European Journal of Preventive Cardiology

Original scientific paper

European Journal of Preventive Cardiology
2015, Vol. 22(3) 335–343

DOI: 10.1177/2047487313514895
ejpc.sagepub.com
SAGE

Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis

LE Clarson[1], P Chandratre[1], SL Hider[1], J Belcher[1], C Heneghan[2], E Roddy[1] and CD Mallen[1]

Abstract

Background: Hyperuricaemia, the biochemical precursor to gout, has been shown to be an independent risk factor for mortality from cardiovascular disease (CVD), although studies examining the clinical phenomenon of gout and risk of CVD mortality report conflicting results. This study aimed to produce a pooled estimate of risk of mortality from cardiovascular disease in patients with gout.

Design: Systematic review and meta-analysis.

Methods: Electronic bibliographic databases were searched from inception to November 2012, with results reviewed by two independent reviewers. Studies were included if they reported data on CVD mortality in adults with gout who were free of CVD at time of entry into the study. Pooled hazard ratios (HRs) for this association were calculated both unadjusted and adjusted for traditional vascular risk factors.

Results: Six papers, including 223,448 patients, were eligible for inclusion (all (CVD) mortality $n = 4$, coronary heart disease (CHD) mortality $n = 3$, and myocardial infarction mortality $n = 3$). Gout was associated with an excess risk of CVD mortality (unadjusted HR 1.51 (95% confidence interval, CI, 1.17–1.84)) and CHD mortality (unadjusted HR 1.59, 95% CI 1.25–1.94)). After adjusting for traditional vascular risk factors, the pooled HR for both CVD mortality (HR 1.29, 95% CI 1.14–1.44) and CHD mortality (HR 1.42, 95% CI 1.22–1.63) remained statistically significant, but none of the studies reported a significant association with myocardial infarction.

Conclusions: Gout increases the risk of mortality from CVD and CHD, but not myocardial infarction, independently of vascular risk factors.

Keywords
Cardiovascular disease, coronary heart disease, gout, mortality, myocardial infarction

Received 30 August 2013; accepted 9 November 2013

Introduction

Gout is the most common form of inflammatory arthritis and is estimated to affect 1.4% of the population in the UK and Germany and 4% in the USA.[1,2] In recent literature, both hyperuricaemia (the biochemical precursor to gout) and other inflammatory arthritides have been shown to be independent risk factors for mortality from cardiovascular disease (CVD).[3–6] Several mechanisms for these associations have been suggested, including immobility resulting from joint pain and the additional cardiovascular risk conferred by medications (such as nonsteroidal anti-inflammatory drugs) used to manage these conditions.[7] Latterly, it has been suggested that systemic inflammation leads to atherogenesis via endothelial dysfunction, decreased arterial compliance, impaired blood flow, and thus a proatherogenic state.[8] Therefore patients with gout may be at increased vascular risk due to both hyperuricaemia and crystal-induced inflammation,

[1]Keele University, Keele, UK
[2]Oxford University, Oxford, UK

Corresponding author:
Lorna Clarson, Research Institute for Primary Care and Health Sciences, Keele University, Keele, Staffordshire, ST5 5BG, UK.
Email: l.clarson@keele.ac.uk

now recognized to persist even in the asymptomatic intercritical period.[9]

However, the precise nature of the relationship remains unclear since gout and CVD share many common risk factors, such as hypertension and obesity,[10] introducing a potential source of confounding.

Epidemiological studies examining the relationship between gout and mortality from CVD have, to date, reported conflicting findings even where they are undertaken in similar populations and geographical areas.[11,12] Although one systematic review has been published, no attempt was made to pool the data described.[13]

For this reason, a systematic review and meta-analysis was undertaken to pool estimates of risk from existing studies in order to examine the relationship between gout and mortality from CVD.

Methods

Data sources and searches

Four electronic databases (MEDLINE, EMBASE, CINAHL, and The Cochrane Library) were searched from their inception until 17 November 2012, for studies of the association between gout and cardiovascular mortality. Search terms describing gout (both free-text and using database specific indexing trees) were combined using the Boolean operator 'AND' with terms describing the outcome of cardiovascular mortality. A full list of search terms is available as an online supplement. Reference lists of relevant reports and review articles were screened to identify additional sources of data.

Study selection

Studies were eligible for inclusion if they were of a trial or epidemiological design (cohort, cross-sectional), included adults aged 18 and over, and examined the association of interest in a cohort of patients free from vascular disease at diagnosis of gout. Case–control studies were not included due to the likelihood of sampling and recall bias associated with this design. No geographical or language restrictions were imposed.

Two authors (LC, PC) independently screened all of the titles and abstracts, after which, for those considered potentially relevant, full-text articles were independently reviewed to determine eligibility for inclusion. A third reviewer (SH) was identified in case of disagreement or uncertainty. Studies reporting different definitions of cardiovascular mortality were grouped according to these definitions for analysis. All studies reported mortality coded according to the International Classification of Disease 9th or 10th revision, with comparisons suggesting both revisions identify a similar prevalence of medical conditions.[14] Studies were included if they reported mortality from any of: any CVD (ICD-9 codes 390–459, ICD-10 codes I00–I99), coronary heart disease (CHD: including myocardial infarction, MI; ICD-9 codes 410–414, ICD-10 codes I20–I25), or specifically MI (ICD-9 code 414, ICD-10 codes I21–I22).

Data extraction and quality assessment

Data extraction and quality assessment was undertaken by two reviewers independently (LC, PC), using a specifically designed data extraction form. Methodological quality assessment criteria were based upon the Newcastle–Ottawa scale.[15] This consists of three components; selection of study group, quality of adjustment for confounding, and ascertainment of the outcome of interest in the cohorts (maximum score of nine). Two additional outcome criteria were added, assessing the appropriateness of statistical methods and the separation of patients with gout from those with asymptomatic hyperuricaemia. Authors were contacted for additional information where necessary. Higher methodological quality is indicated by a higher score.

Data synthesis and analysis

Pooled estimates of hazard ratios (HRs) were calculated using the DerSimonian and Laird random-effects model,[16] for mortality from any CVD or CHD. This technique weights individual studies according to sample size and variance, giving a pooled estimate and 95% confidence interval. A random effects model was chosen due to the number of papers included and the likelihood of heterogeneity across study populations. I^2 was used to calculate heterogeneity between studies, estimating the percentage of variability in results attributed to between-study differences.[17] Statistical analysis was performed using STATA IC 12. Publication bias was assessed using funnel plots. Begg's rank correlation test and Egger's linear regression test were used to detect any asymmetry in the funnel plot that may be due to publication bias.[18,19]

Results

Description of the studies

The initial search identified 1293 potentially relevant papers. After title and abstract screening, 1192 papers were excluded either because they did not examine the association of interest or were editorial or discursive articles. The remaining 101 papers were reviewed in

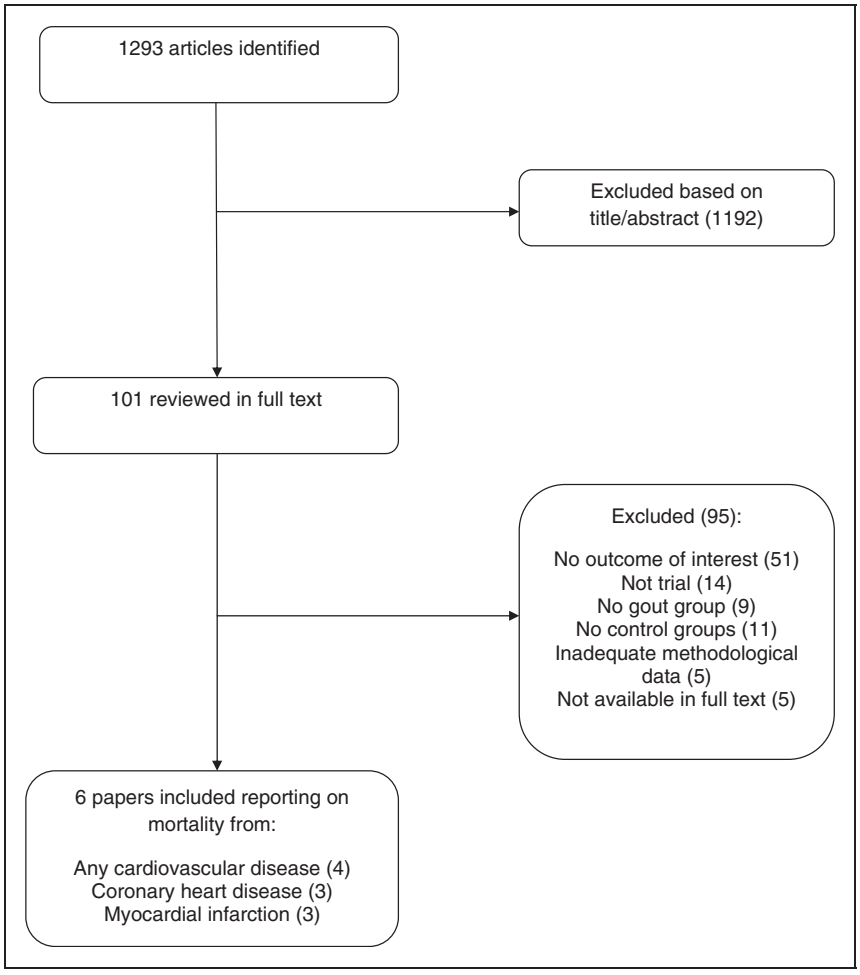

Figure 1. Selection of studies included in the review.

full text, and of these 95 were excluded (Figure 1). Six studies reporting outcomes for 223,448 patients were included: 149,532 men and 73,916 women. Four studies reported on mortality from any CVD,[11,12,20,21] three reported on mortality from CHD,[11,12,20] and three reported on mortality from MI.[11,22,23] Two studies were conducted in Asia[20,21] and four in the USA or Canada.[11,12,22,23] Numbers of participants ranged from 9105[12] to 57,852.[23] Three studies included male-only study populations.[11,12,22] Follow up ranged from 56 months[20] to 17 years.[12] The characteristics of the included studies are described in Table 1.

Scores for methodological quality of studies, where the maximum score was 11, ranged from nine[11,12] to 11,[21] indicating a high level of methodological quality in all included studies.

Gout and mortality from any CVD

The pooled estimate of unadjusted HR for mortality due to any CVD based on four studies was 1.51 (95% CI 1.17–1.84) (comparing patients with gout to those without gout).[11,12,20,21] A significant degree of study heterogeneity was noted ($I^2 = 66.8\%$, $p = 0.029$). Based on the same four studies, after adjustment for vascular risk factors, the pooled multivariate HR for mortality due to any CVD was 1.29 (95% CI 1.13–1.44), with no statistically significant heterogeneity ($I^2 = 0\%$, $p = 0.541$) (Figure 2). The individual vascular risk factors adjusted for in each study are shown in Table 1. Examining the effect of gender on overall CVD mortality, two studies included only men,[11,12] and whilst one study included both men and women, so a separate analysis by gender was not undertaken.[20] One study reported risk of CVD mortality by gender, but did not find increased risk in either gender (men: HR 1.10, 95% CI 0.82–1.46; women: HR 1.51, 95% CI 1.00–2.30).[21]

Gout and mortality from CHD

The pooled estimate of unadjusted HR for mortality due to CHD based on three studies was 1.59 (95% CI 1.25–1.94) (comparing patients with gout to those

Table 1. Characteristics of included studies

Publication	No. of participants (% male)	Age, years (mean + SD)	Follow up (years)	Gout definition	Outcome definition (no. of deaths)	Covariates in multivariable analysis
Krishnan et al.[22]	12,866 (100)	Overall: 46 ± 6 Gout: 47 ± 5 Not gout: 46 ± 6	6.5	Self report of physician diagnosis + documented sustained hyperuricaemia	Fatal acute MI (246)	Clustering within arms of the study, age, blood pressure, serum cholesterol level, serum creatinine level, diabetes, smoking, family history of MI, aspirin use, diuretic use, alcohol use, BMI, serum uric acid level
Choi and Curhan[11]	47,258 (100)	Gout: 59 Not gout: 54 (SD not reported)	12	Self report of physician diagnosis	All cardiovascular deaths (2132) Fatal CHD (1576)	Age, hypertension, hypercholesterolaemia, aspirin/diuretic use, diabetes, smoking, BMI, physical activity, alcohol, family history of MI, energy intake, trans fat, dietary cholesterol, protein, linoleic fatty acid, ratio of polyunsaturated to unsaturated fat
Krishnan et al.[12]	9105 (100)	Gout: 52.9 ± 5.8 Not gout: 52.1 ± 5.9	17	Self report or physician diagnosis + documented sustained hyperuricaemia OR use of gout medication in the preceding 5y OR self report of gout without urate level	Death from any cardiovascular end-point (1241) Fatal MI (360) Fatal CHD (833)	Age, systolic and diastolic blood pressure, low-density lipoprotein cholesterol levels, high-density lipoprotein cholesterol levels, plasma triglyceride levels, serum creatinine levels, fasting glucose level, cigarettes per day, family history of MI, aspirin use, diuretic use, alcoholic drinks per day, BMI
DeVera et al.[23]	57,852 (59.7)	Gout M: 73.9 ± 6.4 F: 75 ± 6.8 Not gout M: 73.3 ± 6.4 F: 75.0 ± 6.8	7	ICD-9 coded	Fatal acute MI (778)	Age, hypertension, diabetes, COPD, hyperlipidaemia, Charlson comorbidity score, monthly prescription drug use of NSAIDs, aspirin, glucocorticoids, statins, anticoagulants, HRT, diuretics

(continued)

Table 1. Continued

Publication	No. of participants (% male)	Age, years (mean + SD)	Follow up (years)	Gout definition	Outcome definition (no. of deaths)	Covariates in multivariable analysis
Kuo et al.[20]	49,332 (53.4)	Gout: 52 ± 11 Not gout: 50 ± 11	4.7	Physican recorded (either crystals present in joint aspirate or ICD-9 gout code) OR self report	Cardiovascular mortality (198)	Normouricaemia/hyperuricaemia/gout, age, gender, number of components of metabolic syndrome, proteinuria
Teng et al.[21]	47,035 (41.4)	Gout: 61.5 ± 7.7 Not gout: 61.6 ± 8.0	8.1	Self report of physician diagnosis + self report of elevated serum urate + self report of dietary advice for gout	All cardiovascular deaths (1526) CHD deaths (855)	Age at follow up, years between baseline and follow up, BMI, gender, dialect group, education, alcohol consumption, physical activity, cigarette smoking, dietary saturated fat density, dietary cholesterol density, hypertension, diabetes

BMI, body mass index; MI, myocardial infarction; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; HRT, hormone-replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.

without gout).[11,12,21] Moderate heterogeneity was noted ($I^2 = 55\%$, $p = 0.108$). Based on the same three studies, after adjustment for vascular risk factors, the pooled multivariate HR for mortality due to CHD was 1.42 (95% CI 1.22–1.63), with no statistically significant heterogeneity ($I^2 = 0\%$, $p = 0.660$) (Figure 3). Two of these studies used a solely male population.[11,12] In the remaining study, an increased risk of mortality from CHD was reported in women, HR 1.81, 95% CI 1.07–3.05), but not men, HR 1.16, 95% CI 0.81–1.67).[21]

Gout and mortality from MI

Three studies report on the association between gout and mortality from MI. However, these studies were unsuitable for meta-analysis due to significant heterogeneity in the statistical analysis undertaken and outcomes reported, and thus are described.

One study, from the USA, reported no increased risk of fatal MI in 1123 men with gout compared to 11,743 age-matched male controls (odds ratio, OR, 0.96, 95% CI 0.66–1.44).[22] However, another paper reporting results from this same study using a smaller population of 655 men with gout compared to 8450 without did report an excess risk of mortality from MI in gout patients (HR 1.46, 95% CI 1.03–2.06).[12] A further study from Canada reported an excess risk of mortality from MI in a mixed population of 9642 gout patients compared to 48210 controls, but reported an increased mortality risk only for women with gout ($n = 3890$) (HR 1.57, 95% CI 1.18–2.09), but not men (HR 1.19, 95% CI 0.96–1.49).[23] After adjustment for vascular risk factors, none of the studies report a statistically significant excess risk of mortality from MI in gout patients of either gender.

Publication bias assessment

No evidence of publication bias was seen for either any CVD mortality (Begg's tests: crude $p = 0.149$, multivariate $p = 0.734$; Egger's tests: crude $p = 0.06$, multivariate $p = 0.442$) or CHD mortality (Begg's tests: crude $p = 0.296$, multivariate $p = 0.296$; Egger's tests: crude $p = 0.164$, multivariate $p = 0.197$).

Discussion

This systematic review and meta-analysis found a significant association between gout and mortality from any CVD and CHD. It does not support an association between gout and mortality from MI based upon current evidence.

Our results are consistent with a previous systematic review of four studies,[13] which concluded that gout is an independent risk factor for cardiovascular mortality.

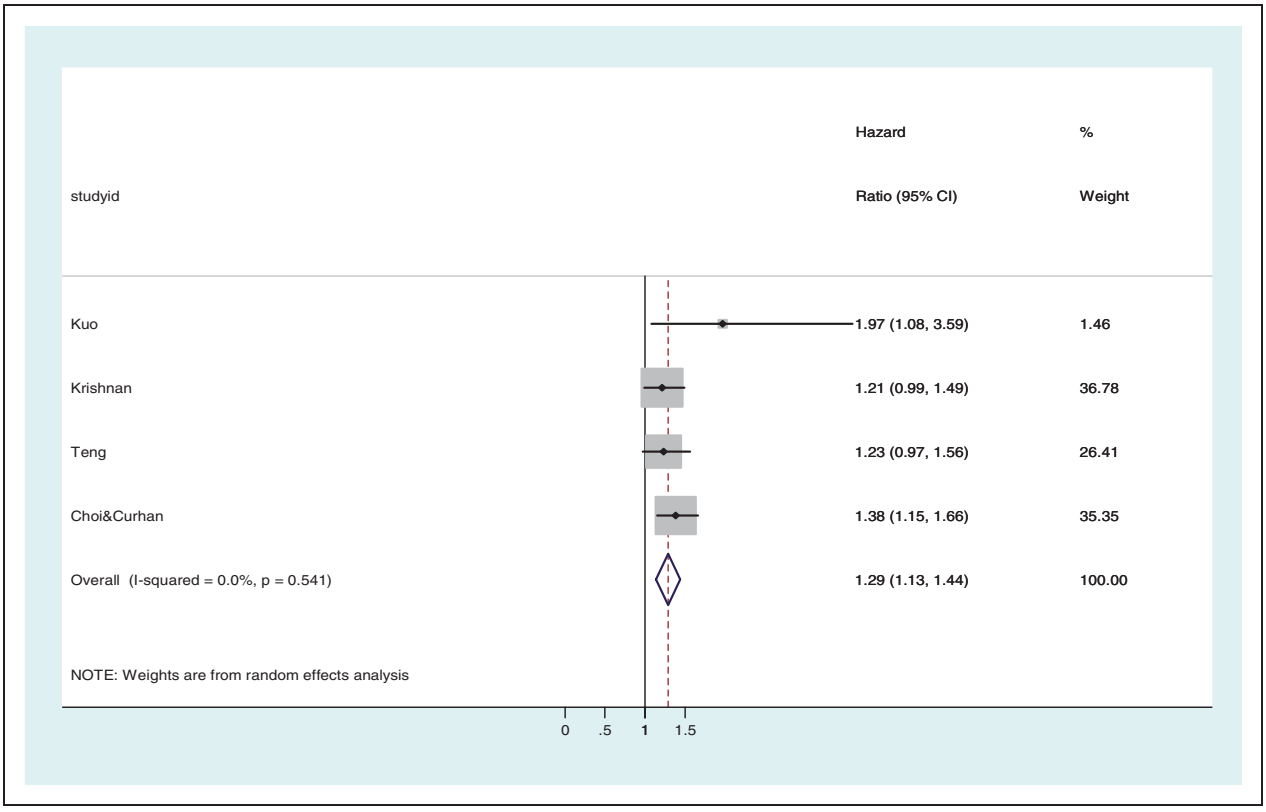

Figure 2. Meta-analysis of adjusted findings of studies reporting mortality from any cardiovascular disease.

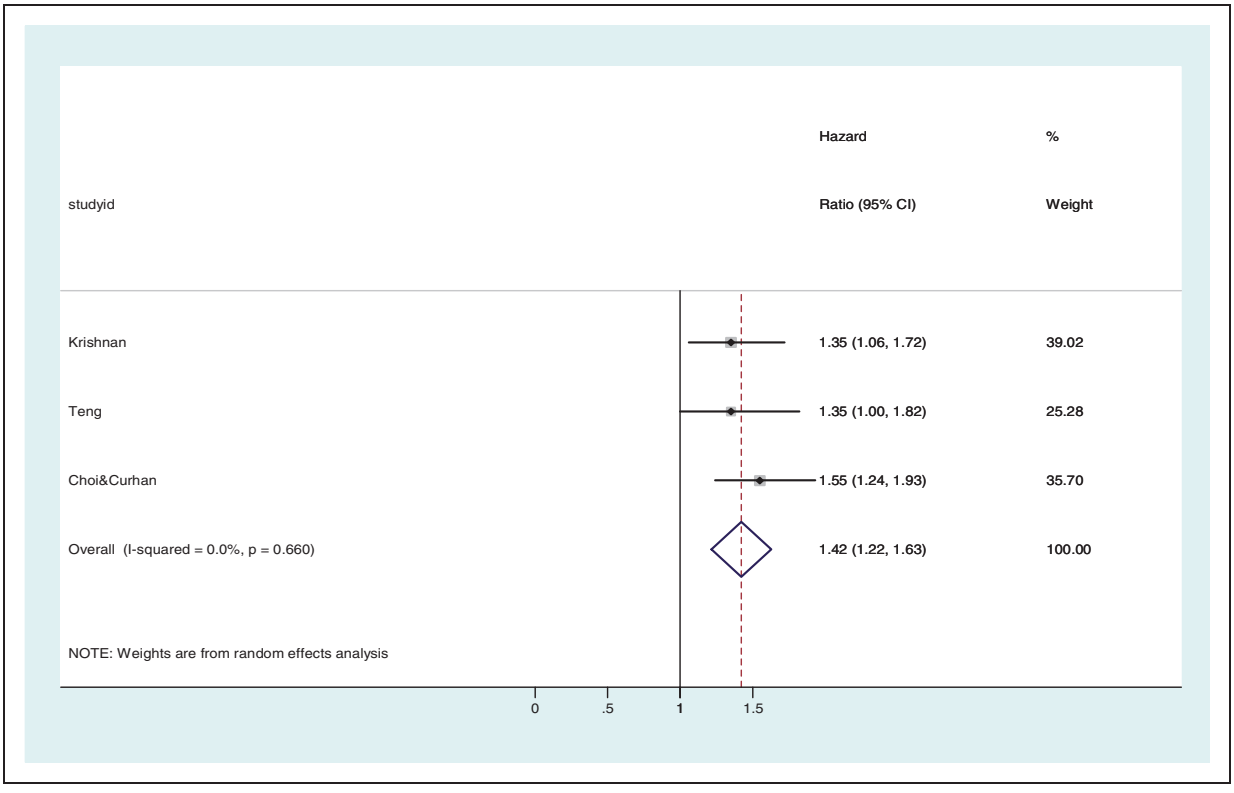

Figure 3. Meta-analysis of adjusted findings of studies reporting mortality from coronary heart disease.

Three of the studies included in that review were included in this meta-analysis;[11,12,20] however, one was excluded[24] as the study population consisted of renal dialysis and transplantation patients, and was not felt to be broadly representative of, or comparable with, the wider gout population, and impaired renal function is itself acknowledged to increase risk of cardiovascular mortality.[25,26] One more recent study was included in our review.[21] Our systematic review builds on the previously published work by conducting the first meta-analysis determining the excess risk of cardiovascular mortality associated with gout.

The precise relationship between gout and CVD remains unclear. The persistence of excess risk of cardiovascular and CHD mortality associated with gout in the pooled multivariate analysis, even after adjustment for traditional vascular risk factors, would suggest there are other important factors which influence this relationship. It is possible that this association is an indirect one, and simply an extension of the increased risk of CVD conferred by hyperuricaemia.[3] This occurs through a mechanism of amplified oxidation of lipids and induction of cellular oxidative stress which contributes to endothelial dysfunction, resulting in decreased arterial compliance, impaired blood flow, and a proatherogenic state.[27] However, since few studies include data on uric acid levels, we are unable to explore this further. Studies have also demonstrated renovascular disease, renal injury, and hypertension can result from this hyperuricaemic-mediated endothelial dysfunction,[28] further contributing to cardiovascular risk. Uric acid is also thought to have direct proinflammatory effects on vascular cells,[29,30] with evidence that reduction of uric acid levels reduces cardiovascular risk.[31] Allopurinol, the most commonly used urate-lowering therapy, has been shown to improve endothelial dysfunction,[32,33] blood pressure,[32,34] and exercise tolerance in patients with chronic stable angina.[35]

However, given that other inflammatory arthritides, such as rheumatoid arthritis and ankylosing spondylitis, not associated with hyperuricaemia also confer increased cardiovascular risk,[4,5] it would seem likely that the relationship is more complex. Common pathways of accelerated atherosclerosis resulting from endothelial dysfunction and impaired arterial compliance, as well as autoimmune inflammatory mechanisms involving proinflammatory cytokines such as tumour necrosis factor α and interleukins 1 and 6, by which inflammatory arthritides increase cardiovascular risk, have been suggested, and inflammatory activity is felt to be the major risk factor for the development of subsequent vascular disease.[36] Monosodium urate crystals deposited in gout have been shown to strongly induce inflammation in humans, through direct neutrophil activation and activation of the NALP3 inflammasome resulting in the release of similar proinflammatory cytokines, during an acute attack.[28] There is growing evidence that this inflammation persists between attacks,[37] with recent ultrasound studies demonstrating the presence of inflammation and synovitis in the intercritical period.[9,38] This recent literature has confirmed that gout should be considered a chronic inflammatory joint disease, and therefore, the possibility that persistent inflammation is one mechanism for increased burden of vascular disease in both gout and rheumatoid arthritis. The effect of inflammation on CVD has prompted the European League Against Rheumatism (EULAR) to publish recommendations for cardiovascular screening and management in both rheumatoid arthritis and gout patients,[39,40] including an aggressive approach to managing both risk factors and inflammatory burden.

However, the reasons for the absence of a similar association with mortality from MI remain unclear. This difference may reflect the presence of alternative underlying factors in the pathogenesis of MI when compared with other forms of CHD. Evidence suggests that coronary artery morphology is the most important factor differentiating patients who experience angina, compared to those with MI.[41] It may also reflect misclassification bias where, in the absence of post-mortem examination, cause of death is recorded as CHD or CVD rather than specifically MI. It may also result from surveillance bias, whereby diagnosis of gout and subsequent monitoring lead to increased likelihood of detection and management of CHD, and better education of patients about the need for prompt medical attention at the onset of symptoms to prevent progression to MI. However, it may simply be that further studies are required to investigate this particular relationship.

The limitations of our review include the small number of papers available for inclusion. However, each of these studies uses a large study population and, combined, the number of patients included in this meta-analysis exceeds 220,000. Moreover, by undertaking the meta-analysis in a stepwise fashion, pooling the studies one-by-one in chronological order, the pooled HR was not significantly altered from the HR reported in the first paper (published in 2007) after the addition of any of the later papers.

Despite a comprehensive search strategy, the possibility remains that some relevant articles may not have been identified. Similarly, papers with negative findings are less likely to be published, although there was no significant indication of publication bias from Begg's and Egger's tests. However, it must be acknowledged that Begg's and Egger's tests have low power to detect biases where study numbers are small.[42]

There was some heterogeneity between papers in the definitions of gout cases and the vascular risk factors included in the multivariate analyses, and unmeasured confounding must be considered given the observational nature of the included studies. Misclassification bias may also occur where studies relied upon diagnostic codes or death certificates to define outcomes.

The strengths of our review are that only large cohort studies are included, with participants being free of CVD at baseline. Data extraction and thorough methodological quality assessment was undertaken by two reviewers independently. Crude and multivariate data were pooled separately and potential sources of heterogeneity examined. Finally, no evidence of publication bias was found in our review.

In conclusion, whilst observational studies cannot demonstrate causation, this meta-analysis of large, high-quality cohort studies strongly supports gout as an independent risk factor for mortality from CVD and CHD. Current evidence does not support such an association with MI. The clinical implications of this review are the need to promote identification and management of cardiovascular risk factors in patients with gout, but also to identify and optimally manage gout in patients at risk of CVD. Further research will be required to establish whether the optimal management of gout, or the aggressive management of cardiovascular risk factors reduces negative outcomes for these patients.

Funding

This work was supported by the National School of Primary Care Research (grant number 88) and an Arthritis Research UK Clinician Scientist Award to CDM.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. *Ann Rheum Dis* 2008; 67: 960–966.
2. Zhu Y, Pandya BJ and Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 2011; 63: 3136–3141.
3. Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res* 2010; 62: 170–180.
4. Avina-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008; 59: 1690–1697.
5. Szabo SM, Levy AR, Rao SR, et al. Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: a population-based study. *Arthritis Rheum* 2011; 63: 3294–3304.
6. Gladman DD, Ang M, Su L, et al. Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 2009; 68: 1131–1135.
7. McGettigan P and Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011; 8: e1001098.
8. Brook RD, Yalavarthi S, Myles JD, et al. Determinants of vascular function in patients with chronic gout. *J Clin Hypertens (Greenwich)* 2011; 13: 178–188.
9. Roddy E, Menon A, Hall A, et al. Polyarticular sonographic assessment of gout: a hospital-based cross-sectional study. *Joint Bone Spine* 80: 295–300.
10. Choi HK, Atkinson K, Karlson EW, et al. Obesity, weight change, hypertension, diuretic use and risk of gout in men: the health professionals follow-up study. *Arch Intern Med* 2005; 165: 742–748.
11. Choi HK and Curhan G. Independent impact of gout on mortality and risk of coronary heart disease. *Circulation* 2007; 116: 894–900.
12. Krishnan E, Svendsen K, Neaton JD, et al; MRFIT Research Group. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med 2008*; 168: 1104–1110.
13. Lottmann K, Chen X and Schadlich PK. Association between gout and all-cause as well as cardiovascular mortality: a systematic review. *Curr Rheumatol Rep* 2012; 14: 195–203.
14. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43: 1130–1139.
15. Wells G, Shea A, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.htm (2008, consulted February 2013).
16. DerSimonian R and Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
17. Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
18. Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
19. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple graphical test. *Br Med J* 1997; 315: 629–634.
20. Kuo CF, See LC, Luo SF, et al. Gout: an independent risk factor for all-cause and cardiovascular mortality. *Rheumatology* 2010; 49: 141–146.
21. Teng GG, Ang LW, Saag KG, et al. Mortality due to coronary heart disease and kidney disease among middle-aged and elderly men and women with gout in the Singapore Chinese Health Study. *Ann Rheum Dis* 2012; 71: 924–928.

22. Krishnan E, Baker JF, Furst DE, et al. Gout and the risk of acute myocardial infarction. *Arthritis Rheum* 2006; 54: 2688–2696.
23. DeVera MA, Rahman MM, Bhole V, et al. Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population-based study. *Ann Rheum Dis* 2010; 69: 1162–1164.
24. Cohen SD, Kimmel PL, Neff R, et al. Association of incident gout and mortality in dialysis patients. *J Am Soc Nephrol* 2008; 19: 2204–2210.
25. Mahmoodi BK, Matsushita K, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet* 2012; 380: 1649–1661.
26. Gaita D, Mihaescu A and Schiller A. Of heart and kidney: a complicated love story. *Eur J Prev Cardiol* 2012; Epub ahead of print.
27. Ceriello A and Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 2004; 24: 816–823.
28. Jin M, Yang F, Yang I, et al. Uric acid, Hyperuricemia and vascular diseases. *Front Biosci* 2012; 17: 656–669.
29. Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 2003; 41: 1287–1293.
30. Kang DH, Park SK, Lee IK, et al. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol* 2005; 16: 3553–3562.
31. Hoieggen A, Alderman MH, Kjeldsen SE, et al; LIFE Study Group. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* 2004; 65: 1041–1049.
32. Kanbay M, Huddam B, Azak A, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemia subjects with normal renal function. *Clin J Am Soc Nephrol* 2011; 6: 1887–1894.
33. Melendez-Ramirez G, Perez-Mendez O, Lopez-Osorio C, et al. Effect of the treatment with allopurinol on the endothelial function in patients with hyperuricemia. *Endocr Res* 2012; 37: 1–6.
34. Kanbay M, Ozkara A, Selcoki Y, et al. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions. *Int Urol Nephrol* 2007; 39: 1227–1233.
35. Noman A, Ang DS, Ogston S, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010; 375: 2161–2167.
36. Soltész P, Kerekes G, Dér H, et al. Comparative assessment of vascular function in autoimmune rheumatic diseases: considerations of prevention and treatment. *Autoimmun Rev* 2011; 10: 416–425.
37. Pascual E. Persistence of monosodium urate crystals and low-grade inflammation in the synovial fluid of patients with untreated gout. *Arthritis Rheum* 1991; 34: 141–145.
38. Filippucci E, Scirè CA, Delle Sedie A, et al. Ultrasound imaging for the rheumatologist. XXV. Sonographic assessment of the knee in patients with gout and calcium pyrophosphate deposition disease. *Clin Exp Rheumatol* 2010; 28: 2–5.
39. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010; 69: 325–323.
40. Zhang W, Doherty M, Bardin T, et al. EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; 65: 1312–1324.
41. Ambrose JA, Winters SL, Arora RR, et al. Coronary angiographic morphology in myocardial infarction: a link between the pathogenesis of unstable angina and myocardial infarction. *J Am Coll Cardiol* 1985; 6: 1233–1238.
42. Sterne JAC, Gavaghan D and Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in literature. *J Clin Epidemiol* 2000; 53: 1119–1129.