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**Original Scientific Paper**

# Serum uric acid and long-term mortality from stroke, coronary heart disease and all causes

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***Background*** **Increased serum uric acid (SUA) levels are linked to obesity, dyslipidemia, diabetes and hypertension. Whether SUA carries a risk for coronary heart disease (CHD) and stroke remains uncertain.**

***Design*** **A prospective cohort study.**

***Methods*** **Of an original cohort of middle-aged workers who were examined in 1963 and followed-up for 23 years, 9125 men, free of CHD at entry, are included in this study. Subjects were divided into quintiles according to baseline SUA levels. Hazard ratios (HR) for all-cause, CHD, and stroke mortality were estimated in SUA quintiles, with the third serving as a referent.**

***Results*** **During follow-up, 2893 deaths were recorded, including 830 ascribed to CHD and 292 to stroke. The HR for all death [1.22, 95% confidence interval (CI) 1.09–1.37] and CHD (1.29, 95% CI 1.05–1.58) were increased in the upper SUA quintile. Fatal stroke showed a U-shaped relationship as both the upper (HR 1.48, 95% CI 1.02–2.17) and bottom (HR 1.43, 95% CI 0.99–2.08) quintiles were associated with a higher risk. Adjustment for confounders reduced the HR of the upper quintile for all outcomes, but did not attenuate the association of the bottom quintile with stroke (HR 1.52, 95% CI 1.04–2.23). When analysed separately by stroke type, the latter association seemed to be stronger for hemorrhagic (HR 3.27, 95% CI 1.14–9.33) than for ischemic stroke (HR 1.34, 95% CI 0.87–2.05).**

***Conclusion*** **In addition to findings supporting increased mortality among hyperuricemic subjects, we identified an association between low SUA levels and fatal stroke, which deserves further investigation.** ***Eur J Cardiovasc Prev Rehabil*** **13:193–198** © **2006 The European Society of Cardiology**

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## Introduction

Serum uric acid (SUA) has long been associated with hypertension, diabetes, dyslipidemia, obesity, and renal failure [1,2]. Many studies have provided strong evidence correlating elevated SUA to coronary heart disease (CHD) [3–7]. However, whether SUA is a risk factor for CHD and the mechanism of this risk remain questionable [8–12]. Several direct and indirect (non-causal) mechanisms relating SUA to CHD risk have been postulated. Hyperuricemia might have deleterious effects on endothelial function, oxidative stress, the formation of free radicals, and platelet adhesiveness [8]. On the other hand, high SUA is correlated with confounding risk factors or may simply reflect an underlying cardiovascular disease [8,13].

Whereas a positive relationship between SUA and the risk of CHD is suggested in several populations, the relationship between SUA and stroke is less clear. High SUA has been associated with stroke risk in several studies [14–17], whereas others found an inverse association [18,19]. In the present study, we analysed data from a large cohort of Israeli male employees in order to assess

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the relationship between SUA levels and mortality from stroke, CHD and all causes.

## Subjects and methods

### Study participants

The original cohort ($n = 10\,059$) was assembled by stratified sampling of tenured civil servants and municipal employees in 1963, based on: (1) men aged 40 years or above on inclusion; (2) place of work limited to the three largest urban areas in Israel (Tel-Aviv, Jerusalem, and Haifa); and (3) sampling fractions aimed at obtaining sufficient numbers of subjects from six areas of birth, approximately proportional to the Israeli male population of this age. Participants underwent clinical, dietary, psychosocial and blood biochemical evaluations in 1963, 1965, and 1968. The response rate to the initial examination was 86%, and 98% of those living in 1965 were re-examined. Similarity was found between the subjects examined and the non-responders with respect to age, area of birth, and socio-economic status. Further details of the study have been described [20,21]. For the current report, men with missing measurements of SUA ($n = 150$) were excluded, as well as individuals with either a history of CHD (defined as confirmed angina pectoris, past hospitalization for myocardial infarction, or electrocardiogram consistent with an old infarction; $n = 444$), or under antihypertensive treatment during the initial 5 years of follow-up ($n = 376$). A total of 934 men with at least one of the above causes were eliminated, leaving 9125 for analysis.

### Mortality data

Mortality follow-up lasted for 23 years (1963–1986). The underlying cause of death was documented on the basis of case-by-case determinations by a review panel until 1970 and by the use of the International Classification of Diseases (ICD) codes thereafter. Deaths from presumed CHD were based on ICD-9 codes 410 to 414, and those ascribed to stroke were based on codes 430 to 438. Information on death was derived from the Israeli Mortality Registry. For all hospital deaths until 1970, a comparison of death certificates with the analyses of hospital records (including physician notes, autopsy reports, and death certificates) by a study panel revealed agreement in over 90% of cases. An analysis of a 254 random sample of hospital deaths versus death certificates showed an agreement of almost 100% for death caused by cancer and 84% for death caused by non-malignant disease.

### Uric acid measurement

SUA was measured by Fister's adaptation of the colorimetric method using phosphotungstic acid in the presence of cyanide and urea. All determinations were performed in duplicate and the mean result of the two tests was used for analysis. One in 20 samples was retested blindly in duplicate. A standard serum was assayed with each run. The standard deviation of duplicates was $\pm 0.21$ mg/dl or 4.4% (the mean value being 4.75 mg/dl) [22].

### Risk factor assessment

Blood pressure (BP) was measured using a standard mercury sphygmomanometer with a 12-cm diameter cuff on the right arm. It was taken twice, in the supine position, 30–45 min after arrival at the clinic and again 15–30 min later. The second measurement was used for the analysis.

Non-fasting serum cholesterol was measured using the Anderson and Keys modification of the Abel method [23]. The control procedures included the use of freshly weighted standards, the daily determination of a specimen derived from pooled adult human serum and duplicate tests on all specimens. The cholesterol value reported for each individual was the average duplicate testing, with a coefficient of variation of approximately 2.4%.

Cigarette smoking was self-reported, and was classified into five groups (never, past, and current one to 10, 11–20, and above 20 cigarettes per day).

Left ventricular hypertrophy (LVH) on electrocardiogram was diagnosed by R wave in lead aVF $\geq 2.0$ mV or lead aVL $\geq 1.3$ mV, S wave in V1 plus R wave in lead V5 or V6 $\geq 4.6$ mV, or S wave in V2 plus R wave in lead V5 or V6 $\geq 4.6$ mV [24].

Other variables included body mass index (BMI; kg/m$^2$), and diabetes mellitus (known treated diabetes or diagnosed by an oral glucose tolerance test) [25].

### Statistical analyses

Subjects were divided into quintiles according to baseline SUA levels. Associations between SUA and cardiovascular risk factors were assessed with the Mantel–Haenszel chi-squared tests for categorical variables and analysis of variance (ANOVA) for continuous variables.

Proportional hazards regression models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for all-cause, CHD, and stroke mortality in SUA quintiles, with the third quintile serving as the reference category. The proportional hazards assumption was tested using the Schoenfeld residuals applying the Stata (version 7) procedures stcox and stphtest. The HR were estimated before and after adjustment for confounding risk factors. Sensitivity analyses included an evaluation of the HR according to diabetes and smoking status. In addition, specific analyses were performed for ischemic and hemorrhagic strokes (defined by ICD-9 codes 433–438 and 430–432, respectively).

Repeated measures of SUA were used to correct for regression dilution bias. Regression dilution factors were

**Table 1 Baseline clinical characteristics by serum uric acid (SUA) quintiles**

| | SUA quintiles (mg/dl) | | | | | *P* value |
|---|---|---|---|---|---|---|
| Baseline characteristics | 1 ($\leq$ 3.9) | 2 (4.0–4.4) | 3 (4.5–4.9) | 4 (5.0–5.5) | 5 ($\geq$ 5.6) | |
| No. of subjects | 1765 | 1930 | 2030 | 1792 | 1608 | |
| Age (years) | 49 (7) | 49 (7) | 49 (7) | 49 (7) | 49 (7) | 0.34 |
| BMI (kg/m$^2$) | 24.2 (3.2) | 25.0 (3.3) | 25.6 (3.2) | 26.3 (3.1) | 27.1 (3.2) | <0.001 |
| SBP (mmHg) | 130 (18) | 132 (18) | 133 (19) | 135 (19) | 138 (20) | <0.001 |
| DBP (mmHg) | 81 (10) | 82 (10) | 83 (10) | 84 (10) | 86 (11) | <0.001 |
| Cholesterol (mg/dl) | 202 (40) | 204 (38) | 208 (40) | 213 (39) | 216 (40) | <0.001 |
| Current smoking (%) | 59 | 57 | 53 | 49 | 44 | <0.001 |
| Diabetes (%) | 8 | 5 | 3 | 3 | 3 | <0.001 |
| LVH on ECG (%) | 1.3 | 1.5 | 1.1 | 1.7 | 2.3 | 0.04 |

Values represent mean (standard deviation) unless specified. BMI, body mass index; DBP, diastolic blood pressure; LVH on ECG, left ventricular hypertrophy on electrocardiogram; SBP, systolic blood pressure.

**Table 2 Relations of uric acid quintiles with mortality from stroke, coronary heart disease (CHD) and all causes**

| | Events | Crude rate | Hazard ratio (95% CI) | |
|---|---|---|---|---|
| SUA quintiles | *n* | (95% CI)[a] | Unadjusted | Multivariable-adjusted[b] |
| Stroke | 292 | | | |
| Quintile 1 | 62 | 17 (13–21) | 1.43 (0.99–2.08) | 1.52 (1.04–2.23) |
| Quintile 2 | 66 | 16 (12–20) | 1.39 (0.96–2.00) | 1.46 (1.00–2.12) |
| Quintile 3 | 50 | 12 (09–15) | 1.00 | 1.00 |
| Quintile 4 | 58 | 15 (12–20) | 1.32 (0.90–1.92) | 1.25 (0.85–1.84) |
| Quintile 5 | 56 | 17 (13–22) | 1.48 (1.01–2.17) | 1.20 (0.81–1.78) |
| CHD | 830 | | | |
| Quintile 1 | 159 | 42 (37–50) | 0.97 (0.79–1.20) | 0.96 (0.77–1.20) |
| Quintile 2 | 145 | 35 (30–41) | 0.81 (0.65–1.00) | 0.84 (0.67–1.05) |
| Quintile 3 | 189 | 44 (38–50) | 1.00 | 1.00 |
| Quintile 4 | 153 | 40 (34–47) | 0.92 (0.74–1.14) | 0.87 (0.70–1.08) |
| Quintile 5 | 184 | 56 (48–64) | 1.29 (1.05–1.58) | 1.12 (0.90–1.38) |
| All causes | 2893 | | | |
| Quintile 1 | 582 | 150 (138–163) | 1.05 (0.94–1.18) | 1.04 (0.92–1.17) |
| Quintile 2 | 610 | 142 (131–154) | 0.99 (0.88–1.11) | 1.00 (0.89–1.12) |
| Quintile 3 | 645 | 143 (132–155) | 1.00 | 1.00 |
| Quintile 4 | 575 | 144 (133–157) | 1.01 (0.90–1.13) | 0.98 (0.87–1.11) |
| Quintile 5 | 605 | 173 (160–188) | 1.22 (1.09–1.37) | 1.15 (1.02–1.29) |

CI, Confidence interval; SUA, serum uric acid. [a]Rates (95% CI) are given per 10 000 person-years. [b]Adjusted for age, body mass index, systolic blood pressure, diabetes, serum cholesterol, smoking, and left ventricular hypertrophy on electrocardiogram.

estimated by dividing the difference in mean SUA between each quintile (i.e. first, second, fourth and fifth) and the third quintile computed from the first measurement (1963) by the corresponding difference in means at the repeated measurement (1968) in identically defined quintiles (1963). Corrections of the proportional hazards regression estimates were made by multiplying the coefficients obtained from the Cox model by the equivalent regression dilution factor, before exponentiation to obtain the estimated HR [24,26].

## Results

### Demographic and clinical characteristics

A total of 9125 men were included in the analysis. Participants were divided into approximate quintiles according to SUA levels. Group characteristics are presented in Table 1. Higher SUA was positively associated with BMI, systolic and diastolic BP, serum cholesterol and LVH on electrocardiogram, and was inversely related to smoking and diabetes. The age distribution was similar across SUA quintiles.

### Mortality rates in serum uric acid quintiles

During the follow-up period (193 337 person-years overall), 2893 deaths were recorded. Of these, 292 (10%) and 830 (29%) were attributed to stroke and CHD, respectively. The crude rates of CHD and all-cause mortality were higher in the upper SUA quintile, whereas a U-shaped relationship was observed between SUA and fatal stroke (Table 2).

### Proportional hazards regression analysis

Cox regression analyses were used to assess the relationships between SUA and mortality from stroke, CHD and all causes. Compared with the average quintile, both the bottom (HR 1.43, 95% CI 0.99–2.08) and upper (HR 1.48, 95% CI 1.02–2.17) quintiles were associated with an increased risk of stroke. Regarding CHD and all-cause mortality, an increased risk was found only in the upper quintile (HR 1.29, 95% CI 1.05–1.58; and HR 1.22, 95% CI 1.09–1.37, respectively). Multivariable adjustment for age, BMI, systolic BP, diabetes, serum cholesterol, smoking and LVH on electrocardiogram diminished the HR associated with the upper SUA quintile to 1.20 (95%

**Table 3 Hazard ratios (95% confidence intervals) for specific stroke types in uric acid quintiles**

| | Ischemic stroke ($n=246$) | | Hemorrhagic stroke ($n=46$) | |
|---|---|---|---|---|
| SUA quintiles | Unadjusted | Adjusted[a] | Unadjusted | Adjusted[a] |
| Quintile 1 | 1.23 (0.82–1.85) | 1.34 (0.87–2.05) | 3.23 (1.16–8.97) | 3.27 (1.14–9.33) |
| Quintile 2 | 1.26 (0.85–1.87) | 1.33 (0.89–2.00) | 2.52 (0.89–7.16) | 2.52 (0.87–7.29) |
| Quintile 3 | 1.00 | 1.00 | 1.00 | 1.00 |
| Quintile 4 | 1.29 (0.86–1.92) | 1.21 (0.81–1.82) | 1.59 (0.50–5.00) | 1.55 (0.49–4.89) |
| Quintile 5 | 1.41 (0.94–2.12) | 1.15 (0.75–1.74) | 2.11 (0.69–6.46) | 1.62 (0.51–5.18) |

SUA, Serum uric acid. [a]Adjusted for age, body mass index, systolic blood pressure, diabetes, serum cholesterol, smoking, and left ventricular hypertrophy on electrocardiogram.

CI 0.81–1.78) for stroke, 1.12 (95% CI 0.90–1.38) for CHD, and 1.15 (95% CI 1.02–1.29) for all-cause mortality. However, the association with stroke of the bottom SUA quintile was not attenuated (HR 1.52, 95% CI 1.04–2.23; Table 2). Further adjustment for fasting glucose and ethnic origin yielded similar results (not shown).

Testing the proportional hazards assumption by use of the Schoenfeld method yielded non-significant results (all $P > 0.15$) for all outcomes in the unadjusted models, indicating the validity of the assumption. However, the inclusion of systolic BP disrupted the proportional hazards assumption in the multivariable model for stroke ($P = 0.02$). Therefore, an additional analysis was performed with systolic BP as a time-dependent covariate (COXREG command, SPSS version 12). This analysis yielded similar estimates of the association between SUA quintiles and stroke (risk factor-adjusted HR 1.52, 1.45, 1.26 and 1.18 for the first, second, fourth and fifth quintiles, respectively).

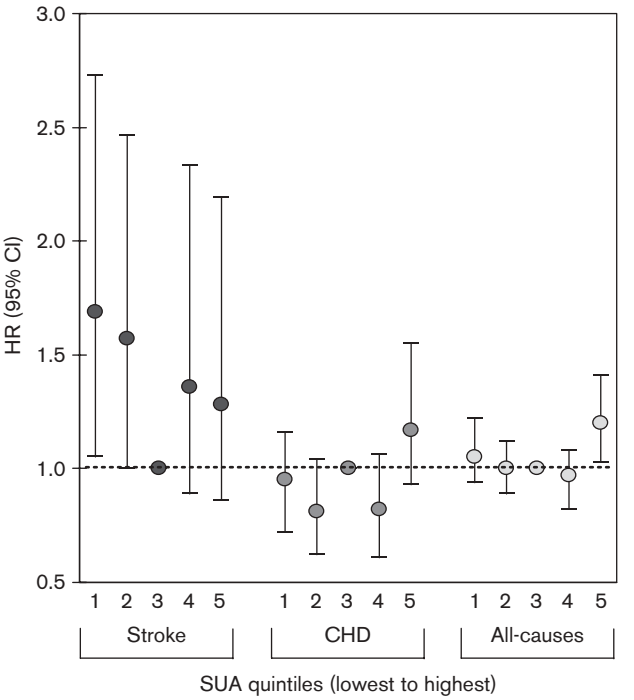
### Sensitivity analyses

The exclusion of subjects with diabetes at entry ($n = 402$) changed the SUA–outcome associations only slightly. The risk factor-adjusted HR in the upper SUA quintile was 1.33 (95% CI 0.88–2.01) for stroke, 1.21 (95% CI 0.97–1.51) for CHD, and 1.21 (95% CI 1.07–1.37) for all-cause mortality, in addition to 1.50 (95% CI 0.99–2.26) for stroke in the lowest quintile. Likewise, in analysis stratified by smoking status, the adjusted HR for stroke, associated with the SUA quintiles, was similar between current and non-current smokers (1.41 versus 1.65 in the bottom quintile, 1.20 versus 1.23 in the upper quintile, respectively). Finally, separate analyses were performed by stroke type. The U-shaped relation of SUA seemed to be stronger in hemorrhagic than in ischemic stroke, although the CI overlapped, indicating the possibility of a chance finding (Table 3).

### Regression dilution correction

As observed regression coefficients might underestimate true regression coefficients for biological variables measured only once, a correction for regression dilution bias was carried out. In multivariable analyses controlling for potential confounders and regression dilution bias, the estimated HR in the upper SUA quintile were 1.28 (95% CI 0.86–2.19) for stroke, 1.17 (95% CI 0.93–1.55) for CHD, and 1.20 (95% CI 1.03–1.41) for all-cause mortality, compared with the average quintile. On the other hand, HR of 1.69 (95% CI 1.05–2.73) and 1.57 (95% CI 1.00–2.46) for fatal stroke were estimated for the first (lowest) and second SUA quintiles, respectively (Fig. 1).

**Fig. 1**




Risk factor-adjusted hazard ratios [HR; 95% confidence intervals (CI)] for stroke, coronary heart disease (CHD) and all-cause mortality in uric acid quintiles, corrected for regression dilution bias. SUA, Serum uric acid.

## Discussion

Two distinct mutations that are thought to have occurred during the Miocene epoch (5 to 20 million years ago) have rendered the urate oxidase (uricase) non-functional

[8]. This enzyme is responsible for the degradation of uric acid to allantoin, which can easily be excreted from the body. As a result, humans have higher SUA than most mammals [8,9]. Normally, only small amounts of uric acid are excreted (5–10%), but the balance is susceptible to disturbances by metabolic disorders that increase production or interfere with clearance [9,13].

### Serum uric acid and coronary heart disease

A link between elevated SUA and increased cardiovascular risk has been recognized for many years [3,7]. Observations carried out in general populations and in groups defined by a specific disease commonly supported a role for SUA as a risk factor for CHD [1]. There is also evidence to suggest that hyperuricemia predicts the development of hypertension [27,28]. Others have considered SUA a part of the metabolic syndrome or simply a marker of other CHD risk factors, such as hypertension, dyslipidemia, obesity, glucose intolerance, and renal disease [29,30].

Culleton *et al.* [10], using the Framingham Heart Study data, reported that elevated baseline SUA levels were not independently associated with an increased risk of cardiovascular mortality. They concluded that the apparent association between SUA and cardiovascular events was probably caused by confounding by other factors, particularly diuretic treatment. Similarly, Wannamethee *et al.* [11] found that among 7688 middle-aged British men followed up for 17 years, the relationship between SUA and CHD risk depended heavily upon the presence of pre-existing myocardial infarction and underlying atherosclerosis as well as the clustering of risk factors. On the other hand, Fang and Alderman [5] reported that among 5926 subjects who participated in the NHANES 1 study (followed up for 16 years) increased SUA was strongly associated with the risk of cardiovascular mortality. This association was independent of cardiovascular risk factors, alcohol intake and diuretic use. Tomita *et al.* [31] analysed the data of nearly 50 000 Japanese male railroad workers. High SUA levels (> 8.5 mg/dl) were associated with an approximately 50% net increase in CHD and all-cause mortality. More recently, Niskanen *et al.* [32], studying 1423 healthy middle-aged Finnish men, reported a 2.5-fold increase in the risk of CHD mortality in the upper versus the lower SUA tertile.

In our study, based on 9125 Israeli working men (after the exclusion of CHD patients and antihypertensive drug users), a high level of SUA was associated with a mild increase in the risk of CHD and overall mortality. Adjustment for a variety of confounding risk factors diminished but did not erase this association: a net 15–20% higher mortality persisted in the upper quintile.

### Serum uric acid and stroke

Controversy exists in the literature as to whether a high level of SUA carries a risk of stroke. Lehto *et al.* [14], studying 1017 diabetic patients, reported a twofold increase in the risk of fatal and non-fatal stroke associated with an SUA level above 5 mg/dl. In the Cardiovascular Study in the Elderly (CASTEL) [15], involving 3282 elderly individuals (aged $\geq$ 65 years) from northern Italian towns, a high level of uric acid was predictive of stroke mortality. Weir *et al.* [17] supported these findings by studying 2500 stroke survivors. In their analysis, the vascular event risk increased by 27% per additional 1.7 mg/dl in the urate level. In contrast, Chamorro and colleagues [18] found a 12% increase in the odds of a good clinical outcome (Mathew score scale > 75) per each mg/dl increase in SUA, based on 881 consecutive patients with acute ischemic stroke. Jee *et al.* [33] recently reported no association between SUA and stroke in a large cohort of Korean men.

In our study, a U-shaped relationship was shown for SUA and fatal stroke. Adjustment for potential confounders, particularly systolic BP and diabetes, accounted for most of the excess risk in the upper quintile, whereas the increased risk associated with low urate levels persisted. However, if a high SUA level promotes hypertension and diabetes [22,27,28], it may not be expected to be independent of these variables while being evaluated as a risk factor. Another interesting finding in our study, although it should be interpreted with caution, is the strong association of low SUA with hemorrhagic rather than ischemic stroke.

### Postulated mechanisms

Several explanations have been suggested for the discrepancies in the reported association between SUA and both CHD and stroke. Johnson *et al.* [8] recently postulated that the increased risk at low levels reflects the decreased plasma antioxidant activity, whereas the increased risk at high levels reflects the role of SUA in inducing vascular disease and hypertension. SUA possesses antioxidant properties, and contributes approximately 60% of the free radical scavenging activity in human serum [34]. Uric acid interacts with peroxynitrite to form a stable nitric oxide donor, promoting vasodilatation and reducing the potential for peroxynitrite-induced oxidative damage [35]. Therefore, uric acid could be expected to protect against oxidative stresses. On the other hand, increased SUA levels might promote the oxygenation of low-density lipoprotein cholesterol and facilitate lipid peroxidation. In addition, increased SUA may be associated with increased platelet adhesiveness, and this effect could potentiate thrombus formation [17]. Each of these factors is known to play a role in the progression of atherosclerosis.

### Study strengths and limitations

The major advantages of our study include the large and well-defined cohort used, and the long follow-up period (overall 2893 fatal events, including 830 CHD and 292 stroke deaths). Extensive baseline measurements allowed

us to adjust for a variety of confounding risk factors. In addition, repeated measures performed during the study enabled us to correct for regression dilution bias.

The disadvantages include the reliance on death certificates, which might lead to misclassification. Assuming that this bias is non-differential with regard to SUA levels, it will underestimate the true HR. Because of the small number of hemorrhagic strokes, and some potential misclassification, differences in the association of SUA by stroke type should be interpreted with caution. Another limitation is the lack of information regarding the use of new treatments introduced during follow-up and their possible interaction with SUA levels. In addition, changes in risk factor status over time [36], and the late development of disease states could not be incorporated. Finally, whereas increased SUA might confer a higher risk in women than in men [37], we were unable to examine this hypothesis as only men were included in this cohort.

### Conclusion

Recent reports linking high SUA levels to cardiovascular and cerebrovascular events have suggested that intervention to reduce urate levels may be warranted [1,16,17,37]. Although our findings support increased mortality in the upper SUA quintile, we also found an association between low urate levels and fatal stroke. This finding needs further clarification, both physiologically and epidemiologically, especially in the light of possible differences in the association of SUA with specific stroke types.

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