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# Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies

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## ABSTRACT

### OBJECTIVE

To map the diverse health outcomes associated with serum uric acid (SUA) levels.

### DESIGN

Umbrella review.

### DATA SOURCES

Medline, Embase, Cochrane Database of Systematic Reviews, and screening of citations and references.

### ELIGIBILITY CRITERIA

Systematic reviews and meta-analyses of observational studies that examined associations between SUA level and health outcomes, meta-analyses of randomised controlled trials that investigated health outcomes related to SUA lowering treatment, and Mendelian randomisation studies that explored the causal associations of SUA level with health outcomes.

### RESULTS

57 articles reporting 15 systematic reviews and 144 meta-analyses of observational studies (76 unique outcomes), 8 articles reporting 31 meta-analyses of randomised controlled trials (20 unique outcomes), and 36 articles reporting 107 Mendelian randomisation studies (56 unique outcomes) met the eligibility criteria. Across all three study types, 136 unique health outcomes were reported. 16 unique outcomes in meta-analyses of observational studies had  $P < 10^{-6}$ , 8 unique outcomes in meta-analyses of randomised controlled trials had  $P < 0.001$ , and 4 unique outcomes in Mendelian randomisation studies had  $P < 0.01$ . Large between study

heterogeneity was common (80% and 45% in meta-analyses of observational studies and of randomised controlled trials, respectively). 42 (55%) meta-analyses of observational studies and 7 (35%) meta-analyses of randomised controlled trials showed evidence of small study effects or excess significance bias. No associations from meta-analyses of observational studies were classified as highly suggestive (increased risk of heart failure, hypertension, impaired fasting glucose or diabetes, chronic kidney disease, coronary heart disease mortality with high SUA levels). Only one outcome from randomised controlled trials (decreased risk of nephrolithiasis recurrence with SUA lowering treatment) had  $P < 0.001$ , a 95% prediction interval excluding the null, and no large heterogeneity or bias. Only one outcome from Mendelian randomisation studies (increased risk of gout with high SUA levels) presented convincing evidence. Hypertension and chronic kidney disease showed concordant evidence in meta-analyses of observational studies, and in some (but not all) meta-analyses of randomised controlled trials with respective intermediate or surrogate outcomes, but they were not statistically significant in Mendelian randomisation studies.

### CONCLUSION

Despite a few hundred systematic reviews, meta-analyses, and Mendelian randomisation studies exploring 136 unique health outcomes, convincing evidence of a clear role of SUA level only exists for gout and nephrolithiasis.

## Introduction

Uric acid was thought to be a biologically inert waste product from purine metabolism, until in the early 1800s it was discovered that an increased serum uric acid (SUA) level was the cause of gout.<sup>1</sup> Subsequently, associations of uric acid concentration with cardiovascular and renal disorders were also observed.<sup>2</sup> These associations were explored in several prospective studies but yielded conflicting results, and therefore the causal role of uric acid in these diseases was widely questioned.<sup>3-6</sup> It was argued that these associations are either confounded by other risk factors, such as obesity and hypertension, or are representative of reverse causality.<sup>4,7</sup> These inconclusive findings led to a shift of interest away from uric acid, and asymptomatic hyperuricemia was not considered as an indication for SUA lowering treatment in patients with cardiovascular and renal diseases.<sup>8,9</sup>

New findings have fuelled enthusiasm to address this longstanding controversy.<sup>10</sup> Recent epidemiological

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies suggest that high serum uric acid (SUA) levels are associated with multiple health outcomes, including cardiovascular and metabolic diseases (increased risk) or neurological diseases (decreased risk), yet it remains to be determined whether these observed associations are causal

Clinical trials of SUA lowering have shown that xanthine oxidase inhibition decreases blood pressure and improves renal function

There is still debate as to whether SUA level is simply a marker of xanthine oxidase activity or a causal factor involved in systemic inflammation

## WHAT THIS STUDY ADDS

Of the 136 health outcomes related to SUA level that were examined in meta-analyses of observational studies, meta-analyses of randomised controlled trials, and Mendelian randomisation studies, convincing evidence of a clear association exists only for gout and nephrolithiasis

The available evidence does not support any change in the existing clinical recommendations in relation to hyperuricemia

**Box 1: Strengths and limitations of study types**

Although none of the following study types are infallible, all are able to provide useful information about causal inference and can complement each other to achieve increasing certainty about causality

**Observational studies**

- Aim to examine the association between an exposure and an outcome and to test whether the association is caused by chance, bias, or confounding
- Typically are affected by residual confounding, undetected bias, or reverse causality, which may generate associations that are not reliable indicators of causality

**Randomised controlled trials**

- An approach to obtain evidence of a causal effect of a treatment or intervention on a disease process
- Eliminates many of the biases and confounding factors that are present in observational studies
- Limitations include non-adherence to the assigned intervention, limited external validity, short term intervention effects, and non-retention, which can all render the results invalid or questionable
- High costs and ethical concerns can also limit the application of the trials in scientific research

**Mendelian randomisation studies**

- Provide a cost effective analogy to a randomised controlled trial by using genetic variants as proxies to test the causality of an association between exposure and outcome
- Is not influenced by the confounding inherent in observational studies and not seriously affected by reverse causality, but does rely on several assumptions (the genetic instruments should be associated with the exposure of interest, they should not be associated with known confounders, and they should affect the outcome solely through the exposure) that can be hard to identify and control
- May lack power when the proportion of trait variance explained by the genetic instruments is small

studies have explored associations of uric acid with a wide range of conditions (cardiovascular diseases, metabolic syndrome, diabetes, and cancer) and some intermediate phenotypes or biomarkers.<sup>11</sup> In an attempt to understand the possible underlying mechanisms, laboratory studies have been carried out and found that uric acid is potentially involved in multiple biological processes, including oxidative stress, systemic inflammation, and intrahepatic fructose metabolism, all mechanisms that could be linked to the development of cardiovascular disease and metabolic syndrome.<sup>12-14</sup> Alternatively, uric acid level may only present a marker of high oxidative stress associated with increased xanthine oxidase activity, instead of being an active agent in the pathogenic processes.<sup>15</sup> Finally, taking into account the antioxidant properties of uric acid (acting as a free radical scavenger), its potential mechanistic roles in these disorders may be complex.<sup>16</sup>

In view of the potential importance of uric acid, assessing the credibility of the observed evidence may have implications both for clinical practice and public health. It is recognised that different types of studies have specific strengths and weaknesses that can be complementary (see box 1). An umbrella review, which collects and evaluates evidence from multiple resources systematically, might therefore help clarify the composite literature. We carried out an umbrella review of meta-analyses of observational studies, meta-analyses of randomised controlled trials, and Mendelian randomisation

studies on associations between SUA level and multiple health outcomes. In particular, we summarised the range of related health outcomes, presented the magnitude, direction, and significance of the reported associations and effects, assessed the potential biases, and identified which associations and effects have the most convincing evidence.

**Methods****Literature search and selection criteria**

We systematically searched Medline, Embase, and the Cochrane Database of Systematic Reviews from inception to 17 July 2016 using a comprehensive search strategy (see table S1 in the web appendix) to identify systematic reviews and meta-analyses of observational studies, meta-analyses of randomised controlled trials, and Mendelian randomisation studies. All identified publications went through a three step parallel review of title, abstract, and full text (performed by XL and XM) based on predefined inclusion and exclusion criteria.

We included systematic reviews and meta-analyses of observational studies that examined associations between serum uric acid (SUA) levels (or hyperuricemia) and health outcomes; meta-analyses of randomised controlled trials that investigated health outcomes related to SUA lowering treatment (intervention with one or a combination of two or more SUA lowering drugs versus placebo or no treatment), including xanthine oxidase inhibitors (allopurinol, febuxostat, or oxypurinol), uricosuric agents (probenecid, benzbromarone, thiazides, or citrates), and uricase analogues (pegloticase or rasburicase); and Mendelian randomisation studies that explored SUA (or hyperuricemia) associations in relation to health outcomes by using genetic instruments influencing SUA levels. The identified health outcomes included a wide range of diseases, intermediate phenotypes, and biomarkers. We excluded studies investigating associations between gout and health outcomes and meta-analyses of randomised controlled trials that used non-drug interventions, such as dietary or lifestyle interventions. We further excluded animal and laboratory studies, meta-analyses on the prevalence of gout and hyperuricemia, and meta-analyses of randomised controlled trials that focused on drug variables, safety, and effects of reducing SUA levels without investigating other health effects.

**Data extraction**

One investigator (XL) extracted data, which were checked by a second investigator (XM). For each eligible study, we extracted the PubMed identification number, lead author's name, journal name, publication year, study population, number of studies included, and outcomes investigated. For meta-analyses investigating more than one health outcome, we recorded each outcome separately. For meta-analyses of observational studies and of randomised controlled trials, we extracted the reported summary risk estimates (risk ratio, odds ratio, hazard ratio, or mean difference) with the 95% confidence intervals and the corresponding number of case and control participants. Furthermore, for each unique outcome we

extracted data from the individual component studies that were included in the meta-analyses for further analysis. This second level extraction included data on study design, number of cases, total number of participants, relative risk estimates, and 95% confidence intervals for each component study. When more than one meta-analysis existed for the same outcome in the same population, we extracted individual component data from the most recent and largest meta-analysis. In a few exceptions where the most recent was not also the largest meta-analysis, we explored the reason for this discrepancy. If the most recent included prospective studies and the largest one had fewer prospective studies plus some retrospective data, we kept the one with the largest amount of prospective data; otherwise we kept the largest meta-analysis. For Mendelian randomisation studies, we extracted data on study population, sample size, genetic instruments, the variance of SUA level explained by the genetic instruments ( $R^2$ ) and Mendelian randomisation effect estimates (odds ratio, hazard ratio, mean difference, or regression coefficient  $\beta$ ), standard deviation of SUA levels, and standard deviation of continuous outcomes.

### Data analysis

For systematic reviews we performed descriptive analyses and presented the authors' conclusions. For each unique meta-analysis of observational studies and of randomised controlled trials, we estimated several metrics, including the summary effect and 95% confidence intervals using a random effect model (DerSimonian Laird method)<sup>17</sup>; the heterogeneity among studies (Q statistic and  $I^2$  metric with 95% confidence intervals); the 95% prediction interval to predict the range of effect size that would be expected in a new original study, after accounting for both the heterogeneity among individual studies and the uncertainty of the summary effect estimated in the random effect model (the calculation of 95% prediction interval is based on the predicted distribution derived from a function of the degree of heterogeneity, number of studies included, and within study standard errors)<sup>18,19</sup>; the presence of small study effects by using the Egger's regression asymmetry test to investigate if small studies tend to give larger estimates of effect size than large studies (significance threshold  $P < 0.10$ )<sup>20</sup>; and the excess significance test to assess if the observed number (O) of studies with significant results was greater than the expected number (E) using the  $\chi^2$  test:  $A = [(O - E)^2 / E + (O - E)^2 / (n - E)]$  (significance threshold  $P < 0.10$ ).<sup>21,22</sup> For the excess significance test, we calculated the expected number (E) of studies with significant findings by using the sum of statistical power estimated for each component study. The statistical power of each component study was calculated with an algorithm that uses a non-central  $t$  distribution, by assuming the true effect size to be the same as that of the largest component study (with smallest variance) in the meta-analysis.<sup>23</sup> If the type of metric in a meta-analysis was mean difference, we firstly calculated Cohen's  $d$  by weighing the pooled standard deviation based on the sample size of individual studies. We then transformed Cohen's  $d$ , Hedges  $g$ , and other

standardised mean difference metrics to odds ratios.<sup>24</sup> We compared the results reported in overlapping meta-analyses to evaluate their concordance in terms of the direction and statistical significance of the observed associations. All statistical analyses were conducted in Stata (StataCorp) version 14.0.

Owing to the extensive differences in genetic instruments used in the Mendelian randomisation studies we did not conduct quantitative syntheses. Instead, we performed and present here a descriptive analysis of the individual studies. When more than one Mendelian randomisation study was conducted for the same outcome, we compared the concordance of the findings for the direction and statistical significance of the reported association and retained the study with the largest number of cases and participants for further analysis and comparison. If all of the information required for calculation was provided (ie, sample size, number of cases,  $R^2$ , estimates of association, standard deviation of continuous outcomes, and standard deviation of SUA levels), we performed a power calculation for the largest Mendelian randomisation studies by using the non-centrality parameter based approach.<sup>25</sup> For Mendelian randomisation studies with missing  $R^2$  values, we performed a crude power estimation by using the  $R^2$  values from other Mendelian randomisation studies that used the same genetic variants as instruments.

### Credibility assessment

As previously proposed,<sup>26</sup> we classified evidence from meta-analyses of observational studies with nominally statistically significant summary results ( $P < 0.05$ ) into four categories (class I, II, III, and IV). Convincing (class I) evidence was assigned to associations with a statistical significance of  $P < 10^{-6}$ , included more than 1000 cases (or more than 20 000 participants for continuous outcomes), had the largest component study reporting a significant result ( $P < 0.05$ ), had a 95% prediction interval that excluded the null, did not have large heterogeneity ( $I^2 < 50\%$ ), and showed no evidence of small study effects ( $P > 0.10$ ) and of excess significance bias ( $P > 0.10$ ). Highly suggestive (class II) evidence was assigned to associations that reported a significance of  $P < 0.001$ , included more than 1000 cases (or more than 20 000 participants for continuous outcomes), and had the largest component study reporting a statistically significant result ( $P < 0.05$ ). Suggestive (class III) evidence was assigned to associations that reported a significance of  $P < 0.01$  with more than 1000 cases (or more than 20 000 participants for continuous outcomes). Weak (class IV) evidence was assigned to the remaining significant associations with  $P < 0.05$ . For each association in the convincing or highly suggestive categories we reassessed the evidence after excluding the retrospective and case-control studies in an attempt to address reverse causality. Finally, for each association in the convincing category we reassessed the evidence after we examined each meta-analysis in depth by assessing the eligibility of the included studies as well as verifying the data used in the meta-analysis.

Evidence from meta-analyses of randomised controlled trials was assessed in terms of the significance of

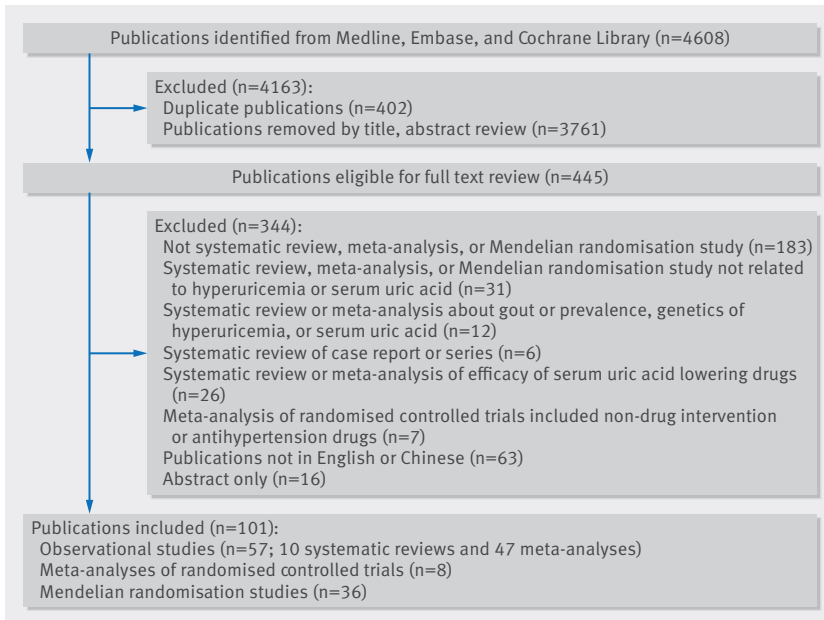


Fig 1 | Study flowchart

the summary effect ( $P < 0.01$ ,  $0.01 \leq P < 0.05$ ,  $P \geq 0.05$ ), 95% prediction interval (excluding the null or not), and presence of large heterogeneity ( $I^2 > 50\%$ ), small study effects ( $P > 0.10$ ), and excess significance ( $P > 0.10$ ). We also noted the conclusions from any evidence classification (GRADE<sup>27</sup> or equivalent system) applied by the original meta-analyses. Finally, we assessed the evidence from individual Mendelian randomisation studies for statistical significance of the effect estimate ( $P < 0.01$ ) and of the statistical power ( $> 80\%$ ).<sup>28</sup>

For overlapping outcomes that were investigated in meta-analyses of observational studies and/or meta-analyses of randomised controlled trials and/or individual Mendelian randomisation studies, we examined if the direction and statistical significance of the associations were reported concordantly across the different study types. We noted the overlapping outcomes that were graded as class I or II in meta-analyses of observational studies and had a 95% prediction interval excluding the null in meta-analyses of randomised controlled trials. For these outcomes we also presented the evidence from Mendelian randomisation studies if available.

### Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

## Results

### Literature review

Overall, the parallel reviews identified 4608 publications across three databases. After applying the inclusion or exclusion criteria, 101 publications were selected for inclusion (fig 1). Specifically, 15 systematic

reviews and 144 meta-analyses of observational studies were reported in 57 articles<sup>29-85</sup>; 31 meta-analyses of randomised controlled trials were reported in 8 articles<sup>86-93</sup>; and 107 Mendelian randomisation studies were reported in 36 articles (see tables S2 to S5, respectively, in web appendix).<sup>94-129</sup> Across all three study types, 136 unique outcomes were reported.

### Meta-analyses of observational studies

Overall, 144 meta-analyses of observational studies were identified (see table S3 in web appendix). The median number of studies included in meta-analyses was 5 (range 2-31), the median number of participants was 7932 (129-1 017 810), and the median number of cases was 1176 (49-34 370). More than one meta-analysis was conducted for 16 outcomes (see table S3 in web appendix). The direction and statistical significance of the reported associations in overlapping meta-analyses were concordant for 14 (88%) outcomes: atrial fibrillation incidence (n=3),<sup>39 52 82</sup> coronary heart disease (n=4),<sup>41 72 76 83</sup> hypertension incidence (n=3),<sup>44 74 85</sup> stroke incidence (n=2),<sup>48 75</sup> diabetes (n=3),<sup>49 50 79</sup> chronic kidney disease (n=3),<sup>54 55 77</sup> mild cognitive impairment (n=2),<sup>58 80</sup> Parkinson's disease (n=3),<sup>58 59 81</sup> multiple sclerosis (n=2),<sup>60 78</sup> coronary heart disease mortality (n=3),<sup>41 72 76</sup> cardiovascular disease mortality (n=2),<sup>65 84</sup> stroke mortality (n=2),<sup>48 75</sup> all cause mortality in patients with heart failure (n=2),<sup>43 67</sup> and all cause mortality in the general population (n=2).<sup>65 84</sup> Discordance in the statistical significance was present for two outcomes: diabetic neuropathy (n=2)<sup>51 53</sup> and Alzheimer's disease (n=4).<sup>57 58 73 80</sup>

After removing the overlapping meta-analyses (which were conducted in the same population for the same outcome), 76 unique meta-analyses were retained. The meta-analyses reported a wide range of outcomes (table 1): cardiovascular outcomes (n=13), diabetes related outcomes (n=9), kidney disorders (n=7), neurocognitive disorders (n=11), cancer outcomes (n=6), all cause or cause specific mortality (n=22), and other outcomes (n=8). Overall, 58 (76%) of the 76 non-overlapping meta-analyses reported nominally significant summary results ( $P < 0.05$ ). Figures 1 and 2 in the web appendix show the summary effects of the unique meta-analyses of observational studies. Of these, 12 (92%) meta-analyses in cardiovascular outcomes, 8 (89%) in diabetes related outcomes, all 7 (100%) in kidney disorders, 1 (9%) in neurocognitive disorders, 1 (17%) in cancer outcomes, 15 (68%) in all cause and cause specific mortality, and 6 (75%) in other outcomes reported summary estimates with  $P < 0.05$  and suggested that high levels of SUA were associated with an increased risk of disease. In addition, 7 (64%) meta-analyses in neurocognitive disorders and 1 (12%) in other outcomes (composite of adverse outcomes (death or major adverse cardiovascular event) in patients with acute ischaemic stroke) reported summary estimates with  $P < 0.05$  and suggested inverse associations with SUA level.

We then applied our evidence classification criteria. Sixteen (21%) meta-analyses had  $P < 10^{-6}$ , 10 (13%) had a 95% prediction interval that excluded the null, 27 (36%)

Table 1 | Health outcomes and evidence class reported in meta-analyses (MA) of observational studies

Outcomes	Population	Study design included in MA	Comparison	No of studies	No of participants	No of cases	Type of metric	Relative risk (95% CI)	P value	I <sup>2</sup> (95% CI)	P value for Egger test	P value for excess significance test	95% prediction interval	Evidence class <sup>a</sup>
<b>Cardiovascular outcomes</b>														
AF <sup>39</sup>	General	Prospective cohort	Hyper v normal	6	426159	7595	RR	1.49 (1.24 to 1.79)	2.50E-05	79 (42 to 89)	0.01	0.22	0.87 to 2.53	III
AF recurrence <sup>40</sup>	Patients with AF	Prospective or retrospective cohort	Hyper v normal	4	1298	393	OR	1.52 (1.19 to 1.94)	8.25E-04	89 (61 to 95)	0.72	0.26	0.27 to 7.01	IV
Coronary heart disease incidence <sup>41</sup>	General	Prospective cohort	Hyper v normal	13	70382	6666	aRR	1.13 (1.05 to 1.21)	7.70E-04	38 (0 to 64)	0.27	<0.001	0.94 to 1.34	III
Cardiovascular disease <sup>42</sup>	Patients with hypertension	Prospective cohort	Hyper v normal	6	19546	1054	aHR	1.17 (1.07 to 1.27)	3.56E-04	67 (0 to 84)	0.05	0.04	0.90 to 1.52	III
Heart failure incidence <sup>43</sup>	General	Prospective cohort	Hyper v normal	5	427917	10171	HR	1.65 (1.41 to 1.94)	1.77E-09	72 (7 to 86)	0.49	0.31	1.05 to 2.61	II
Hypertension incidence <sup>44</sup>	General	Prospective cohort or nested case-control	Hyper v normal	17	71630	18751	aRR	1.48 (1.33 to 1.65)	3.99E-12	79 (65 to 85)	0.06	NP	0.99 to 2.23	II
Prehypertension <sup>45</sup>	General	Cross sectional	Highest v lowest SUA category	8	44095	20832	OR	1.84 (1.42 to 2.38)	4.88E-06	91 (86 to 94)	0.10	NP	0.81 to 4.01	III
Left atrial thrombus or spontaneous echo contrast <sup>39</sup>	Patients with heart diseases	Prospective or retrospective cohort	Highest v lowest SUA category	6	2381	241	OR	1.59 (1.13 to 2.23)	7.51E-03	85 (66 to 91)	0.02	NP	0.54 to 4.70	IV
MACE <sup>46</sup>	Patients after PCI	Prospective or retrospective cohort	Hyper v normal	2	3054	NA	RR	1.78 (1.26 to 2.52)	1.16E-03	NA	NA	NP	NA	IV
Medium term MACE <sup>47</sup>	Patients with AMI	Prospective or retrospective cohort	Highest v lowest SUA category	4	4299	1240	OR	1.93 (1.36 to 2.74)	2.56E-04	74 (0 to 89)	0.81	NP	0.46 to 8.21	III
Short term MACE <sup>47</sup>	Patients with AMI	Prospective or retrospective cohort	Highest v lowest SUA category	7	6470	787	OR	2.46 (1.84 to 3.27)	1.93E-09	63 (0 to 82)	0.25	NP	1.06 to 5.71	IV
Stroke <sup>42</sup>	Hypertensive patients	Prospective or retrospective cohort	Continuous SUA level	3	9978	217	aHR	1.11 (0.98 to 1.26)	0.10	70 (0 to 89)	0.22	0.06	0.26 to 4.77	NS
Stroke incidence <sup>48</sup>	General	Prospective cohort	Highest v lowest SUA category	5	24548	1290	aRR	1.22 (1.02 to 1.46)	0.03	53 (0 to 75)	0.03	NP	0.73 to 2.04	IV
<b>Diabetes related outcomes</b>														
T2DM <sup>49</sup>	General	Prospective or retrospective cohort	1 mg/dL SUA increase	11	42834	3305	RR	1.17 (1.09 to 1.25)	8.97E-06	75 (54 to 84)	0.07	0.002	0.92 to 1.47	III
Impaired fasting glucose or T2DM <sup>50</sup>	General	Prospective or retrospective cohort	Highest v lowest SUA category	12	62834	6340	RR	1.57 (1.39 to 1.77)	1.12E-12	42 (0 to 67)	0.09	NP	1.10 to 2.23	II
Diabetes incidence <sup>42</sup>	Patients with hypertension	Prospective or retrospective cohort	Hyper v normal	2	8247	564	aHR	1.84 (1.02 to 3.30)	0.04	NA	NA	0.42	NA	IV
Diabetic nephropathy <sup>51</sup>	Patients with T2DM	Case-control	Continuous or categorical SUA level	3	3166	196	OR	1.72 (1.07 to 2.76)	0.03	84 (12 to 93)	0.04	NP	0.01 to 382.85	IV

(Continued)

Table 1 Health outcomes and evidence class reported in meta-analyses (MA) of observational studies

Outcomes	Population	Study design included in MA	Comparison	No of studies	No of participants	No of cases	Type of metric	Relative risk (95% CI)	P value	I <sup>2</sup> (95% CI)	P value for Egger test	P value for excess significance test	95% prediction interval	Evidence class <sup>*</sup>
Diabetic microvascular complications <sup>51</sup>	Patients with T2DM	Case-control	Continuous or categorical SUA level	5	4513	854	OR	1.42 (1.11 to 1.83)	0.006	83 (61 to 90)	0.08	NP	0.68 to 2.95	IV
Diabetic vascular complications <sup>52</sup>	Patients with T2DM	Case-control	Continuous or categorical SUA level	6	5017	967	OR	1.27 (1.11 to 1.45)	4.86E-04	77 (57 to 86)	0.02	0.51	0.87 to 1.86	IV
Diabetic peripheral neuropathy <sup>53</sup>	Patients with diabetes	Cohort or case-control	Hyper v normal	5	4097	894	RR	2.83 (2.13 to 3.76)	2.91E-12	78 (23 to 89)	0.94	0.93	1.05 to 7.62	IV
Diabetic macrovascular complications <sup>51</sup>	Patients with T2DM	Case-control	Continuous or categorical SUA level	3	2538	187	OR	1.03 (1.00 to 1.06)	0.05	48 (0 to 79)	0.45	0.01	0.56 to 2.30	IV
Diabetic retinopathy <sup>51</sup>	Patients with T2DM	Case-control	Continuous or categorical SUA level	2	1739	311	OR	1.23 (0.81 to 1.87)	0.34	NA	NA	NP	NA	NS
<b>Kidney disorders</b>														
CKD incidence <sup>54</sup>	Middle aged populations	Prospective or retrospective cohort	1 mg/dL SUA increase	15	99 205	3492	RR	1.22 (1.16 to 1.28)	1.61E-14	66 (39 to 78)	0.22	0.12	1.02 to 1.44	II
CKD new onset incidence <sup>55</sup>	Non-CKD population	Prospective or retrospective cohort	1 mg/dL SUA increase	7	153 620	7014	HR	1.13 (1.04 to 1.22)	2.74E-03	83 (63 to 90)	0.12	0.24	0.88 to 1.44	IV
CKD new onset incidence <sup>55</sup>	Patients with diabetes	Prospective or retrospective cohort	Hyper v normal	2	NA	NA	HR	1.90 (1.30 to 2.78)	9.76E-04	NA	NA	0.94	NA	IV
Estimated glomerular filtration rate <sup>56</sup>	Renal transplant recipients	Prospective or retrospective cohort	Hyper v normal	8	2075	NA	MD to OR	0.36 (0.26 to 0.52)	1.48E-08	66 (3 to 82)	0.35	0.81	0.13 to 1.06	IV
Serum creatinine <sup>56</sup>	Renal transplant recipients	Prospective or retrospective cohort	Hyper v normal	5	873	NA	MD to OR	2.45 (1.69 to 3.54)	2.77E-06	40 (0 to 77)	0.15	0.65	0.88 to 6.81	IV
Graft loss <sup>56</sup>	Renal transplant recipients	Prospective or retrospective cohort	Hyper v normal	3	910	154	OR	2.28 (1.54 to 3.38)	4.66E-05	0 (0 to 73)	0.57	NP	0.18 to 29.36	IV
Chronic allograft nephropathy <sup>56</sup>	Renal transplant recipients	Prospective or retrospective cohort	Hyper v normal	4	1057	113	OR	2.81 (1.65 to 4.77)	1.52E-04	26 (0 to 75)	0.92	NP	0.53 to 14.76	IV
<b>Neurocognitive disorders</b>														
Alzheimer's disease <sup>57</sup>	General	Cohort or case-control	SUA level (mg/dL)	21	3617	1128	MD to OR	0.29 (0.11 to 0.76)	0.012	97 (96 to 97)	0.30	NP	0.01 to 8.97	IV
Dementia or cognitive impairment <sup>58</sup>	General	Cohort or case-control	SUA level (mg/dL)	31	7021	2681	SMD to OR	0.58 (0.41 to 0.83)	0.003	89 (86 to 91)	0.01	0.004	0.08 to 4.48	IV
VaD <sup>58</sup>	Patients with VaD v controls	Cohort or case-control	SUA level (mg/LI)	7	597	272	SMD to OR	0.92 (0.20 to 4.12)	0.92	94 (90 to 96)	0.45	<0.001	0.01 to 200.17	NS
MCI <sup>58</sup>	Patients with MCI v controls	Cohort or case-control	SUA level (mg/dL)	4	731	515	SMD to OR	0.65 (0.20 to 2.17)	0.49	92 (83 to 95)	0.36	0.52	0.01 to 63.36	NS

(Continued)

Table 1 | Health outcomes and evidence class reported in meta-analyses (MA) of observational studies

Outcomes	Population	Study design included in MA	Comparison	No of studies	No of participants	No of cases	Type of metric	Relative risk (95% CI)	P value	I <sup>2</sup> (95% CI)	P value for Egger test	P value for excess significance test	95% prediction interval	Evidence class <sup>a</sup>
Parkinson's disease incidence <sup>59</sup>	General	Cohort and nested case-control	Hyper v normal	6	33 185	578	RR	0.65 (0.43 to 0.97)	0.04	42 (0 to 73)	0.39	NP	0.24 to 1.77	IV
MS <sup>60</sup>	Patients with MS v control	Case-control	SUA level (µmol/L)	10	2216	1308	SMD to OR	0.49 (0.27 to 0.87)	0.02	92 (88 to 94)	0.11	NP	0.05 to 4.96	IV
NMO <sup>60</sup>	Patients with NMO v control	Case-control	SUA level (µmol/L)	3	1137	229	SMD to OR	0.22 (0.10 to 0.45)	9.07E-05	82 (49 to 91)	0.65	0.93	0.02 to 3.14	IV
ALS <sup>61</sup>	Patients with ALS v controls	Case-control	SUA level (mg/dL)	3	826	311	Hedge's G to OR	0.21 (0.14 to 0.32)	6.33E-13	51 (0 to 82)	0.43	NP	0.04 to 1.05	IV
Schizophrenia (chronic) v controls <sup>62</sup>	Patients with chronic schizophrenia v controls	Case-control	SUA level (mg/dL)	2	274	155	Hedge's G to OR	0.72 (0.43 to 1.21)	0.22	NA	NA	NP	NA	NS
Schizophrenia (first episode psychosis) v controls <sup>62</sup>	Patients with schizophrenia in first episode psychosis v controls	Case-control	SUA level (mg/dL)	3	277	103	Hedge's G to OR	0.37 (0.23 to 0.59)	4.16E-05	0 (0 to 73)	0.50	0.21	0.02 to 7.75	IV
Bipolar disorder v controls <sup>63</sup>	Patients with bipolar disorder v controls	Case-control	SUA level (mg/dL)	9	1127	619	SMD to OR	3.23 (1.82 to 5.73)	7.09E-05	83 (66 to 89)	0.19	NP	0.65 to 12.39	IV
<b>Cancer outcomes</b>														
Cancer incidence <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	5	456053	14 355	RR	1.04 (0.99 to 1.08)	0.08	45 (0 to 78)	0.30	0.16	0.93 to 1.14	NS
Cancer incidence in digestive organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	3	266347	2521	RR	1.06 (0.96 to 1.18)	0.27	53 (0 to 79)	0.58	0.65	0.81 to 1.40	NS
Cancer incidence in lymphoid and haematopoietic system <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	2	86739	397	RR	1.39 (1.13 to 1.71)	0.002	NA	NA	NP	NA	IV
Cancer incidence in male genital organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	3	162022	2634	RR	1.08 (0.96 to 1.21)	0.19	61 (0 to 87)	0.45	0.63	0.28 to 4.18	NS
Cancer incidence in respiratory system and intrathoracic organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	4	456053	2941	RR	1.05 (0.93 to 1.18)	0.43	71 (0 to 87)	0.62	0.49	0.72 to 1.54	NS
Cancer incidence in urinary organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	2	86739	536	RR	1.17 (0.44 to 3.15)	0.77	NA	NA	0.02	NA	NS
<b>All cause and cause specific mortality</b>														
Coronary heart disease mortality <sup>41</sup>	General	Prospective cohort	Hyper v normal	13	876584	24198	aRR	1.27 (1.16 to 1.39)	3.46E-07	65 (36 to 78)	0.10	NP	0.96 to 1.69	II
CVD mortality <sup>65</sup>	General	Prospective cohort	Highest v lowest SUA category	9	165 806	6121	RR	1.37 (1.19 to 1.57)	1.07E-05	54 (0 to 74)	0.59	NP	0.92 to 2.03	III
CVD mortality <sup>43</sup>	Patients with heart failure	Prospective cohort	Hyper v normal	2	2250	NA	HR	1.45 (1.18 to 1.78)	4.25E-04	NA	NA	NP	NA	IV

(Continued)



Table 1 Health outcomes and evidence class reported in meta-analyses (MA) of observational studies

Outcomes	Population	Study design included in MA	Comparison	No of studies	No of participants	No of cases	Type of metric	Relative risk (95% CI)	P value	I <sup>2</sup> (95% CI)	P value for Egger test	P value for excess significance test	95% prediction interval	Evidence class <sup>*</sup>
CVD mortality <sup>42</sup>	Patients with hypertension	Prospective or retrospective cohort	Hyperv v normal	3	NA	NA	aHR	1.31 (0.96 to 1.78)	0.09	NA	NA	NA	NA	NS
Stroke mortality <sup>48</sup>	General	Prospective cohort	Highest v lowest SUA category	9	1 017 810	21 281	aRR	1.32 (1.23 to 1.41)	1.11E-14	30 (0 to 65)	0.92	NP	1.13 to 1.56	I†
CKD mortality <sup>46</sup>	General	Prospective cohort	1 mg/dL SUA increase	21	23 443	3904	aHR	1.07 (1.04 to 1.11)	5.46E-05	82 (74 to 87)	0.04	0.03	0.93 to 1.24	III
Cancer mortality <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	12	632 472	NA	RR	1.17 (1.04 to 1.32)	0.01	66 (25 to 80)	0.36	NP	0.82 to 1.69	IV
Cancer mortality in digestive organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	4	187 886	855	RR	1.22 (0.86 to 1.74)	0.27	55 (0 to 80)	0.99	NP	0.45 to 3.31	NS
Cancer mortality in bone, connective tissue, soft tissue, and skin <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	NA	112 296	NA	RR	0.94 (0.47 to 1.87)	0.87	NA	NA	NA	NA	NS
Cancer mortality in lymphoid and haematopoietic systems <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	NA	112 296	NA	RR	1.18 (0.82 to 1.70)	0.38	NA	NA	NA	NA	NS
Cancer mortality in male genital organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	NA	88 033	NA	RR	0.51 (0.07 to 3.85)	0.52	NA	NA	NA	NA	NS
Cancer mortality in respiratory system and intrathoracic organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	2	116 646	164	RR	1.08 (0.61 to 1.91)	0.80	NA	NA	NP	NA	NS
Cancer mortality in urinary organs <sup>64</sup>	General	Prospective cohort	Highest v lowest SUA category	2	112 296	NA	RR	1.35 (0.88 to 2.07)	0.17	NA	NA	NP	NA	NS
All cause mortality <sup>43</sup>	Patients with heart failure	Cohort or case-control	Hyperv v normal	11	12 444	1888	HR	2.15 (1.64 to 2.83)	6.64E-08	81 (67 to 88)	0.01	0.37	0.87 to 5.31	II
Short term mortality <sup>47</sup>	Patients with AMI	Prospective or retrospective cohort	Highest v lowest SUA category	8	6805	396	OR	3.24 (2.47 to 4.27)	3.75E-16	31 (0 to 69)	0.83	NP	1.74 to 6.06	IV
Medium term mortality <sup>47</sup>	Patients with AMI	Prospective or retrospective cohort	Highest v lowest SUA category	5	5194	565	OR	2.69 (2.00 to 3.62)	1.75E-10	55 (0 to 81)	0.66	NP	1.09 to 6.67	IV
In hospital mortality <sup>68</sup>	Patients with AMI	Cohort	Hyperv v normal	6	5686	218	RR	2.10 (1.03 to 4.26)	0.04	81 (51 to 90)	0.86	NP	0.21 to 20.66	IV
All cause mortality <sup>51</sup>	Patients with T2DM	Cohort or case-control	Hyperv v normal	3	5534	NA	HR	1.09 (1.03 to 1.17)	0.008	19 (0 to 73)	0.49	NP	0.90 to 1.33	IV
All cause mortality <sup>65</sup>	General	Prospective cohort	Highest v lowest SUA category	10	143 483	7031	RR	1.23 (1.08 to 1.39)	0.001	75 (56 to 84)	0.51	NP	0.79 to 1.90	IV
All cause mortality <sup>66</sup>	Patients after PCI	Prospective or retrospective cohort	Hyperv v normal	9	17 268	NA	RR	1.52 (1.28 to 1.81)	2.95E-06	64 (3 to 81)	0.002	NP	0.98 to 2.24	IV
All cause mortality <sup>42</sup>	Hypertensive patients	Prospective or retrospective cohort	Hyperv v normal	4	46 103	5820	aHR	1.12 (1.02 to 1.23)	0.02	26 (0 to 76)	0.77	0.93	0.86 to 1.49	IV

(Continued)

Table 1 Health outcomes and evidence class reported in meta-analyses (MA) of observational studies

Outcomes	Population	Study design included in MA	Comparison	No of studies	No of participants	No of cases	Type of metric	Relative risk (95% CI)	P value	I <sup>2</sup> (95% CI)	P value for Egger test	P value for excess significance test	95% prediction interval	Evidence class*
All cause mortality <sup>62</sup>	Patients with CKD	Prospective or retrospective cohort	Hyperv normal	5	1789	609	RR	1.67 (1.29 to 2.16)	1.09E-04	NA	NA	NA	NA	IV
<b>Other outcomes</b>														
Medium or long term occurrence of death or MACE <sup>67</sup>	Patients with AMI	Prospective or retrospective cohort	50 µmol/L increase	4	3533	NA	aHR	1.19 (1.03 to 1.37)	0.02	84 (47 to 92)	0.03	NP	0.65 to 2.18	IV
Short term occurrence of death or MACE <sup>67</sup>	Patients with AMI	Prospective or retrospective cohort	Highest v lowest SUA category	4	3625	336	aOR	2.26 (1.85 to 2.77)	1.61E-14	0 (0 to 68)	0.97	0.23	1.45 to 3.53	IV
Combined death or cardiac events <sup>63</sup>	Patients with heart failure	Cohort, case-control and post hoc RCT	Hyper v normal	9	12 699	1765	HR	1.39 (1.18 to 1.63)	7.44E-05	66 (13 to 82)	0.001	0.12	0.89 to 2.07	III
Adverse outcomes (mortality, MACE, in stent restenosis) <sup>66</sup>	Patients after PCI	Prospective or retrospective cohort	Hyper v normal	12	21 030	NA	RR	1.46 (1.29 to 1.65)	3.63E-09	59 (3 to 77)	<0.001	NP	1.05 to 1.95	IV
Occurrence of poor outcomes <sup>69</sup>	Patients with acute ischaemic stroke	Prospective or retrospective cohort, or nested case-control	Highest v lowest SUA category	9	7932	NA	HR	0.77 (0.68 to 0.88)	8.12E-05	44 (0 to 73)	0.30	NP	0.56 to 1.06	IV
Psoriasis <sup>70</sup>	Patients with psoriasis v controls	Case-control	SUA level (mg/dl)	13	29 037	1644	MD to OR	4.46 (1.57 to 12.62)	0.005	98 (98 to 99)	0.41	<0.001	0.06 to 320.30	IV
Severe psoriasis <sup>70</sup>	Patients with severe psoriasis v controls	Case-control	SUA level (mg/dl)	3	300	104	MD to OR	1.57 (0.25 to 9.80)	0.64	92 (78 to 96)	0.20	<0.001	0.00 to 1.52E-10	NS
Non-alcoholic fatty liver disease <sup>71</sup>	General	Prospective or retrospective cohort, or case-control	Highest v lowest SUA category	9	55 573	10 581	OR	1.92 (1.59 to 2.31)	2.51E-11	78 (61 to 86)	0.02	NP	0.99 to 3.74	II

AF=atrial fibrillation; Hyper=hyperuricemia; RR=relative risk; OR=odds ratio; aRR=adjusted relative risk; CVD=cardiovascular disease; aHR=adjusted hazard ratio; HR=hazard ratio; NP=not pertinent (because the number of expected significant studies was larger than the number of observed significant studies); SUA=serum uric acid; MACE=major adverse cardiovascular events; PCI=percutaneous coronary intervention; NA=not available; AMI=acute myocardial infarction; T2DM=type 2 diabetes; NS=not significant; CKD=chronic kidney disease; MD=mean difference; SMD=standardised mean difference; Vab=vascular dementia; MC=mild cognitive impairment; MS=multiple sclerosis; NMO=neuromyelitis optica; ALS=amyotrophic lateral sclerosis; aOR=adjusted odds ratio.

\*Evidence class criteria: class I (convincing); statistical significance with  $P < 10^{-6}$ , more than 1000 cases (or >20000 participants for continuous outcomes), the largest component study reported statistically significant effect ( $P < 0.05$ ); 95% prediction interval excluded the null; no large heterogeneity ( $I^2 < 50\%$ ), no evidence of small study effects ( $P > 0.10$ ) and excess significance bias ( $P > 0.10$ ); class II (highly suggestive); statistical significance with  $P < 10^{-6}$ , more than 1000 cases (or >20000 participants for continuous outcomes), the largest component study reported statistically significant effect ( $P < 0.05$ ); class III (suggestive); statistical significance with  $P < 10^{-3}$ , more than 1000 cases (or >20000 participants for continuous outcomes); class IV (weak); the remaining statistically significant associations with  $P < 0.05$ .

†The heterogeneity ( $I^2$ ), Egger's test, or 95% prediction interval could not be calculated, either because data about the individual component studies were insufficient or because the number of studies included in meta-analyses was less than three. #Evidence was reassessed by examining the meta-analyses in depth to verify the eligibility or appropriateness of the data included in analysis and errors were corrected, the association became non-statistically significant.

Table 2 | Reassessing the credibility of associations with class I and II evidence reported in meta-analyses (MA) of observational studies

Outcomes	Population	Study design included in MA	Comparison	No of studies	No of participants	No of cases	Type of metric	Relative risk (95% CI)	P value	I <sup>2</sup> (95% CI)	P value for Egger test	P value for excess significance test	95% prediction interval	Evidence class*
Stroke mortality	General	Prospective cohort	Highest v lowest SUA category	8	600 076	5205	aRR	1.17 (0.91 to 1.51)	0.22	84 (73 to 89)	0.44	NP	0.46 to 2.98	NS (changed from II)
Heart failure incidence	General	Prospective cohort	Hyper v normal	5	427 917	10 171	HR	1.65 (1.41 to 1.94)	1.77E-09	72 (7 to 86)	0.49	0.31	1.05 to 2.61	II
Hypertension incidence	General	Prospective cohort	Hyper v normal	12	68 401	16 132	aRR	1.42 (1.27 to 1.59)	2.16E-09	76 (53 to 85)	0.04	NP	0.98 to 2.05	II
IFG/T2DM	General	Prospective cohort	Highest v lowest SUA category	13	561 130	5629	RR	1.62 (1.47 to 1.77)	1.25E-22	0 (0 to 49)	0.07	NP	1.45 to 1.79	II
CKD incidence	Middle aged populations	Prospective cohort	1 mg/dL SUA increase	12	78 205	2793	RR	1.19 (1.12 to 1.25)	1.26E-09	67 (34 to 80)	0.10	0.15	0.99 to 1.42	II
CHD mortality	General	Prospective cohort	Hyper v normal	13	876 584	24 198	aRR	1.27 (1.16 to 1.39)	3.47E-07	65 (36 to 78)	0.10	NP	0.96 to 1.69	II
All cause mortality	Patients with HF	Prospective cohort	Hyper v normal	6	9608	1474	HR	2.38 (1.59 to 3.56)	2.98E-05	88 (77 to 92)	0.05	0.39	0.61 to 9.35	III (changed from II)
Non-alcoholic fatty liver disease†	General	Prospective cohort	Highest v lowest SUA category	2	12 631	2530	OR	1.43 (1.20 to 1.71)	8.63E-05	NA	NA	NP	NA	III (changed from II)

SUA=serum uric acid; aRR=adjusted relative risk; NP=not pertinent (because the number of expected significant studies was larger than the number of observed significant studies); NS=not significant; Hyper=hyperuricemia; HR=hazard ratio; IFG=impaired fasting glucose; T2DM=type 2 diabetes; RR=relative risk; CKD=chronic kidney disease; CHD=coronary heart disease; HF=heart failure; OR=odds ratio; NA=not available.

\*Evidence class criteria: class I (convincing): statistical significance with  $P < 10^{-6}$ , more than 1000 cases (or >20000 participants for continuous outcomes), the largest component study reported statistically significant effect ( $P < 0.05$ ); 95% prediction interval excluded the null value; no large heterogeneity ( $I^2 < 50\%$ ); no evidence of small study effects ( $P > 0.10$ ) and excess significance bias ( $P > 0.10$ ); class II (highly suggestive): statistical significance with  $P < 10^{-6}$ , more than 1000 cases (or >20000 participants for continuous outcomes), the largest component study reported statistically significant effect ( $P < 0.05$ ); class III (suggestive): statistical significance with  $P < 10^{-3}$ , more than 1000 cases (or >20000 participants for continuous outcomes).

†The heterogeneity ( $I^2$ ), Egger's test, and 95% prediction interval could not be calculated, because the number of studies included in meta-analyses was less than three.

had more than 1000 cases (or more than 20 000 participants for continuous outcomes), 15 (20%) had no large heterogeneity ( $I^2 < 50\%$ ), and 34 (45%) had neither small study effects nor excess significant bias. Based on these metrics, only one of 76 (1%) outcomes presented convincing evidence (class I: stroke mortality in general population), 7 (9%) outcomes presented highly suggestive evidence (class II: heart failure incidence, hypertension incidence, impaired fasting glucose or diabetes, chronic kidney disease incidence, coronary heart disease mortality, all cause mortality in patients with heart failure, and non-alcoholic fatty liver disease), and 9 (12%) outcomes presented suggestive evidence (class III: atrial fibrillation, coronary heart disease incidence, cardiovascular disease, prehypertension, medium term major adverse cardiac event, type 2 diabetes, cardiovascular disease mortality, chronic kidney disease mortality, death, or cardiac events). The remaining 41 (54%) statistically significant outcomes presented weak evidence (class IV).

We performed a thorough examination and reassessed the meta-analyses of stroke mortality<sup>48</sup> (class I) and found that data from the largest study were incorrect (the events represented stroke incidence cases rather than stroke deaths and the included study had not published data on stroke mortality).<sup>130</sup> Furthermore, the data from two individual studies reported comparisons of SUA categories that differed from other studies (the highest sextile versus the second or third sextile rather than the lowest),<sup>131 132</sup> and a fourth study had been using only data on ischaemic stroke deaths but missing the data on haemorrhagic stroke deaths.<sup>133</sup> When we excluded the stroke incidence study, used the proper comparison for the other two studies, and added the missing data in the fourth study, the association with stroke mortality was not statistically significant (table 2). For the highly suggestive outcomes (class II), when we limited the data to prospective cohort studies, all associations retained their ranking, except for all cause mortality in patients with heart failure and non-alcoholic fatty liver disease, which were downgraded to class III (table X in the web appendix).

### Meta-analyses of randomised controlled trials

We identified 31 meta-analyses of randomised controlled trials on SUA lowering treatment from eight publications (see table S4 in web appendix). The median number of studies included in the meta-analyses was 5 (range 2-10) and the median number of participants was 216 (41-738). More than one meta-analysis was found for five outcomes (see table S4 in web appendix). The direction and statistical significance of the effects in overlapping meta-analyses were in concordance only for one (20%) outcome: serum creatinine level ( $n=2$ ).<sup>88 89</sup> Discordance in either the direction and/or the statistical significance was found for the remaining four outcomes: glomerular filtration rate ( $n=2$ ),<sup>88 89</sup> end stage kidney disease ( $n=2$ ),<sup>88 89</sup> systolic blood pressure ( $n=2$ ),<sup>89 93</sup> and diastolic blood pressure ( $n=2$ ).<sup>89 93</sup>

Twenty unique meta-analyses (table 3) were identified for the outcomes in relation to kidney disorders

Table 3 | Health outcomes reported in meta-analyses of randomised controlled trials

Outcomes	Population	SUA lowering treatment	No of studies	No of participants	Type of metric	Relative risk (95% CI)	P value	I <sup>2</sup> (95% CI)	P value for Egger's test	P value for excess significance test	95% prediction interval
<b>Kidney disorders</b>											
Recurrence of nephrolithiasis* <sup>†86</sup>	Patients with nephrolithiasis	Allopurinol	2	152	RR	0.59 (0.42 to 0.84)	2.90E-03	NA	NA	0.39	NA
Recurrence of nephrolithiasis* <sup>†86</sup>	Patients with nephrolithiasis	Thiazides	5	300	RR	0.52 (0.39 to 0.69)	9.00E-06	0 (0 to 64)	0.06	0.11	0.33 to 0.82
Recurrence of nephrolithiasis* <sup>†86</sup>	Patients with nephrolithiasis	Cit rates	4	197	RR	0.26 (0.15 to 0.45)	2.84E-06	0 (0 to 68)	0.19	NP	0.08 to 0.88
Serum creatinine <sup>87</sup>	General	All active treatment	9	580	SMD to OR	0.10 (0.03 to 0.39)	4.64E-04	93 (90 to 95)	0.39	NP	0.01 to 13.21
Serum creatinine <sup>88</sup>	Patients with CKD	Allopurinol	6	354	MD to OR	0.16 (0.08 to 0.34)	1.00E-06	70 (0 to 85)	0.01	0.59	0.02 to 1.76
eGFR <sup>87</sup>	General	All active treatment	3	218	SMD to OR	2.22 (1.21 to 4.06)	9.79E-03	29 (0 to 80)	0.24	NP	0.01 to 497.40
eGFR <sup>89</sup>	Patients with CKD or decreased kidney function	Allopurinol	5	346	MD to OR	1.18 (0.97 to 1.42)	0.09	0 (0 to 64)	0.29	NP	0.86 to 1.60
Proteinuria <sup>89</sup>	Patients with CKD or decreased kidney function	Allopurinol	5	250	MD to OR	0.91 (0.73 to 1.12)	0.40	0 (0 to 64)	0.42	NP	0.64 to 1.28
Blood urea nitrogen <sup>88</sup>	Patients with CKD	Allopurinol	3	169	MD to OR	0.18 (0.10 to 0.32)	1.47E-08	0 (0 to 73)	0.88	0.67	0.01 to 7.16
End stage renal disease <sup>88</sup>	Patients with CKD	Allopurinol	5	267	RR	0.33 (0.21 to 0.51)	1.38E-06	0 (0 to 64)	0.01	0.07	0.16 to 0.68
<b>Endothelial function</b>											
Flow mediated dilatation <sup>90</sup>	Population with vascular disease or risk factors	Allopurinol or oxypurinol	5	144	MD to OR	4.38 (1.85 to 10.38)	8.76E-04	60 (0 to 83)	0.23	0.24	0.27 to 70.69
Forearm blood flow <sup>90</sup>	Population with vascular disease or risk factors	Allopurinol or oxypurinol	5	148	MD to OR	2.69 (1.22 to 5.93)	0.014	53 (0 to 81)	0.09	0.61	0.24 to 307.3
<b>Mortality</b>											
Death during neonatal period or infancy <sup>92</sup>	All infants	Allopurinol	3	114	RR	0.87 (0.43 to 1.75)	0.71	34 (0 to 81)	0.49	NP	0.01 to 952.4
Death during neonatal period or infancy <sup>192</sup>	Infants with severe hypoxic-ischaemic encephalopathy	Allopurinol	2	41	RR	0.92 (0.39 to 2.15)	0.86	NA	NA	NP	NA
Death or severe neurodevelopmental disability <sup>92</sup>	All infants	Allopurinol	3	110	RR	0.85 (0.63 to 1.15)	0.29	0 (0 to 73)	0.12	NP	0.12 to 5.98
Death or severe neurodevelopmental disability <sup>192</sup>	Infants with severe hypoxic-ischaemic encephalopathy	Allopurinol	2	41	RR	0.93 (0.67 to 1.30)	0.68	NA	NA	NP	NA
<b>Other outcomes</b>											
Severe quadriplegia <sup>92</sup>	Surviving infants with hypoxic-ischaemic encephalopathy	Allopurinol	3	73	RR	0.58 (0.27 to 1.26)	0.17	0 (0 to 73)	0.69	NP	0.01 to 86.99
Seizures in neonatal period <sup>92</sup>	Surviving infants with hypoxic-ischaemic encephalopathy	Allopurinol	3	114	RR	0.98 (0.84 to 1.15)	0.81	0 (0 to 73)	0.15	NP	0.35 to 2.79
Systolic blood pressure <sup>93</sup>	Patients with increased SUA or kidney dysfunction	Allopurinol	10	738	MD (mm Hg)	-3.33 (-5.25 to -1.42)	0.001	87 (79 to 91)	0.60	NP	-13.61 to 6.94
Diastolic blood pressure <sup>93</sup>	Patients with increased SUA or kidney dysfunction	Allopurinol	10	738	MD (mm Hg)	-1.29 (-2.48 to -0.10)	0.03	82 (68 to 88)	0.38	NP	-8.22 to 5.65

SUA=serum uric acid; RR=relative risk; NA=not applicable (did not calculate with only 2 studies); NP=not pertinent (because the number of expected significant studies was larger than the number of observed significant studies); SMD=standardised mean difference; OR=odds ratio; CKD=chronic kidney disease; MD=mean difference; eGFR=estimated glomerular filtration rate.

\*The heterogeneity (I<sup>2</sup>), Egger's test, or 95% prediction interval could not be calculated, because the number of studies included in meta-analyses was less than 3.

†The strength of evidence was graded based on the evidence based practice centre approach (conceptually similar to the GRADE ranking system); recurrence of nephrolithiasis (with allopurinol, thiazides, or citrates treatment) was all considered with moderate evidence in original meta-analyses.

#Meta-analyses included one prospective study.

(n=10), endothelial function (n=2), all cause and cause specific mortality (n=4), and other outcomes (n=4). Figure 3 in the web appendix shows the summary effects of the unique meta-analyses of randomised controlled trials. Overall, 12 (60%) reported a nominally significant summary result at  $P<0.05$  (8 had  $P<0.001$ ). Only three (15%) meta-analyses had a 95% prediction interval that excluded the null (two nephrolithiasis outcomes (with thiazide and citrate treatment) and one renal function outcome), 11 (55%) meta-analyses showed no large heterogeneity ( $I^2<50\%$ ), and 13 (65%) meta-analyses showed neither small study effects nor excess significant bias.

Only one outcome (recurrence of nephrolithiasis with citrates treatment) reported a  $P<0.001$ , had a 95% prediction interval excluding the null, and had no evidence of large heterogeneity or bias. In the original meta-analyses, the strength of evidence was graded collectively for three nephrolithiasis outcomes (thiazide, citrate, or allopurinol treatment) by using an approach conceptually similar to the GRADE ranking system,<sup>134</sup> and evidence for these three nephrolithiasis outcomes was graded as moderate.

#### Mendelian randomisation studies

A total of 107 Mendelian randomisation analyses were identified from 36 publications (see table S5 in web appendix). The median number of participants was 7158 (range 343-206 822) and median number of cases was 2225 (19-65 877). The proportion of variance in SUA level ( $R^2$ ) explained by genetic instruments was 2-6%. More than one Mendelian randomisation study was identified for 14 outcomes (see table S5 in web appendix). Discordance in either the direction and/or the statistical significance of association among overlapping Mendelian randomisation existed for all the identified outcomes: body mass index (n=7),<sup>95 96 101 102 110 115 121</sup> bone mineral density in femoral neck (n=2),<sup>97 98</sup> coronary heart disease (n=5),<sup>96 100 106 118 126</sup> diastolic blood pressure (n=7),<sup>96 101 106 110 119 121 124</sup> systolic blood pressure (n=7),<sup>96 101 106 110 119 121 124</sup> metabolic syndrome (n=2),<sup>107 120</sup> glucose level (n=3),<sup>96 106 121</sup> triglyceride level (n=3),<sup>96 121 123</sup> diabetes (n=6),<sup>96 99 105 100 122 127</sup> serum creatinine level (n=2),<sup>110 129</sup> estimated glomerular filtration rate (n=5),<sup>106 110 121 128 129</sup> Parkinson's disease (n=5),<sup>111 112 116 117 125</sup> memory performance (n=2),<sup>114</sup> and gout (n=3).<sup>99 100 106</sup>

The 56 unique outcomes (table 4) investigated in individual Mendelian randomisation studies belonged to the following categories: anthropometric variables (n=9), cardiovascular outcomes (n=15), kidney disorders (n=6), metabolic disorders (n=5), neurocognitive disorders (n=5), metabolites (n=11), all cause and cause specific mortality (n=3), and other outcomes (n=2). Only nine (16%) outcomes (diabetic macrovascular disease, arterial stiffness (internal diameter of carotid artery), adverse renal events, Parkinson's disease, lifetime anxiety disorders, memory performance, cardiovascular disease mortality, sudden cardiac death, and gout) presented significant associations of  $P<0.05$ . Three Mendelian randomisation studies (on memory performance, Parkinson's disease, and gout) reported discordant

results in the direction and/or statistical significance in other Mendelian randomisation studies. Of note, only four outcomes (diabetic macrovascular disease, arterial stiffness (internal diameter of carotid artery), renal events, and gout) reported a  $P<0.01$ , and only that for gout was based on convincing evidence ( $P=3.55E-40$ ,  $n=71\,501$ , power  $>99\%$ ).

#### Comparison of findings from meta-analyses

Table 5 summarises the outcomes reported in meta-analyses of observational studies with highly suggestive evidence or meta-analyses of randomised controlled trials with 95% prediction intervals excluding the null. Among these outcomes, hypertension and chronic kidney disease showed concordant evidence between meta-analyses of observational studies and the selected (largest) meta-analyses of randomised controlled trials on their corresponding intermediate traits or surrogate outcomes (eg, systolic blood pressure, diastolic blood pressure, serum creatinine level, estimated glomerular filtration rate, and end stage renal disease) but had discordant evidence from Mendelian randomisation studies. Moreover, even for these outcomes there were additional meta-analyses of randomised controlled trials that had found discordant effects in terms of direction and/or statistical significance for all these intermediate traits or surrogate outcomes, with the exception of serum creatinine level. Heart failure, impaired fasting glucose or diabetes, and coronary heart disease mortality showed no evidence from meta-analyses of randomised controlled trials, and Mendelian randomisation studies reported discordant evidence on the corresponding outcomes, the intermediate traits, or the surrogate outcomes. Recurrence of nephrolithiasis was only reported in meta-analysis of randomised controlled trials, and no evidence was found from meta-analyses of observational studies or Mendelian randomisation studies.

#### Discussion

In this study, we provide a comprehensive overview of reported associations between serum uric acid (SUA) levels and a wide range of health outcomes by incorporating evidence from systematic reviews and meta-analyses of observational studies, meta-analyses of randomised controlled trials, and Mendelian randomisation studies. We also further evaluated the reported evidence by following criteria that we have previously applied to appraise the epidemiological credibility in several research specialties.<sup>26 135 136</sup> Our study comprised 76 unique meta-analyses of observational studies, 20 unique meta-analyses of randomised controlled trials, and 56 unique individual Mendelian randomisation studies, which overall covered 136 unique health outcomes.

#### Main findings and possible explanations

Most health outcomes that were reported to be associated with SUA level were identified from meta-analyses of observational studies, but after the application of our criteria none of them were classified as convincing

Table 4 | Health outcomes reported in Mendelian randomisation studies

Outcomes	Population	No./No of Events (No of studies)*	Genetic instruments (GI)	SUA variance (R <sup>2</sup> ) explained by GI (%)	Type of metric	Estimate of effect (95% CI)	P value	Statistical power†
<b>Anthropometric variables</b>								
Appendicular lean mass (kg) <sup>94</sup>	UK	3953	rs737267 in <i>SCL2A9</i>	NA	β	0.013 (NA)	0.51	NA
Fat mass (kg) <sup>95</sup>	Switzerland	6184	rs6855911 in <i>SCL2A9</i>	3.2	β	0.05 (-0.10 to 0.19)	0.52	0.07
Body mass index (kg/m <sup>2</sup> ) <sup>96</sup>	Europe	127 600 (64)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	-0.0003 (-0.0008 to 0.0002)	NA	NA
Waist circumference (cm) <sup>95</sup>	Switzerland	6184	rs6855911 in <i>SCL2A9</i>	3.2	β	0.08 (-0.05 to 0.21)	0.24	0.06
BMD in femoral neck (g/cm <sup>2</sup> ) <sup>97</sup>	USA	2501	Genetic risk score of 5 SUA related SNPs	3.3	β	-0.27 (-0.58 to 0.03)	0.08	0.07
BMD in L1-L4 (g/cm <sup>2</sup> ) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	0.39 (-0.26 to 0.98)	0.26	0.19
BMD in spine (g/cm <sup>2</sup> ) <sup>97</sup>	USA	2501	Genetic risk score of 5 SUA related SNPs	3.3	β	0.08 (-0.32 to 0.48)	0.68	0.18
BMD in total femur (g/cm <sup>2</sup> ) <sup>97</sup>	USA	2501	Genetic risk score of 5 SUA related SNPs	3.3	β	-0.29 (-0.60 to 0.01)	0.06	0.11
BMD in total hip (g/cm <sup>2</sup> ) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	0.19 (-0.36 to 0.74)	0.50	0.19
<b>Cardiovascular outcomes</b>								
Arrhythmia <sup>99</sup>	Germany	3060/444	Genetic risk score of 8 SUA related SNPs	NA	OR	0.98 (0.88 to 1.08)	0.64	0.05\$
Atrial fibrillation <sup>99</sup>	Germany	3060/368	Genetic risk score of 8 SUA related SNPs	NA	OR	1.03 (0.93 to 1.15)	0.57	0.05\$
Cardiomyopathy <sup>99</sup>	Germany	3060/316	Genetic risk score of 8 SUA related SNPs	NA	OR	1.00 (0.89 to 1.12)	0.93	0.05\$
Coronary heart disease <sup>96</sup>	Europe	206 822/65 877 (58)*	Genetic risk score of 31 SUA related SNPs	4.2	OR	1.05 (0.92 to 1.18)	0.49	0.57
Heart failure <sup>100</sup>	Pakistan	22926/4526 (2)*	Genetic risk score of 14 SUA related SNPs	3.1	OR	1.07 (0.88 to 1.30)	0.51	0.11
Ischaemic heart disease <sup>101</sup>	Denmark	68 674/3742 (2)*	rs742295 in <i>SCL2A9</i>	2.2	HR	0.93 (0.79 to 1.09)	0.38	0.10
Hypertension <sup>99</sup>	Germany	3060/2225	Genetic risk score of 8 SUA related SNPs	NA	OR	0.98 (0.90 to 1.06)	0.56	0.05\$
Ischaemic stroke <sup>100</sup>	Pakistan	82 091/14 779 (2)*	Genetic risk score of 14 SUA related SNPs	3.1	OR	0.99 (0.88 to 1.12)	0.93	0.05\$
Peripheral vascular disease <sup>99</sup>	Germany	3060/295	Genetic risk score of 8 SUA related SNPs	NA	OR	0.92 (0.82 to 1.04)	0.18	0.06\$
Valve disease <sup>99</sup>	Germany	3060/538	Genetic risk score of 8 SUA related SNPs	NA	OR	1.08 (0.99 to 1.19)	0.10	0.07\$
Diabetic macrovascular disease <sup>103</sup>	Patients with T2DM in China	3207	Genetic risk score of 3 SUA related SNPs	NA	OR	1.18 (1.06 to 1.33)	0.004	NA
cIMT (mm) <sup>102</sup>	Finland (male)	1985	rs13129697 in <i>SCL2A9</i>	NA	β	<0.0001 (NA)	0.99	NA
Arterial stiffness (internal diameter of carotid artery (mm)) <sup>104</sup>	Italy	449	rs734553 in <i>SCL2A9</i>	NA	β	0.48 (NA)	0.003	NA
Diastolic blood pressure (mm Hg) <sup>96</sup>	Europe	89 667 (37)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	0.005 (0.003 to 0.007)	NA	NA
Systolic blood pressure (mm Hg) <sup>96</sup>	Europe	89 667 (37)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	0.005 (0.003 to 0.006)	NA	NA
<b>Metabolic disorders</b>								
Type 2 diabetes <sup>100</sup>	Pakistan	110 452/26 488 (2)*	Genetic risk score of 14 SUA related SNPs	3.1	OR	0.95 (0.86 to 1.05)	0.28	0.24
Diabetes <sup>105</sup>	Europe	165 482/41 508 (2)*	Genetic risk score of 24 SUA related SNPs	4.0	OR	0.99 (0.92 to 1.06)	0.79	0.06
Fasting glucose (mmol/L) <sup>96</sup>	Europe	57 397 (28)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	-0.001 (-0.003 to 0.001)	NA	NA
Fasting insulin† <sup>106</sup>	USA	19 899 (5)*	Genetic risk score of 8 SUA related SNPs	6.0	Z statistic	-0.015 (NA)	0.99	NA
Metabolic syndrome <sup>107</sup>	China	7827	Genetic risk score of 2 SNPs (rs117 222 28 in <i>SCL2A9</i> and rs2231142 in <i>ABCG2</i> )	2.1	OR	1.03 (0.98 to 1.09)	0.23	NA
<b>Kidney disorders</b>								
Chronic kidney disease <sup>106</sup>	USA	23 387/3092 (5)*	Genetic risk score of 8 SUA related SNPs	6.0	OR	1.20 (0.96 to 1.50)	0.12	0.70
Acute kidney injury <sup>108</sup>	USA	7 553/823	Genetic risk score of 8 SUA related SNPs	6.0	HR	1.01 (0.77 to 1.34)	0.92	0.05
Adverse renal events <sup>109</sup>	Italy	7 55/244	rs734553 in <i>GLUT9</i>	NA	HR	2.35 (1.25 to 4.42)	0.01	NA

(Continued)

Table 4 | Health outcomes reported in Mendelian randomisation studies

Outcomes	Population	No/No of Events (No of studies)*	Genetic instruments (GI)	SUA variance (R <sup>2</sup> ) explained by GI (%)	Type of metric	Estimate of effect (95% CI)	P-value	Statistical power†
Log eGFR (mL/min/1.73 m <sup>2</sup> ) <sup>106</sup>	USA	23844 (5)*	Genetic risk score of 8 SUA related SNPs	6.0	β	0.001 (−0.01 to 0.02)	0.91	0.05
serum creatinine (mmol/L) <sup>110</sup>	Europe (Caucasian)	7979 (2)*	Genetic risk score of 5 SUA related SNPs	2.3	β	−19.23 (−40.32 to 1.86)	0.07	NA
Albumin/creatinine ratio <sup>129</sup>	USA (Indian American)	3604 (3)*	Genetic risk score of 5 SUA related SNPs	5.3	Residual variance**	Overall P>0.05		NA
<b>Neurocognitive disorders</b>								
Parkinson's disease <sup>116</sup>	UK	1815/1061	Genetic risk score of 8 SUA related SNPs	NA	OR	1.55 (1.10 to 2.18)	0.01	0.59§
Age at onset of Parkinson's disease <sup>112</sup>	Europe	664 (3)*	4 SNPs in <i>SLC2A9</i> rs737267	NA	Null after multiple testing correction			
			rs6449213	NA	β	−1.18 (−4.96 to 2.59)	0.04	NA
			rs1014290	NA	β	−4.56 (−8.13 to −1.00)	0.01	0.54
			rs733175	NA	β	3.59 (0.67 to 6.51)	0.02	0.01
Lifetime anxiety disorders <sup>113</sup>	Switzerland	3716	rs6855911 in <i>SLC2A9</i>	3.2	OR (male)	1.40 (1.07 to 1.84)	0.02	0.11
					OR (female)	0.97 (0.80 to 1.17)	0.73	0.05
Current anxiety disorders <sup>113</sup>	Switzerland	3716	rs6855911 in <i>SLC2A9</i>	3.2	OR (male)	1.42 (0.99 to 2.03)	0.06	0.12
					OR (female)	0.84 (0.66 to 1.06)	0.14	0.07
Memory performance <sup>114</sup>	Europe: Population 1	1091	4 SNPs in <i>SLC2A9</i>	NA	β	Overall P<0.05		NA
	Europe: Population 2	1066	4 SNPs in <i>SLC2A9</i>	NA	β	Overall P>0.05		NA
<b>Metabolites</b>								
High density lipoprotein cholesterol (mmol/L) <sup>96</sup>	Europe	196621 (68)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	−0.008 (−0.010 to −0.006)	NA	NA
Low density lipoprotein cholesterol (mmol/L) <sup>96</sup>	Europe	196621 (68)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	−0.001 (−0.003 to 0.001)	NA	NA
Total cholesterol (mmol/L) <sup>96</sup>	Europe	196621 (68)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	0.000 (−0.002 to 0.002)	NA	NA
Triglyceride (mmol/L) <sup>96</sup>	Europe	196621 (68)*	Genetic risk score of 31 SUA related SNPs	4.2	MD†	0.01 (0.01 to 0.02)	NA	NA
Parathyroid hormone (pg/mL) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	−0.63 (−2.12 to 0.85)	0.40	0.05
Phosphorus (mmol/L) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	−0.16 (−0.74 to 0.42)	0.59	0.05
C-reactive protein (mg/L) <sup>115</sup>	Europe	7158	Genetic risk score of 29 SUA related SNPs	NA	β	−0.05 (−0.15 to 0.05)	0.37	NA
Calcium (mmol/L) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	0.06 (−0.10 to 0.21)	0.48	0.20
Tropocollagen type 1 N-terminal propeptide (ng/L) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	0.11 (−1.53 to 1.75)	0.90	0.05
β-crosslaps of type I collagen containing cross-linked C telopeptide (ng/L) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	−1.45 (−3.17 to 0.27)	0.10	0.05
Calcifediol (ng/mL) <sup>98</sup>	China	1667	Genetic risk score of 5 SUA related SNPs	1.8	β	0.76 (−0.63 to 2.15)	0.28	0.05
<b>All cause and cause specific mortality</b>								
Cardiovascular mortality <sup>99</sup>	Germany	3060/NA	Genetic risk score of 8 SUA related SNPs	NA	aHR	1.11 (1.02 to 1.21)	0.02	NA
All cause mortality <sup>99</sup>	Germany	3060/NA	Genetic risk score of 8 SUA related SNPs	NA	aHR	1.02 (0.95 to 1.09)	0.59	NA
Sudden cardiac death <sup>99</sup>	Germany	3060/NA	Genetic risk score of 8 SUA related SNPs	NA	aHR	1.18 (1.03 to 1.35)	0.02	NA
<b>Other outcomes</b>								
Cancer <sup>99</sup>	Germany	3060/226	Genetic risk score of 8 SUA related SNPs	NA	OR	0.95 (0.83 to 1.08)	0.41	0.05§
Gout <sup>100</sup>	Pakistan	71501/3151 (2)*	Genetic risk score of 14 SUA related SNPs	3.1	OR	5.84 (4.56 to 7.49)	3.55E-40	1.00

SUA=serum uric acid; NA=not available; β=regression coefficient; SNPs=single-nucleotide polymorphisms; MD=mean difference; OR=odds ratio; HR=hazard ratio; T2DM=type 2 diabetes; cIMT=carotid intima-media thickness; eGFR=estimated glomerular filtration rate; aHR=adjusted hazard ratio.  
 \*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.  
 †When Mendelian randomisation studies did not provide other necessary information for calculation (eg, standard deviation of serum uric acid levels, standard deviation of outcomes, or the number of cases), the statistical power was not calculated (reported as NA).  
 ‡MD (mean difference) represented the difference in mean caused by per inverse variance weighted allele estimated from pooled analysis.  
 §The statistical power was a crude estimation, as the Mendelian randomisation studies failed to report R<sup>2</sup>; we used the extrapolated R<sup>2</sup> from other Mendelian randomisation studies that used the same genetic variants as instruments for calculation.  
 ¶Because of the lack of a standard to convert insulin in different studies to the same scale, sample size-weighted pooled analysis were performed and Z statistics were reported instead of the β coefficient.  
 \*\*Residual variance represented the proportion of residual variance explained by the SUA related SNPs.

Table 5 | Summary of evidence grading and comparison of multiple evidence

Outcomes	Meta-analysis of observational studies	Meta-analysis of randomised controlled trials*	Mendelian randomisation studies
Heart failure	Class II	NA	Heart failure: n=22 926, P=0.51, power=0.11),
Hypertension†	Class II	Systolic blood pressure: P=0.001, 95% PI included null; diastolic blood pressure: P=0.03, 95% PI included null	Hypertension: n=3060, P=0.56, power=0.05
Impaired fasting glucose or diabetes	Class II	NA	Diabetes: n=165 482, P=0.79, power=0.06); fasting glucose: n=57 397, P>0.05; fasting insulin: n=19 899, P=0.99
Chronic kidney disease†	Class II	Serum creatinine: P<0.001, 95% PI included null; estimated glomerular filtration rate: P=0.010, 95% PI included null; end stage renal disease: P<0.001, 95% PI excluded null	Chronic kidney disease: n=23 387; P=0.12, power=0.70; adverse renal events: n=755, P=0.01; serum creatinine: n=7979, P=0.07; estimated glomerular filtration rate: n=23 844, P=0.91, power=0.05
Coronary heart disease mortality†	Class II (general population)	NA	Coronary heart disease incidence: n=206 822, P=0.49, power=0.57
Recurrence of nephrolithiasis	NA	Citrates treatment: P<0.001, 95% PI excluded null; thiazides treatment: P<0.001, 95% PI excluded null	NA

NA=not applicable; PI=prediction interval.

\*Data presented on largest meta-analysis of randomised controlled trials for each outcome.

†If there were no identical outcomes investigated in meta-analyses of randomised controlled trials and/or Mendelian randomisation studies to match with class I or II observational associations, the corresponding intermediate traits were juxtaposed as surrogates for comparison.

(class I). Highly suggestive evidence (class II) existed for five health outcomes, including heart failure, hypertension, impaired fasting glucose or diabetes, chronic kidney disease, and coronary heart disease mortality in the general population. Notably, a large proportion (80%) of the examined meta-analyses displayed substantial heterogeneity ( $I^2 > 50\%$ ), indicating that these associations should be interpreted with caution. Possible sources of the observed heterogeneity include the mixture of prospective, retrospective, or case-control studies and the mixture of different comparison groups, since some meta-analyses synthesised individual studies with diverse contrasted categories of SUA levels (eg, various choices of tertiles, quartiles, quintiles, or sextiles of SUA levels). Likewise, although the outcomes with class I or II evidence fulfilled the criteria of credibility assessment for meta-analyses of observational studies, it would be inadvisable to conclude causation on this basis alone, owing to the inherent limitations of unmeasured confounding, undetected bias, or reverse causality in observational studies. In relation to reverse causality for example, some of the associations that were initially classified as class II (eg, all cause mortality in patients with heart failure and non-alcoholic fatty liver disease), were no longer highly suggestive (and were downgraded to class III) when focusing on prospective observational data and excluding the retrospective studies.

Current evidence from meta-analyses of randomised controlled trials was limited to the beneficial effects of SUA lowering treatment on some intermediate traits or biomarkers related to cardiovascular and renal disorders (eg, blood pressure, endothelial functions, and renal function). However, when multiple meta-analyses of randomised controlled trials existed for traits or markers, often the results were not concordant in direction of effect and/or statistical significance. Although 12 health outcomes had  $P < 0.05$ , only recurrence of nephrolithiasis with citrate treatment achieved  $P < 0.001$ , with 95% prediction interval excluding the null. Two additional health outcomes (recurrence of

nephrolithiasis using thiazides and end stage renal disease in patients with coronary heart disease using allopurinol) also had a 95% prediction interval excluding the null. Large heterogeneity and evidence of bias were common even in meta-analyses of randomised controlled trials (in 45% of meta-analyses and 35% of randomised controlled trials). When incorporating evidence from meta-analyses of randomised controlled trials with that from meta-analyses of observational studies, there was a notable gap, as health outcomes that were investigated in meta-analyses of observational studies and classified as class I or II have generally not been evaluated in meta-analyses of randomised controlled trials. In a few cases, data from randomised controlled trials on surrogate outcomes (eg, systolic blood pressure, diastolic blood pressure, and renal function tests) that corresponded to disease outcomes in observational studies (hypertension, chronic kidney disease) were available, but conclusions from extrapolation of surrogate outcomes, which were evaluated in short term trials, to long term clinical outcomes should be treated with caution.

As an alternative to randomised controlled trials, the Mendelian randomisation design has been developed for exploring the causal effect of biomarkers on health outcomes. Fifty six Mendelian randomisation studies were identified that explored the causal role of SUA in cardiovascular, metabolic, neurocognitive, and renal disorders or related traits and biomarkers. In contrast with the meta-analyses of observational studies where most of the results (76%) were significant at  $P < 0.05$ , most (84%) health outcomes investigated in Mendelian randomisation studies were not statistically significant. The generally negative results across so many health outcomes suggest that the large effects have probably not been missed, but most of the included Mendelian randomisation studies could have been underpowered to detect modest effects. When retaining the largest Mendelian randomisation study for each health outcome, significant results with  $P < 0.05$  were only reported for nine health outcomes, and only four of these health



outcomes (diabetic macrovascular disease, arterial stiffness (internal diameter of carotid artery), renal events, and gout) had  $P < 0.01$ , whereas only the gout outcome was based on evidence from a Mendelian randomisation study with adequate power. Of the other five health outcomes with  $P < 0.05$ , Parkinson's disease and memory performance had at least one other Mendelian randomisation study that was not significant or had an association in the opposite direction.

Several instrumental variable assumptions need to be fulfilled for the results of a Mendelian randomisation analysis to be valid. The first assumption states that the genetic instrument should be strongly associated with the intermediate phenotype. SUA level has an evident heritable component with an overall heritability of 40-60%,<sup>137</sup> but the strength of genetic instruments used in Mendelian randomisation studies was small or moderate, accounting for only 2-6% of SUA variance. Currently, the proportion of SUA variance explained by all common genetic variants identified by a genome wide association study remains relatively small (7%).<sup>138</sup> This limits the power of genetic instruments to detect causal associations with SUA level. The second and third assumptions (the instrument is associated with the outcome through the studied exposure only and the genotype is independent of other factors that affect the outcome) are more difficult to evaluate given the largely unknown complexity and interconnectedness of biological pathways underlying the genetic variants related to SUA level. The included Mendelian randomisation studies tried to validate these assumptions either by excluding single nucleotide polymorphisms related to other known confounding factors, by excluding single nucleotide polymorphisms that had potential pleiotropic effects, or by applying new Mendelian randomisation methods to account for pleiotropic effects (eg, Egger Mendelian randomisation analysis or network Mendelian randomisation).

#### Clinical implications and future research

Current recommendations on the drug treatment of hyperuricemia are related to gout or nephrolithiasis.<sup>8</sup> Since a wide range of health outcomes has been identified to be associated with SUA level, a renewed interest in whether individuals with asymptomatic hyperuricemia should be treated with SUA lowering drugs for the prevention or treatment of associated cardiovascular and metabolic diseases. In this study we raised large uncertainty about the potential therapeutic benefits of an expansion of SUA lowering treatment. Although we identified some highly suggestive associations from observational studies, there was a lack of concordance with clinically relevant endpoints from randomised controlled trials or surrogate endpoints from Mendelian randomisation studies, and therefore evidence is insufficient to support any SUA lowering drug intervention for these outcomes. Furthermore, the adverse effects of SUA lowering drugs should be taken into consideration (eg, an estimated 0.1% of patients treated with allopurinol, the first line SUA lowering drug,

develop allopurinol hypersensitivity syndrome, which can be life threatening).<sup>9</sup>

Our study does not support one of the recommendations in the recently updated European League Against Rheumatism gout treatment guidelines, which suggest that SUA level  $< 3.0$  mg/dL is not recommended for gout management in the long term.<sup>139</sup> This recommendation is based on several observational studies in which low SUA levels were associated with increased risk of multiple neurological diseases, including Alzheimer's disease and Parkinson's disease.<sup>140-142</sup> However, in our umbrella review a number of meta-analyses reported nominally statistically significant associations of low SUA levels with increased risk of multiple neurological diseases, but several other meta-analyses (9 out of 28) did not support these findings. Moreover, our credibility assessment showed that the nominally significant associations were consistent with class IV evidence, and a causal effect has not consistently been established for any neurological disease in Mendelian randomisation studies. Therefore, there is no adequate evidence against lowering SUA levels in patients with gout because of an increased risk of neurological diseases.

For future research, efforts to address the limitations and caveats in current evidence will be beneficial. In particular, as the current clinical trials of SUA lowering treatment largely focus on the effect of allopurinol on some intermediate traits or biomarkers, the effect of SUA reduction on clinically relevant endpoints of the convincing and highly suggestive associations might be worth further investigation. In addition, efforts to evaluate whether other SUA lowering agents have the same effect as xanthine oxidase inhibitors will help to determine if these effects are truly due to the SUA reduction itself rather than the mechanisms of xanthine oxidase inhibition. Finally, noting the largely discordant evidence in Mendelian randomisation studies, better designed such studies with collaboration of large international consortiums might assist in deciding whether the lack of replication of highly suggestive findings of observational studies is owing to low power to detect moderate or small effects, or owing to truly negative effects.

#### Strengths and weaknesses of this review

The strengths of umbrella reviews have been described in detail.<sup>26 135 136</sup> Here we summarised and presented the evidence of the associations between SUA level and a wide spectrum of health related outcomes systematically and thoroughly by incorporating information from meta-analyses of observational studies, meta-analyses of randomised controlled trials, and Mendelian randomisation studies. We then calculated a number of additional metrics and applied well defined criteria to assess the credibility of the observed associations.

In relation to study weaknesses, umbrella reviews focus on existing meta-analyses and therefore outcomes that were not assessed in a meta-analysis are not included in the review. For example, we found no formal meta-analysis of observational studies on SUA level and urolithiasis or gout, even though these associations

are well established. Although there are some differences in SUA levels between men and women, there is not sufficient evidence at a meta-analysis level and therefore we did not attempt to perform subgroup analyses by sex. To avoid subjectivity, we did not include reviews without explicit systematic literature searches, but this could limit the breadth of the results to some extent, if some non-systematic reviews cover questions that have not been addressed by systematic reviews.<sup>143 144</sup> Furthermore, we did not appraise the quality of the individual studies, since this should be the responsibility of the authors of the original meta-analysis and it was beyond the scope of the current umbrella review.

We adopted credibility assessment criteria, which were based on established tools for observational evidence, and their individual limitations have been summarised previously.<sup>26 135 136</sup> None of the components of these criteria provides firm proof of lack of reliability, but they cumulatively map the possibility that the results are susceptible to bias and uncertainty. Given the wide variety of study designs and populations considered in several of the meta-analyses, one might claim that large heterogeneity in particular may not necessarily be worrisome. However, considering it is difficult to differentiate the real heterogeneity from the heterogeneity that reflects some forms of bias or uncertainty, we applied  $I^2 < 50\%$  as one of the criteria for class I evidence (convincing) for meta-analyses of observational studies, so as to assign the top evidence grade only to associations that are most robust and without hints of bias. In most cases  $I^2 > 50\%$  indicates the presence of component studies with opposite effects or of component studies with and without statistically significant associations. However, nine meta-analyses of observational studies classified as class II, III, or IV had an  $I^2 > 50\%$ , with all component studies reporting a statistically significant association of the same direction. Only one of these nine meta-analyses (heart failure incidence) would be upgraded from class II to class I if we did not consider the heterogeneity criterion, since the other eight also failed additional class I criteria. No meta-analyses of randomised controlled trials had an  $I^2 > 50\%$  with all component studies reporting a statistically significant association with the same direction.

Finally, another limitation of the umbrella review approach is the use of existing meta-analyses taking their results at face value. Meta-analyses are known to have common flaws<sup>145</sup> and their results may also depend on choices made about what estimates to select from each primary study and how to represent them in the meta-analysis (eg, in what contrast of exposure levels). This may be a common problem when the factor of interest is continuous, as in the case of SUA level, and where different comparisons of levels of the risk factor may be selected to express risk.<sup>146</sup> We therefore decided to investigate any meta-analyses with seemingly convincing evidence in more detail. In this process, the only meta-analysis that seemed to achieve convincing evidence (class I: stroke mortality) was found to actually have major flaws. Recalculation of the results

showed that the evidence was downgraded to not statistically significant. It is possible that similar thorough evaluations might have downgraded the credibility of some additional meta-analyses. In addition, we noted that many primary studies are represented in the calculations of meta-analyses by using only a small subset of the data of extreme groups (eg, as the risk ratio for an event in extreme quintiles of SUA levels). In these cases, the number of events pertinent to these extreme groups may be much fewer than the total number of events used in calculating the amount of evidence criteria. Therefore, some meta-analyses that seemingly include studies with more than 1000 cases may actually capture fewer than 1000 cases in the main calculations and thus their grading appraisal should have been weaker. These flaws and deficiencies are difficult to decipher without a thorough reconstruction of all observational meta-analyses, and they may explain why observational evidence for SUA associations generally did not show good concordance with evidence from randomised controlled trials and Mendelian randomisation studies in our umbrella evaluation.

Meta-analyses of observational data for SUA level and other risk factors need to be strengthened. For continuous putative risk factors such as SUA concentration, a consensus on the categorisation of levels of interest would be useful. This might be achieved by careful meta-analyses of individual level data in inclusive consortiums. This approach would allow a more accurate and reliable exploration of both linear and non-linear associations (eg, the possibility of U-shaped associations with increased risk at both very high and very low levels). Currently available data from meta-analyses do not allow for consistent handling and assessment of such non-linear relations. Conversely, data dredging using different categorisations of SUA levels for comparison is likely to fuel a literature with spurious associations.<sup>147</sup>

## Conclusion

This comprehensive umbrella review will help investigators to judge the relative priority of health outcomes related to SUA level for future research and clinical management of disease. In summary, despite a few hundred systematic reviews, meta-analyses, and Mendelian randomisation studies exploring 136 unique health outcomes, convincing evidence of a clear role of SUA level only exists for gout and nephrolithiasis. Concordant evidence between observational studies and randomised controlled trials existed for hypertension and chronic kidney disease, but a potential causal role of SUA level for these outcomes has not been verified by current Mendelian randomisation studies and even for these two outcomes not all meta-analyses of randomised controlled trials are concordant among themselves and with observational evidence. Therefore, the available evidence does not support any change in the existing clinical recommendations in relation to hyperuricemia.

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extraction. XL performed the statistical analysis. XL and ET wrote the manuscript. HC, JP, KKT, MT, and IT critically reviewed the manuscript and contributed important intellectual content. All authors have read and approved the final manuscript as submitted. ET is the guarantor.

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### Appendix: Supplementary materials