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 convincing; five associations 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.1 Subsequently, associations of uric acid concentration with cardiovascular and renal disorders were also observed.2 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.3 4 5 6 It was argued that these associations are either confounded by other risk factors, such as obesity and hypertension, or are representative of reverse causality.4 7 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.3 9

New findings have fuelled enthusiasm to address this longstanding controversy.10 Recent epidemiological 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.11 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.12 13 14 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.15 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.16

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, benz bromarone, 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 (R²) and Mendelian randomisation effect estimates (odds ratio, hazard ratio, mean difference, or regression coefficient β), 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)17; the heterogeneity among studies (Q statistic and F 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)\(^13\)\(^15\), 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 \(P<0.10\))\(^20\); 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 \(t\) test:  
\[
A=\frac{(O-E)}{\sqrt{E+2(O-E)/n}} \quad \text{(significance threshold \(P<0.10\))}\]
\[
\text{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.}\]

\(^7\) 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.\(^4\)

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.\(^27\)

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,\(^28\) 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 \(P<10^{-8}\), 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 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 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\(^23\) 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%).

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, 31 meta-analyses of randomised controlled trials were reported in 8 articles, and 107 Mendelian randomisation studies were reported in 36 articles (see tables S2 to S5, respectively, in web appendix). Across all three study types, 136 unique outcomes were reported.

Meta-analyses of observational studies

Over all, 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 (seetable 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), coronary heart disease (n=4), hypertension incidence (n=3), stroke incidence (n=2), diabetes (n=3), chronic kidney disease (n=3), mild cognitive impairment (n=2), Parkinson’s disease (n=3), multiple sclerosis (n=2), coronary heart disease mortality (n=3), cardiovascular disease mortality (n=2), stroke mortality (n=2), all cause mortality in patients with heart failure (n=2), and all cause mortality in the general population (n=2). Discordance in the statistical significance was present for two outcomes: diabetic neuropathy (n=2) and Alzheimer’s disease (n=4). 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, 7 (100%) in kidney disorders, 1 (9%) in neurocognitive disorders, 1 (17%) in cancer outcomes, and 7 (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 I (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 association with SUA level.

We then applied our evidence classification criteria. Sixteen (21%) meta-analyses had P<10−4, 10 (13%) had a 95% prediction interval that excluded the null, 27 (36%) had more than 1000 cases (or more than 20 000 participants for continuous outcomes), 15 (20%) had no large heterogeneity (I²<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 mortality48 (class I) and found that data from the largest study were incorrect (the events and the represented stroke incidence cases rather than stroke deaths and the included study had not published data on stroke mortality). 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).131 132 and a fourth study had been using only data on ischaemic stroke deaths but missing the data on haemorrhagic stroke deaths.133 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 (41-736). 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).60 66 Discordance in either the direction and/or the statistical significance was found for the remaining four outcomes: glomerular filtration rate (n=2),80 89 end stage kidney disease (n=2),80 89 systolic blood pressure (n=2),90 93 and diastolic blood pressure (n=2).90 93

Twenty unique meta-analyses (table 3) were identified for the outcomes in relation to kidney disorders (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 (I²<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,114 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 343-20682) and median number of cases was 2225 (19-65877). The proportion of variance in SUA level (R²) 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),79 80 86 101 102 110 115 127 bone mineral density in femoral neck (n=2),79 80 coronary heart disease (n=5),76 96 100 110 118 126 diastolic blood pressure (n=7),76 96 101 106 110 119 123 systolic blood pressure (n=7),76 96 101 106 110 119 123 metabolic syndrome (n=2),90 120 glucose level (n=3),90 106 123 triglyceride level (n=3),90 123 diabetes (n=6),76 99 105 100 122 127 serum creatinine level (n=2),110 129 estimated glomerular filtration rate (n=5),90 106 131 129 Parkinson’s disease (n=5),111 112 116 117 125 memory performance (n=2),114 and gout (n=3),90 106 108

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 andmeta-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.26 115 116 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 (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 (I²>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%, 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%). 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 hyperuricaemia are related to gout or nephrolithiasis. Since a wide range of health outcomes has been identified to be associated with SUA level, a renewed interest in whether individuals with asymptomatic hyperuricaemia 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). 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. 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. 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. 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 uricosteatosis 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. 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. 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 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. 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, 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.


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. For 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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Data sharing: No additional data available.

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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 reduced disease), 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 nephropathisis.

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

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 (95% CI) | f² | P value for Egger test | P value for excess significance test | 95% prediction interval | Evidence class |
|---------------------------------|--------------|----------------------------|------------|---------------|-------------------|-------------|----------------|----------------------|-------------------|-----|------------------------|--------------------------------------|--------------------------|---------------|
| **Cardiovascular outcomes**     |              |                            |            |               |                   |             |                |                      |                   |     |                        |                                      |                          |               |
| AF†                             | General      | Prospective cohort         | Hyper v normal | 6             | 426 159          | 7595        | RR             | 1.49 (1.24 to 1.79) | 2.50E-05 (79)  | 0.01 | 0.22                   | 0.87 to 2.53                      | III                       |               |
| AF recurrence†                  | 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)  | 0.72 | 0.26                   | 0.27 to 7.01                    | IV                        |               |
| Coronary heart disease incidence‡| General      | Prospective cohort         | Hyper v normal | 13            | 70 382           | 6666        | aRR            | 1.13 (1.05 to 1.21) | 7.70E-04 (38)  | 0.27 | <0.001                 | 0.94 to 1.34                     | III                       |               |
| Cardiovascular disease‡         | Patients with hypertension | Prospective cohort         | Hyper v normal | 6             | 19 546           | 1054        | aHR            | 1.17 (1.07 to 1.27) | 3.56E-04 (67)  | 0.05 | 0.04                   | 0.90 to 1.52                     | III                       |               |
| 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)  | 0.49 | 0.31                   | 1.05 to 2.61                     | II                        |               |
| Hypertension incidence‡         | General      | Prospective cohort or nested case-control | Hyper v normal | 17            | 71 630           | 18 751      | aRR            | 1.48 (1.33 to 1.65) | 3.99E-12 (79)  | 0.06 | NP                     | 0.99 to 2.23                     | II                        |               |
| Prehypertension§ General        | Cross sectional |                            | Highest v lowest SUA category | 8             | 44 095           | 20 832      | OR             | 1.84 (1.42 to 2.38) | 4.88E-06 (91)  | 0.10 | NP                     | 0.81 to 4.01                     | III                       |               |
| Left atrial thrombus or spontaneous echo contrast‡| 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)  | 0.02 | NP                     | 0.54 to 4.70                     | IV                        |               |
| MACE†‡                          | 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   | NA                     | NA                                      | NA                       | IV             |
| Medium term MACE‡                | 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)  | 0.81 | NP                     | 0.46 to 8.21                     | III                       |               |
| Short term MACE‡                | 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)  | 0.25 | NP                     | 1.06 to 5.71                     | IV                        |               |
| Stroke‡                         | Hypertensive patients | Prospective or retrospective cohort | Continuous SUA level | 3             | 9978             | 217         | aHR            | 1.11 (0.98 to 1.26) | 0.10 (NA)       | 0.22 | 0.06                   | 0.26 to 4.77                     | NS                       |               |
| Stroke incidence§ General       | Prospective cohort | Highest v lowest SUA category |                      | 5             | 24 548           | 1290        | aRR            | 1.22 (1.02 to 1.46) | 0.03 (3)        | 0.03 | NP                     | 0.73 to 2.04                     | IV                        |               |
| **Diabetes related outcomes**   |              |                            |            |               |                   |             |                |                      |                   |     |                        |                                      |                          |               |
| T2DM‡                           | General      | Prospective or retrospective cohort | 1 mg/dL SUA increase | 11            | 42 834           | 3305        | RR             | 1.17 (1.09 to 1.25) | 8.97E-06 (75)  | 0.07 | 0.002                  | 0.92 to 1.47                     | III                       |               |
| Impaired fasting glucose or T2DM§| General      | Prospective or retrospective cohort | Highest v lowest SUA category | 12            | 62 834           | 6340        | RR             | 1.57 (1.39 to 1.77) | 1.12E-12 (42)  | 0.09 | NP                     | 1.10 to 2.23                     | II                        |               |
Table 1 (continued)

| 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 | I² (95% CI) | P value for excess significance test | 95% prediction interval | Evidence classification |
|-----------------------------------|-----------------------------------|-----------------------------|-------------------|---------------|-------------------|-------------|----------------|-----------------------|---------|------------|--------------------------------------|------------------------|------------------------|
| Diabetes incidence†‡              | 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                                   | NA                     | IV                     |
| Diabetic nephropathy§             | 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) | NA                                   | NA                     | IV                     |
| Diabetic microvascular complications§ | Patients with T2DM                | Case-control                | Continuous or categorical SUA level | 5             | 4513              | 854         | OR              | 1.42 (1.11 to 1.85)   | 0.006   | 83 (61 to 90) | NA                                   | NA                     | IV                     |
| Diabetic vascular complications§  | Patients with T2DM                | Case-control                | Continuous or categorical SUA level | 6             | 5017              | 967         | OR              | 1.27 (1.11 to 1.45)   | 4.36E-04| 77 (57 to 86) | 0.02                                | 0.51 (0.87 to 1.86)  | IV                     |
| Diabetic peripheral neuropathy§   | Patients with diabetes            | Cohort or case-control      | Hyper v normal    | 5             | 4097              | 894         | RR              | 2.83 (2.13 to 3.76)   | 0.04    | 78 (23 to 89) | 0.94                                | 0.93 (1.05 to 7.62)  | IV                     |
| Diabetic macrovascular complications§ | 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§             | 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                                   | NA                     | NS                     |

### Kidney disorders

| CKD incidence†§                   | Middle aged populations          | Prospective or retrospective cohort | Hyper v normal | 15            | 99205            | 3492        | RR              | 1.22 (1.16 to 1.28)   | 0.22    | NA         | 0.12 (0.94 to 1.44)  | 0.01 (0.88 to 1.44)  | IV                     |
| CKD new onset incidence§         | Non-CKD population               | Prospective or retrospective cohort | Hyper v normal | 7             | 153620           | 7014        | HR              | 1.13 (1.04 to 1.22)   | 0.13    | 83 (63 to 90) | 0.24                                | 0.88 (0.88 to 1.44)  | IV                     |
| CKD new onset incidence†§        | Patients with diabetes           | Prospective or retrospective cohort | Hyper v normal | 2             | NA               | NA          | HR              | 1.90 (1.30 to 2.78)   | 0.90    | NA         | 0.94 (NA to NA)       | 0.94 (NA to NA)       | IV                     |
| Estimated glomerular filtration rate§ | Renal transplant recipients     | Prospective or retrospective cohort | Hyper v normal | 8             | 2075             | NA          | MD to OR       | 0.36 (0.26 to 0.52)   | 0.36    | 66 (39 to 79) | 0.81                                | 0.13 (0.81 to 1.06)  | IV                     |
| Serum creatinine§                 | Renal transplant recipients      | Prospective or retrospective cohort | Hyper v normal | 5             | 873              | NA          | MD to OR       | 2.45 (0.35 to 3.54)   | 0.15    | 40 (0 to 77) | 0.65                                | 0.88 (0.68 to 0.88)  | IV                     |
| Graft loss§                       | Renal transplant recipients      | Prospective or retrospective cohort | Hyper v normal | 3             | 910              | 154         | OR              | 4.26 (1.54 to 3.38)   | 0.56    | 0 (0 to 73) | 0.05                                | 0.18 (0.18 to 29.36) | IV                     |
| Chronic allograft nephropathy§    | Renal transplant recipients      | Prospective or retrospective cohort | Hyper v normal | 4             | 1057             | 113         | OR              | 2.81 (1.65 to 4.75)   | 0.92    | 26 (0 to 75) | 0.53                                | 0.53 (0.53 to 14.76) | IV                     |

### Neurocognitive disorders

| Alzheimer’s disease§             | 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                                | 0.01 (0.89)          | IV                     |
| Dementia or cognitive impairment§ | General                          | Cohort or case-control          | SUA level (mg/dL) | 31            | 7021             | 2681        | SM to OR      | 0.58 (0.41 to 0.83)   | 0.003   | 89 (86 to 91) | 0.01                                | 0.04 (0.08 to 4.48)  | IV                     |
Table 1 (continued)

| 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^2 (%) | P value for excess significance test | P value for trend | 95% prediction interval | Evidence class |
|-----------------------------------------------|-------------------------------------|-----------------------------|-----------------------|---------------|--------------------|-------------|-----------------|-----------------------|----------|---------|--------------------------------------|--------------------|------------------------|----------------|
| Venous Thromboembolism                        | Patients with VT v control          | Cohort or nested case-control | SUA level (µmol/L)    | 4             | 731                | 515         | SMD to OR      | 0.65 (0.20 to 2.17)  | 0.49     | 92      | 0.01 to 0.06                         | NS                 | 0.01 to 200.17          | IV              |
| Parkinson’s disease incidence                 | Patients with PD v controls         | Cohort or nested case-control | Hyper G to OR (mg/dL) | 6             | 33 185             | 578         | RR              | 0.65 (0.43 to 0.97)  | 0.04     | 42      | 0.24 to 1.77                         | NS                 | 0.05 to 4.96            | IV              |
| Multiple sclerosis                            | 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      | 0.02 to 3.14                         | IV                 | 0.04 to 1.05            | IV              |
| NMO***                                        | Patients with NMN v controls        | Case-control                | SUA level (µmol/L)    | 3             | 1137               | 229         | SMD to OR      | 0.22 (0.10 to 0.45)  | 9.07E-05 | 82      | 0.02 to 3.14                         | IV                 | 0.04 to 1.05            | IV              |
| ALS***                                        | Patients with ALS v controls        | Case-control                | SUA level (µmol/L)    | 3             | 826                | 311         | SMD to OR      | 0.21 (0.14 to 0.32)  | 6.33E-13 | 51      | 0.04 to 7.46                         | IV                 | 0.07 to 4.96            | IV              |
| Schizophrenia (chronic)†                      | Patients with schizophrenia v controls | Case-control                | SUA level (µmol/L)    | 2             | 274                | 155         | Hedge's G to OR| 0.72 (0.43 to 1.21) | 0.22     | NA      | NA                                   | NS                 | NA         | NS             |
| Schizophrenia (first episode psychosis)†       | Patients with schizophrenia v controls | Case-control                | SUA level (µmol/L)    | 3             | 277                | 103         | Hedge's G to OR| 0.37 (0.23 to 0.59)  | 4.16E-05 | 0       | 0.02 to 7.75                         | IV                 | 0.02 to 7.75            | IV              |
| Bipolar disorder**                           | Patients with bipolar disorder v controls | Case-control                | SUA level (µmol/L)    | 9             | 1127               | 619         | SMD to OR      | 3.23 (1.82 to 5.73)  | 7.09E-05 | 83      | 0.65 to 12.39                        | IV                 | 0.02 to 12.39           | IV              |

Cancer outcomes

| Cancer incidence***                          | General prospective cohort         | Highest v lowest SUA category | RR (95% CI) | P value | I^2 (%) | P value for excess significance test | 95% prediction interval | Evidence class |
|---------------------------------------------|-----------------------------------|-------------------------------|-------------|----------|---------|--------------------------------------|------------------------|----------------|
| Cancer incidence in digestive organs***     | General prospective cohort        | Highest v lowest SUA category | 1.04 (0.99 to 1.08) | 0.08     | 45      | 0.16                                 | 0.93 to 1.14           | NS              |
| Cancer incidence in lymphoid and haematopoietic system*** | General prospective cohort        | Highest v lowest SUA category | 1.01 (0.96 to 1.07) | 0.19     | 53      | 0.36                                 | 0.81 to 1.05           | NS              |
| Cancer incidence in male genital organs***  | General prospective cohort        | Highest v lowest SUA category | 1.05 (0.99 to 1.21) | 0.43     | 61      | 0.63                                 | 0.28 to 1.05           | NS              |
| Cancer incidence in respiratory system and intrathoracic organs*** | General prospective cohort        | Highest v lowest SUA category | 1.05 (0.99 to 1.21) | 0.43     | 61      | 0.63                                 | 0.28 to 1.05           | NS              |
| Cancer incidence in urinary organs***       | General prospective cohort        | Highest v lowest SUA category | 1.04 (0.99 to 1.18) | 0.19     | 53      | 0.36                                 | 0.81 to 1.05           | NS              |

All cause and cause specific mortality
### Table 1 (continued)

| 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 | P value for excess significance test | 95% prediction interval | Evidence class |
|---------------------------------|--------------------------|-----------------------------|-------------------------|---------------|--------------------|-------------|-----------------|-------------------------|---------|-------------------------------------|------------------------|----------------|
| Coronary heart disease mortality† | General                  | Prospective cohort          | Hyper v normal          | 13            | 876 584             | 24          | RR              | 1.27 (1.16 to 1.39) | 3.46E-07 | 0.10                               | 0.96 to 1.69          | II |
| CVD mortality†                  | General                  | Prospective cohort          | Highest v lowest SUA category | 9             | 165 806             | 6121        | RR              | 1.37 (1.19 to 1.57) | 1.07E-05 | 0.59                               | 0.92 to 2.03           | III |
| CVD mortality†† Patients with heart failure | Prospective cohort | Hyper v normal           | 2                  | NA            | 2250               | NA          | HR              | 1.45 (1.18 to 1.78) | 4.25E-04 | NA                                  | NA                    | NA |
| CVD mortality†† Patients with hypertension  | Prospective or retrospective cohort | Hyper v normal           | 3                  | NA            | NA                 | NA          | aHR             | 1.31 (0.96 to 1.78) | 0.09    | NA                                  | NA                    | NA |
| Stroke mortality†                | General                  | Prospective cohort          | Highest v lowest SUA category | 9             | 1 017 810           | 21          | RR              | 1.32 (1.23 to 1.41) | 1.11E-14 | 0.92                               | 1.13 to 1.56           | III |
| CKD mortality†                  | General                  | Prospective cohort          | 1 mg/dl SUA increase  | 21            | 23 443             | 3904        | aHR             | 1.07 (1.04 to 1.11) | 5.46E-05 | 0.04                               | 0.93 to 1.24           | III |
| Cancer mortality‡                | General                  | Prospective cohort          | Highest v lowest SUA category | 12            | 632 472             | NA          | RR              | 1.17 (1.04 to 1.32) | 0.01    | 0.36                               | 0.82 to 1.69           | IV |
| Cancer mortality in digestive organs† | General                  | Prospective cohort          | Highest v lowest SUA category | 4             | 187 886             | 855         | RR              | 1.22 (0.86 to 1.74) | 0.27    | 0.99                               | 0.45 to 3.31           | NS |
| Cancer mortality in bone, connective tissue, soft tissue, and skin†† | 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 |
| Cancer mortality in lymphoid and haematopoietic systems†† | 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 |
| Cancer mortality in male genital organs†| General                  | Prospective cohort          | Highest v lowest SUA category | NA            | 88 033             | NA          | RR              | 0.51 (0.07 to 3.65) | 0.52    | NA                                  | NA                    | NA |
| Cancer mortality in respiratory system and intrathoracic organs†† | General                  | Prospective cohort          | Highest v lowest SUA category | 2             | 116 646             | 164         | RR              | 1.08 (0.61 to 1.91) | 0.80    | NA                                  | NA                    | NA |
| Cancer mortality in urinary organs†| General                  | Prospective cohort          | Highest v lowest SUA category | 2             | 112 296             | NA          | RR              | 1.35 (0.88 to 2.07) | 0.17    | NA                                  | NP                    | NA |
| All cause mortality†             | Patients with heart failure | Cohort or case-control    | Hyper v normal          | 11            | 12 444             | 1888        | HR              | 2.15 (1.64 to 2.83) | 6.64E-08 | 0.01                               | 0.87 to 5.31           | II |
| Short term mortality†             | 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 | 0.83                               | 1.74 to 6.06           | IV |
| Medium term mortality†           | 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 | 0.66                               | 1.09 to 6.67           | IV |
Table 1 (continued)

| 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 | I² (%) | P value for excess significance test | P value for Egger test | 95% prediction interval | Evidence class |
|-----------------------------------|-----------------------------|-----------------------------|------------|---------------|-------------------|-------------|-----------------|------------------------|---------|--------|--------------------------------------|------------------------|------------------------|-------------------|
| In hospital mortality†            | Patients with AMI           | Cohort                      | Hyper 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†              | Patients with T2DM         | Cohort or case-control      | Hyper 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†              | 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†              | Patients after PCI         | Prospective or retrospective cohort | Hyper 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†              | Hypertensive patients      | Prospective or retrospective cohort | Hyper 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                  |
| All cause mortality†              | Patients with CKD          | Prospective or retrospective cohort | Hyper v normal | 5               | 1789             | 609         | RR              | 1.67 (1.29 to 2.16)    | 1.09E−04 | NA     | NA                                    | NA                     | NA                     | NA                | IV                  |
| Other outcomes                    |                             |                             |            |               |                   |             |                 |                        |         |        |                                      |                       |                        |                   |
| Medium or long term occurrence of death or MACE† | 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† | 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† | Patients with heart failure | Cohort, case-control, or 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)† | 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†     | 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†                        | 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†                 | 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† | General                   | Prospective or retrospective cohort, or case-control | Highest v lowest SUA category | 9               | 55 573           | 10          | 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; VaD = vascular dementia; MCI = 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 more than 1000 cases in one single study, respectively).
Table 1 (continued)

| 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 | I² (95% CI) | P value for excess significance test | P value for Egger test | 95% prediction interval | Evidence class |
|----------|------------|-----------------------------|------------|---------------|-------------------|-------------|----------------|------------------------|---------|-------------|----------------------------------|----------------------|-------------------------|------------------|

>20 000 participants for continuous outcomes), the largest component study reported statistically significant effect (P<0.05); 95% prediction interval excluded the null; no large heterogeneity (I² <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 >20 000 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 >20 000 participants for continuous outcomes); class IV (weak): the remaining statistically significant associations with P<0.05.

†The heterogeneity (I²), 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 found. When errors and analyses 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 | No of metrics | Type of metric | Relative risk (95% CI) | P value for excess significance test | P value for Egger test | P value | 95% prediction interval | Evidence class |
|---------------------------|----------------|-----------------------------|------------|---------------|--------------------|-------------|---------------|----------------|------------------------|------------------------------|-----------------------|----------|--------------------------|---------------|
| Stroke mortality          | General        | Prospective cohort          | Highest v lowest SUA category | 8            | 600 076           | 5205        | aRR           | (0.91 to 1.51) | 0.22                   | 0.44                         | NS                    | 0.46 to 2.98              | NS (changed from I) |
| Heart failure incidence   | General        | Prospective cohort          | Hyper v normal | 5            | 427 917           | 117         | HR            | (1.41 to 1.94) | 1.77E-09               | 0.49                         | 0.31                  | 1.05 to 2.61              | II             |
| Hypertension incidence    | General        | Prospective cohort          | Hyper v normal | 12           | 68 401            | 16          | aRR           | (1.27 to 1.59) | 2.16E-09               | 0.04                         | NP                    | 0.98 to 2.05              | II             |
| IFG/T2DM                  | General        | Prospective cohort          | Highest v lowest SUA category | 13           | 56 130            | 5629        | RR            | (1.47 to 1.77) | 1.25E-22               | 0.07                         | NP                    | 1.45 to 1.79              | II             |
| CKD incidence             | Middle aged populations | Prospective cohort          | Highest v lowest SUA category | 12           | 78 205            | 2793        | RR            | (1.12 to 1.25) | 1.26E-09               | 0.10                         | 0.15                  | 0.99 to 1.42              | II             |
| CHD mortality             | General        | Prospective cohort          | Hyper v normal | 13           | 876 584           | 24          | aRR           | (1.16 to 1.39) | 3.47E-07               | 0.10                         | NP                    | 0.96 to 1.69              | II             |
| All cause mortality       | Patients with HF | Prospective cohort          | Hyper v normal | 6            | 9608              | 1474        | HR            | (1.59 to 3.56) | 2.98E-05               | 0.05                         | 0.39                  | 0.61 to 9.35              | (changed from II) |
| Non-alcoholic fatty liver disease† | General | Prospective cohort          | Highest v lowest SUA category | 2            | 12 631            | 2530        | OR            | (1.20 to 1.71) | 8.63E-05               | NA                           | NA                    | NA                   | (changed from III) |

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 >20 000 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^{-4}, more than 1000 cases (or >20 000 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 >20 000 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.
| Outcomes                          | Population                             | Treatment | SUA lowering treatment | No of studies | No of participants | No of participants | Type of metric | Relative risk (95% CI) | P value for excess significance test | I² (95% CI) | P value for Egger's test | P value for SMD to OR | 95% prediction interval |
|----------------------------------|----------------------------------------|-----------|------------------------|---------------|-------------------|-------------------|----------------|-----------------------|--------------------------------------|-------------|------------------------|---------------------|------------------------|
| Kidney disorders                 |                                        |           |                        |               |                   |                   |                |                       |                                      |             |                        |                     |                        |
| Recurrence of nephrolithiasis†   | Patients with nephrolithiasis          | Allopurinol |                        | 2             | 152               |                   | RR             | 0.59 (0.42 to 0.84)  | 2.90E-03                         | NA          | NA                     | NA                  | NA                     |
| Recurrence of nephrolithiasis‡   | Patients with nephrolithiasis          | Thiazides  |                        | 5             | 300               |                   | RR             | 0.52 (0.39 to 0.69)  | 9.00E-06                         | 0.06        | 0.11                   | 0.33 to 0.82         |                       |
| Recurrence of nephrolithiasis‡   | Patients with nephrolithiasis          | Citrates   |                        | 4             | 197               |                   | RR             | 0.26 (0.15 to 0.45)  | 2.84E-06                         | 0.19        | NP                     | 0.08 to 0.88          |                       |
| Serum creatinine†                | General                                | All active treatment |                | 9             | 580               |                   | SMD to OR       | 0.10 (0.03 to 0.39)  | 4.64E-04                         | 0.39        | NP                     | 0.01 to 13.21         |                       |
| Serum creatinine**               | Patients with CKD                      | Allopurinol |                        | 6             | 354               |                   | MD to OR        | 0.16 (0.08 to 0.34)  | 1.00E-06                         | 0.01        | 0.59                   | 0.02 to 1.76          |                       |
| eGFR†                            | General                                | All active treatment |                | 3             | 218               |                   | SMD to OR       | 2.22 (1.21 to 4.06)  | 9.79E-03                         | 0.24        | NP                     | 0.01 to 497.40        |                       |
| eGFR‡                            | Patients with CKD or decreased kidney function | Allopurinol |                        | 5             | 346               |                   | MD to OR        | 1.18 (0.97 to 1.42)  | 0.09                  | 0.0 (0 to 64)         | 0.29        | NP                     | 0.86 to 1.60          |                       |
| Proteinuria†                     | Patients with CKD or decreased kidney function | Allopurinol |                        | 5             | 250               |                   | MD to OR        | 0.91 (0.73 to 1.12)  | 0.40                  | 0.0 (0 to 64)         | 0.42        | NP                     | 0.64 to 1.28          |                       |
| Blood urea nitrogen†             | Patients with CKD                      | Allopurinol |                        | 3             | 169               |                   | MD to OR        | 0.18 (0.10 to 0.32)  | 1.47E-08                         | 0.88        | 0.67                   | 0.01 to 7.16          |                       |
| End stage renal disease**        | Patients with CKD                      | Allopurinol |                        | 5             | 267               |                   | RR             | 0.33 (0.21 to 0.51)  | 1.38E-06                         | 0.01        | 0.07                   | 0.16 to 0.68          |                       |
| Endothelial function             |                                        |           |                        |               |                   |                   |                |                       |                                      |             |                        |                     |                        |
| Flow mediated dilatation*        | 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                         | 0.23        | 0.24                   | 0.27 to 70.69         |                       |
| Forearm blood flow‡              | 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 30.73         |                       |
| Mortality                        |                                        |           |                        |               |                   |                   |                |                       |                                      |             |                        |                     |                        |
| Death during neonatal period or infancy† | 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‡ | 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 serve neurodevelopmental disability† | 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 serve neurodevelopmental disability‡ | Infants with severe hypoxic-ischaemic encephalopathy | Allopurinol |                        | 2             | 41                |                   | RR             | 0.93 (0.67 to 1.30)  | 0.68                  | NA                    | NA         | NP                     | NA                  |                       |
| Other outcomes                   |                                        |           |                        |               |                   |                   |                |                       |                                      |             |                        |                     |                        |
| Severe quadriplegia†             | 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‡     | 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‡         | 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        |                       |
Table 3 (continued)

| Outcomes                  | Population                                    | SUA lowering treatment | No of studies | No of participants | Type of metric | Relative risk (95% CI) | P value for excess significance test | P value for Egger’s test | I² (95% CI) | P value | 95% prediction interval |
|---------------------------|------------------------------------------------|------------------------|---------------|--------------------|----------------|------------------------|-------------------------------------|-------------------------|-------------|---------|------------------------|
| Diastolic blood pressure‡ | 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 (I²), 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.
| Outcomes                                      | Population     | No/No of Events (No of studies)* | Genetic instruments (GI)                      | SUA variance (R²) explained by GI (%) | Type of metric | Estimate of effect (95% CI) | P value | Statistical power † |
|----------------------------------------------|----------------|----------------------------------|-----------------------------------------------|----------------------------------------|----------------|-----------------------------|---------|----------------------|
| **Anthropometric variables**                 |                |                                  |                                               |                                        |                |                             |         |                      |
| Appendicular lean mass (kg)†                 | UK             | 3953                             | rs737267 in SCL2A9                             | NA                                     | β              | 0.013 (NA)                  | 0.51    | NA                   |
| Fat mass (kg)‡                               | Switzerland    | 6184                             | rs6855911 in SCL2A9                            | 3.2                                    | β              | 0.05 (−0.10 to 0.19)       | 0.52    | 0.07                 |
| Body mass index (kg/m²)‡                     | 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)‡                    | Switzerland    | 6184                             | rs6855911 in SCL2A9                            | 3.2                                    | β              | 0.08 (−0.05 to 0.21)       | 0.24    | 0.06                 |
| BMD in femoral neck (g/cm²)†                 | 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/cm²)‡                        | 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/cm²)‡                        | USA            | 2501                             | Genetic risk score of 5 SUA related SNPs       | 3.3                                    | β              | 0.06 (−0.32 to 0.48)       | 0.68    | 0.18                 |
| BMD in total femur (g/cm²)‡                  | 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/cm²)‡                    | China          | 1667                             | Genetic risk score of 5 SUA related SNPs       | 1.8                                    | β              | 0.19 (−0.36 to 0.74)       | 0.50    | 0.19                 |
| **Cardiovascular outcomes**                  |                |                                  |                                               |                                        |                |                             |         |                      |
| Arrhythmia‡                                  | 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‡                         | 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‡                              | 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‡                      | Europe         | 206 822/85 877 (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‡                               | Pakistan       | 22 926/4526 (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‡                     | Denmark        | 68 674/3742 (2)*                 | rs7442295 in SCL2A9                            | 2.2                                    | HR             | 0.93 (0.79 to 1.09)        | 0.38    | 0.10                 |
| Hypertension‡                                | 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‡                            | 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‡                 | 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‡                               | 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‡              | 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)†                                   | Finland (male) | 1985                             | rs13129697 in SCL2A9                           | NA                                     | β              | <0.0001 (NA)               | 0.99    | NA                   |
| Arterial stiffness (internal diameter of carotid artery (mm))† | Italy | 449                               | rs734553 in SCL2A9                             | NA                                     | β              | 0.48 (NA)                  | 0.003   | NA                   |
| Diastolic blood pressure (mm Hg)‡            | 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)‡             | Europe         | 89 667 (37)*                     | Genetic risk score of 31 SUA related SNPs      | 4.2                                    | MD‡            | 0.005 (0.003 to 0.006)     | NA      | NA                   |
| **Metabolic disorders**                      |                |                                  |                                               |                                        |                |                             |         |                      |
| Type 2 diabetes‡                             | Pakistan       | 110 452/26 488 (2)*              | Genetic risk score of 14 SUA related SNPs      | 3.1                                    | OR             | 0.96 (0.86 to 1.05)        | 0.28    | 0.24                 |

† Statistical power calculated using R software.
| Outcomes | Population | No/No of Events (No of studies)* | Genetic instruments (GI) | SUA variance (R²) explained by GI (%) | Type of metric | Estimate of effect (95% CI) | P value | Statistical power† |
|----------|------------|----------------------------------|--------------------------|---------------------------------------|----------------|---------------------------|---------|-------------------|
| Diabetes* | 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)* | 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* | USA | 19,899 (5)* | Genetic risk score of 8 SUA related SNPs | 6.0 | Z statistic | −0.015 (NA) | 0.99 | NA |
| Metabolic syndrome* | China | 7827 | Genetic risk score of 2 SNPs (rs11722228 in SLC2A9 and rs2311142 in ABCG2) | 2.1 | OR | 1.03 (0.98 to 1.09) | 0.23 | NA |

**Kidney disorders**

| Chronic kidney disease* | 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* | USA | 7553/2823 | 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* | Italy | 755/244 | rs734553 in GLUT9 | NA | HR | 2.35 (1.25 to 4.42) | 0.01 | NA |
| Log eGFR (mL/min/1.73 m²)* | USA | 23,844 (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)* | 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* | USA (Indian American) | 3604 (3)* | Genetic risk score of 5 SUA related SNPs | 5.3 | Residual variance | Overall P>0.05 | NA | |

**Neurocognitive disorders**

| Parkinson’s disease* | 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* | Europe | 664 (3)* | 4 SNPs in SLC2A9 | NA | β | Null after multiple testing correction | 3.10 (0.17 to 6.03) | 0.04 | NA |
| | | | rs732767 | NA | | | | 3.03 (0.87 to 10.95) | 0.32 | NA |
| | | | rs6449213 | NA | | | | | |
| | | | rs1014290 | NA | | | | | |
| | | | rs733175 | NA | | | | | |
| Lifetime anxiety disorders* | Switzerland | 3716 | rs6855911 in SLC2A9 | 3.2 | OR (male) | 1.40 (1.07 to 1.84) | 0.02 | 0.11 |
| | | | rs6855911 in SLC2A9 | 3.2 | OR (female) | 0.97 (0.80 to 1.17) | 0.73 | 0.05 |
| Current anxiety disorders* | Switzerland | 3716 | rs6855911 in SLC2A9 | 3.2 | OR (male) | 1.42 (0.99 to 2.03) | 0.06 | 0.12 |
| | | | rs6855911 in SLC2A9 | 3.2 | OR (female) | 0.84 (0.66 to 1.06) | 0.14 | 0.07 |
| Memory performance* | Europe: Population 1 | 1091 | 4 SNPs in SLC2A9 | NA | β | Overall P>0.05 | NA | |
| | Europe: Population 2 | 1066 | 4 SNPs in SLC2A9 | NA | β | Overall P>0.05 | NA | |

**Metabolites**

| High density lipoprotein cholesterol (mmol/L)* | Europe | 196,621 (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)* | Europe | 196,621 (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)* | Europe | 196,621 (68)* | Genetic risk score of 31 SUA related SNPs | 4.2 | MD‡ | 0.000 (−0.002 to 0.002) | NA | NA |
| Triglyceride (mmol/L)* | Europe | 196,621 (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)* | 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)* | China | 1667 | Genetic risk score of 5 SUA related SNPs | 1.8 | β | −0.16 (−0.74 to 0.42) | 0.59 | 0.05 |
Table 4 (continued)

| Outcomes | Population | No/No of Events (No of studies)* | Genetic instruments (GI) | SUA variance (R²) explained by GI (%) | Type of metric | Estimate of effect (95% CI) | P value | Statistical power† |
|----------|------------|----------------------------------|--------------------------|--------------------------------------|----------------|---------------------------|---------|-------------------|
| C-reactive protein (mg/L)*| 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)*| 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)*| 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)*| China | 1667 | Genetic risk score of 5 SUA related SNPs | 1.8 | β | −1.45 (−3.17 to 0.27) | 0.10 | 0.05 |
| Calcifiedol (ng/mL)*| China | 1667 | Genetic risk score of 5 SUA related SNPs | 1.8 | β | 0.76 (−0.63 to 2.15) | 0.28 | 0.05 |

All cause and cause specific mortality

| Outcomes | Population | No/No of Events (No of studies)* | Genetic instruments (GI) | SUA variance (R²) explained by GI (%) | Type of metric | Estimate of effect (95% CI) | P value | Statistical power† |
|----------|------------|----------------------------------|--------------------------|--------------------------------------|----------------|---------------------------|---------|-------------------|
| Cardiovascular mortality* | 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* | 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* | Germany | 3060/NA | Genetic risk score of 8 SUA related SNPs | NA | aHR | 1.18 (1.03 to 1.35) | 0.02 | NA |

Other outcomes

| Outcomes | Population | No/No of Events (No of studies)* | Genetic instruments (GI) | SUA variance (R²) explained by GI (%) | Type of metric | Estimate of effect (95% CI) | P value | Statistical power† |
|----------|------------|----------------------------------|--------------------------|--------------------------------------|----------------|---------------------------|---------|-------------------|
| Cancer* | 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** | Pakistan | 71 501/3151 (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; BMD=bone mineral density; 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 R²; we used the extrapolated R² 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.
| 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.
## Figure

**Fig 1** Study flowchart

| Publications identified from Medline, Embase, and Cochrane Library (n=4608) |
|---|
| Excluded (n=4163): |
| Duplicate publications (n=402) |
| Publications removed by title, abstract review (n=3761) |
| Publications eligible for full text review (n=445) |
| Excluded (n=344): |
| Not systematic review, meta-analysis, or Mendelian randomisation study (n=183) |
| Systematic review, meta-analysis, or Mendelian randomisation study not related to hyperuricemia or serum uric acid (n=31) |
| Systematic review or meta-analysis about gout or prevalence, genetics of hyperuricemia, or serum uric acid (n=12) |
| Systematic review of case report or series (n=6) |
| Systematic review or meta-analysis of efficacy of serum uric acid lowering drugs (n=26) |
| Meta-analysis of randomised controlled trials included non-drug intervention or antihypertension drugs (n=7) |
| Publications not in English or Chinese (n=63) |
| Abstract only (n=16) |

Publications included (n=101):
- Observational studies (n=57; 10 systematic reviews and 47 meta-analyses)
- Meta-analyses of randomised controlled trials (n=8)
- Mendelian randomisation studies (n=36)