



**Centre for Clinical Effectiveness**

Enhancing patient outcomes through clinical application of the best available evidence

**EVIDENCE CENTRE  
CRITICAL APPRAISAL  
AND LITERATURE  
SEARCH**

Series 2002: Aetiology

# **Are Gout or Increased Uric Acid Levels Risk Factors for Cardiac Disease?**

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April 2002

*Southern Health*

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April 2002

## **SUMMARY STATEMENT**

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## **REQUEST**

Is gout or an increased uric acid level a cardiac risk factor?

## **REQUESTED BY**

**Stephen Kennett**, RN, CCU, Monash Medical Centre, Clayton.

## **METHODOLOGY**

### **Search Strategy**

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

### **Details of Evidence Request**

Patients (Subjects): All

Exposure: Gout or increased uric acid levels

Comparisons: None

Outcomes: Cardiac disease

### **Search terms**

(see Appendix 2 for exact search strategy)

Exposure: gout, arthritis gouty, uric acid, risk, risk factors

Outcome: cardiovascular disease, CAD

## **Resources Searched**

We searched the following databases and Internet websites:

The Cochrane Library – 2002, Issue 1

Medline (OVID)- 1996 to April week 1 2002/1993-1995/1989-1992

CINAHL (OVID)- 1982 to February week 4 2002

Current Contents (OVID)- 1993 Week 27 to 2002 Week 16

PREMEDLINE (OVID)- April 12<sup>th</sup> 2002

PubMed Clinical Queries

## **Refinements, Searching & Reporting Constraints**

We included items of evidence that were available to us on 12 April 2002. We restricted our search to humans and the English language and only included articles published since 1990. Due to the broad subject area of the request and the large amount of literature obtained assessing the association of high uric acid levels and cardiac disease, detailed critical appraisal of the available studies has not been carried out. The results of the literature search are attached to this report. Critical appraisal of the literature concerning gout specifically as a risk factor for cardiac disease has however been included.

## RESULTS

### Gout as a Risk Factor for Cardiac Disease (Critical Appraisal)

From our sources we identified 1 potentially relevant article. We obtained the full text of this article to determine its relevance.

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	0
Pseudo-randomised controlled trials	0
<b>Controlled trials, cohort or case-control analytic studies</b>	1
<b>Total</b>	1

Based on our refinements, searching and reporting constraints we are reasonably confident this article represents the most relevant findings published to date.

The article (Gelber *et al*, 1997) reports the results of two prospective longitudinal cohort studies specifically designed to assess risk factors for cardiovascular disease. After controlling for co-morbid risk factors both studies found no association with gout and cardiovascular disease. Indeed, when the results of the two studies were combined in a meta-analysis this conclusion remained unchanged.

### Increased Uric Acid Level as a Risk Factor for Cardiac Disease (Literature Search)

Each citation includes a listing of the title, authors and source – and the abstract if available. Each citation has been assigned a “level of evidence” as defined by the NHMRC (see Appendix 1) as reliably as could be determined from the available evidence. The majority of the trials included were cohort or case control studies (level III). Although relevant cross-sectional studies and surveys were identified they were not included in this report due to the less stringent nature of these studies.

Due to the large number of references initially identified certain inclusion and exclusion criteria were used. Included studies include those specifically assessing potential risk factors for cardiac disease. One of the problems with assessing the effect of increased uric acid levels on the risk of cardiac disease are that increased levels often occur with other co-morbid conditions and confounding factors. Therefore, we have excluded citations analysing increased uric acid levels with other co morbid conditions such as, metabolic syndrome, insulin-resistance syndrome and uncontrolled hypertension. In addition, studies assessing increased uric acid levels in combination with other cardiac risk factors have also been excluded. Overall, the results from the studies appear to be equivocal, therefore they have been sub-divided into studies concluding that increased uric acid levels are independently associated with cardiac disease, studies which concluded that increased levels are not independently associated with cardiac disease and studies failing to establish any firm conclusions.

## **EVIDENCE SUMMARIES (for gout as a risk factor only)**

### **Format**

Evidence summaries are presented as spreadsheets attached to this report. Each spreadsheet contains the article citation, details of the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

## **REFERENCES**

### **ARTICLES CRITICALLY APPRAISED FOR THIS REPORT**

Gelber, A. C., Klag, M. J., Mead, L. A., Thomas, J., Thomas, D. J., Pearson, T. A. and Hochberg, M. C. (1997) Gout and Risk for Subsequent Coronary Heart Disease. Archives of Internal Medicine, 157, 1436-1440.

# APPENDIX 1

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## Levels Of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

Level I Evidence obtained from a systematic review (or meta-analysis) of all relevant randomised controlled trials.

Level II Evidence obtained from at least one randomised controlled trial.

Level III -1 Evidence obtained from pseudo-randomised controlled trials (alternate allocation or some other method).

-2 Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case control studies or interrupted time series with a control group.

-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.

Level IV Evidence obtained from case series, either post-test or pre-test/post-test.

## APPENDIX 2

### Search strategy

	Search terms for MEDLINE
1	Gout/ or arthritis, gouty/
2	Gout.tw
3	(arthritis adj3 gout\$.tw
4	Exp uric acid/
5	Uric acid.tw
6	Hyperuricemia.mp or hyperuricaemia.tw [mp=title, abstract, cas registry/ec number word, mesh subject heading]
7	Cardiovascular diseases/ or cardiovascular abnormalities/ or heart diseases/
8	Cardiovascular disease\$.tw
9	Cardiovascular abnormalit\$.tw
10	Cardiac.tw
11	Coronary.tw
12	Heart.tw
13	CAD.tw
14	Exp cohort studies/
15	Exp risk/
16	Risk factor\$.tw
17	Risk\$.tw
18	(relative and risk).mp [mp=title, abstract, cas registry/ec number word, mesh subject heading]
19	(odds and ratio\$.mp [mp=title, abstract, cas registry/ec number word, mesh subject heading]
20	(case and control\$.mp [mp=title, abstract, cas registry/ec number word, mesh subject heading]
21	Or/1-6
22	Or/7-13
23	Or/14-20
24	21 and 22
25	23 and 24
26	Limit 25 to (human and English language)

## **Citations concluding that elevated uric acid levels are a risk factor for cardiac disease**

### **Cohort Studies**

#### *Level III*

(Below study includes controlled hypertensive patients)

Alderman, M. H., H. Cohen, et al. (1999). "Serum uric acid and cardiovascular events in successfully treated hypertensive patients." *Hypertension* 34(1): 144-50.

To determine whether pre-treatment and/or in-treatment serum uric acid (SUA) is independently and specifically associated with cardiovascular events in hypertensive patients, we examined the 20-year experience of 7978 mild-to-moderate hypertensive participants in a systematic worksite treatment program. Clinical evaluation and treatment were protocol-directed. SUA was measured at entry and annually thereafter. Subjects were stratified according to gender-specific quartile of baseline SUA. Blood pressures at entry and in-treatment were, respectively, 152.5/95.6 and 138.9/85.4 mm Hg. SUA was normally distributed with a mean of 0.3990.0893 and 0.3210.0833 mmol/L for men and women, respectively. Subjects with highest SUA were heavier, had greater evidence of cardiovascular disease (CVD), higher systolic blood pressure, higher creatinine, more frequent diuretic use, and lower prevalence of diabetes. During an average follow-up of 6.6 years (52 751 patient-years), 548 CVD events (183 mortal) and 116 non-CVD events occurred. In bivariate analysis, the association of SUA to CVD was more robust in nonwhites than whites and in patients at low versus high CVD risk. In multivariate analysis, CVD incidence was significantly associated with SUA with a hazard ratio of 1.22 (95% confidence interval 1.11 to 1.35), controlling for other known cardiovascular risk factors, including serum creatinine, body mass index, and diuretic use. Despite blood pressure control, SUA levels increased during treatment and were significantly and directly associated with CVD events, independently of diuretic use and other cardiovascular risk factors.

Bernhardt, R., Z. Feng, et al. (1991). "Incidence and mortality rates of myocardial infarction in Chinese workers aged 40-59 in relation to coronary risk factors. Results of a Chinese prospective study (Wuhan Study) in comparison to the Gottingen Risk Incidence and Prevalence Study (GRIPS)." *Klinische Wochenschrift* 69(5): 201-12.

Some 2045 male Chinese industrial workers aged 40-59 years living in the city of Wuhan in the People's Republic of China were examined for coronary risk factors in the year 1983. The investigation included a patient history, clinical examination, and ECG and laboratory tests, with special attention to serum lipids. After 5 years, a follow-up investigation of the study group was carried out. The results were compared to the similarly designed German GRIPS project. In comparison to the German population, significantly lower levels for total-, LDL-, and VLDL-cholesterol, apolipoprotein B, triglycerides, uric acid, body mass index, and diastolic blood pressure were found in China. The percentage of smokers, however, was remarkably higher in China than in the Federal Republic of Germany. During the 5 year observation period in the Chinese sample, four subjects suffered from sudden death and four from nonfatal myocardial infarction; in the German study group three times as many fatal myocardial infarction and cases of sudden death and 7.5 times as many nonfatal myocardial infarctions were recorded. Nonfatal coronary heart disease and peripheral vascular disease were also observed less often in China. The incidence of cerebrovascular diseases was 1.5 times higher in China than in Germany. Whereas in Germany, total-, and LDL-cholesterol values were the major distinguishing parameters between infarction and reference

groups, in China these values have thus far had no significant influence on the level of risk. Instead in the Chinese incidence group, significantly higher levels for blood pressure, body mass index, uric acid, and the ratio LDL/HDL-cholesterol were found.

Bickel, C., H. J. Rupprecht, et al. (2002). "Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease." *American Journal of Cardiology* 89(1): 12-7.

It is a matter of controversy as to whether uric acid is an independent predictor of mortality in patients with coronary artery disease (CAD) or whether it represents only an indirect marker of adverse outcome by reflecting the association between uric acid and other cardiovascular risk factors. Therefore, we studied the influence of uric acid levels on mortality in patients with CAD. In 1,017 patients with angiographically proven CAD, classic risk factors and uric acid levels were determined at enrolment. A follow-up over a median of 2.2 years (maximum 3.1) was performed. Death from all causes was defined as an end point of the study. In CAD patients with uric acid levels  $<303 \mu\text{mol/L}$  (5.1 mg/dl) (lowest quartile) compared with those with uric acid levels  $>433 \mu\text{mol/L}$  (7.1 mg/dl) (highest quartile), the mortality rate increased from 3.4% to 17.1% (fivefold increase). After adjustment for age, both sexes demonstrated an increased risk for death with increasing uric acid levels (female patients: hazard ratio [HR] 1.30, 95% confidence intervals [CI] 1.14 to 1.49,  $p < \text{or} = 0.001$ ; male patients: HR 1.39 [95% CI 1.21 to 1.59],  $p < \text{or} = 0.001$ ). In multivariate Cox regression analysis performed with 12 variables that influence overall mortality-including diuretic use-elevated levels of uric acid demonstrated an independent, significant positive relation to overall mortality (HR 1.23 [95% CI 1.11 to 1.36],  $p < 0.001$ ) in patients with CAD. Thus, uric acid is an independent predictor of mortality in patients with CAD.

Fang, J. and M. H. Alderman (2000). "Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey." *JAMA* 283(18): 2404-10.

CONTEXT: Although many epidemiological studies have suggested that increased serum uric acid levels are a risk factor for cardiovascular mortality, this relationship remains uncertain. OBJECTIVE: To determine the association of serum uric acid levels with cardiovascular mortality. DESIGN AND SETTING: Cross-sectional population-based study of epidemiological follow-up data from the First National Health and Nutrition Examination Survey (NHANES I) from 1971-1975 (baseline) and data from NHANES I Epidemiologic Follow-up Study (NHEFS). PARTICIPANTS: A total of 5926 subjects who were aged 25 to 74 years and had serum uric acid level measurements at baseline. MAIN OUTCOME MEASURES: Ischemic heart disease mortality, total cardiovascular mortality, and all-cause mortality, compared by quartiles of serum uric acid level. RESULTS: In an average of 16.4 years of follow-up, 1593 deaths occurred, of which 731 (45.9%) were ascribed to cardiovascular disease. Increased serum uric acid levels had a positive relationship to cardiovascular mortality in men and women and in black and white persons. Deaths due to ischemic heart disease in both men and women increased when serum uric acid levels were in the highest quartile compared with the lowest quartile (men,  $>416$  vs.  $<321 \mu\text{mol/L}$ ; risk ratio, 1.77 [95% confidence interval [CI], 1.08-3.98]; women,  $>333$  vs.  $<238 \mu\text{mol/L}$ ; risk ratio, 3.00 [95% CI, 1.45-6.28]). Cox regression analysis showed that for each 59.48-micromol/L increase in uric acid level, cardiovascular mortality and ischemic heart disease mortality increased. Hazard ratios for men were 1.09 (95% CI, 1.02-1.18) and 1.17 (95% CI, 1.06-1.28), and for women were 1.26 (95% CI, 1.16-1.36) and 1.30 (95% CI, 1.17-1.45), respectively, after adjustment for age, race, body mass index, smoking status, alcohol consumption, cholesterol level, history of hypertension and diabetes, and diuretic use. Further analysis, stratifying by cardiovascular risk status, diuretic use, and menopausal status, confirmed a significant association of uric acid and cardiovascular mortality in all subgroups except among men

using diuretics (n=79) and men with 1 or more cardiovascular risk factors (n=1140).  
CONCLUSION: Our data suggest that increased serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality.

Longo-Mbenza, B., E. L. Luila, et al. (1999). "Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans?" *International Journal of Cardiology* 71(1): 17-22.

BACKGROUND: Uric acid stabilizes platelet aggregation and enhances thrombotic tendency. OBJECTIVE: To examine the relationship between raised serum uric acid and subsequent cardiovascular events (mortality, myocardial infarction, stroke). METHODS: This is a longitudinal study in a small random number (418) of patients in Kinshasa, Congo. In this hospital-based study, uricemia was determined with respect to gender, obesity and hypertension as well correlated with traditional cardiovascular risk factors. A univariate regression model was used to investigate the association of serum uric acid with the incidence of mortality, stroke and myocardial infarction. RESULTS: Serum uric acid was higher ( $P < 0.05$ ) in obese women and men as well in hypertensives, than in their controls. The significant ( $P < 0.05$  and  $0.001$ ) highest frequency of hyperuricemia was observed in both diabetic and hypertensive patients. Blood pressure (BP) was higher ( $P < 0.001$ ) in patients with hyperuricemia than in those with normal serum uric acid. Serum uric acid was significantly correlated with body weight, BP, glucose, fibrinogen, urea, creatinine and total cholesterol. In men, hyperuricemia was significantly ( $P < 0.01$ ) associated with a twofold increased risk of both myocardial infarction and stroke incidence. However, hyperuricemia was significantly related to a double risk of all mortality and stroke onset. CONCLUSION: Our results indicate that hyperuricemia among African patients is a strong predictor of myocardial infarction in men, stroke in both sexes and all causes of mortality in women.

Puddu, P. E., M. Lanti, et al. (2001). "Serum uric acid for short-term prediction of cardiovascular disease incidence in the Gubbio population Study." *Acta Cardiologica* 56(4): 243-51.

OBJECTIVE: The Gubbio Study is an Italian population study measuring risk factors for and incidence of major cardiovascular diseases. This analysis investigates the association of serum uric acid with the incidence of coronary and cardiovascular events. METHODS: A population sample of 2469 men and women aged 35-74 years, free from major cardiovascular diseases and in whom serum uric acid was measured in 1983 along with other standard risk factors, were followed up for 6 years and the incidence of coronary heart disease (CHD) and all cardiovascular atherosclerotic (CVD) events, both fatal and non-fatal, was computed. Proportional hazards models were used for the prediction of these events. RESULTS: In six years 61 CHD hard criteria, 109 CHD any criterion and 149 CVD events were recorded. Age-adjusted rates per 1000 of the 3 event categories were computed in sex-specific quintiles (Q) of serum uric acid with 428 76 (Q5) and 198 42 (Q1)  $\mu\text{mol/l}$ , respectively. Although higher rates were seen in Q5 as compared to Q1 for all three first event categories considered (relative risks 6.2, 3.6 and 3.7, respectively), a statistically significant trend was seen only for CVD all criteria ( $t = 3.63$ ,  $p < 0.036$ ). These trends were borderline significant for CHD any criterion ( $t = 2.92$ ,  $p < 0.06$ ) and not significant for CHD hard criteria ( $t = 2.23$ ,  $p < 0.11$ ). In multivariate models, adjusted for 8 other risk factors, serum uric acid showed a statistically significant contribution to predict CVD incidence [relative risk (RR) for 92  $\mu\text{mol/l}$  difference of 1.24 with 95% confidence intervals (CI) 1.05-1.45], whereas the statistical contribution to predict CHD any criterion (RR = 1.19 with CI 0.98-1.45) and CHD hard criteria (RR = 1.20 with CI 0.93-1.55) was not significant. Diuretic treatment and blood urea, as further confounders, were positively and significantly related to event incidence (RR ranging from 1.21 to 2.00) but serum uric acid maintained its independent and statistically significant role in the prediction of CVD events (RR = 1.18 with CI 1.00-

1.39). Presence of specific treatments to lower serum uric acid levels (in 1.13% of the population), tested as final confounders, was not statistically contributory.

CONCLUSIONS: Increased serum uric acid levels are independently and significantly associated with risk of CVD events in the 6-year follow-up of the Gubbio Study. Longer follow-up is needed before the contributory role of serum uric acid can be properly assessed to explain CHD incidence.

Tomita, M., S. Mizuno, et al. (2000). "Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers." *Journal of Epidemiology* 10(6): 403-9.

A positive association between hyperuricemia and cardiovascular disease has been reported, but no study has evidenced yet the precise role of serum uric acid in the development of cardiovascular disease. In addition, no epidemiological studies have so far documented a decreased risk of cancer among people with hyperuricemia, even though the antioxidant action of uric acid has recently been stressed to inhibit DNA damage. The present prospective cohort study investigates the relationship between hyperuricemia and health hazards in a Japanese working population. The subjects were 49,413 Japanese male railroad workers, aged 25-60 years at enrolment. Serum uric acid and other baseline data were provided by annual health-survey records from 1975 to 1982. The vital status of the subjects was traced until the end of 1985 for those who remained alive. During an average 5.4-year study period, 984 deaths were recorded. Those with serum uric acid over 8.5 mg/dl showed elevated relative risks (RRs) of death in all causes (RR 1.62,  $p < 0.01$ ), coronary heart disease (RR 1.52), stroke (RR 2.33,  $p < 0.01$ ), hepatic disease (RR 3.58,  $p < 0.01$ ), and renal failure (RR 8.52,  $p < 0.01$ ), as compared with those with serum uric acid levels of 5.0-6.4mg/dl. The RR of death in all causes still remains statistically significant when adjusted by age and serum total cholesterol (2.00,  $p < 0.01$ ), age and alcohol intake (1.85,  $p < 0.001$ ), age and smoking (1.69,  $p < 0.001$ ), age and gout treatment (1.61,  $p < 0.05$ ), and also age and BMI (1.50,  $p < 0.05$ ). On the other hand, the RR of all causes decreased but was still above 1.0 when adjusted by age and blood glucose (1.62), age and systolic blood pressure (1.32), age and GOT (1.23), and also age and history of cardiovascular disease (1.17). These results showed that hyperuricemia has a strong association with the RRs of death in all causes, coronary heart disease, stroke, hepatic disease and renal failure, and indicated that serum uric acid seems to be a considerable risk factor for reduced life expectancy.

## Case control studies

### *Level III*

Ahmed, A. F., S. A. Abdelsalam, et al. (1993). "A case-control study of the incidence of coronary heart disease risk factors in Saudis at Almadina Almounawarah." *Saudi Medical Journal* 14(2): 146-151.

A total of 136 Saudi subjects (68 patients with coronary heart disease (CHD) and an equal number of age- and sex-matched controls) were studied in detail for the incidence of CHD risk factors. The following are the percentages of patients with risk factors found significantly more frequently than in controls (together with p-value and 95% confidence interval): hypertension 42%,  $< 0.01$  (6-37%); diabetes mellitus 41%,  $< 0.046$  (2-33%); cigarette smoking 24%,  $< 0.046$  (2-27%); hypertriglyceridaemia 32%,  $< 0.001$  (1-37%); hyperuricaemia 45%,  $< 0.001$  (19-50%). The incidence of the following risk factors were not significantly different in patients and controls: alcohol consumption; family history of premature CHD; lack of physical activity; raised total cholesterol (TC) and low density lipoprotein (LDL) and obesity as assessed by the mean Body Mass Index (BMI). Perhaps the recently reported qualitative blood lipid abnormalities, e.g. apolipoprotein, need to be investigated in Saudis with CHD.

Cadeddu G, F. P. A. R. G. P. M. G. R. (1995). "[Hyperuricemia and cardiac risk factors: epidemiologic study in the aged]. [Italian]." *Minerva Cardioangiologica*. 43(1-2):29-34, 1995 Jan-Feb.

The aim of our study is to evaluate whether hyperuricemia may be considered a cardiovascular risk factor also in the elderly. 370 subjects over 60-years-old of both sexes were examined of which 148 presented an ischemic heart disease and 222, age and sex homogeneous, were considered as control group. Serum uric acid was determined. A strong difference between the two groups ( $p < 0.001$ ) was statistically demonstrated. Such modifications were sex independent. A strict correlation of hyperuricemia and hypertriglyceridemia was present; in fact high uric acid levels were mostly found in the group with triglycerides  $> 200$  mg/dl ( $p < 0.02$ ). In the whole group and in males a stability of uric acid was noted. In females a significant increase between the first (60-69 years) and the second (70-79 years) age class was present. In conclusion, a positive role of hyperuricemia in the ischemic heart disease pathogenesis is possible.

## **Citations concluding that elevated uric acid levels are not a risk factor for cardiac disease**

### **Cohort Studies**

#### *Level III*

Culleton, B. F., M. G. Larson, et al. (1999). "Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study." *Annals of Internal Medicine* 131(1): 7-13.

**BACKGROUND:** Hyperuricemia is associated with risk for cardiovascular disease and death. However, the role of uric acid independent of established risk factors is uncertain. **OBJECTIVE:** To examine the relation of serum uric acid level to incident coronary heart disease, death from cardiovascular disease, and death from all causes. **DESIGN:** Community-based, prospective observational study. **SETTING:** Framingham, Massachusetts. **PATIENTS:** 6763 Framingham Heart Study participants (mean age, 47 years). **MEASUREMENTS:** Serum uric acid level at baseline (1971 to 1976); event rates per 1000 person-years by sex-specific uric acid quintile. **RESULTS:** During 117,376 person-years of follow-up, 617 coronary heart disease events, 429 cardiovascular disease deaths, and 1460 deaths from all causes occurred. In men, after adjustment for age, elevated serum uric acid level was not associated with increased risk for an adverse outcome. In women, after adjustment for age, uric acid level was predictive of coronary heart disease ( $P = 0.002$ ), death from cardiovascular disease ( $P = 0.009$ ), and death from all causes ( $P = 0.03$ ). After additional adjustment for cardiovascular disease risk factors, uric acid level was no longer associated with coronary heart disease, death from cardiovascular disease, or death from all causes. In a stepwise Cox model, diuretic use was identified as the covariate responsible for rendering serum uric acid a statistically non-significant predictor of outcomes. **CONCLUSIONS:** These findings indicate that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes. Any apparent association with these outcomes is probably due to the association of uric acid level with other risk factors.

Hu, P. F., T. E. Seeman, et al. (2001). "Is serum uric acid level associated with all-cause mortality in high-functioning older persons: MacArthur studies of successful aging?" *Journal of the American Geriatrics Society* 49(12): 1679-1684.

**OBJECTIVES:** To explore the effect of serum uric acid level on subsequent all-cause mortality in high-functioning community-dwelling older persons. It is controversial whether high serum uric acid level is a true independent risk factor for cardiovascular and total mortality or the association is due to other confounding variables. Furthermore, it remains unclear whether the predictive value of uric acid level on mortality observed in younger cohorts can be extended to older people. **DESIGN:** Prospective cohort study. **SETTING:** A sample of community-dwelling older people. **PARTICIPANTS:** A cohort of 870 participants from the MacArthur Studies of Successful Aging. **MEASUREMENTS:** Baseline information was obtained for serum uric acid level, C-reactive protein (CRP), interleukin-6 (IL-6), prevalent medical conditions, and health behaviours. Crude and multivariate logistic regression analyses were used to examine the association between serum uric acid levels and 7-year all-cause mortality, while adjusting for potential confounders. **RESULTS:** In men, the multiply adjusted risk ratios for 7-year total mortality were 1.07 (95% CI = 0.61-1.88) for the mid tertile of uric acid level and 1.24 (95% CI = 0.70-2.20) for the top tertile. In women, the multiply adjusted risk ratios were 0.58 (95% CI = 0.29-1.18) and 0.47 (95% CI = 0.22-0.99), for the mid and top tertiles, respectively. CRP and IL-6 were important confounders in the relationship between serum uric acid and overall mortality. **CONCLUSIONS:** High serum uric acid level is not independently associated with increased total mortality in high-functioning older men and women. When evaluating the association between serum uric acid and mortality, the potential confounding effect of underlying inflammation and other risk factors must be considered. [References: 18]

Menotti, A., A. Spagnolo, et al. (1992). "Multivariate prediction of coronary deaths in a 10 year follow-up of an Italian occupational male cohort." *Acta Cardiologica* 47(4): 311-20.

3395 men aged 46-65 belonging to occupational groups in Rome were examined in 1980 for the measurement of a number of potential coronary risk factors and of other personal characteristics. They represented the 76.5% of the enrolled roster. In 2853 men free from previous major coronary events and with all the measurements available, 98 died from CHD in the next 10 years. The multivariate analysis performed by the Cox model showed the significant predictive role of age, systolic blood pressure, non-HDL cholesterol, blood glucose and heart rate. The relative risk (for a distance of 2 standard deviations from the mean) was of 2.3, 2.1, 1.4, 1.7 and 1.4 respectively. Smoking habits, body mass index, xanthelasma, leisure physical activity, serum triglycerides, uric acid and a stress score did not contribute to the prediction of coronary deaths. HDL cholesterol produced a negative but not significant coefficient. As compared to the previously available Italian risk functions the role of non-HDL cholesterol and of blood glucose represents the most remarkable contribution.

Moriarty, J. T., A. R. Folsom, et al. (2000). "Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study." *Annals of Epidemiology* 10(3): 136-43.

**PURPOSE:** Approximately half of previous studies on serum uric acid have reported it to be an independent risk factor for coronary heart disease (CHD). We tested this hypothesis in the Atherosclerosis Risk in Communities (ARIC) Study. **METHODS:** A total of 13,504 healthy middle-aged men and women were followed prospectively for up to eight years. We identified 128 fatal and nonfatal CHD events in women and 264 in men. **RESULTS:** The age-, race-, and ARIC field center-adjusted relative risk of CHD for sex-specific quartiles of serum uric acid were 1.0, 1.39, 1.08, and 2.35 in women (p for trend = 0.009) and 1.0, 1.03, 0.89, and 1.21 in men (p for trend = 0.44), respectively. However, serum uric acid was correlated positively with many risk factors, and after multivariable adjustment, there was little evidence of an association of uric acid with CHD

in either sex. CONCLUSIONS: Our results are not consistent with serum uric acid being an independent risk factor for CHD.

Sakata, K. T Hashimoto et al. Nippon Data Research Group (2001). "Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980-1994. National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in the Aged." *European Journal of Epidemiology*. 17(5):461-8, 2001.

Although elevated serum uric acid has been associated with an increased risk of cardiovascular disease, its importance as a risk factor is still controversial. The authors examined the relationship between serum uric acid levels and death from all causes, including cardiovascular disease and stroke. The baseline data were collected in the National Cardiovascular Survey in 1980. The survey was carried out for all household members aged 30 years or older in 300 districts, which were randomly selected throughout Japan. The number who participated in the survey was 10,897. The vital status was ascertained in 1994. Finally, 8172 subjects were available for the analyses. There were 108,284 person-years of follow-up, and 960 deaths from all causes, 249 deaths from cardiovascular disease, and 174 deaths from stroke. After adjustment for age and other cardiovascular disease risk factors, uric acid levels were not associated with mortality from all causes, cardiovascular disease, or stroke. These findings indicate that serum uric acid levels are not related to increased risk for death from all causes, including cardiovascular disease and stroke in a Japanese population.

## **Citations with equivocal results concerning the role of elevated uric acid levels as a risk factor for cardiac disease**

### **Cohort Studies**

#### *Level III*

Freedman, D. S., D. F. Williamson, et al. (1995). "Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study." *American Journal of Epidemiology* 141(7): 637-44.

Although hyperuricemia is frequently found among persons with ischemic heart disease, its importance as a risk factor remains uncertain. The authors examined this relation among 5,421 persons in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study; baseline data were collected in 1971-1975 and follow-up was through 1987. No associations were seen among men, but, among women, the serum uric acid level was predictive of mortality from all causes and from ischemic heart disease. These associations persisted even after excluding the first 10 years of follow-up and were independent of use of antihypertensive agents and diuretics, diastolic blood pressure, overweight, and other characteristics. A dose-response relation was evident for mortality from ischemic heart disease: each 1-mg/dl change in uric acid (about two thirds of the standard deviation) among women increased the rate by 1.48 (95% confidence interval 1.3-1.7). Furthermore, as compared with women who had a uric acid level < 4 mg/dl, those with a level > or = 7 mg/dl had a 4.8-fold (95% confidence interval 1.9-12) higher rate of ischemic heart disease mortality. In contrast, the uric acid level showed a weaker relation with disease incidence among women, with a rate ratio of 1.14 for each 1-mg/dl change. Although the biologic mechanism is unclear, further investigation into the possible role of uric acid in the development of ischemic heart disease is needed.

Iribarren, C., D. S. Sharp, et al. (1996). "High uric acid: a metabolic marker of coronary heart disease among alcohol abstainers." *Journal of Clinical Epidemiology* 49(6): 673-8.

The association between serum uric acid level and risk of coronary heart disease (CHD) over 21 years was investigated among 6411 middle-aged Japanese-American men who were participants in the Honolulu Heart Program. In an age-stratified Cox regression model, high serum uric acid (quartile 4 [ $>6.7$  mg/dl], relative to quartile 1 [ $<5.0$  mg/dl]) was a significant predictor of definite CHD (RR = 1.33; 95% confidence interval = 1.08-1.63;  $p = 0.006$ ). However, when adjustment for confounders (body mass index, heavy alcohol consumption, triglycerides, diastolic blood pressure, blood glucose, and the ratio of animal to vegetable protein) was made, the association of high uric acid with coronary events was substantially reduced and became non-significant (RR = 1.14; 95% confidence interval = 0.92-1.42;  $p = 0.21$ ). There was a significant interaction between serum uric acid and drinking status ( $P = 0.03$ ). Thus, the risk of definite CHD associated with high urate levels (quartile 4), relative to low levels (quartile 1), was elevated in the abstainers (RR = 1.40; 95% confidence interval = 1.01-1.93;  $p = 0.02$ ), but not in light and moderate drinkers (RR = 1.11; 95% confidence interval = 0.79-1.55;  $p = 0.58$ ) or among the heavy drinkers ( $>40$  ml of ethanol/day; RR = 0.57; 95% confidence interval = 0.27-1.21;  $p = 0.08$ ). It is concluded that elevated uric acid may be associated with higher CHD among alcohol abstainers. Whether raised urate is an etiological factor for CHD or a manifestation of existing arterial disease in non-drinkers deserves further investigation.

Liese, A. D., H. W. Hense, et al. (1999). "Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases." *Epidemiology* 10(4): 391-7.

Because previous findings have been inconsistent, we explored the association of serum concentrations of uric acid with all-cause and cardiovascular disease mortality and myocardial infarction prospectively. We used data from 1,044 men who are members of the World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA) Augsburg cohort. The men, 45-64 years of age in 1984-1985, were followed through 1992. There were 90 deaths, 44 of which were related to cardiovascular disease; 60 men developed incident nonfatal or fatal myocardial infarction. We estimated hazard rate ratios from Cox proportional hazard models. Uric acid levels  $\geq 373$   $\mu\text{mol/liter}$  (fourth quartile) vs.  $< 319$   $\mu\text{mol/liter}$  (first and second quartile) independently predicted all-cause mortality [hazard rate ratio = 2.8; 95% confidence interval (CI) = 1.6-5.0] after adjustment for alcohol, total cholesterol/high-density lipoprotein cholesterol ratio, hypertension, use of diuretic drugs, smoking, body mass index, and education. The adjusted risk of cardiovascular disease mortality was 2.2 (95% CI = 1.0-4.8), and that of myocardial infarction was 1.7 (95% CI = 0.8-3.3). Although residual confounding cannot be excluded, our results are among the few, in men, demonstrating a strong positive association of elevated serum uric acid with all-cause mortality. Future investigations may be able to evaluate whether uric acid contributes independently to the development of cardiovascular disease or is simply a component of the atherogenic metabolic condition known as the insulin resistance syndrome.

## Case control studies

### *Level III*

Hoschoian, J. C., S. D. Catz, et al. (1993). "Evaluation of the blood components considered as risk predictors in coronary heart disease." *Medicina* 53(1): 13-20.

The study included 249 patients two days before cardiovascular surgery and 73,915 control subjects. Results obtained were analyzed by grouping the individuals according to sex and age. In coronary heart disease (CHD) in males, total cholesterol was found higher than in controls (mean D.S.: 241.9 44.7 vs. 223.6 43.0 mg/dl,  $p < 0.01$ ) between 25 and 49 years of age, this significance being lost with age. Triglycerides were also higher (197 107.3 vs. 161.6 97.7 mg/dl,  $p < 0.01$ ) in the CHD male population between ages 25 and 69. In CHD females, triglycerides were higher (116.9 56.2 vs. 91.5 43.3 mg/dl,  $p < 0.05$ ) between ages 25 and 49; cholesterol showed no difference at any of the ages studied. HDL-C was much lower in both sexes of CHD patients at all ages studied ( $p < 0.001$ ). Uric acid was higher in CHD males between ages 25 and 49 ( $p < 0.05$ ), this significance being lost in the older age CHD group. Other components such as glycated hemoglobin, glucose and ionized calcium, were not different from those of the control group.

Nakamura, T., Y. Tsubono, et al. (2001). "Magnitude of sustained multiple risk factors for ischemic heart disease in Japanese employees: a case-control study." *Japanese Circulation Journal* 65(1): 11-7.

A case-control study was performed to clarify the cause of ischemic heart disease (IHD), such as acute myocardial infarction and angina pectoris, in Japanese employees. Among 122,051 workers from 31 industries, 94 cases of IHD were the subjects of the study, and a total of 191 age-matched subjects from the same department, but who did not develop IHD, served as the controls. Compared with the control group, body mass index, blood pressure, fasting plasma glucose, serum total cholesterol and serum triglyceride were significantly higher, and cigarette consumption and serum uric acid also tended to be higher, in the patient group from at least 10 years prior to onset. The frequency of moderate-drinkers tended to be lower in the case group. Electrocardiograms showed that, compared with the control group, the frequency of myocardial ischemia was higher in the case group from 9 years prior to onset and further rapidly increased from 3 years prior. The frequency of subjects with arrhythmia was the same as the control group until 3 years before onset and increased rapidly from 2 years prior. The frequency of subjects with multiple risk factors, particularly obesity, hypertension, hyperlipidemia and hyperglycemia, was consistently higher in the case group compared with the control group from 10 years prior to onset. Conditional logistic regression analysis demonstrated that having more than one risk factor greatly increased the risk; in particular, the combination of 3 or more factors increased the relative risk to 10.56 (95% confidence interval: 3.30-33.78). These findings suggest that a long duration of multiple risks is involved in the onset of IHD in Japanese employees, and that annual ECG monitoring as part of the medical examination was important in the prognosis.

<p style="text-align: center;"><b>Evidence Summary</b></p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> <p style="text-align: center;">Gout As A Risk Factor For Cardiac Disease</p> </div>	<p style="text-align: center;"><b>Study 1</b></p> <p style="text-align: center;">Gelber A, Klag M, Mead L <i>et al.</i> (1997). Gout and Risk for Subsequent Coronary Heart Disease: The Meharry-Hopkins Study. Arch Intern Med.157: 1436-1440.</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVELS OF EVIDENCE</b></p>	<p>Two prospective longitudinal cohort studies (Level III-2)</p>
<p><b>DESCRIPTION:</b> Patient (subjects), Exposure, Outcomes, Inclusion &amp; Exclusion Criteria</p>	<p><b>Patients (Subjects):</b> Former medical students from two studies; The Meharry Cohort Study - 371-black men and The John Hopkins Precursors Study - 1181 white men.  <b>Exposure:</b> Gout  <b>Outcomes:</b> Coronary heart disease including myocardial infarction, sudden death, angina pectoris, chronic ischaemic heart disease and other types of symptomatic coronary disease that requiring coronary surgery.  <b>Incl and Excl criteria:</b> White male graduating students from medical school (John Hopkins Study) and black male graduating students from medical school without hypertension (Meharry Cohort Study).</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection, analysis</p>	<p><b>Focused question:</b> The John Hopkins study was designed to identify the precursors of cardiovascular disease, and the Meharry study was designed to identify risk factors for the development of hypertension and coronary artery disease  <b>Assessed validity:</b> All self-reports of gout were reviewed by an Endpoint Assessment Committee according to the American college of Rheumatology Preliminary Survey Criteria for the Classification of Gout. Self-report of coronary disease was also verified.  <b>Appropriate analysis of results:</b> The studies consisted of fairly select cohorts including men of higher socioeconomic status who were at a low risk of cardiovascular disease, therefore the generalisability of the results to other groups of patients is uncertain.</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>During a median follow-up of 30 years, there were 38 gout cases and 44 coronary heart disease cases among the Meharry men, and 68 gout cases and 138 coronary heart disease cases among the Hopkins men. Gout was not associated with an increased risk for coronary heart disease in either study (The Meharry study; unadjusted relative risk =1.20; 95% confidence interval, 0.37-3.92 and The Hopkins study; unadjusted relative risk =0.66; 95% confidence interval, 0.24-1.79). A meta-analysis of the two studies also failed to show any association (unadjusted relative risk =0.85; 95% confidence interval, 0.40-1.81). Multivariate analysis adjusted for known coronary heart disease risk factors did not alter these findings.</p>
<p><b>AUTHORS COMMENTS:</b> Limitations, implications for practice and research</p>	<p>The study concludes that after adjusting for known risk factors there is no evidence to support gout as a risk factor for coronary heart disease in black and white male physicians.</p>
<p><b>OUR COMMENTS:</b> Opportunity for bias, weakness and strength</p>	<p><b>Potential for bias: Yes.</b></p> <ul style="list-style-type: none"> <li>• It is not stated if the students selected for the cohort were all or a subset of those graduating at the time of enrolment.</li> <li>• Physicians self-reported the incidences of gout and coronary heart disease and it is unclear whether they were aware of the ultimate purpose of the study.</li> </ul> <p><b>Weakness/s:</b></p> <ul style="list-style-type: none"> <li>• Women were not included in the studies due to the numbers of female medical students at the time of enrolment being too low to draw any meaningful comparisons</li> <li>• The studies consisted of select cohorts of patients who were of high socioeconomic status, in good health and at a low risk for cardiovascular disease</li> <li>• Relatively low incidence of gout and cardiovascular incidence in the cohorts limits the power of the results</li> </ul> <p><b>Strength/s:</b></p> <ul style="list-style-type: none"> <li>• Prospective longitudinal cohort design with patients enrolled before the onset of disease</li> <li>• High rate (greater than 90%) and long duration of follow-up</li> <li>• Self reporting by physicians</li> <li>• Similar results were obtained from the two cohorts</li> </ul>

Is gout or an increased uric acid level a cardiac risk factor?