Serum urate and the risk of major coronary heart disease events

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Abstract

Objective—To examine the relation between serum urate and the risk of major coronary heart disease events.

Design—A prospective study of a male cohort.

Setting—One general practice in each of 24 British towns.

Subjects—7688 men aged 40–59 years at screening.

Main outcome measures—Fatal and non-fatal coronary heart disease events.

Results—There were 1085 major coronary heart disease events during the average follow up period of 16.8 years. Serum urate was significantly associated with a wide range of cardiovascular risk factors including body mass index, alcohol intake, antihypertensive treatment, pre-existing coronary heart disease, serum triglycerides, cholesterol, and diastolic blood pressure. There was a significant positive association between serum urate and risk of coronary heart disease after adjustment for lifestyle factors and disease indicators. This relation was attenuated to non-significance upon additional adjustment for diastolic blood pressure and serum total cholesterol: cholesterol appeared to be the critical factor in attenuating this relation. When the association between serum urate and risk of coronary heart disease was examined by presence and grade of pre-existing coronary heart disease, a positive association was seen only in men with previous definite myocardial infarction, even after full adjustment ($P = 0.07$).

Conclusions—The relation between serum urate and the risk of coronary heart disease depends heavily upon the presence of pre-existing myocardial infarction and widespread underlying atherosclerosis as well as the clustering of risk factors. Thus serum urate is not a truly independent risk factor for coronary heart disease. Raised serum urate appears to be an integral part of the cluster of risk factors associated with the insulin resistance syndrome that include obesity, raised serum triglycerides, and serum cholesterol.

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Raised serum urate concentrations have been associated with increased risk of coronary heart disease events.^{1–3} However, hyperuricaemia has also been shown to be associated with many cardiovascular risk factors, in particular raised blood pressure, pre-existing ischaemic heart disease, hyperlipidaemia, and the use of antihypertensive treatment.^{3–9} Thus the role of serum urate in the development of coronary heart disease remains uncertain. There is increasing evidence that the relation between hyperuricaemia and the risk of coronary heart disease in men is dependent on the association between urate and other cardiovascular risk factors.^{2–4 6–8} However, it is uncertain whether the observed relation is related to raised blood pressure or to the presence of established coronary heart disease. Hyperuricaemia is commonly found in people with coronary heart disease and although several studies have either excluded or adjusted for pre-existing coronary heart disease in multivariate analysis, few studies have examined the role of urate separately in the presence or absence of coronary heart disease. In those that have done so, the findings have been inconsistent.^{4 7} We have therefore examined the relation between serum urate and subsequent risk of coronary heart disease in a prospective study of over 7000 middle aged men followed up for an average of 16.8 years. This paper focuses on the role of other cardiovascular risk factors in the relation between urate and risk of coronary heart disease and on the role of urate as a predictor of coronary heart disease events in men with and without the presence of pre-existing coronary heart disease.

Methods

The British Regional Heart Study is a large prospective study of cardiovascular disease in 7735 men aged 40–59 years selected from the age/sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland (78% response rate). The criteria for selecting the town, the general practice, and the subjects, as well as the methods of data collection, have been reported.¹⁰ Research nurses administered a standard questionnaire to each man, which included questions on smoking habits, alcohol intake, physical activity, and medical history. Several physical measurements were made, and blood samples (non-fasting) were taken throughout the day between 0830 and 1830. Thirteen biochemical measurements, including serum urate,

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were made on each serum sample using a Technicon SMA 12/60 autoanalyser (Technicon Instruments, Tarrytown, New York, USA) at the Wolfson Research Laboratories, Queen Elizabeth Hospital, Birmingham.

Details of blood pressure, blood lipid, and heart rate measurements¹¹⁻¹³ and classification methods for alcohol consumption, occupation (social class), smoking habits, and physical activity have been reported.^{10,14} Heavy drinking is defined as consumption of more than six drinks daily or on most days (1 drink = 8–10 g alcohol). Forced expiratory volume in one second (FEV₁) was measured with a Vitalograph spirometer (Vitalograph Medical Instrumentation, Buckingham, UK) with the subjects seated and FEV₁ measurements were height standardised to the average height of the men in the study.

TRIGLYCERIDE AND SERUM INSULIN

Triglyceride and insulin measurements were available in 18 towns (n = 5664 and n = 5649, respectively) and were adjusted for the marked diurnal variation observed in both variables.¹⁵

PRE-EXISTING DISEASE AND DRUG TREATMENT

The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (heart attack, coronary thrombosis), stroke, diabetes, and several other disorders. They were also asked for details of any regular drug treatment including use of antihypertensive drugs. Only 375 men reported regular use of antihypertensive drugs. Men on diuretics who did not recall a diagnosis of hypertension or cardiovascular disease were not included in the group on antihypertensive drugs. The WHO (Rose) chest pain questionnaire¹⁶ was administered to all men at the initial examination and a three-orthogonal lead electrocardiogram was recorded at rest.

Pre-existing coronary heart disease

The men were separated into three groups according to the evidence of coronary heart disease at screening.

(1) No evidence of coronary heart disease on WHO chest pain questionnaire or electrocardiogram and no recall of a doctor diagnosis of ischaemic heart disease (n = 5757).

(2) Men with evidence suggesting coronary heart disease short of a definite myocardial infarction. This group contains those with electrocardiographic evidence of possible or definite myocardial ischaemia or possible myocardial infarction, those with angina or a possible myocardial infarction on WHO (Rose) chest pain questionnaire, or with recall of a doctor diagnosis of angina (n = 1508).

(3) Men with a previous definite myocardial infarction on electrocardiogram or who recalled a doctor diagnosis of a myocardial infarction ("heart attack") (n = 425).

FOLLOW UP

All men were followed up for all cause mortality and for cardiovascular morbidity.¹⁷ All car-

diovascular events occurring in the period up to December 1995 are included in the study, an average follow up of 16.8 years (range 15.5–18.0 years) and follow up has been achieved for 99% of the cohort. Information on death was collected through the established "tagging" procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland). Non-fatal events were ascertained by direct reports from general practitioners and by regular reviews of the patients' notes. A non-fatal myocardial infarction was diagnosed according to WHO criteria, which included any report of myocardial infarction accompanied by at least two of the following: a history of severe chest pain, electrocardiographic evidence of myocardial infarction, and cardiac enzyme changes associated with myocardial infarction. Fatal coronary heart disease events were defined as deaths from coronary heart disease (ICD 9th revision, codes 410–414) as the underlying cause.

STATISTICAL METHODS

Cox proportional hazards model was used to estimate the relative risks adjusted for age, smoking, alcohol intake, body mass index, presence of diabetes, pre-existing coronary heart disease, heart rate, FEV₁, and diastolic blood pressure.¹⁸ Relative risks for the five urate groups were obtained by fitting urate as four dummy variables (for the five urate groups). Tests for trend were carried out fitting urate in its original continuous form. In the adjustment, age, body mass index, cholesterol, FEV₁, and diastolic blood pressure were fitted as continuous variables. Smoking (five levels: never, ex-, light, moderate, and heavy), alcohol (five levels: none, occasional, light, moderate, heavy), pre-existing coronary heart disease (three levels: none, group 1 and group 2), use of antihypertensive treatment (yes/no), and history of diabetes (yes/no) were fitted as categorical variables.

Results

During the mean follow up period of 16.8 years there were 1085 major coronary heart disease events (fatal and non-fatal) in the 7688 men with available data on serum urate. The mean (SD) serum urate concentration in these 7688 men was 358.8 (69.8) $\mu\text{mol/l}$, range 91 to 995 $\mu\text{mol/l}$.

URATE AND CORONARY HEART DISEASE RISK FACTORS

Urate was strongly associated with body mass index (BMI) ($r = 0.29$; $P < 0.0001$) but no association was seen with age.

Lifestyle factors and pre-existing disease

Table 1 shows the age and BMI adjusted mean serum urate concentrations by personal characteristics and disease status. Anti-hypertensive treatment and pre-existing coronary heart disease were significantly associated with higher levels of serum urate after adjustment for age and BMI. Urate levels increased

Table 1 Mean serum urate by levels of personal characteristics and pre-existing disease. Body mass index (BMI) adjusted for age, all others adjusted for age and BMI

Factors	n	Adjusted mean (SE)	Test for difference between groups
BMI (kg/m ²)			
< 20	266	314.7 (4.10)	P < 0.0001
20–	698	326.1 (2.53)	
22–	1537	343.5 (1.71)	
24–	2069	357.2 (1.47)	
26–	1629	368.8 (1.66)	
28–	1486	389.0 (1.73)	
Antihypertensive treatment			
No	7313	356.3 (0.77)	P < 0.0001
Yes	375	406.7 (3.45)	
Pre-existing IHD			
None	5755	357.0 (0.88)	P < 0.0001
Grade II	1508	361.9 (1.72)	
Def MI	425	371.7 (3.26)	
Diabetes			
No	7571	359.4 (0.77)	P < 0.0001
Yes	117	320.2 (6.16)	
Smoking			
Never	1812	360.7 (1.57)	P < 0.0001
Ex–	2700	366.1 (1.29)	
1–19*	1176	354.1 (1.95)	
20*	833	348.0 (2.31)	
21–*	1151	351.2 (1.97)	
Alcohol			
None	461	344.7 (3.05)	P < 0.0001
Occasional	1831	343.0 (1.53)	
Light	2531	356.8 (1.30)	
Moderate	2030	366.7 (1.46)	
Heavy	829	387.8 (2.28)	

IHD, ischaemic heart disease; Def MI, definite myocardial infarction.

*Cigarettes per day.

progressively with increasing alcohol intake. Current smoking and diabetes were associated with significantly lower levels of serum urate. No association was seen with social class or physical activity (data not shown). The significant positive associations with antihypertensive treatment, pre-existing ischaemic heart diseases, and alcohol intake and the inverse association with smoking and history of diabetes persisted even after adjustment for each of the other factors.

Biological factors

After adjustment for age and BMI there were small but significant correlations with triglyceride ($r = 0.15$; $P < 0.0001$), cholesterol ($r = 0.10$; $P < 0.0001$), diastolic blood pressure ($r = 0.08$; $P < 0.0001$), systolic blood pressure ($r = 0.05$; $P < 0.0001$), serum insulin ($r = 0.08$; $P < 0.0001$), packed cell volume ($r = 0.06$; $P < 0.0001$), FEV₁ ($r = -0.06$; $P < 0.0001$), and heart rate ($r = 0.04$; $P = 0.0004$). No association was seen with high density lipoprotein (HDL) cholesterol ($r = 0.01$). Although no significant correlation was seen with blood glucose ($r = -0.02$), a previous report from this study has shown a non-linear relation between serum urate and blood glucose. There was a positive relation between blood glucose and serum urate up to a blood

glucose concentration of about 8.0 mmol/l; at higher levels of glucose, serum urate decreased.¹⁹

With the exception of blood pressure, the associations with biological factors persisted even after additional adjustment for pre-existing coronary heart disease, antihypertensive treatment, diabetes, alcohol intake, and smoking. The correlations between urate and blood pressure were weakened ($r = 0.04$ and $r = 0.02$ for diastolic and systolic blood pressure, respectively) although the correlation remained significant for diastolic blood pressure. Since cholesterol and triglyceride are strongly correlated ($r = 0.37$) we examined the relation between urate and cholesterol and triglyceride adjusting in addition for each of the other factors. Triglyceride remained strongly associated with urate but the relation with cholesterol, although statistically significant, was markedly attenuated ($r = 0.05$).

SERUM URATE AND RISK OF CORONARY HEART DISEASE

In order to determine the role of confounding factors and because the biological factors such as blood lipids and blood pressure may be mediating factors, we have examined the relation between serum urate and risk of coronary heart disease by quintiles of serum urate (table 2) adjusting successively and cumulatively for potential confounding variables: (A) age only, (B) lifestyle factors, (C) disease indicators, and (D) biological factors (cholesterol and diastolic blood pressure). In this study serum triglyceride is not an independent risk factor for coronary heart disease once blood cholesterol has been taken into account, and it has therefore not been included in the adjustment.²⁰ A strong and significant positive association was seen between urate and risk of coronary heart disease after adjustment for age (table 2; A). Further adjustment for lifestyle factors shown to be associated with urate—smoking, BMI, and alcohol—made little difference to the relation (B). Additional adjustment for disease indicators, that is, pre-existing coronary heart disease, use of antihypertensive treatment, and lung function, attenuated the positive relation slightly but the trend remained significant (C). Finally, adjustment for diastolic blood pressure and blood cholesterol considerably weakened the relation (D). Although men in the lowest quintile of serum urate showed significantly lower risk than the rest, there was no difference between the other groups and a test for trend was not

Table 2 Serum urate and age adjusted coronary heart disease (CHD) rates/1000 person-years and adjusted relative risk of coronary heart disease, with 95% confidence intervals

Urate fifths	n	Age adjusted cases rate/1000 person-years		A	B	C	D
1	1530	173	7.4	1.00	1.00	1.00	1.00
2	1537	214	9.6	1.30 (1.07 to 1.59)	1.33 (1.08 to 1.62)	1.36 (1.10 to 1.66)	1.32 (1.07 to 1.62)
3	1533	208	9.2	1.27 (1.04 to 1.56)	1.32 (1.08 to 1.63)	1.36 (1.11 to 1.69)	1.28 (1.04 to 1.58)
4	1572	236	10.1	1.39 (1.14 to 1.69)	1.42 (1.15 to 1.74)	1.42 (1.15 to 1.74)	1.29 (1.05 to 1.59)
5	1516	254	11.5	1.55 (1.29 to 1.89)	1.58 (1.30 to 1.95)	1.42 (1.16 to 1.76)	1.27 (1.03 to 1.57)
Test for trend				P < 0.0001	P < 0.0001	P = 0.007	P = 0.12

A, adjusted for age; B, adjusted for A, smoking, body mass index, and alcohol intake; C, adjusted for A, B, and antihypertensive treatment, pre-existing ischaemic heart disease, diabetes, and lung function; D, adjusted for A, B, C, and diastolic blood pressure and cholesterol.

significant ($P = 0.12$). To assess whether diastolic blood pressure or blood cholesterol in particular attenuated this relation, these two factors were entered separately in the model. Blood cholesterol emerged as the critical factor in attenuating the relation. The adjusted relative risk when only blood cholesterol was included in addition to lifestyle factors and indicators of disease was 1.00, 1.34, 1.30, 1.32, and 1.30 for the five groups, respectively. Thus additional inclusion of diastolic blood pressure had little further effect on the relation.

URATE AND RISK OF CORONARY HEART DISEASE BY EVIDENCE OF PRE-EXISTING CORONARY HEART DISEASE

Because of the strong association between serum urate and presence of coronary heart disease, we examined the relation between serum urate by grades of pre-existing coronary heart disease at baseline, adjusting first (A) for lifestyle factors and disease indicators and then (B) in addition for blood cholesterol and diastolic blood pressure (table 3). In men with no pre-existing disease, after adjustment for lifestyle factors and disease indicators (column A), a positive association was seen, but this was considerably attenuated after further adjustment for cholesterol and diastolic blood pressure (column B). In men with pre-existing coronary heart disease short of a definite myocardial infarction, risk was lowest in men with low urate but there was no difference between the other groups. A positive association was seen in men with pre-existing definite myocardial infarction even after adjustment for diastolic blood pressure and cholesterol and the trend was of marginal significance ($P = 0.07$).

Exclusion of men with definite myocardial infarction on antihypertensive treatment ($n = 92$) increased the positive association seen in men in group 3 (test for trend $P = 0.02$), with those in the top quintile showing an almost twofold increase in risk of subsequent major

coronary heart disease events compared to men in the lowest quintile after adjustment for diastolic blood pressure and cholesterol (adjusted relative risk (RR) = 1.95; 95% confidence interval (CI) 1.07 to 3.56). This positive association was still seen even after exclusion of cases which occurred within the first five years of follow up (adjusted RR = 1.73, 95% CI 0.83 to 2.10; test for trend $P = 0.09$) although the trend was not significant, possibly due to the small numbers involved (266 men; 84 cases).

SERUM URATE AND RISK SCORE FOR CORONARY HEART DISEASE IN ABSENCE OF PRE-EXISTING CORONARY HEART DISEASE

If serum urate is integrally related to many of the risk factors for major coronary heart disease events, then as overall risk of major coronary heart disease as manifest by a clustering of risk factors (risk score) increases, one would expect levels of serum urate to increase even in the absence of evidence of pre-existing coronary heart disease. In table 4, all men with pre-existing coronary heart disease (groups 2 and 3) were excluded and serum urate levels were examined in relation to progressively increasing risk of coronary heart disease as assessed by a multifactorial risk score, which includes age, smoking, systolic blood pressure, cholesterol, ECG ischaemia, ECG definite myocardial infarction, diagnosis of coronary heart disease, current angina, diabetes, and parental history of heart disease.²¹ Mean serum urate increased significantly with increasing risk score even in the absence of underlying coronary heart disease.

ALL CAUSE MORTALITY

There were 1510 deaths from all causes during the follow up period. The relation between serum urate and all cause mortality was examined by evidence of pre-existing coronary heart disease. No association was seen in any of the three groups after adjustment for age, lifestyle factors, disease indicators, diastolic blood pressure, and cholesterol.

RENAL FUNCTION AND RISK OF CORONARY HEART DISEASE

Serum urate was significantly correlated with serum creatinine and urea even after adjustment for age and BMI ($r = 0.29$ and $r = 0.13$, respectively). This correlation was seen in men with and without pre-existing coronary

Table 3 Serum urate and risk of coronary heart disease (CHD) by grades of pre-existing CHD adjusted for (A) age, smoking, body mass index, and alcohol intake, antihypertensive treatment, history of diabetes, lung function, and (B) in addition for diastolic blood pressure and cholesterol. 7578 men with data on all covariates

Urate fifths	n	Age adjusted rate per 1000 person-years	Adjusted RR (95% CI)	
			A	B
None (618/5677)				
1	1162	6.4	1.00	1.00
2	1132	7.0	1.15	1.10 (0.84 to 1.41)
3	1196	7.8	1.34	1.25 (0.97 to 1.61)
4	1107	7.8	1.32	1.18 (0.89 to 1.52)
5	1080	7.6	1.27	1.11 (0.84 to 1.46)
Test for trend			$P = 0.09$	NS
Group 2 (269/1485)				
1	261	6.9	1.00	1.00
2	321	15.4	2.30	2.22 (1.44 to 3.43)
3	253	11.4	1.72	1.62 (1.00 to 2.60)
4	309	11.4	1.69	1.56 (0.99 to 2.47)
5	341	15.3	1.86	1.71 (1.08 to 2.69)
Test for trend			NS	NS
Group 3 (definite MI) (177/416)				
1	73	23.9	1.00	1.00
2	65	28.7	1.14	1.13 (0.64 to 1.99)
3	63	25.5	1.11	1.05 (0.59 to 1.86)
4	82	38.9	1.56	1.53 (0.91 to 2.57)
5	133	38.1	1.51	1.46 (0.88 to 2.44)
Test for trend			$P = 0.05$	$P = 0.07$

MI, myocardial infarction.

Table 4 Mean serum urate ($\mu\text{mol/l}$) by BRHS full score† ranked by fifth of the whole distribution. Men with pre-existing ischaemic heart disease (grades II and III) were excluded after this ranking

BRHS score (fifths)	No of men	Mean urate (SE)
1	1377	348.6 (1.71)
2	1291	355.9 (1.81)
3	1207	359.2 (2.02)
4	1107	358.2 (2.04)
5	636	362.1 (2.91)
Test for trend		$P < 0.0001$

†Full score includes age, smoking, systolic blood pressure, cholesterol, ECG ischaemia, ECG definite myocardial infarction, diagnosis of ischaemic heart disease, current angina, diabetes, and parental history.

heart disease. However, no association was seen between blood urea and risk of coronary heart disease or between creatinine and risk of coronary heart disease. In particular no association was seen between these renal factors and risk of coronary heart disease in men with definite myocardial infarction, unlike that seen with serum urate.

HISTORY OF GOUT

Serum urate concentration was significantly raised in the 197 men who recalled a doctor diagnosis of gout (age and BMI adjusted urate concentration 415.4 v 357.3 $\mu\text{mol/l}$; $P < 0.0001$). However, there was little association between a history of gout and subsequent risk of coronary heart disease, even after adjusting only for age (age adjusted RR 1.19 , 95% CI 0.85 to 1.66).

Discussion

In this study of middle aged men, raised serum urate was associated with a significant increase in risk of heart attacks after adjustment for age, as has been observed in other prospective studies. However, as in several other large population studies, we found that serum urate was associated with many of the cardiovascular risk factors, in particular obesity, use of antihypertensive treatment, alcohol intake, hyperlipidaemia, and the presence of coronary heart disease.^{3-6 22-25} Although several epidemiological and clinical studies have reported a significant association between hyperuricaemia and hypertension, in our study there was only a weak association between serum urate and blood pressure (diastolic only) after adjusting for BMI and other lifestyle factors. Several population studies have also noted weak^{6 7} or no association between uric acid and blood pressure after BMI or antihypertensive treatment is taken into account in multivariate analyses.²⁴ The negative association between smoking and serum urate levels observed in this study has also been reported by others.² Although raised serum urate has been shown to be associated with an increased risk of development of diabetes,^{26 27} diabetics have significantly lower mean urate concentrations, a phenomenon also observed in a study of 10 000 Israeli men.²⁶ We found no association between urate and HDL cholesterol after adjustment for BMI.

SERUM URATE AS AN INDEPENDENT RISK FACTOR

Although it has become increasingly recognised that the relation between raised serum urate and risk of coronary heart disease in men is mediated through other risk factors, it is still uncertain whether the observed relation is related to hypertension or use of antihypertensive treatment, hyperlipidaemia, or the presence of established coronary heart disease. In this study, serum urate was significantly and positively associated with risk of coronary heart disease, even after adjustment for lifestyle factors and disease indicators including pre-existing coronary heart disease and use

of antihypertensive treatment. However, this relation was attenuated to non-significance after further adjustment for diastolic blood pressure and blood cholesterol. While several studies have found the increased risk to be related to use of thiazide diuretics^{4 8} or pre-existing coronary heart disease,⁷ we found the relation to be statistically independent of these factors in multivariate analyses, but the positive relation was more concentrated in men with pre-existing coronary heart disease. The Framingham study also found the relation to be independent of use of antihypertensive treatment but it was attenuated upon adjustment for other cardiovascular risk factors, including blood pressure and cholesterol.⁴ The NHANES study²⁸ and the Chicago Heart Association detection project in industry⁶ both found the relation between uric acid and risk of coronary heart disease to be attenuated after adjustment for a range of other cardiovascular risk factors, but neither of these studies ascertained which factors were responsible for the attenuation. The increased risk of coronary heart disease observed in our total study population appeared to be largely mediated by the association between hyperuricaemia and serum cholesterol.

HYPERURICAEMIA AND HYPERLIPIDAEMIA

Hyperlipidaemia is commonly associated with hyperuricaemia.^{4 5 29 30} In this study we observed a significant association between urate and serum triglycerides and cholesterol. Raised triglyceride is often accompanied by a rise in cholesterol and in our study the relation between raised urate and raised cholesterol appeared to be largely mediated through triglycerides. Although our findings are based on non-fasting triglyceride concentrations, the stronger association with uric acid and triglycerides than with cholesterol has also been observed in another large prospective study⁵ and in studies which have used fasting triglyceride concentrations.^{29 30} It is not clear why hyperuricaemia is associated with a clustering of risk factors but it has been suggested that serum uric acid, together with increased small dense low density lipoprotein cholesterol particles, may be part of the insulin resistance syndrome,³¹⁻³⁴ which in turn leads to coronary heart disease.^{33 34} It is therefore possible that the association between urate and coronary heart disease is largely mediated by triglyceride metabolism.³⁴

PRE-EXISTING CORONARY HEART DISEASE

Uric acid is often raised in patients with established coronary heart disease, as seen in this study. Although no independent association was seen between serum urate and risk of coronary heart disease in the total study population, when the relation was examined separately by grades of pre-existing coronary heart disease a significant positive association was seen in men with definite myocardial infarction, even after full adjustment. This association was strengthened upon exclusion of men on antihypertensive treatment. Men in the top fifth of the distribution showed nearly a

twofold increase risk of coronary heart disease compared to those in the bottom fifth. In men with no evidence of coronary heart disease, a weaker but positive association was seen in the age adjusted analysis, which was attenuated after adjustment. However, in these men with no evidence of pre-existing coronary heart disease, mean serum urate concentrations increased progressively, albeit moderately, as overall risk determined by a multifactorial score increased.

Few studies have examined the role of uric acid separately by presence or absence of coronary heart disease and in the two that have done so the findings have been inconsistent. In the US coronary drug project no association was seen between raised serum uric acid and risk of non-fatal myocardial infarction in men with pre-existing myocardial infarction followed up for three years.⁴ In a Finnish study of 3195 men, no association was seen between serum uric acid and risk of cardiovascular mortality in men without known heart disease.⁷ In men with known heart disease hyperuricaemia was associated with an increase in cardiovascular mortality. Although the findings were not statistically significant after adjustment for other cardiovascular risk factors including antihypertensive medication and heart enlargement, there was still a nearly twofold increase in risk of cardiovascular mortality.

GOUT AND CORONARY HEART DISEASE

It is widely accepted that gout is a risk factor for coronary heart disease, although few prospective population studies have examined this relation. In the Framingham study, based on a 32 year follow up, men with gout ($n = 92$) experienced a 60% excess of coronary heart disease, predominantly in the form of angina pectoris. Adjustment for other atherogenic risk factors (systolic blood pressure, total cholesterol, alcohol, BMI, diabetes) did not alter the risk of coronary heart disease in men. In women ($n = 19$), in whom gout occurred infrequently, there was no significant association between gout and CHD.³⁵ In the present study we found no increased risk of coronary heart disease in the men with recall of a diagnosis of gout ($n = 187$) despite their raised serum urate concentrations. There also appears to be no conclusive evidence that raised serum urate in hypertensive subjects, even when induced by diuretics, worsens vascular risk.^{36 37}

CONCLUSIONS

The significant positive association observed in the total cohort between serum urate and the risk of a major coronary heart disease event persisted after adjustment for age, lifestyle factors, and disease indicators. However, after additional adjustment for total cholesterol the increased risk was attenuated to a non-significant level. Furthermore, the relation between serum urate and major coronary heart disease events was only observed, after full adjustment, in men with previous definite myocardial infarction. The findings in this study

strongly suggest that the relation observed between serum urate and the risk of major coronary heart disease events depends heavily upon the increased risk in those with previous definite myocardial infarction and severe underlying atherosclerosis. It also appears that raised serum urate is an integral part of the cluster of risk factors associated with the insulin resistance syndrome, particularly obesity, raised serum triglycerides, and raised serum cholesterol.

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- 1 Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. *Ann Intern Med* 1951;34:1421-31.
- 2 Beard JT. Serum uric acid and coronary heart disease. *Am Heart J* 1983;106:397-400.
- 3 Brand FN, McGee DL, Kannel WB, Stokes J, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: the Framingham Study. *Am J Epidemiol* 1985;121:11-18.
- 4 The Coronary Drug Project Research Group. Serum uric acid: its association with other risk factors and with mortality in coronary heart disease. *J Chron Dis* 1976;29:557-69.
- 5 Yano K, Rhoads GC, Kagan A. Epidemiology of serum uric acid among 8000 Japanese-American Men in Hawaii. *J Chron Dis* 1977;30:171-84.
- 6 Persky VW, Dyer AR, Idris Soven E, Stamler J, Shekelle RB, Schoenberger JA, et al. Uric acid: a risk factor for coronary heart disease? *Circulation* 1979;59:969-77.
- 7 Reunanen A, Takkunen, Knekt P, Aromaa A. Hyperuricaemia as a risk factor for cardiovascular mortality. *Acta Med Scand (Suppl)* 1982;668:49-59.
- 8 Yano K, Reed DM, McGee DL. Ten year incidence of coronary heart disease in the Honolulu Heart Program: relationship to biologic and lifestyle characteristics. *Am J Epidemiol* 1984;119:653-66.
- 9 Selby JV, Friedman GD, Quesenberry CP. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol levels, and other serum chemistries. *Am J Epidemiol* 1990;131:1017-27.
- 10 Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. *BMJ* 1981;283:179-86.
- 11 Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. *J Hypertens* 1988;6:375-80.
- 12 Thelle DS, Shaper AG, Whitehead TP, Bullock DG, Ashby D, Patel I. Blood lipids in middle-aged British men. *Br Heart J* 1983;49:205-13.
- 13 Shaper AG, Wannamethee G, MacFarlane PW, Walker M. Heart rate, ischaemic heart disease and sudden cardiac death in middle-aged British men. *Br Heart J* 1993;70:49-55.
- 14 Shaper AG, Wannamethee G. Physical activity and ischaemic heart disease in middle-aged British men. *Br Heart J* 1991;66:384-94.
- 15 Perry IJ, Wannamethee SG, Whincup PH, Shaper AG, Walker M, Alberti KGM. Serum insulin and incident coronary heart disease in middle-aged British men. *Am J Epidemiol* 1996;144:224-34.
- 16 Cook DG, Shaper AG, Macfarlane PW. Using the WHO (Rose) angina questionnaire in cardiovascular epidemiological studies. *Int J Epidemiol* 1989;18:607-13.
- 17 Walker M, Shaper AG. Follow-up of subjects in prospective studies based in general practices. *J R Coll Gen Pract* 1984;34:365-70.
- 18 Cox DR. Regression models and life tables. *J R Stat Soc (B)* 1972;34:187-220.
- 19 Cook DG, Shaper AG, Thelle DS, Whitehead TP. Serum uric acid, serum glucose and diabetes: relationships in a population study. *Postgrad Med J* 1986;62:1001-6.
- 20 Pocock SJ, Shaper AG, Phillips AN. Concentrations of high density lipoprotein cholesterol, triglycerides, and total cholesterol in ischaemic heart disease. *BMJ* 1989;298:998-1002.
- 21 Shaper AG, Pocock SJ, Phillips AN, Walker M. A scoring system to identify men at high risk of a heart attack. *Health Trends* 1987;19:37-3.
- 22 Klein R, Klein B, Cornoni JC, Maready J, Cassel JC, Tyroler HA. Serum uric acid: its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia. *Arch Intern Med* 1973;132:401-10.
- 23 Iribarren C, Sharp DS, Curb JD, Yano K. High uric acid: a metabolic marker of coronary heart disease among alcohol abstainers. *J Clin Epidemiol* 1996;49:673-8.
- 24 Okada M, Takeshita M, Ueda K, Omae T, Hirota Y. Factors influencing the serum uric acid level. A study based on a population survey in Hisayama town, Kyushu, Japan. *J Chronic Dis* 1980;33:607-12.

- 25 Goldbourt U, Medalie JH, Herman JB, Neufeld HN. Serum uric acid: correlation with biochemical, anthropometric, clinical and behavioural parameters in 10,000 Israeli men. *J Chron Dis* 1980;33:435-43.
- 26 Medalie JH, Papier C, Herman JB, Goldbourt U, Tamir S, Neufeld HN, *et al.* Diabetes mellitus among 10 000 adult men: Israeli Study. *Isr J Med Sci* 1974;10:681-97.
- 27 Perry IJ, Wannamethee SG, Walker M, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle-aged British men. *BMJ* 1995;310:560-4.
- 28 Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischaemic heart disease: the NHANES I epidemiologic follow-up study. *Am J Epidemiol* 1995;141:637-44.
- 29 Berkowitz D. Blood lipid and uric acid interrelationships. *JAMA* 1964;190:120-2.
- 30 Zalokar J, Lellough J, Claude JR, Kuntz D. Epidemiology of serum uric acid and gout in Frenchmen. *J Chron Dis* 1974 27:59-75.
- 31 Modan M, Halkin H, Karasik A, Lusky A. Elevated serum uric acid—a facet of hyperinsulinaemia. *Diabetologia* 1987;30:713-8.
- 32 Facchini F, Chen Y-D, Hollenbeck CB. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA* 1991;266:3008-11.
- 33 Lee J, Sparrow D, Vokonas PS, Landsberg L, Weiss ST. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. *Am J Epidemiol* 1995;142:288-94.
- 34 Krentz AJ. Insulin resistance. *BMJ* 1996;313:1385-9.
- 35 Abbott RD, Brand FN, Kannel WB, Castelli WP. Gout and coronary heart disease: the Framingham study. *J Clin Epidemiol* 1988;41:237-42.
- 36 Hypertension and uric acid [editorial]. *Lancet* 1981;i:365-6.
- 37 Uric acid in hypertension [editorial]. *Lancet* 1987;i:1124.