concordance in overlapped MA
Cardiovascular outcomes											
Tamariz[11]	2014	Atrial fibrillation incidence	General	Highest vs lowest SUA category	3	138,306	3,466	RR	Random	1.67 (1.23, 2.27)	**YES[11-13]**
Xu[12]	2015	Atrial fibrillation incidence	General	Hyper vs normal	7	85,530	NA	RR	Random	1.80 (1.37, 2.38)	
Xu[12]	2015	Atrial fibrillation new-onset	General	Hyper vs normal	5	84,837	NA	RR	Random	1.66 (1.22, 2.26)	
Zhang[13]	2016	Atrial fibrillation incidence	General	Hyper vs normal	6	426,159	7,595	RR	Random	1.49 (1.24, 1.79)	
Tamariz[11]	2014	Atrial fibrillation	Atrial fibrillation vs controls	SUA level (mg/dl)	6	7,930	1,603	SMD	Random	0.42 (0.27, 0.58)	
Zhao[14]	2016	Atrial fibrillation recurrence	Atrial fibrillation patients	Hyper vs normal	4	1,298	393	OR	Random	1.37 (0.98, 1.93)	
Xu[12]	2015	Atrial fibrillation recurrence	General	Hyper vs normal	2	61,955	NA	aRR	Random	2.07 (1.61, 2.67)	
Wheeler[15]	2005	CHD incidence	General	Highest vs lowest SUA category	16	164,542	9,485	RR	Random	1.13 (1.07, 1.20)	**YES[15-18]**
Kim[16]	2010	CHD	General	Hyper vs normal	9	53,750	5,113	aRR	Random	1.09 (1.03, 1.16)	
Braga[17]	2015	CHD incidence	General	Hyper vs normal	9	457,915	19,119	RR	Random	1.21 (1.07, 1.36)	
Li[18]	2016	CHD incidence	General	Hyper vs normal	13	70,382	6,666	aRR	Random	1.13 (1.05, 1.21)	
Qin[19]	2016	CVD	Hypertensive patients	Hyper vs normal	6	19,546	1,054	aHR	Random	1.17 (1.07, 1.27)	
Qin[19]	2016	CVD	Hypertensive patients	Continuous SUA	4	NA	NA	aHR	Random	1.51 (1.13, 2.03)	
Huang[20]	2014	Heart failure incidence	General	Hyper vs normal	5	427,917	101,71	HR	Random	1.65 (1.41, 1.94)	
Huang[20]	2014	Heart failure incidence	General	Highest vs lowest SUA category	4	NA	NA	HR	Random	1.64 (1.39, 1.94)	
Huang[20]	2014	Heart failure incidence	General	1 mg/dl SUA increase	3	420,756	9,812	HR	Fixed	1.19 (1.17, 1.21)	
Zhang[21]	2009	Hypertension	General	Highest vs lowest SUA category	8	28,657	NA	RR	Random	1.55 (1.32, 1.82)	**YES[21-23]**

Grayson[22]	2011	Hypertension incidence	General	Hyper vs normal	12	32,390	NA	RR	Random	1.81 (1.55, 2.07)	
Grayson[22]	2011	Hypertension incidence	General	Hyper vs normal	11	33,925	NA	aRR	Random	1.41 (1.23, 1.58)	
Grayson[22]	2011	Hypertension incidence	General	1 mg/dl SUA increase	6	23,018	NA	aRR	Random	1.13 (1.06, 1.20)	
Grayson[22]	2011	Hypertension incidence	General	1 SD SUA increase	8	30,492	NA	RR	Random	1.16 (1.07, 1.26)	
Wang[23]	2014	Hypertension incidence	General	Hyper vs normal	17	71,630	18,751	aRR	Random	1.48 (1.33, 1.65)	
Wang[23]	2014	Hypertension incidence	General	1 SD SUA increase	10	37,125	7,584	aRR	Random	1.19 (1.11, 1.28)	
Wang[23]	2014	Hypertension incidence	General	1 mg/dl SUA increase	5	15,951	4,941	aRR	Random	1.15 (1.06, 1.26)	
Jiang[24]	2016	Prehypertension	General	Highest vs lowest SUA category	8	44,095	20,832	OR	Random	1.84 (1.42, 2.38)	
Zhang[13]	2016	Left atrial thrombus or spontaneous echo contrast (LATH/LASEC)	Patients with mitral stenosis, sinus rhythm or atrial fibrillation	Highest vs lowest SUA category	6	2,381	241	OR	Random	1.59 (1.13, 2.23)	
Yan[25]	2014	Major adverse cardiovascular events (MACE)	Acute myocardial infarction (AMI) patients vs controls	Hyper vs normal	6	2,406	651	RR	Fixed	3.44 (2.33, 5.08)	
Song[26]	2015	MACE	Patients after PCI	Hyper vs normal	2	3,054	NA	RR	Fixed	1.78 (1.26, 2.52)	
Trkulja[27]	2012	Medium term MACE	Patients with acute myocardial infarction	Highest vs lowest SUA category	4	4,299	1,240	OR	Random	1.62 (1.20, 2.19)	
Trkulja[27]	2012	Short term MACE	Patients with acute myocardial infarction	Highest vs lowest SUA category	7	6,470	787	OR	Random	2.21 (1.64, 2.97)	
Qin[19]	2016	Stroke	Hypertensive patients	Hyper vs normal	5	NA	NA	HR	Random	0.94 (0.67, 1.33)	
Qin[19]	2016	Stroke	Hypertensive patients	Continuous SUA level	3	9,978	217	aHR	Random	1.11 (0.98, 1.16)	
Kim[28]	2009	Stroke incidence	General	Hyper vs normal	6	11,495	NA	RR	Random	1.41 (1.05, 1.76)	**YES[28 29]**
Li[29]	2014	Stroke incidence	General	Hyper vs normal	5	24,548	1,290	aRR	Random	1.22 (1.02, 1.46)	
Diabetes related outcomes											
Jia[30]	2013	Impaired fasting glucose or T2DM	General	Highest vs lowest SUA category	12	62,834	6,340	RR	Random	1.57 (1.39, 1.77)	
Kodama[31]	2009	Type 2 diabetes	General	1 mg/dl SUA increase	11	42,834	3,305	RR	Random	1.17 (1.09,	**YES[30-32]**

		(T2DM)								1.25)	
Jia[30]	2013	T2DM	General	Highest vs lowest SUA category	9	48,808	5,115	RR	Fixed	1.67 (1.51, 1.86)	
Lv[32]	2013	T2DM incidence	General without diabetes	Hyper vs normal	8	32,016	2,930	RR	Fixed	1.56 (1.39, 1.76)	
Lv[32]	2013	T2DM incidence	General without diabetes	1 mg/dl SUA increase	6	21,592	2,203	RR	Fixed	1.06 (1.04, 1.07)	
Qin[19]	2016	Diabetes incidence	Hypertensive patients	Hyper vs normal	2	8,247	564	aHR	Random	1.84 (1.02, 3.30)	
Qin[19]	2016	Diabetes incidence	Hypertensive patients	Continuous SUA level	2	NA	NA	aHR	Random	1.28 (1.18, 1.38)	
Xu[33]	2013	Diabetic nephropathy	T2DM patients	Continuous/categorical SUA level	3	3,166	196	OR	Random	1.91 (1.07, 3.42)	
Xu[33]	2013	Diabetic retinopathy	T2DM patients	Continuous/categorical SUA level	2	1,739	311	OR	Random	1.23 (0.81, 1.87)	
Xu[33]	2013	Diabetic vascular complications	T2DM patients	Continuous/categorical SUA level	6	5,017	967	OR	Random	1.28 (1.12, 1.46)	
Xu[33]	2013	Diabetic microvascular complications	T2DM patients	Continuous/categorical SUA level	5	4,513	854	OR	Random	1.47 (1.11, 1.94)	
Xu[33]	2013	Peripheral vascular disease	T2DM patients	Continuous/categorical SUA level	3	2,538	151	OR	Random	1.27 (0.91, 1.78)	
Xu[33]	2013	Diabetic Macrovascular disease	T2DM patients	Continuous/categorical SUA level	3	2,538	187	OR	Fixed	1.03 (1.00, 1.06)	
Xu[33]	2013	Diabetic neuropathy	T2DM patients	Continuous/categorical SUA level	2	2,034	231	OR	Random	1.19 (0.61, 2.32)	**NO**[33 34] (discordance in statistical significance)
Yu[34]	2016	Diabetic peripheral neuropathy	Diabetic peripheral peuropathy patients vs diabetic controls	SUA level (μmol/L)	7	2,035	464	MD	Random	50.03 (22.14, 77.93)	
Yu[34]	2016	Diabetic peripheral neuropathy	Diabetic peripheral peuropathy patients vs diabetic controls	Hyper vs normal	5	4,097	894	RR	Random	2.83 (2.13, 3.76)	
Kidney disorders											
Li[35]	2011	Impaired kidney function	General	Hyper vs normal	3	3,004	NA	RR	Random	1.35 (1.12, 1.63)	
Li[35]	2011	CKD incidence	General	Hyper vs normal	10	276,801	3,730	aRR	Random	1.49 (1.27, 1.75)	**YES**[35-37]
Zhu[37]	2014	CKD incidence	Middle-aged Populations	1 mg/dL SUA increase	15	99,205	3,492	RR	Random	1.22 (1.16, 1.28)	
Li[36]	2014	CKD new-onset incidence	Non-CKD population	Hyper vs normal	6	28,256	NA	HR	Fixed	2.59 (2.14, 3.13)	

Li[36]	2014	CKD new-onset incidence	Non-CKD population	1 mg/dl SUA increase	7	153,620	7,014	HR	Random	1.06 (1.04, 1.08)	
Li[36]	2014	CKD new-onset incidence	Healthy population	Hyper vs normal	4	NA	NA	HR	Random	2.86 (2.30, 3.56)	
Li[36]	2014	CKD new-onset incidence	Diabetic patients	Hyper vs normal	2	NA	NA	HR	Random	1.90 (1.30, 2.78)	
Huang[38]	2012	eGFR (mL/min·1.73 m^2)	Renal transplant recipients	Hyper vs normal	8	2,075	NA	MD	Random	-11.24 (-16.34, -6.14)	
Huang[38]	2012	SCr (μmol/L)	Renal transplant recipients	Hyper vs normal	5	873	NA	MD	Fixed	0.24 (0.17, 0.31)	
Huang[38]	2012	Graft loss	Renal transplant recipients	Hyper vs normal	3	910	154	OR	Fixed	2.29 (1.55, 3.39)	
Huang[38]	2012	Graft loss	Renal transplant recipients	1 mg/dl SUA increase	3	1,050	NA	aHR	Fixed	1.21 (1.08, 1.37)	
Huang[38]	2012	Chronic allograft nephropathy	Renal transplant recipients	Hyper vs normal	4	1,057	113	OR	Fixed	2.85 (1.85, 4.38)	
Neurocognitive disorders											
Khan[39]	2013	Alzheimer's disease (AD)	AD patients vs controls	SUA level (mg/dl)	17	3,447	1,153	SMD	Random	-0.42 (-0.62, -0.21)	**NO**[39-42] (discordance in statistical significance)
Schrag[40]	2013	Alzheimer's disease (AD)	AD patients vs controls	SUA level (mg/dl)	10	900	453	Hedge's G	Random	-0.59 (-1.26, -0.09)	
Chen[41]	2014	Alzheimer's disease (AD)	AD patients vs controls	SUA level (mg/dl)	11	2,708	647	SMD	Random	-0.50 (-1.23, 0.22)	
Du[42]	2016	Alzheimer's disease (AD)	AD patients vs controls	SUA level (mg/dl)	21	3,617	1,128	MD	Random	-0.77 (-1.18, -0.36)	
Du[42]	2016	Alzheimer's disease (AD)	Alzheimer's patients vs controls	Highest vs lowest SUA category	3	7,372	NA	RR	Fixed	0.66 (0.52, 0.85)	
Bartoli[43]	2016	Bipolar disorder	Bipolar disorder vs controls	SUA level (mg/dl)	9	1,127	619	SMD	Random	0.65 (0.33, 0.97)	
Bartoli[43]	2016	Bipolar disorder	Bipolar disorder vs major depression	SUA level (mg/dl)	5	735	399	SMD	Random	0.46 (0.16, 0.75)	
Bartoli[43]	2016	Bipolar disorder phase (Depressive vs euthymic phase)	Depressive vs euthymic phase	SUA level (mg/dl)	6	375	NA	SMD	Random	-0.11 (-0.33, 0.11)	
Bartoli[43]	2016	Bipolar disorder phase	Manic/mixed vs depressive phase	SUA level (mg/dl)	7	472	NA	SMD	Random	0.34 (0.02, 0.66)	
Bartoli[43]	2016	Bipolar disorder phase	Manic/mixed vs euthymic phase	SUA level (mg/dl)	6	402	NA	SMD	Random	0.19 (-0.10, 0.49)	
Khan[39]	2013	Dementia/cognitive impairment	Dementia/cognitive impairment patients vs controls	SUA level (mg/dl)	31	7,021	2,681	SMD	Random	-0.33 (-0.48, -0.17)	
Khan[39]	2013	Dementia/cognitive impairment	Dementia/cognitive impairment	Highest vs lowest SUA category	5	3,281	489	OR	Random	1.18 (0.96, 1.46)	

			patients vs controls								
Khan[39]	2013	Vascular dementia (VaD)	Vascular dementia patients vs controls	SUA level (mg/dl)	7	597	272	SMD	Random	-0.05 (-0.88, 0.78)	
Schrag[40]	2013	Mild cognitive impairment (MCI)	MCI patients vs controls	SUA level (mg/dl)	2	129	49	Hedge's G	Random	-0.73 (-2.7, 1.24)	**YES[39 40]**
Khan[39]	2013	Mild cognitive impairment (MCI)	MCI patients vs controls	SUA level (mg/dl)	4	731	515	SMD	Random	-0.24 (-0.90, 0.42)	
Khan[39]	2013	Mixed or undifferentiated dementia	Mixed or undifferentiated dementia vs controls	SUA level (mg/dl)	4	1,998	NA	SMD	Random	0.19 (-0.17, 0.54)	
Khan[39]	2013	Parkinson's disease (PD)	PD patients vs controls	SUA level (mg/dl)	7	1,008	514	SMD	Random	-0.67 (-1.05, -0.29)	**YES[39 44 45]**
Shen[44]	2013	Parkinson's disease (PD)	PD patients vs controls	SUA level (μM/L)	6	2,493	1,217	SMD	NA	-0.52 (-0.72, -0.31)	
Shen[44]	2013	Parkinson's disease (PD)	General	Hyper vs normal	6	33,185	578	RR	Random	0.65 (0.43, 0.97)	
Shen[44]	2013	Parkinson's disease (PD)	General	Hyper vs normal	3	11,795	NA	RR(dose-respond)	NA	0.77 (0.68, 0.88)	
Shen[45]	2013	PD progression	PD patients	Hyper vs normal	2	1,578	NA	RR	Fixed	0.56 (0.43, 0.72)	
Liu[46]	2012	Multiple sclerosis (MS)	MS patients vs controls	SUA level (umol/L)	8	1,037	556	SMD	Random	-0.68 (-0.82, -0.55)	**YES[46 47]**
Wang[47]	2016	Multiple sclerosis (MS)	MS patients vs control	SUA level (μmol/L)	10	2,216	1,308	SMD	Random	-0.40 (-0.73, -0.07)	
Wang[47]	2016	Neruomyelistsopticis (NMO)	NMO patients vs control	SUA level (μmol/L)	3	1,137	229	SMD	Random	-0.85 (-1.24, -0.46)	
Wang[47]	2016	MS and NMO	MS+NMO patients vs control	SUA level (μmol/L)	13	2,445	1,537	SMD	Random	-0.52 (-0.81, -0.24)	
Abraham[48]	2014	Amyotrophic lateral sclerosis (ALS)	ALS patients vs controls	SUA level (mg/dl)	3	826	311	Hedge's G	NA	0.84 (NA, NA)	
Flatow[49]	2013	Schizophrenia (Chronic)	Chronic Schizophrenia patients vs controls	SUA level (mg/dl)	3	241	103	Hedge's G	Random	p=0.15	
Flatow[49]	2013	Schizophrenia (First-Episode Psychosis)	Schizophrenia patients in First-Episode Psychosis vs controls	SUA level (mg/dl)	2	274	155	Hedge's G	Random	p<0.01	
Cancer outcomes											
Yan[50]	2015	Cancer incidence	General	Highest vs lowest SUA category	5	456,053	14,355	RR	Fixed	1.03 (1.01, 1.05)	
Yan[50]	2015	Cancer in Digestive	General	Highest vs lowest	3	266,347	2,521	RR	Random	1.08 (0.94,	

		organs incidence		SUA category						1.25)	
Yan[50]	2015	Cancer in Lymphoid and hematopoietic systems incidence	General	Highest vs lowest SUA category	2	86,739	397	RR	Fixed	1.71 (1.10, 2.68)	
Yan[50]	2015	Cancer in Male genital organs incidence	General	Highest vs lowest SUA category	3	162,022	2,634	RR	Fixed	1.06 (1.00, 1.13)	
Yan[50]	2015	Cancer in Respiratory system and intrathoracic organs incidence	General	Highest vs lowest SUA category	4	456,053	2,941	RR	Random	1.05 (0.93, 1.19)	
Yan[50]	2015	Cancer in Urinary organs incidence	General	Highest vs lowest SUA category	2	86,739	536	RR	Random	1.17 (0.44, 3.15)	
All-cause and cause-specific mortality											
Kim[16]	2010	CHD mortality	General	Hyper vs normal	8	253,336	4,473	aRR	Random	1.16 (1.01, 1.30)	**YES[16-18]**
Kim[16]	2010	CHD mortality	General	1 mg/dl SUA increase	4	102,342	770	aRR	Random	1.12 (1.05, 1.19)	
Braga[17]	2015	CHD mortality	General	Hyper vs normal	6	237,421	5,572	RR	Random	1.21 (1.00, 1.46)	
Li[18]	2016	CHD Mortality	General	Hyper vs normal	13	876,584	24,198	aRR	Random	1.27 (1.16, 1.39)	
Li[18]	2016	CHD Mortality	General	1 mg/dl SUA increase	6	NA	NA	RR	Random	1.15 (1.09, 1.21)	
Qin[19]	2016	CVD mortality	Hypertensive patients	Hyper vs normal	3	NA	NA	aHR	Random	1.31 (0.96, 1.78)	
Huang[20]	2014	CVD mortality	Heart failure patients	Hyper vs normal	2	2,250	NA	HR	Random	1.45 (1.18, 1.78)	
Zhao[51]	2014	CVD mortality	General	Highest vs lowest SUA category	9	165,806	6,121	RR	Random	1.37 (1.19, 1.57)	**YES[51 52]**
Yang[52]	2015	CVD mortality	General	Highest vs lowest SUA category	3	105,329	1,829	RR	Random	1.25 (1.00, 1.56)	
Kim[28]	2009	Stroke mortality	General	Hyper vs normal	6	45,751	NA	aRR	Random	1.26 (1.12, 1.39)	**YES[28 29]**
Li[29]*	2014	Stroke mortality	General	Hyper vs normal	9	1,017,810	21,281	aRR	Random	1.33 (1.24, 1.43)	
Qin[19]	2016	Stroke mortality	Hypertensive patients	Continuous SUA level	2	NA	NA	aHR	Random	1.20 (0.95, 1.51)	
Xia[53]	2016	CKD mortality	General	Highest vs lowest SUA category	14	15,930	3,245	aHR	Random	1.52 (1.33, 1.73)	
Xia[53]	2016	CKD mortality	General	1 mg/dl SUA increase	21	23,443	3,904	aHR	Random	1.08 (1.04, 1.11)	

Yan[50]	2015	Cancer mortality	General	Highest vs lowest SUA category	12	632,472	NA	RR	Random	1.17 (1.04, 1.32)	
Yan[50]	2015	Cancer mortality in bone, connective tissue, soft tissue, and skin	General	Highest vs lowest SUA category	NA	112,296	NA	RR	Fixed	0.94 (0.47, 1.87)	
Yan[50]	2015	Cancer mortality in digestive organs	General	Highest vs lowest SUA category	4	187,886	855	RR	Fixed	1.27 (1.08, 1.49)	
Yan[50]	2015	Cancer mortality in lymphoid and hematopoietic systems	General	Highest vs lowest SUA category	NA	112,296	NA	RR	Fixed	1.18 (0.82, 1.70)	
Yan[50]	2015	Cancer mortality in male genital organs	General	Highest vs lowest SUA category	NA	88,033	NA	RR	Random	0.51 (0.07, 3.85)	
Yan[50]	2015	Cancer mortality in respiratory system and intrathoracic organs	General	Highest vs lowest SUA category	2	116,646	164	RR	Random	1.08 (0.61, 1.91)	
Yan[50]	2015	Cancer mortality in urinary organs	General	Highest vs lowest SUA category	2	112,296	NA	RR	Fixed	1.35 (0.88, 2.07)	
Tamariz[54]	2009	All-cause mortality	Heart failure patients	Hyper vs normal	6	1,456	NA	RR	Fixed	2.13 (1.78, 2.55)	**YES[20 54]**
Tamariz[54]	2009	All-cause mortality	Acute heart failure patients	Hyper vs normal	4	772	NA	RR	Fixed	2.40 (1.50, 3.70)	
Tamariz[54]	2009	All-cause mortality	Chronic heart failure patients	Hyper vs normal	2	772	NA	RR	Fixed	2.10 (1.50, 2.90)	
Huang[20]	2014	All-cause mortality	Heart failure patients	Hyper vs normal	11	12,444	1,888	HR	Random	2.15 (1.64, 2.83)	
Huang[20]	2014	All-cause mortality	Heart failure patients	1 mg/dl SUA increase	10	21,119	5,755	HR	Random	1.04 (1.02, 1.06)	
Li[35]	2011	All-cause mortality	CKD population	Hyper vs normal	5	1,789	609	RR	Random	1.67 (1.29, 2.16)	
Trkulja[27]	2012	Short-term mortality	AMI patients	Highest vs lowest SUA category	8	6,805	396	OR	Random	2.95 (2.29, 3.80)	
Trkulja[27]	2012	Medium term mortality	AMI patients	Highest vs lowest SUA category	5	5,194	565	OR	Random	2.28 (1.82, 2.86)	
Yan[25]	2014	In-hospital mortality	AMI patients vs controls	Hyper vs normal	6	5,686	218	RR	Random	2.10 (1.03, 4.26)	
Xu[33]	2013	Mortality	T2DM patients	Hyper vs normal	3	5,534	NA	HR	Random	1.09 (1.03, 1.16)	
Zhao[51]	2014	All-cause mortality	General	Highest vs lowest SUA category	10	143,483	7,031	RR	Random	1.24 (1.09, 1.42)	**YES[51 52]**
Yang[52]	2015	All-cause mortality	General	Highest vs lowest SUA category	6	126,702	12,863	RR	Random	1.17 (1.03, 1.32)	

Song[26]	2015	Mortality	Patients after PCI	Hyper vs normal	9	17,268	NA	RR	Fixed	1.31 (1.21, 1.42)	
Song[26]	2015	Mortality	Patients after PCI	1 mg/dl SUA increase	3	NA	NA	RR	Random	1.25 (1.13, 1.39)	
Qin[19]	2016	All-cause mortality	Hypertensive patients	Hyper vs normal	4	46,103	5,820	aHR	Random	1.12 (1.02, 1.23)	
Qin[19]	2016	All-cause mortality	Hypertensive patients	Continuous SUA level	3	NA	NA	aHR	Random	1.05 (0.98, 1.13)	
Other outcomes											
Trkulja[27]	2012	Medium/long-term occurrence of poor outcomes (death/MACE)	AMI patients	Highest vs lowest SUA category	3	2,683	NA	HR	Random	1.30 (1.01, 1.68)	
Trkulja[27]	2012	Medium/long-term occurrence of poor outcomes (death/MACE)	AMI patients	50 μmol/L increase	4	3,533	NA	aHR	Random	1.19 (1.03, 1.37)	
Trkulja[27]	2012	Short-term occurrence of poor outcomes (death/MACE)	AMI patients	Highest vs lowest SUA category	4	3,625	336	aOR	Random	2.26 (1.85, 2.77)	
Huang[20]	2014	Combined death or cardiac events	Heart failure patients	Hyper vs normal	9	12,699	1,765	HR	Random	1.39 (1.18, 1.63)	
Huang[20]	2014	Combined death or cardiac events	Heart failure patients	1 mg/dl SUA increase	4	2,514	NA	HR	Random	1.28 (0.97, 1.70)	
Song[26]	2015	Adverse outcomes (mortality, MAGE, In-stent restenosis)	Patients after PCI	Hyper vs normal	12	21,030	NA	RR	Random	1.46 (1.29, 1.65)	
Wang[55]	2016	Occurrence of poor outcomes	Acute ischemic stroke patients	Highest vs lowest SUA category	9	7,932	NA	HR	Random	0.77 (0.68, 0.88)	
Wang[55]	2016	Occurrence of poor outcomes	Acute ischemic stroke patients	SUA level (μmol/L)	4	1,879	631	MD	Fixed	30.61 (20.13, 41.08)	
Li[56]	2016	Psoriasis	Psoriasis patients vs controls	SUA level (mg/dl)	13	29,037	1,644	MD	Random	0.89 (0.05, 1.73)	
Li[56]	2016	Psoriasis severity	Sever psoriasis patients vs controls	SUA level (mg/dl)	3	300	104	MD	Random	0.53 (-1.04, 2.10)	
Zhou[57]	2016	Non-alcoholic fatty liver disease (NAFLD)	General	Highest vs lowest SUA category	9	55,573	10,581	OR	Random	1.92 (1.59, 2.31)	

Abbreviations: MA, meta-analysis; CHD, coronary heart disease; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; T2DM, Type 2 diabetes; CKD, chronic kidney disease; AD, Alzheimer's disease; PD, Parkinson's disease; VaD, Vascular dementia; MCI, mild cognitive impairment; MS, multiple sclerosis; NMO, neruomyelistsopticis; ALS, amyotrophic lateral sclerosis; NAFLD, non-alcoholic fatty liver disease; MD, mean difference; SMD, standard mean difference; NA, not available.

* We corrected the errors and inappropriateness of the original meta-analysis, when conducted the quantitative analysis.

Supplementary table S4 General characteristics and main findings of the 31 meta-analyses of RCTs

Author	Year	Population	SUA-lowering therapy	Versus	Outcome	N studies	N participants	N Cases	Type of metric	Effect model	Reported summary effect (95%)	Concordance in overlapped MA
Kidney diseases												
Fink[58]	2013	Nephrolithiasis patients	Thiazides	Placebo/no treatment	Nephrolithiasis recurrence	5	300	151	RR	Random	0.52 (0.39, 0.69)	
Fink[58]	2013	Nephrolithiasis patients	Citrates	Placebo/no treatment	Nephrolithiasis recurrence	4	197	90	RR	Random	0.25 (0.14, 0.44)	
Fink[58]	2013	Nephrolithiasis patients	Allopurinol	Placebo/no treatment	Nephrolithiasis recurrence	2	152	78	RR	Random	0.59 (0.42, 0.84)	
Wang[59]	2013	General	All active therapy	Placebo/no treatment	SCr (mg/dL)	9	580	NA	SMD	Random	-1.25 (-1.98, -0.52)	
Wang[59]	2013	General	All active therapy	Placebo/no treatment	eGFR (ml/min/1.73m^2)	3	218	NA	SMD	Fixed	0.41 (0.14, 0.68)	
Zhang[60]	2014	CKD Patients	Allopurinol	Placebo/no treatment	SCr (μmol/L)	6	354	177	MD	Random	-62.55 (-98.10, -26.99)	YES[60 61]
Bose[61]	2014	Patients with CKD or decreased kidney function	Allopurinol	Placebo/no treatment	SCr (mg/dL)	3	130	NA	MD	Random	-0.40 (-0.80, 0.00)	
Zhang[60]	2014	CKD Patients	Allopurinol	Placebo/no treatment	eGFR (ml/min/1.73m^2)	2	184	96	MD	Fixed	5.65 (1.88, 9.41)	NO[60 61] (discordance in statistical significance)
Bose[61]	2014	Patients with CKD or decreased kidney function	Allopurinol	Placebo/no treatment	eGFR (ml/min/1.73m^2)	5	346	NA	MD	Random	3.10 (-0.90, 7.10)	
Zhang[60]	2014	CKD Patients	Allopurinol	Placebo/no treatment	End-stage renal disease	5	267	132	RR	Fixed	0.30 (0.19, 0.46)	NO[60 61] (discordance in direction and statistical significance)
Bose[61]	2014	Patients with CKD or decreased kidney function	Allopurinol	Placebo/no treatment	End-stage kidney disease	2	164	NA	RR	Random	1.01 (0.15, 6.98)	
Zhang[60]	2014	CKD Patients	Allopurinol	Placebo/no treatment	Blood urea nitrogen (mmol/L)	3	169	83	MD	Fixed	-6.15 (-8.17, -4.13)	
Zhang[60]	2014	CKD Patients	Allopurinol	Placebo/no treatment	24-h urinary protein (g/day)	3	184	94	MD	Fixed	0.13 (0.28, 0.02)	
Zhang[60]	2014	CKD Patients	Allopurinol	Placebo/no treatment	Stable renal function	5	267	132	RR	Fixed	1.73 (1.44, 2.09)	
Bose[61]	2014	Patients with CKD or decreased kidney function	Allopurinol	Placebo/no treatment	Proteinuria (g/day)	5	250	NA	MD	Random	-0.20 (-0.60, 0.10)	

Endothelial function												
Higgins[62]	2010	Population with vascular diseases	Xanthine Oxidase	Placebo/no treatment	Flow-mediated dilatation (%)	5	144	75	MD	Random	2.50 (0.15, 4.84)	
Higgins[62]	2010	Population with vascular diseases	Xanthine Oxidase	Placebo/no treatment	Forearm blood flow	5	148	74	MD	Random	68.80 (18.70, 118.90)	
Kanbay[63]*	2014	General	Allopurinol	Placebo/no treatment	Flow-mediated dilatation (%)	6	285	142	MD	Fixed	2.75 (2.49, 3.01)	
Kanbay[63]*	2014	General	Allopurinol	Placebo/no treatment	Forearm blood flow (%)	5	130	71	MD	Fixed	2.62 (2.32, 2.91)	
Kanbay[63]*	2014	General	Allopurinol	Placebo/no treatment	Endothelial-dependent dilatation (%)	11	415	213	MD	Fixed	2.69 (2.49, 2.89)	
Kanbay[63]*	2014	General	Allopurinol	Placebo/no treatment	Endothelial independent dilatation (%)	5	216	113	MD	Fixed	0.20 (-0.20, 0.61)	
Mortality												
Chaudhari[64]	2012	Infants with hypoxic-ischaemic encephalopathy	Allopurinol	Placebo/no treatment	Death during neonatal or infancy	3	114	58	RR	Fixed	0.88 (0.56, 1.38)	
Chaudhari[64]	2012	Infants with hypoxic-ischaemic encephalopathy	Allopurinol	Placebo/no treatment	Death during neonatal or infancy	2	41	20	RR	Fixed	0.97 (0.62, 1.51)	
Chaudhari[64]	2012	Infants with hypoxic-ischaemic encephalopathy	Allopurinol	Placebo/no treatment	Death or serve neurodevelopmental disability in survivors	3	110	56	RR	Fixed	0.78 (0.56, 1.08)	
Chaudhari[64]	2012	Infants with hypoxic-ischaemic encephalopathy	Allopurinol	Placebo/no treatment	Death or serve neurodevelopmental disability in survivors	2	41	20	RR	Fixed	0.92 (0.66, 1.30)	
Other outcomes												
Chaudhari[64]	2012	Infants with hypoxic-ischaemic encephalopathy	Allopurinol	Placebo/no treatment	Severe quadriplegia in surviving infants	3	73	38	RR	Fixed	0.59 (0.28, 1.27)	
Chaudhari[64]	2012	Infants with hypoxic-ischaemic encephalopathy	Allopurinol	Placebo/no treatment	Seizures in neonatal period	3	114	58	RR	Fixed	0.93 (0.75, 1.16)	
Agarwal[65]	2013	Patients with elevated SUA or kidney	Allopurinol	Placebo/no treatment	SBP (mmHg)	10	738	NA	MD	Random	-3.33 (-5.25, -1.42)	NO[61 65] (discordance in statistical

		dysfunction										significance)
Bose[61]	2014	Patients with CKD or decreased kidney function	Allopurinol	Placebo/no treatment	SBP (mmHg)	5	309	NA	MD	Random	-2.70 (-7.30, 1.90)	
Agarwal[65]	2013	Patients with elevated SUA or kidney dysfunction	Allopurinol	Placebo/no treatment	DBP (mmHg)	10	738	NA	MD	Random	-1.29 (-2.48, -0.10)	NO[61 65] (discordance in statistical significance)
Bose[61]	2014	Patients with CKD or decreased kidney function	Allopurinol	Placebo/no treatment	DBP (mmHg)	5	309	NA	MD	Random	-1.90 (-4.90, 1.20)	

Abbreviations: MA, meta-analysis; CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; MD, mean difference; SMD, standard mean difference; NA, not available.
* Quantitative analyses were not performed, because we suspected some of the reported data misused standard error as standard deviation.

Supplementary table S5 General characteristics and main findings of the 107 Mendelian randomisation studies*

Author	Year	Population	N/n Events (N studies)*	Outcomes	Genetic instruments (GI)	SUA variance (R2) explained by GI	Type of metric	Estimate effect (95%CI)	P value	Concordance in overlapped MR
Anthropometric variables										
Korostishevsky[66]	2016	UK	3,953	Appendicular lean mass (kg)	rs737267 in *SCL2A9*	NA	β	0.01 (NA, NA)	0.51	
Lyngdoh[67]	2012	Switzerland	6,184	Fat mass (kg)	rs6855911 in *SCL2A9*	3.2%	β	0.05 (-0.10, 0.19)	0.52	
Burgess[68]	2015	European	7,158	BMI (kg/m^2)	Genetic risk score of 29 SUA-related SNPs	NA	β	-0.12(-0.53, 0.29)	0.57	NO[67-73] (discordance in direction)
Palmer[69]	2013	Danish	68,674 (2)*	BMI (kg/m^2)	rs7442295 in *SCL2A9*	2.2%	MD	-0.04 (-0.25, 0.16)	NA	
Hughes[70]	2013	European	7,979 (2)*	BMI (kg/m^2)	Genetic risk score of 5 SUA-related SNPs	2.3%	β	-0.05 (-0.12, 0.01)	0.11	
Lyngdoh[67]	2012	Switzerland	6,184	BMI (kg/m^2)	rs6855911 in *SCL2A9*	3.2%	β	-0.01 (-0.16, 0.14)	0.94	
Oikonen[71]	2012	Finnish (male)	1,985	BMI (kg/m^2)	rs13129697 in *SCL2A9*	NA	β	0.04 (NA, NA)	0.82	
Parsa[72]	2012	USA	868	BMI (kg/m^2)	rs16890979 in SCL2A9	NA	MD	0.24 (-0.33, 0.81)	0.39	
White[73]	2016	European	127,600 (64)*	BMI (kg/m^2)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	-0.0003 (-0.0008, 0.0002)	NA	
Lyngdoh[67]	2012	Switzerland	6,184	Waist circumference (cm)	rs6855911 in *SCL2A9*	3.2%	β	0.08 (-0.05, 0.21)	0.24	
Xiong[74]	2016	Chinese	1,667	BMD in femoral neck (g/cm^2)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	0.19 (-0.42, 0.81)	0.53	NO[74 75] (discordance in direction)
Dalbeth[75]	2015	USA	2,501	BMD in femoral neck (g/cm^2)	Genetic risk score of 5 SUA-related SNPs	3.3%	β	-0.27 (-0.58, 0.03)	0.08	
Xiong[74]	2016	Chinese	1,667	BMD in L1–L4 (g/cm^2)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	0.39 (-0.26, 0.98)	0.26	
Dalbeth[75]	2015	USA	2,501	BMD in spine (g/cm^2)	Genetic risk score of 5 SUA-related SNPs	3.3%	β	0.08 (-0.32, 0.48)	0.68	
Dalbeth[75]	2015	USA	2,501	BMD in total femur (g/cm^2)	Genetic risk score of 5 SUA-related SNPs	3.3%	β	-0.29 (-0.60, 0.01)	0.06	
Xiong[74]	2016	Chinese	1,667	BMD in total hip (g/cm^2)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	0.19 (-0.36, 0.74)	0.50	
Cardiovascular outcomes										
Kleber[76]	2015	Germany	3,060/444	Arrhythmia	Genetic risk score of 8 SUA-related SNPs	NA	OR	0.98 (0.88, 1.08)	0.64	
Kleber[76]	2015	Germany	3,060/368	Atrial fibrillation	Genetic risk score of 8 SUA-related SNPs	NA	OR	1.03 (0.93, 1.15)	0.57	
Kleber[76]	2015	Germany	3,060/316	Cardiomyopathy	Genetic risk score of 8 SUA-related SNPs	NA	OR	1.00 (0.89, 1.12)	0.93	

White[73]	2016	European	206,822/65,877 (58)*	CHD	Genetic risk score of 31 SUA-related SNPs	4.2%	OR	1.05 (0.92, 1.20)	0.49	NO[73 77-80] (discordance in direction)
Keenan[77]	2016	Pakistan	122,776/54,501 (2)*	Coronary heart disease	Genetic risk score of 14 SUA-related SNPs	3.1%	OR	1.02 (0.92, 1.12)	0.73	
Kleber[76]	2015	Germany	3,060/2,418	Coronary artery disease (CAD)	Genetic risk score of 8 SUA-related SNPs	NA	OR	0.99 (0.91, 1.09)	0.90	
Han[78]	2015	Chinese	2,292/1,123	CHD	rs11722228 in *SLC2A9*	NA	OR	1.09 (0.88, 1.35)	0.43	
					rs4148152 in *ABCG2*	NA	OR	0.84 (0.70, 1.11)	0.31	
Yang[79]	2010	American	23,362/3,050 (5)*	CHD incidence	Genetic risk score of 8 SUA-related SNPs	6.0%	OR	1.03 (0.85, 1.25)	0.76	
Stark[80]	2009	Germany	2,714/1,473	CAD	10 SUA-related SNPs:	NA	OR	Overall P>0.05		
					rs12129861			1.04 (0.93, 1.15)	0.54	
					rs780094			0.95 (0.85, 1.06)	0.39	
					rs734553			1.14 (1.00, 1.29)	0.06	
					rs734553			1.14 (0.96, 1.36)	0.13	
					rs742132			0.98 (0.87, 1.10)	0.74	
					rs1183201			0.96 (0.86, 1.07)	0.48	
					rs12356193			0.94 (0.81, 1.09)	0.42	
					rs17300741			1.08 (0.97, 1.21)	0.15	
					rs505802			1.04 (0.93, 1.17)	0.5	
Keenan[77]	2016	Pakistan	22,926/4,526 (2)*	Heart failure	Genetic risk score of 14 SUA-related SNPs	3.1%	OR	1.07 (0.88, 1.30)	0.51	
Palmer[69]	2013	Danish	68,674/3,742 (2)*	Ischemic heart disease	rs7442295 in SCL2A9	2.2%	HR	0.93 (0.79, 1.09)	0.38	
Kleber[76]	2015	Germany	3,060/2,225	Hypertension	Genetic risk score of 8 SUA-related SNPs	NA	OR	0.98 (0.90, 1.06)	0.56	
Keenan[77]	2016	Pakistan	82,091/14,779 (2)*	Ischemic stroke	Genetic risk score of 14 SUA-related SNPs	3.1%	OR	0.99 (0.88, 1.12)	0.93	
Kleber[76]	2015	Germany	3,060/295	Peripheral vascular disease	Genetic risk score of 8 SUA-related SNPs	NA	OR	0.92 (0.82, 1.04)	0.18	
Kleber[76]	2015	Germany	3,060/538	Valve disease	Genetic risk score of 8 SUA-related SNPs	NA	OR	1.08 (0.99, 1.19)	0.10	
Yan[81]	2016	Chinese female T2DM patients	3,207	Diabetic macrovascular	Genetic risk score of 3 SUA-related SNPs	NA	OR	1.18 (1.06, 1.33)	0.004	

Oikonen[71]	2012	Finnish (male)	1,985	Carotid artery intima-media thickness (cIMT) (mm)	rs13129697 in *SCL2A9*	NA	β	<0.0001	0.99	
Mallamaci[82]	2015	Italian	449	cIMT (mm)	rs734553 in SLC2A9	NA	β	0.40 (NA, NA)	<0.001	
Mallamaci[82]	2015	Italian	449	Arterial stiffness (internal diameter) (mm)	rs734553 in SLC2A9	NA	β	0.48 (NA, NA)	0.003	
White[73]	2016	European	89,667 (37)*	DBP (mm Hg)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	0.005 (0.003, 0.007)	NA	NO[69 70 72 73 79 83 84] (discordance in direction and statistical significance)
Sedaghat[83]	2014	Netherlander	5,974	DBP (mm Hg)	Genetic risk score of 30 SUA-related SNPs	4.2%	β	-0.42 (-0.72, -0.13)	0.01	
Mallamaci[84]	2014	Italian	449	DBP (mm Hg)	rs734553 in *SCL2A9*	NA	MD	NA	0.02	
Palmer[69]	2013	Danish	68,674 (2)*	DBP (mm Hg)	rs7442295 in *SCL2A9*	2.2%	MD	0.63 (-0.04, 1.29)	NA	
Hughes[70]	2013	European Caucasian	7,979 (2)*	DBP (mm Hg)	Genetic risk score of 5 SUA-related SNPs	2.3%	β	-0.002 (-0.13, 0.13)	0.97	
Yang[79]	2010	American	20,699 (5)*	DBP (mm Hg)	Genetic risk score of 8 SUA-related SNPs	6.0%	β	-0.34 (-1.04, 0.35)	0.33	
Parsa[72]	2012	USA	868	DBP-Clinic visit 1 (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	0.52 (-0.62, 1.66)	0.36	
Parsa[72]	2012	USA	868	DBP-High-salt 24-h (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	0.42 (-0.56, 1.40)	0.41	
Parsa[72]	2012	USA	868	DBP-Low-salt 24-h (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	0.19 (-0.75, 1.13)	0.69	
Parsa[72]	2012	USA	868	DBP-Salt sensitivity 24-h (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	-0.01 (-0.62, 0.60)	0.99	
White[73]	2016	European	89,667 (37)*	SBP (mm Hg)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	0.005 (0.003, 0.006)	NA	NO[69 70 72 73 79 83 84] (discordance in direction and statistical significance)
Sedaghat[83]	2014	Netherlander	5,974	SBP (mm Hg)	Genetic risk score of 30 SUA-related SNPs	4.2%	β	-0.75 (-1.31, -0.19)	0.01	
Mallamaci[84]	2014	Italian	449	SBP (mm Hg)	rs734553 in SLC2A9	NA	β	NA	0.02	
Palmer[69]	2013	Danish	68,674 (2)*	SBP (mm Hg)	rs7442295 in *SCL2A9*	2.2%	MD	0.65 (-0.54, 1.85)	NA	
Hughes[70]	2013	European Caucasian	7,979 (2)*	SBP (mm Hg)	Genetic risk score of 5 SUA-related SNPs	2.3%	β	0.07 (-0.12, 0.26)	0.47	
Yang[79]	2010	American	20,673 (5)*	SBP (mm Hg)	Genetic risk score of 8 SUA-related SNPs	6.0%	β	-0.83 (-1.96, 0.30)	0.15	
Parsa[72]	2012	USA	868	SBP-Clinic visit 1 (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	0.08 (-1.70, 1.86)	0.38	
Parsa[72]	2012	USA	868	SBP-High-salt 24-h (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	2.20 (0.65, 3.75)	0.01	
Parsa[72]	2012	USA	868	SBP-Low-salt 24-h (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	1.48 (0.09, 2.87)	0.04	

Parsa[72]	2012	USA	868	SBP-Salt sensitivity 24-h (mm Hg)	rs16890979 in *SCL2A9*	NA	MD	0.62 (-0.34, 1.58)	0.21	
Metabolic disorders										
White[73]	2016	European	84,638/15,360 (20)*	Diabetes	Genetic risk score of 31 SUA-related SNPs	4.2%	OR	0.99 (0.99, 1.01)	0.82	NO[73 76 85 77 86 87] (discordance in direction and statistical significance)
Kleber[76]	2015	Germany	3,060/1,236	Diabetes	Genetic risk score of 8 SUA-related SNPs	NA	OR	0.94 (0.88, 1.01)	0.10	
Sluijs[85]	2015	European	165,482/41,508 (2)*	Diabetes	Genetic risk score of 24 SUA-related SNPs	4.0%	OR	0.99 (0.92, 1.06)	0.79	
Keenan[77]	2016	Pakistan	110,452/26,488 (2)*	T2DM	Genetic risk score of 14 SUA-related SNPs	3.1%	OR	0.95 (0.86, 1.05)	0.28	
Pfister[86]	2012	UK	16,064/7,504 (4)*	T2DM	Genetic risk score of 8 SUA-related SNPs	NA	OR	0.99 (0.94, 1.04)	0.68	
Sun[87]	2015	Chinese	5,198/2,999	T2DM	15 SUA-related SNPs	NA	OR	No overall result		
					rs12129861			1.03 (0.92, 1.16)	0.59	
					rs780094			1.22 (1.11, 1.35)	3.94E-05	
					rs2544390			0.97 (0.88, 1.06)	0.50	
					rs11722228			1.01 (0.91, 1.12)	0.83	
					rs16890979			0.98 (0.66, 1.45)	0.91	
					rs3775948			1.03 (0.93, 1.13)	0.59	
					rs10489070			0.96 (0.84, 1.10)	0.54	
					rs2231142			0.94 (0.85, 1.04)	0.21	
					rs742132			1.01 (0.91, 1.13)	0.80	
					rs1183201			0.98 (0.86, 1.11)	0.75	
					rs1165205			0.98 (0.87, 1.11)	0.75	
					rs1333049			1.024 (0.93, 1.12)	0.61	
					rs17300741			0.97 (0.80, 1.19)	0.78	
					rs506338			0.99 (0.89, 1.10)	0.87	
					rs606458			1.11 (1.01, 1.22)	0.04	
Yang[79]	2010	American	25,877 (5)*	Fasting glucose (mmol/L)	Genetic risk score of 8 SUA-related SNPs	6.0%	β	-0.06 (-0.13, 0.02)	0.13	NO[72 73 79] (discordance in

White[73]	2016	European	57,397 (28)*	Fasting glucose (mmol/L)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	-0.001 (-0.003, 0.001)	NA	direction)
Parsa[72]	2012	USA	868	Glucose (mmol/L)	rs16890979 in *SCL2A9*	NA	β	0.78 (-0.87, 2.43)	0.36	
Yang[79]	2010	American	19,899 (5)*	Fasting insulin†	Genetic risk score of 8 SUA-related SNPs	6.0%	Z statistics	-0.015 (NA, NA)	0.99	
Dai[88]	2013	Chinese	7,827	Metabolic syndrome	Genetic risk score of 2 SNPs (rs11722228 in *SLC2A9* and rs2231142 in *ABCG2*)	2.1%	OR	1.03 (0.98, 1.09)	0.23	NO[88 89] (discordance in statistical significance)
McKeigue[89]	2010	Scottish	1,017/203	Metabolic syndrome	Genetic risk score of 6 SNPs in *SCL2A9*	NA	NA	NA	>0.05	
Kidney disorders										
Yang[79]	2010	American	23,387/3,092 (5)*	CKD	Genetic risk score of 8 SUA-related SNPs	6.0%	OR	1.20 (0.96, 1.50)	0.12	
Greenberg[90]	2015	USA	7,553/823	Acute kidney injury	Genetic risk score of 8 SUA-related SNPs	6.0%	HR	1.01 (0.77, 1.34)	0.92	
Testa[91]	2014	Italy	755/244	Renal events	rs734553 in *GLUT9*	NA	HR	2.35 (1.25, 4.42)	0.01	
Hughes[70]	2013	European Caucasian	7,979 (2)*	eGFR (mL/min/1.73 m^2)	Genetic risk score of 5 SUA-related SNPs	2.3%	β	12.20 (-11.50, 35.90)	0.31	NO[70 72 79 92 93] (discordance in direction and statistical significance)
Parsa[72]	2012	USA	868	eGFR (mL/min/1.73 m^2)	rs16890979 in *SCL2A9*	NA	MD	0.42 (-1.78, 2.62)	0.71	
Yang[79]	2010	American	23,844 (5)*	Log eGFR (mL/min/1.73 m^2)	Genetic risk score of 8 SUA-related SNPs	6.0%	β	0.001 (-0.01, 0.02)	0.91	
Tabara[92]	2010	Japanese	5,165 (2)*	eGFR (mL/min/1.73 m^2)	Genetic risk score of 3 SUA-related SNPs	NA	β	-0.11 (NA, NA)	<0.001	
Voruganti[93]	2014	American Indians	3,604 (3)*	eGFR (mL/min/1.73 m^2)	7 SNPs in *SCL2A9:*	5.3%	Residual variance[¶]	No overall result		
					rs16890979			0.52 (NA, NA)	0.002	
					rs6832439			0.52 (NA, NA)	0.002	
					rs6449213			0.22 (NA, NA)	0.08	
					rs13131257			0.58 (NA, NA)	0.001	
					rs737267			0.44 (NA, NA)	0.004	
					rs10805346			0.69 (NA, NA)	<0.001	
					rs12498956			0.24 (NA, NA)	0.05	
Voruganti[93]	2014	American Indians	3,604 (3)*	SCr (mmol/L)	7 SNPs in *SCL2A9:*	5.3%	Residual variance[¶]	No overall result		NO[70 93] (discordance in statistical significance)
					rs16890979			0.53 (NA, NA)	0.001	

					rs6832439			0.54 (NA, NA)	0.002	
					rs6449213			0.27 (NA, NA)	0.003	
					rs13131257			0.60 (NA, NA)	0.000	
					rs737267			0.46 (NA, NA)	0.004	
					rs10805346			0.68 (NA, NA)	0.000	
					rs12498956			0.23 (NA, NA)	0.06	
Hughes[70]	2013	European Caucasian	7,979 (2)*	SCr (mmol/L)	Genetic risk score of 5 SUA-related SNPs	2.3%	β	-19.23 (-40.32, 1.86)	0.07	
Voruganti[93]	2014	American Indians	3,604 (3)*	Albumin/creatinine ratio	7 SNPs in *SCL2A9:*	5.3%	Residual variance[¶]	Overall P>0.05		
					rs16890979			0.13 (NA, NA)	0.07	
					rs6832439			0.16 (NA, NA)	0.05	
					rs6449213			0.01 (NA, NA)	0.64	
					rs13131257			0.14 (NA, NA)	0.05	
					rs737267			0.14 (NA, NA)	0.06	
					rs10805346			0.14 (NA, NA)	0.10	
					rs12498956			0.07 (NA, NA)	0.15	
All-cause and cause-specific mortality										
Kleber[76]	2015	Germany	3,060/na	Cardiovascular mortality	Genetic risk score of 8 SUA-related SNPs	NA	aHR	1.11 (1.02, 1.21)	0.02	
Kleber[76]	2015	Germany	3,060/na	All-cause mortality	Genetic risk score of 8 SUA-related SNPs	NA	aHR	1.02 (0.95, 1.09)	0.59	
Kleber[76]	2015	Germany	3,060/na	Sudden cardiac death	Genetic risk score of 8 SUA-related SNPs	NA	aHR	1.18 (1.03, 1.35)	0.02	
Metabolites										
White[73]	2016	European	196,621 (68)*	HDL-C (mmol/L)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	-0.008 (-0.010, -0.006)	NA	
White[73]	2016	European	196,621 (68)*	LDL-C (mmol/L)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	-0.001 (-0.003, 0.001)	NA	
White[73]	2016	European	196,621 (68)*	TC (mmol/L)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	0.000 (-0.002, 0.002)	NA	
White[73]	2016	European	196,621 (68)*	TG (mmol/L)	Genetic risk score of 31 SUA-related SNPs	4.2%	MD[§]	0.014 (0.013, 0.016)	NA	NO[72 73 94] (discordance in

Rasheed[94]	2014	European	8,208 (2)*	TG (mmol/L)	Genetic risk score of 5 SUA-related SNPs	1.7%	β	−1.01 (-2.57, 0.56)	0.21	direction)
Parsa[72]	2012	USA	868	TG (mmol/L)	rs16890979 in *SCL2A9*	NA	MD	2.38 (-2.87, 7.63)	0.35	
Xiong[74]	2016	Chinese	1,667	Parathyroid hormone (pg/mL)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	-0.63 (-2.12, 0.85)	0.40	
Xiong[74]	2016	Chinese	1,667	Phosphorus (mmol/L)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	-0.16 (-0.74, 0.42)	0.59	
Burgess[68]	2015	European	7,158	C-reactive protein (CRP) (mg/L)	Genetic risk score of 29 SUA-related SNPs	NA	β	-0.05 (-0.15, 0.05)	0.37	
Xiong[74]	2016	Chinese	1,667	Calcium (mmol/L)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	0.06 (-0.10, 0.21)	0.48	
Xiong[74]	2016	Chinese	1,667	Tropocollagen type 1 N-terminal propeptide (ng/L)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	0.11 (-1.53, 1.75)	0.90	
Xiong[74]	2016	Chinese	1,667	β-crosslaps of type I collagen containing cross-linked Ctelopeptide (ng/L)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	-1.45 (-3.17, 0.27)	0.10	
Xiong[74]	2016	Chinese	1,667	25(OH)D (ng/mL)	Genetic risk score of 5 SUA-related SNPs	1.8%	β	0.76 (-0.63, 2.15)	0.28	
Neurocognitive disorders										
Gonzalez-Aramburu[95]	2014	Spain	343	Dementia in PD	Genetic risk score of 8 SUA-related SNPs	NA	OR	1.05 (0.70, 3.00)	0.31	NO[95-99] (discordance in direction and statistical significance)
Simon[96]	2014	USA	808 (2)*	PD progression	Genetic risk score of 3 SNPs in *SCL2A9*	NA	HR	1.16 (1.00, 1.35)	0.06	
Gao[97]	2013	American	1,699	Parkinson's disease	12 SNPs in *SCL2A9*	NA	OR	Overall P>0.05		
					rs16890979			1.06 (0.90, 1.24)	0.51	
					rs13129697			0.99 (0.85, 1.16)	0.91	
					rs737267			1.01 (0.86, 1.18)	0.91	
					rs6855911			1.00 (0.85, 1.18)	0.98	
					rs4697700			1.03 (0.88, 1.22)	0.69	
					rs4481233			1.01 (0.85, 1.21)	0.90	
					rs7442295			1.06 (0.90, 1.26)	0.50	
					rs6449213			1.01 (0.85, 1.21)	0.88	
					rs1014290			1.04 (0.88, 1.22)	0.67	

					rs12509955			0.99 (0.84, 1.18)	0.93	
					rs17251963			1.05 (0.88, 1.25)	0.59	
					rs12510549			0.96 (0.81, 1.14)	0.65	
Gonzalez-Aramburu[98]	2013	UK	1,061	Parkinson's disease	Genetic risk score of 9 SUA-related SNPs	NA	OR	1.55 (1.10, 2.18)	0.01	
Facheris[99]	2011	European	664 (3)*	Age at onset of PD	4 SNPs in *SCL2A9*	NA	β	Null after multiple testing correction		
					rs737267	NA		3.10 (0.17, 6.03)	0.04	
					rs6449213	NA		-1.18 (-4.96, 2.59)	0.54	
					rs1014290	NA		-4.56 (-8.13, -1.00)	0.01	
					rs733175	NA		3.59 (0.67, 6.51)	0.02	
Lyngdoh[100]	2013	Switzerland	3,716/660	Lifetime anxiety disorders	rs6855911 in SLC2A9	3.2%	OR (male)	1.40 (1.07, 1.84)	0.02	
							OR (female)	0.97 (0.80, 1.17)	0.73	
Lyngdoh[100]	2013	Switzerland	3,716/370	Current anxiety disorders	rs6855911 in SLC2A9	3.2%	OR (male)	1.42 (0.99, 2.03)	0.06	
							OR (female)	0.84 (0.66, 1.06)	0.14	
Houlihan[101]	2010	European (Population 1: LBC1936)	1,091	Memory performance	4 SNPs in *SCL2A9*	NA	β	Overall P<0.05		NO[101] (discordance in statistical significance)
					rs733175			-0.10 (NA, NA)	2.00E-04	
					rs1014290			-0.07 (NA, NA)	0.01	
					rs6449213			-0.07 (NA, NA)	0.01	
					rs6449213			-0.07 (NA, NA)	0.01	
Houlihan[101]	2010	European (Population 2: ET2DS)	1,066	Memory performance	4 SNPs in *SCL2A9*	NA	β	Overall P>0.05		
					rs733175			-0.03 (NA, NA)	0.27	
					rs1014290			-0.04 (NA, NA)	0.22	
					rs6449213			-0.03 (NA, NA)	0.41	
					rs6449213			-0.04 (NA, NA)	0.19	
Other outcomes										

Kleber[76]	2015	Germany	3,060/226	Cancer	Genetic risk score of 8 SUA-related SNPs	NA	OR	0.95 (0.83, 1.08)	0.41	
Keenan[77]	2016	Pakistan	71,501/3,151 (2)*	Gout	Genetic risk score of 14 SUA-related SNPs	3.1%	OR	5.84 (4.56,0 7.49)	3.55E-40	NO[76 77 79] (discordance in statistical significance)
Kleber[76]	2015	Germany	3,060/19	Gout	Genetic risk score of 8 SUA-related SNPs	NA	OR	1.15 (0.72, 1.82)	0.56	
Yang[79]	2010	American	25,982/1,033 (5)*	Gout	Genetic risk score of 8 SUA-related SNPs	6.0%	OR	12.40 (8.50, 18.00)	3.00E-39	

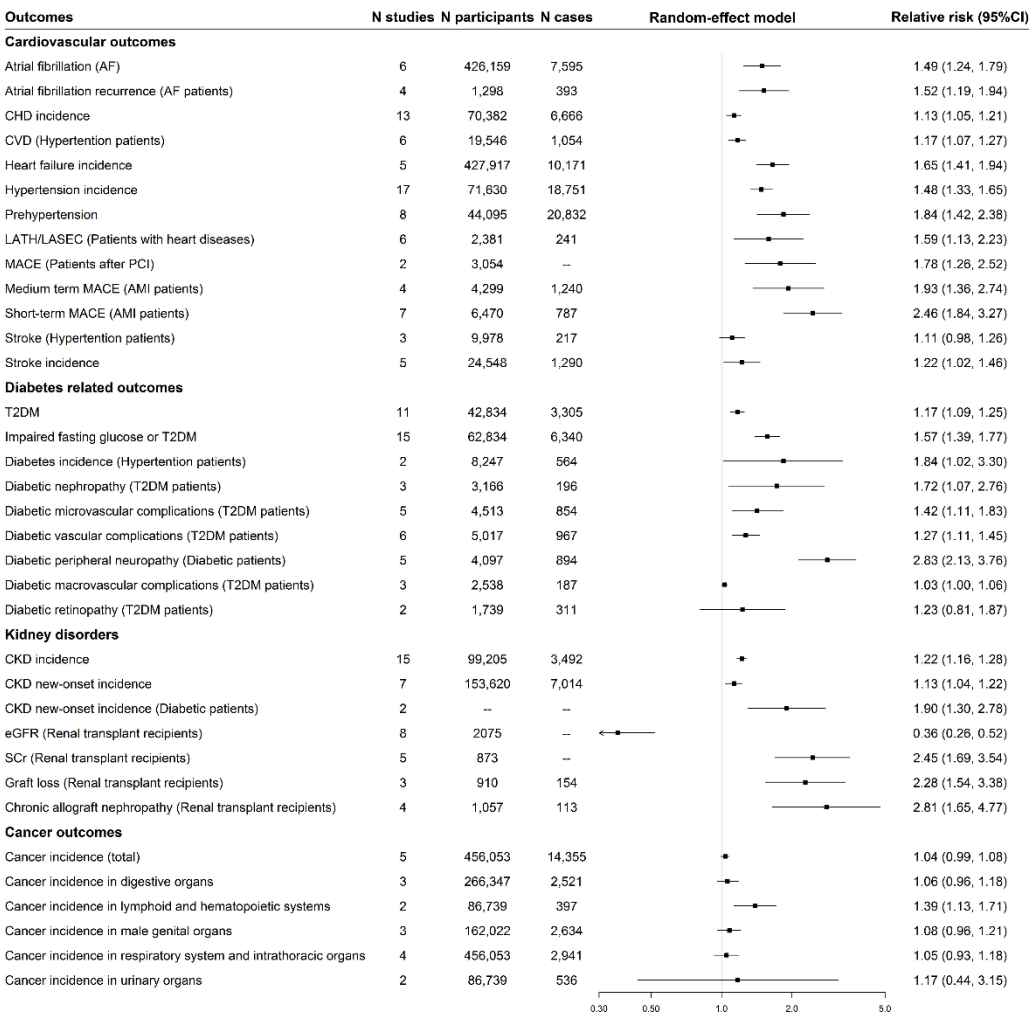
Abbreviations: MR, Mendelian randomisation study; BMI, body mass index; BMD, bone mineral density; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; IMT, intima-media thickness; CVD, cardiovascular disease; T2DM, Type 2 diabetes; CKD, chronic kidney disease; SCr, serum creatinine; eGFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; PD, Parkinson's disease; LBC1936, the Lothian birth cohort; ET2DS, the Edinburgh type 2 diabetes study; MD, mean difference; NA, not available.

* If the outcomes were reported from Mendelian randomisation analysis with pooling multiple studies, the number of studies included in pooled analysis was displayed in brackets.

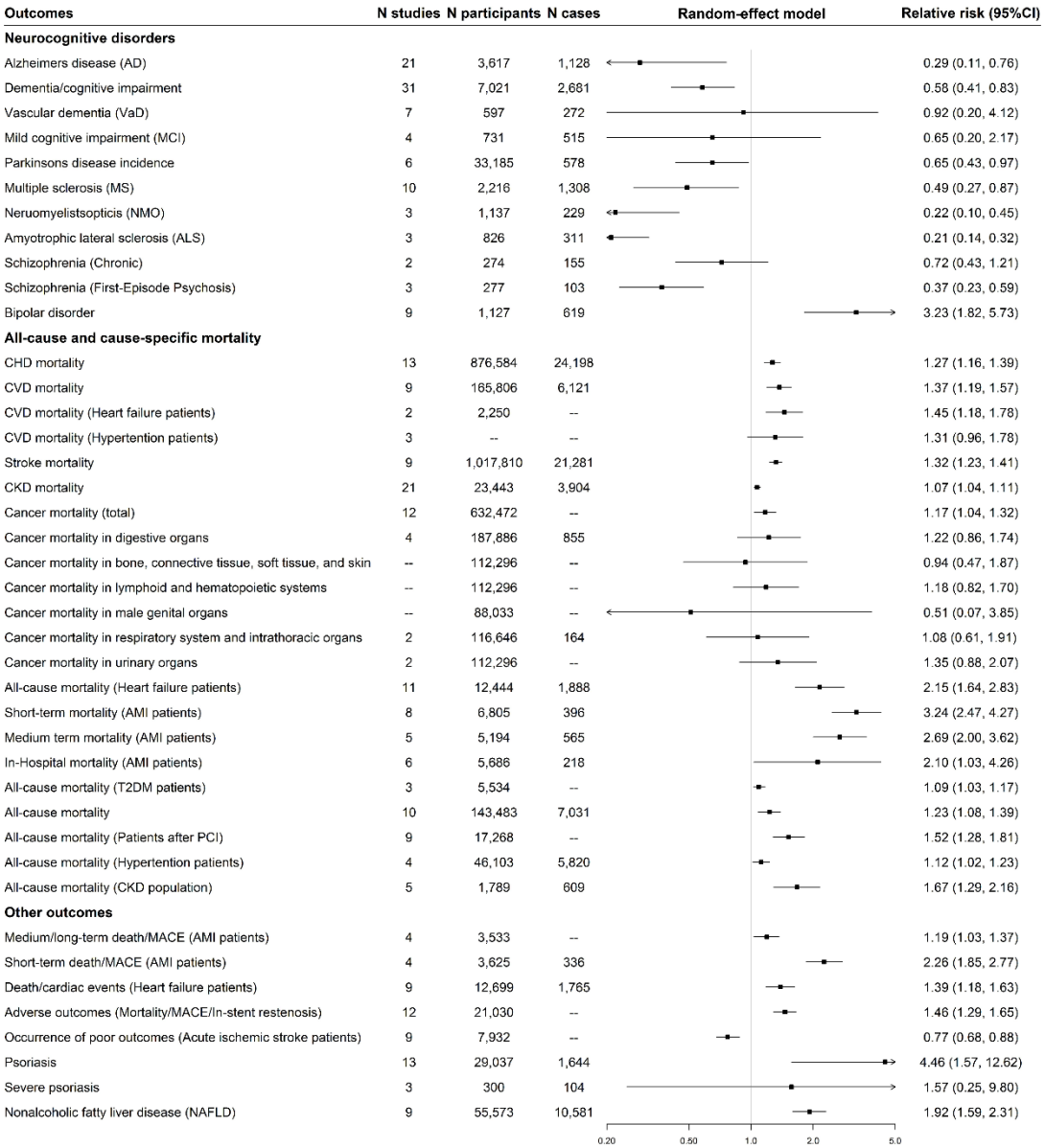
† Because of the lack of a standard to covert insulin in different studies to the same scale, sample size-weighted pooled meta-analyses were performed and Z statistics were reported instead of the β coefficient.

§ MD (mean difference) represented the difference in mean caused by per inverse variance weighted allele estimated from meta-analyses.

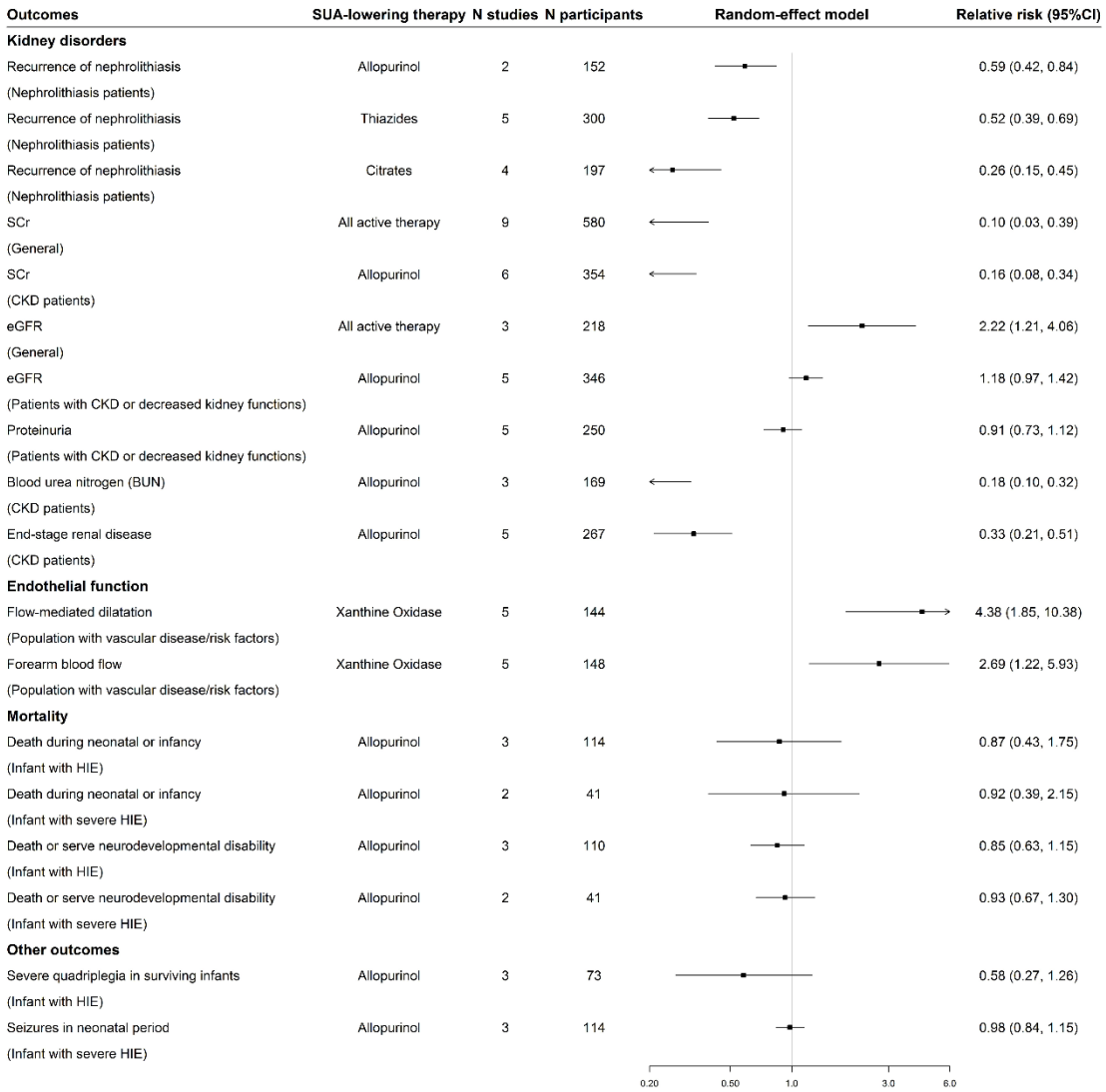
¶ Residual variance represented the proportion of residual variance explained by the SUA related SNPs.



Supplementary Fig 1 Summary random-effect estimates of cardiovascular, diabetes, kidney disorders and cancer outcomes reported in meta-analyses of observational studies. (Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CVD, cardiovascular disease; LATH/LASEC, left atrial thrombus or spontaneous echo contrast; PCI, percutaneous coronary intervention; MACE, major adverse cardiovascular events; AMI, acute myocardial infarction; T2DM, type 2 diabetes; CKD, chronic kidney disease; SCr, serum creatinine; eGFR, glomerular filtration rate)



Supplementary Fig 2 Summary random-effect estimates of neurocognitive disorders, all-cause and cause-specific mortality, and other outcomes reported in meta-analyses of observational studies. (Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; T2DM, type 2 diabetes; MACE, major adverse cardiovascular events; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease



Supplementary Fig 3 Summary random-effect estimates of health outcomes reported in meta-analyses of RCTs. (Abbreviations: CKD, chronic kidney disease; SCr, serum creatinine; eGFR, glomerular filtration rate; HIE, hypoxic-ischaemic encephalopathy)

References

1. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? *American Journal of Medicine* 2005;**118**(8):816-26.
2. Strazzullo P, Puig JG. Uric acid and oxidative stress: relative impact on cardiovascular risk? *Nutrition Metabolism & Cardiovascular Diseases* 2007;**17**(6):409-14.
3. Barron E, Lara J, White M, Mathers JC. Blood-borne biomarkers of mortality risk: Systematic review of cohort studies. *PLoS ONE* 2015;**10**(6).
4. Dimitroula HV, Hatzitolios AI, Karvounis HI. The role of uric acid in stroke: the issue remains unresolved. *Neurologist* 2008;**14**(4):238-42.
5. Hwu CM, Lin KH. Uric acid and the development of hypertension. *Medical Science Monitor* 2010;**16**(10):RA224-30.
6. Avram Z, Krishnan E. Hyperuricaemia - Where nephrology meets rheumatology. *Rheumatology* 2008;**47**(7):960-64.
7. Feig DI. Uric acid: a novel mediator and marker of risk in chronic kidney disease? *Current Opinion in Nephrology & Hypertension* 2009;**18**(6):526-30.
8. Alonso A, Sovell KA. Gout, hyperuricemia, and Parkinson's disease: a protective effect? *Current Rheumatology Reports* 2010;**12**(2):149-55.
9. Chang YT, Chang WN, Tsai NW, Huang CC, Kung CT, Su YJ, et al. The roles of biomarkers of oxidative stress and antioxidant in alzheimer's disease: A systematic review. *BioMed Research International* 2014;**2014**(182303).
10. Cnossen JS, de Ruyter-Hanhijarvi H, van der Post JA, Mol BW, Khan KS, ter Riet G. Accuracy of serum uric acid determination in predicting pre-eclampsia: a systematic review. *Acta Obstetricia et Gynecologica Scandinavica* 2006;**85**(5):519-25.
11. Tamariz L, Hernandez F, Bush A, Palacio A, Hare JM. Association between serum uric acid and atrial fibrillation: A systematic review and meta-analysis. *Heart Rhythm* 2014;**11**(7):1102-08.
12. Xu X, Du N, Wang R, Wang Y, Cai S. Hyperuricemia is independently associated with increased risk of atrial fibrillation: A meta-analysis of cohort studies. *International Journal of Cardiology* 2015;**184**(1):699-702.
13. Zhang CH, Huang DS, Shen D, Zhang LW, Ma YJ, Wang YM, et al. Association Between Serum Uric Acid Levels and Atrial Fibrillation Risk. *Cell Physiol Biochem* 2016;**38**(4):1589-95.
14. Zhao J, Liu T, Korantzopoulos P, Letsas KP, Zhang E, Yang Y, et al. Association between serum uric acid and atrial fibrillation recurrence following catheter ablation: A meta-analysis. *Int J Cardiol* 2016;**204**:103-5.
15. Wheeler JG, Juzwishin KDM, Eiriksdottir G, Gudnason V, Danesh J. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: Prospective study and meta-analysis. *PLoS Medicine* 2005;**2**(3):0236-43.
16. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis (Provisional abstract). Arthritis Care and Research 2010; 62(2).
17. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia (HUA) as an independent risk factor for coronary heart disease (CHD) in the general population: A systematic review and meta-analysis. *Clinical Chemistry and Laboratory Medicine* 2015;**53**:S1199.
18. Li M, Hu X, Fan Y, Li K, Zhang X, Hou W, et al. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. *Sci Rep* 2016;**6**:19520.
19. Qin T, Zhou X, Wang J, Wu X, Li Y, Wang L, et al. Hyperuricemia and the Prognosis of Hypertensive Patients: A Systematic Review and Meta-Analysis. *J Clin Hypertens (Greenwich)* 2016.
20. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, et al. Uric acid and risk of heart failure: A systematic review and meta-analysis. *European Journal of Heart Failure* 2014;**16**(1):15-24.
21. Zhang W, Sun K, Yang Y, Zhang H, Hu FB, Hui R. Plasma uric acid and hypertension in a Chinese community: prospective study and metaanalysis. *Clinical Chemistry* 2009;**55**(11):2026-34.
22. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis care & research* 2011;**63**(1):102-10.
23. Wang J, Qin T, Chen J, Li Y, Wang L, Huang H, et al. Hyperuricemia and risk of incident hypertension: A systematic review and meta-analysis of observational studies. *PLoS ONE* 2014;**9**(12).
24. Jiang M, Gong D, Fan Y. Serum uric acid levels and risk of prehypertension: a meta-analysis. *Clin Chem Lab Med* 2016.
25. Yan L, Liu Z, Zhang C. Uric acid as a predictor of in-hospital mortality in acute myocardial infarction: a meta-analysis. *Cell biochemistry and biophysics* 2014;**70**(3):1597-601.

26. Song X, Hou X, Che K, Wang R, Liu Y, Wang Y, et al. Association between hyperuricemia and clinical adverse outcomes after percutaneous coronary intervention: A meta-analysis. *International Journal of Cardiology* 2015;**201**:658-62.
27. Trkulja V, Car S. On-admission serum uric acid predicts outcomes after acute myocardial infarction: systematic review and meta-analysis of prognostic studies. *Croatian Medical Journal* 2012;**53**(2):162-72.
28. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis & Rheumatism* 2009;**61**(7):885-92.
29. Li M, Hou W, Zhang X, Hu L, Tang Z. Hyperuricemia and risk of stroke: A systematic review and meta-analysis of prospective studies. *Atherosclerosis* 2014;**232**(2):265-70.
30. Jia Z, Zhang X, Kang S, Wu Y. Serum uric acid levels and incidence of impaired fasting glucose and type 2 diabetes mellitus: A meta-analysis of cohort studies. *Diabetes Research and Clinical Practice* 2013;**101**(1):88-96.
31. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* 2009;**32**(9):1737-42.
32. Lv Q, Meng XF, He FF, Chen S, Su H, Xiong J, et al. High Serum Uric Acid and Increased Risk of Type 2 Diabetes: A Systemic Review and Meta-Analysis of Prospective Cohort Studies. *PLoS ONE* 2013;**8**(2).
33. Xu Y, Zhu J, Gao L, Liu Y, Shen J, Shen C, et al. Hyperuricemia as an independent predictor of vascular complications and mortality in type 2 diabetes patients: a meta-analysis. *PloS one* 2013;**8**(10):e78206.
34. Yu S, Chen Y, Hou X, Xu D, Che K, Li C, et al. Serum Uric Acid Levels and Diabetic Peripheral Neuropathy in Type 2 Diabetes: a Systematic Review and Meta-analysis. *Mol Neurobiol* 2016;**53**(2):1045-51.
35. Li YL, Wang L, Li J, Huang Y, Yuan WM. [The correlation between uric acid and the incidence and prognosis of kidney diseases: a systematic review and meta-analysis of cohort studies]. [Chinese]. *Zhonghua nei ke za zhi [Chinese journal of internal medicine]* 2011;**50**(7):555-61.
36. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: A systematic review and meta-analysis based on observational cohort studies. *BMC Nephrology* 2014;**15**(1).
37. Zhu P, Liu Y, Han L, Xu G, Ran JM. Serum uric acid is associated with incident chronic kidney disease in middle-aged populations: A meta-analysis of 15 cohort studies. *PLoS ONE* 2014;**9**(6).
38. Huang Y, Li YL, Huang H, Wang L, Yuan WM, Li J. Effects of hyperuricemia on renal function of renal transplant recipients: A systematic review and Meta-analysis of cohort studies. *PLoS ONE* 2012;**7**(6).
39. Khan A, T JQ, Dawson J. Serum uric acid level and cognitive function; A systematic review and meta-analysis. *Cerebrovascular Diseases* 2013;**35**:821.
40. Schrag M, Mueller C, Zabel M, Crofton A, Kirsch WM, Ghribi O, et al. Oxidative stress in blood in Alzheimer's disease and mild cognitive impairment: A meta-analysis. *Neurobiology of Disease* 2013;**59**:100-10.
41. Chen X, Guo X, Huang R, Chen Y, Zheng Z, Shang H. Serum uric acid levels in patients with Alzheimer's disease: A meta-analysis. *PLoS ONE* 2014;**9**(4).
42. Du N, Xu D, Hou X, Song X, Liu C, Chen Y, et al. Inverse Association Between Serum Uric Acid Levels and Alzheimer’s Disease Risk. *Molecular Neurobiology* 2016;**53**(4):2594-99.
43. Bartoli F, Crocamo C, Mazza MG, Clerici M, Carrà G. Uric acid levels in subjects with bipolar disorder: A comparative meta-analysis. *Journal of Psychiatric Research* 2016.
44. Shen C, Guo Y, Luo W, Lin C, Ding M. Serum urate and the risk of Parkinson's disease: Results from a meta-analysis. *Canadian Journal of Neurological Sciences* 2013;**40**(1):73-79.
45. Shen L, Ji HF. Low uric acid levels in patients with Parkinson's disease: Evidence from meta-analysis. *BMJ Open* 2013;**3**(11).
46. Liu B, Shen Y, Xiao K, Tang Y, Cen L, Wei J. Serum uric acid levels in patients with multiple sclerosis: A meta-analysis. *Neurological Research* 2012;**34**(2):163-71.
47. Wang L, Hu W, Wang J, Qian W, Xiao H. Low serum uric acid levels in patients with multiple sclerosis and neuromyelists opticis: An updated meta-analysis. *Multiple Sclerosis and Related Disorders* 2016;**9**:17-22.
48. Abraham A, Drory VE. Influence of serum uric acid levels on prognosis and survival in amyotrophic lateral sclerosis: a meta-analysis. *Journal of neurology* 2014;**261**(6):1133-38.
49. Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. *Biological Psychiatry* 2013;**74**(6):400-09.
50. Yan S, Zhang P, Xu W, Liu Y, Wang B, Jiang T, et al. Serum Uric Acid Increases Risk of Cancer Incidence and Mortality: A Systematic Review and Meta-Analysis. *Mediators of Inflammation* 2015;**2015**(764250).

51. Zhao G. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: A meta-analysis of prospective studies. *Cardiology (Switzerland)* 2014;**129**:47.
52. Yang Y, Fan Y, Li J, Liu B, Shao Y, Cao H, et al. Serum uric acid as a predictor for cardiovascular and all-cause mortality in women versus men. *International Journal of Cardiology* 2015;**185**:125-28.
53. Xia X, Luo Q, Li B, Lin Z, Yu X, Huang F. Serum uric acid and mortality in chronic kidney disease: a systematic review and meta-analysis. *Metabolism* 2016;**65**(9):1326-41.
54. Tamariz L, Harzand A, Verma S, Jones J, Hare J. Uric acid as a predictor of mortality in congestive heart failure: A meta-analysis. *Journal of the American College of Cardiology* 2009;**53 (10)**:A169.
55. Wang Z, Lin Y, Liu Y, Chen Y, Wang B, Li C, et al. Serum Uric Acid Levels and Outcomes After Acute Ischemic Stroke. *Mol Neurobiol* 2016;**53**(3):1753-9.
56. Li X, Miao X, Wang H, Wang Y, Li F, Yang Q, et al. Association of Serum Uric Acid Levels in Psoriasis: A Systematic Review and Meta-Analysis. *Medicine (Baltimore)* 2016;**95**(19):e3676.
57. Zhou Y, Wei F, Fan Y. High serum uric acid and risk of nonalcoholic fatty liver disease: A systematic review and meta-analysis. *Clin Biochem* 2016;**49**(7-8):636-42.
58. Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, et al. Medical management to prevent recurrent nephrolithiasis in adults: A systematic review for an American College of Physicians Clinical Guideline. *Annals of Internal Medicine* 2013;**158**(7):535-43.
59. Wang H, Wei Y, Kong X, Xu D. Effects of urate-lowering therapy in hyperuricemia on slowing the progression of renal function: A meta-analysis. *Journal of Renal Nutrition* 2013;**23**(5):389-96.
60. Zhang YF, He F, Ding HH, Dai W, Zhang Q, Luan H, et al. Effect of uric-acid-lowering therapy on progression of chronic kidney disease: a meta-analysis. *Journal of Huazhong University of Science and Technology Medical Sciences* 2014;**34**(4):476-81.
61. Bose B, Badve SV, Hiremath SS, Boudville N, Brown FG, Cass A, et al. Effects of uric acid-lowering therapy on renal outcomes: A systematic review and meta-analysis. *Nephrology Dialysis Transplantation* 2014;**29**(2):406-13.
62. Higgins P, Dawson J, Lees KR, McArthur K, Quinn TJ, Walters MR. Xanthine oxidase inhibition for the treatment of cerebrovascular and cardiovascular disease: A systematic review and meta-analysis. *Cerebrovascular Diseases* 2010;**29**:321.
63. Kanbay M, Siriopol D, Nistor I, Elcioglu OC, Telci O, Takir M, et al. Effects of allopurinol on endothelial dysfunction: A meta-analysis. *American Journal of Nephrology* 2014;**39**(4):348-56.
64. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy. Cochrane Database of Systematic Reviews 2012; (7).
65. Agarwal V, Hans N, Messerli FH. Effect of Allopurinol on Blood Pressure: A Systematic Review and Meta-Analysis. *Journal of Clinical Hypertension* 2013;**15**(6):435-42.
66. Korostishevsky M, Steves CJ, Malkin I, Spector T, Williams FM, Livshits G. Genomics and metabolomics of muscular mass in a community-based sample of UK females. *Eur J Hum Genet* 2016;**24**(2):277-83.
67. Lyngdoh T, Vuistiner P, Marques-Vidal P, Rousson V, Waeber G, Vollenweider P, et al. Serum uric acid and adiposity: deciphering causality using a bidirectional Mendelian randomization approach. *PLoS One* 2012;**7**(6):e39321.
68. Burgess S, Daniel RM, Butterworth AS, Thompson SG. Network Mendelian randomization: using genetic variants as instrumental variables to investigate mediation in causal pathways. *Int J Epidemiol* 2015;**44**(2):484-95.
69. Palmer TM, Nordestgaard BG, Benn M, Tybjaerg-Hansen A, Davey Smith G, Lawlor DA, et al. Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts. *BMJ* 2013;**347**:f4262.
70. Hughes K, Flynn T, de Zoysa J, Dalbeth N, Merriman TR. Mendelian randomization analysis associates increased serum urate, due to genetic variation in uric acid transporters, with improved renal function. *Kidney Int* 2014;**85**(2):344-51.
71. Oikonen M, Wendelin-Saarenhovi M, Lyytikainen LP, Siitonen N, Loo BM, Jula A, et al. Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study. *Atherosclerosis* 2012;**223**(2):497-503.
72. Parsa A, Brown E, Weir MR, Fink JC, Shuldiner AR, Mitchell BD, et al. Genotype-based changes in serum uric acid affect blood pressure. *Kidney Int* 2012;**81**(5):502-7.
73. White J, Sofat R, Hemani G, Shah T, Engmann J, Dale C, et al. Plasma urate concentration and risk of coronary heart disease: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol* 2016;**4**(4):327-36.
74. Xiong A, Yao Q, He J, Fu W, Yu J, Zhang Z. No causal effect of serum urate on bone-related outcomes among a population of postmenopausal women and elderly men of Chinese Han ethnicity--a Mendelian randomization study. *Osteoporos Int* 2016;**27**(3):1031-9.

75. Dalbeth N, Topless R, Flynn T, Cadzow M, Bolland MJ, Merriman TR. Mendelian randomization analysis to examine for a causal effect of urate on bone mineral density. *J Bone Miner Res* 2015;**30**(6):985-91.
76. Kleber ME, Delgado G, Grammer TB, Silbernagel G, Huang J, Kramer BK, et al. Uric Acid and Cardiovascular Events: A Mendelian Randomization Study. *J Am Soc Nephrol* 2015;**26**(11):2831-8.
77. Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, et al. Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study. *J Am Coll Cardiol* 2016;**67**(4):407-16.
78. Han X, Gui L, Liu B, Wang J, Li Y, Dai X, et al. Associations of the uric acid related genetic variants in SLC2A9 and ABCG2 loci with coronary heart disease risk. *BMC Genet* 2015;**16**:4.
79. Yang Q, Kottgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet* 2010;**3**(6):523-30.
80. Stark K, Reinhard W, Grassl M, Erdmann J, Schunkert H, Illig T, et al. Common polymorphisms influencing serum uric acid levels contribute to susceptibility to gout, but not to coronary artery disease. *PLoS One* 2009;**4**(11):e7729.
81. Yan D, Wang J, Jiang F, Zhang R, Wang T, Wang S, et al. A causal relationship between uric acid and diabetic macrovascular disease in Chinese type 2 diabetes patients: A Mendelian randomization analysis. *Int J Cardiol* 2016;**214**:194-9.
82. Mallamaci F, Testa A, Leonardis D, Tripepi R, Pisano A, Spoto B, et al. A genetic marker of uric acid level, carotid atherosclerosis, and arterial stiffness: a family-based study. *Am J Kidney Dis* 2015;**65**(2):294-302.
83. Sedaghat S, Pazoki R, Uitterlinden AG, Hofman A, Stricker BH, Ikram MA, et al. Association of uric acid genetic risk score with blood pressure: the Rotterdam study. *Hypertension* 2014;**64**(5):1061-6.
84. Mallamaci F, Testa A, Leonardis D, Tripepi R, Pisano A, Spoto B, et al. A polymorphism in the major gene regulating serum uric acid associates with clinic SBP and the white-coat effect in a family-based study. *J Hypertens* 2014;**32**(8):1621-8; discussion 28.
85. Sluijs I, Holmes MV, van der Schouw YT, Beulens JW, Asselbergs FW, Huerta JM, et al. A Mendelian Randomization Study of Circulating Uric Acid and Type 2 Diabetes. *Diabetes* 2015;**64**(8):3028-36.
86. Pfister R, Barnes D, Luben R, Forouhi NG, Bochud M, Khaw KT, et al. No evidence for a causal link between uric acid and type 2 diabetes: a Mendelian randomisation approach. *Diabetologia* 2011;**54**(10):2561-9.
87. Sun X, Zhang R, Jiang F, Tang S, Chen M, Peng D, et al. Common variants related to serum uric acid concentrations are associated with glucose metabolism and insulin secretion in a Chinese population. *PLoS One* 2015;**10**(1):e0116714.
88. Dai X, Yuan J, Yao P, Yang B, Gui L, Zhang X, et al. Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. *Eur J Epidemiol* 2013;**28**(8):669-76.
89. McKeigue PM, Campbell H, Wild S, Vitart V, Hayward C, Rudan I, et al. Bayesian methods for instrumental variable analysis with genetic instruments ('Mendelian randomization'): example with urate transporter SLC2A9 as an instrumental variable for effect of urate levels on metabolic syndrome. *Int J Epidemiol* 2010;**39**(3):907-18.
90. Greenberg KI, McAdams-DeMarco MA, Kottgen A, Appel LJ, Coresh J, Grams ME. Plasma Urate and Risk of a Hospital Stay with AKI: The Atherosclerosis Risk in Communities Study. *Clin J Am Soc Nephrol* 2015;**10**(5):776-83.
91. Testa A, Mallamaci F, Spoto B, Pisano A, Sanguedolce MC, Tripepi G, et al. Association of a polymorphism in a gene encoding a urate transporter with CKD progression. *Clin J Am Soc Nephrol* 2014;**9**(6):1059-65.
92. Tabara Y, Kohara K, Kawamoto R, Hiura Y, Nishimura K, Morisaki T, et al. Association of four genetic loci with uric acid levels and reduced renal function: the J-SHIPP Suita study. *Am J Nephrol* 2010;**32**(3):279-86.
93. Voruganti VS, Franceschini N, Haack K, Laston S, MacCluer JW, Umans JG, et al. Replication of the effect of SLC2A9 genetic variation on serum uric acid levels in American Indians. *Eur J Hum Genet* 2014;**22**(7):938-43.
94. Rasheed H, Hughes K, Flynn TJ, Merriman TR. Mendelian randomization provides no evidence for a causal role of serum urate in increasing serum triglyceride levels. *Circ Cardiovasc Genet* 2014;**7**(6):830-7.
95. Gonzalez-Aramburu I, Sanchez-Juan P, Sierra M, Fernandez-Juan E, Sanchez-Quintana C, Berciano J, et al. Serum uric acid and risk of dementia in Parkinson's disease. *Parkinsonism Relat Disord* 2014;**20**(6):637-9.
96. Simon KC, Eberly S, Gao X, Oakes D, Tanner CM, Shoulson I, et al. Mendelian randomization of serum urate and parkinson disease progression. *Ann Neurol* 2014;**76**(6):862-8.

97. Gao J, Xu H, Huang X, Chen H. Short communication: genetic variations of SLC2A9 in relation to Parkinson's disease. *Transl Neurodegener* 2013;**2**(1):5.
98. Gonzalez-Aramburu I, Sanchez-Juan P, Jesus S, Gorostidi A, Fernandez-Juan E, Carrillo F, et al. Genetic variability related to serum uric acid concentration and risk of Parkinson's disease. *Mov Disord* 2013;**28**(12):1737-40.
99. Facheris MF, Hicks AA, Minelli C, Hagenah JM, Kostic V, Campbell S, et al. Variation in the uric acid transporter gene SLC2A9 and its association with AAO of Parkinson's disease. *J Mol Neurosci* 2011;**43**(3):246-50.
100. Lyngdoh T, Bochud M, Glaus J, Castelao E, Waeber G, Vollenweider P, et al. Associations of serum uric acid and SLC2A9 variant with depressive and anxiety disorders: a population-based study. *PLoS One* 2013;**8**(10):e76336.
101. Houlihan LM, Wyatt ND, Harris SE, Hayward C, Gow AJ, Marioni RE, et al. Variation in the uric acid transporter gene (SLC2A9) and memory performance. *Hum Mol Genet* 2010;**19**(11):2321-30.