

Uric Acid Level as a Risk Factor for Cardiovascular and All-Cause Mortality in Middle-aged Men

A Prospective Cohort Study

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Background: Despite abundant epidemiologic evidence, the role of elevated serum uric acid level as a cardiovascular risk factor is controversial. We assessed the predictive value of serum uric acid levels for cardiovascular and overall mortality.

Methods: A population-based prospective cohort study was performed of 1423 middle-aged Finnish men initially without cardiovascular disease, cancer, or diabetes. The main outcome measure was death from cardiovascular disease and any cause.

Results: The mean follow-up was 11.9 years. There were 157 deaths during follow-up, of which 55 were cardiovascular. In age-adjusted analyses, serum uric acid levels in the upper third were associated with a greater than 2.5-fold higher risk of death from cardiovascular disease than levels in the lower third. Taking into account cardiovascular risk factors and variables commonly associated with

gout increased the relative risk to 3.73. Further adjustment for factors related to the metabolic syndrome strengthened the risk to 4.77. Excluding the 53 men using diuretics did not alter the results. In age-adjusted analyses, men with serum uric acid levels in the upper third were 1.7-fold more likely to die of any cause than men with levels in the lower third. Adjustment for further risk factors strengthened the association somewhat.

Conclusions: Serum uric acid levels are a strong predictor of cardiovascular disease mortality in healthy middle-aged men, independent of variables commonly associated with gout or the metabolic syndrome. Serum uric acid measurement is an easily available and inexpensive risk marker, but whether its relationship to cardiovascular events is circumstantial or causal remains to be answered.

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THE ROLE OF URIC ACID AS AN independent marker of cardiovascular risk has been controversial for decades. At physiologic pH values, serum monoanionic uric acid is the major product of purine metabolism in humans and higher primates and is formed from xanthine, a reaction catalyzed by xanthine dehydrogenase/oxidase.^{1,2} Several epidemiologic studies have shown elevated uric acid levels to predict increased risk of cardiovascular events,³⁻¹² although lack of an independent relationship has also been found.^{3,10}

It is conceivable that the interpretation of the "independent" role of uric acid is further complicated by the use of diuretics and by the very close correlation of uric acid levels with established cardiovascular risk factors such as hypertension,^{13,14} obesity, low levels of high-density lipoprotein cholesterol, hypertriglyceridemia, hyperinsulinemia,

and reduced insulin sensitivity,¹⁵⁻¹⁹ all of which are components of the metabolic or insulin resistance syndrome.²⁰ Moreover, there are other features of atherosclerosis, such as inflammation,²¹ oxidative stress,²² and endothelial dysfunction,²³ that have also been associated with increased serum uric acid levels. Furthermore, clinical ischemic heart,²⁴ cerebrovascular,²⁵ and even mild renal²⁶ disease are all associated with increased uric acid levels.

Recently, the massive 16.4-year follow-up of the National Health and Nutrition Examination Survey I (NHANES I),¹¹ consisting of 5926 subjects, has convincingly established the role of serum uric acid as an independent predictor of cardiovascular mortality in subjects older than 45 years regardless of sex, menopausal status, diuretic use, presence of cardiovascular disease (CVD), or race. However, NHANES I did not adjust for the essential components of the metabolic syndrome, like waist circumference and lev-

els of glucose, insulin, high-density lipoprotein cholesterol, and triglycerides. Furthermore, the baseline serum creatinine level was unknown in 60% of the participants.

As determination of serum uric acid is widely available and inexpensive, a better understanding of its role as a risk factor is certainly warranted. Therefore, we studied the predictive role of uric acid levels in a population-based sample of 1423 healthy (free of CVD, diabetes, or cancer) middle-aged men with respect to 12-year cardiovascular and total mortality.

METHODS

The Kuopio Ischaemic Heart Disease Risk Factor Study is a prospective population-based study.²⁷ The study population comprised a random age-stratified sample of 2682 men living in eastern Finland who were 42, 48, 54, or 60 years old at baseline between 1984 and 1989. The University of Kuopio Research Ethics Committee approved the study. All subjects gave their written informed consent.

For the present study, 1123 men with a history of CVD (excluding hypertension), cancer, or diabetes mellitus at baseline were excluded. Men with missing measurements of serum uric acid were also excluded (n=136), leaving 1423 men for the analyses.

Body mass index was computed as weight in kilograms divided by the square of height in meters. Blood pressure was measured with a random-zero mercury sphygmomanometer (Hawksley & Sons Ltd, Lancing, England). Waist circumference was calculated as the average of one measurement taken after inspiration and one taken after expiration at the level of middistance between the bottom of the rib cage and the top of the iliac crest. The protocol for blood pressure measurement included, after supine rest of 5 minutes, 3 measurements while supine, 1 while standing, and 2 while sitting at 5-minute intervals. The mean of all 6 measurements was used as the systolic and diastolic blood pressure. Hypertension was defined as blood pressure of 140/90 or greater, or use of blood pressure medication.²⁸⁻³⁰

Subjects were asked to fast and refrain from smoking for 12 hours and to avoid alcohol intake for 3 days before blood sampling. Blood glucose was measured at baseline by means of a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. Diabetes was defined as a fasting blood glucose level of 110 mg/dL (6.1 mmol/L) or greater, or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment.^{31,32}

The serum samples for insulin determination were stored at -80°C. Serum insulin level was determined with a radioimmunoassay kit (Novo Nordisk; Novo Biolabs, Bagsvaerd, Denmark). Low-density lipoprotein and high-density lipoprotein fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triglyceride levels were measured enzymatically. Measurement of fibrinogen and white blood cell count has been described previously.³³ Routine biochemistry tests also included serum creatinine. The serum urate level was determined photometrically by the hydroxylamine method.³⁴

The validated Kuopio Ischaemic Heart Disease Risk Factor Study 12-month Leisure-Time Physical Activity Questionnaire was used to assess physical activity as described previously.³⁵ A graded symptom-limited maximal exercise test with direct measurement of oxygen was carried out on an electrically braked cycle ergometer as previously described.³⁵

Assessment of medical history and medications, family history of diseases, smoking,³⁶ and alcohol consumption³⁷ has been described previously.

ASCERTAINMENT OF ALL-CAUSE AND CVD DEATHS

Deaths were ascertained by computer linkage to the national death registry by means of the Finnish social security number. There were no losses to follow-up. All deaths that occurred between study entry (from March 1, 1984, to December 31, 1989) and December 31, 1998, were included. Deaths coded with the *International Classification of Diseases, Ninth Revision*, codes 390 to 459 were considered CVD deaths. Death codes as coronary heart disease (CHD) (410-414) or stroke (430-436) were all validated according to the international criteria adopted by the World Health Organization MONICA (*Monitoring of Trends and Determinants of Cardiovascular Disease*) Project.³⁸⁻⁴⁰ The province of Kuopio participated in the multinational MONICA project between 1982 and 1992,³⁹ during which CHD deaths were determined by the FINMONICA coronary registry group.⁴⁰ Data on fatal acute coronary events between January 1, 1993, and December 31, 1998, were obtained by computer linkage to the national computerized hospital discharge registry. Diagnostic information was collected from hospitals and classified by one internist (T.A.L.) using identical diagnostic criteria.⁴¹

STATISTICAL ANALYSIS

The associations of clinical, biochemical, anthropometric, and lifestyle variables with cardiovascular and all-cause mortality were assessed with univariate Cox proportional hazards models. Associations of serum uric acid levels categorized into thirds with cardiovascular and overall mortality were also analyzed with forced Cox proportional hazards models, with adjustment for age (model 1); adjusted for age, examination year, smoking (cigarettes per day), low-density lipoprotein cholesterol level, family history of CHD, systolic blood pressure, use of diuretics, use of β -blockers, use of other blood pressure medications, body mass index, alcohol intake, serum creatinine level, and adult socioeconomic class (model 2); and fasting serum insulin, triglyceride, and high-density lipoprotein cholesterol concentrations, fasting blood glucose levels, conditioning exercise (kilocalories per day), and cardiorespiratory fitness in addition to the covariates in model 2 (model 3). Triglyceride and insulin concentrations and alcohol intake were corrected for skewing by means of log transformation but are presented with untransformed values. Significance was considered to be $P < .05$. All statistical analyses were performed with SPSS 11.0 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

The mean follow-up was 11.9 years (range of follow-up for survivors from baseline to the end of follow-up, 9.1-14.8 years). There were 157 deaths (9.6/1000 patient-years) during follow-up. Of these, there were 55 CVD deaths (3.4/1000 patient-years). In univariate Cox proportional hazards analyses, age, smoking, alcohol intake, and low socioeconomic class were associated with a higher risk of death from CVD and any cause during the follow-up (**Table 1**). Blood pressure and hypertension were associated with CVD and death from any cause, whereas use of any hypertensive medications and use of diuretics were associated with all-cause mortality. An increased body mass index was associated with CVD mortality, whereas waist circumference was associated with death from any cause. The serum fibrinogen level, white blood cell count, serum creatinine level, and cardiorespiratory fitness were associated with both CVD and all-

Table 1. Baseline Characteristics of All Men Who Were Initially Free of CVD, Cancer, and Diabetes, and Those Who Died of CVD and Any Cause During Follow-up*

	Entire Cohort (N = 1423)	CVD Death (n = 55)	All Death (n = 157)
Age, y	52.3 (5.3)	54.2 (4.5)†	54.1 (3.9)†
Adult socioeconomic standing	8.0 (4.1)	9.8 (4.0)†	9.8 (4.3)†
Smokers, %	31	54‡	50‡
Alcohol consumption, g/wk	33 (6-90)	44 (4-145)‡	55 (10-166)‡
Family history of CHD, %	45	44	44
Systolic blood pressure, mm Hg	133 (16)	143 (16)‡	138 (16)‡
Diastolic blood pressure, mm Hg	88 (10)	93 (10)†	90 (11)§
Blood pressure medication, %	10	14	17†
Diuretics	4	7	8†
β-Blockers	7	7	11
Hypertension, %	50	75‡	63‡
BMI	26.5 (3.3)	27.4 (4.1)§	27.0 (3.7)
Waist circumference, cm	90.1 (9.3)	92.5 (12.2)	92.5 (10.9)†
Serum LDL cholesterol level, mg/dL	104 (26)	106 (8)	106 (8)
Serum HDL cholesterol level, mg/dL	34 (8)	36 (8)	34 (8)
Serum triglycerides level, mg/dL	88 (67-128)	86 (58-136)	86 (65-131)
Fasting blood glucose level, mg/dL	82 (8)	83 (8)	84 (8)
Fasting serum insulin level, μU/mL	9.4 (7.3-12.4)	10.9 (7.5-14.4)	10.4 (7.3-13.5)§
White blood cell count, ×10 ³ /μL	5.5 (1.5)	6.0 (1.5)§	6.3 (1.9)‡
Plasma fibrinogen level, mg/dL	300 (50)	320 (70)‡	320 (70)‡
Serum creatinine level, mg/dL	1.01 (0.15)	0.96 (0.15)†	0.96 (0.14)‡
Conditioning physical activity, kcal/d	83 (28-180)	90 (19-193)	73 (13-160)
VO ₂ max, mL·kg ⁻¹ ·min ⁻¹	32.5 (7.5)	28.4 (6.6)‡	28.4 (6.5)‡
Serum uric acid level, mg/dL	5.67 (1.01)	5.95 (1.31)§	5.80 (1.16)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VO₂max, maximal oxygen consumption.

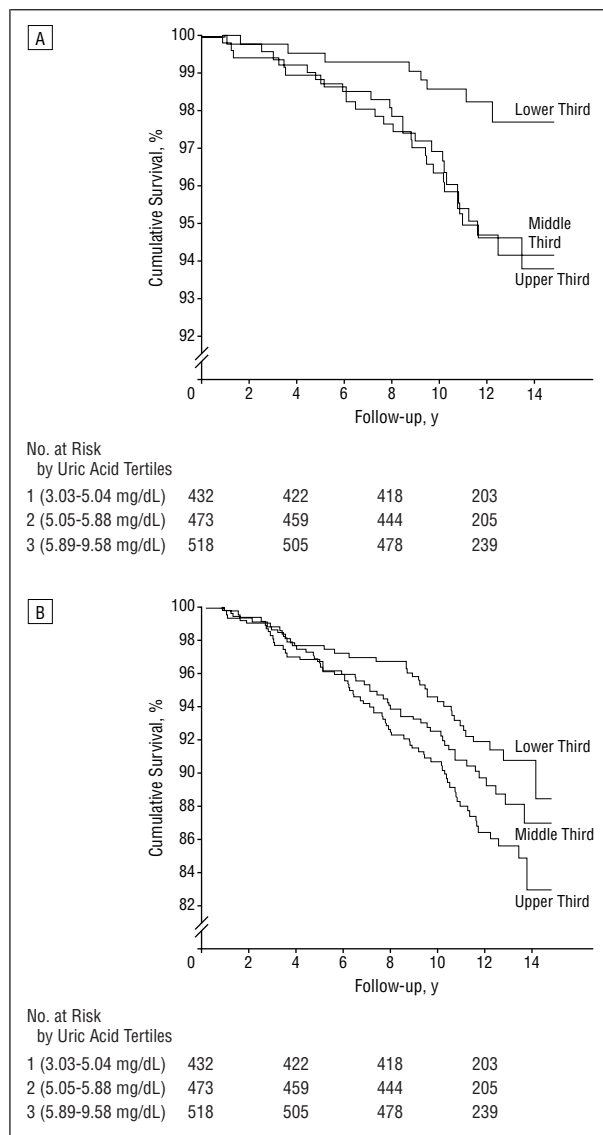
SI conversion factors: To convert cholesterol (LDL and HDL) to millimoles per liter, multiply by 0.0259; creatinine to micromoles per liter, multiply by 88.4; fibrinogen to micromoles per liter, multiply by 0.0294; glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945; triglycerides to millimoles per liter, multiply by 0.0113; uric acid to micromoles per liter, multiply by 59.48.

*Values are mean (SD) except for alcohol intake, fasting serum triglycerides, insulin, and conditioning leisure-time physical activity, which are presented as medians (interquartile ranges). P values are by univariate Cox proportional hazards analysis.

†P = .001 to .01.

‡P < .001.

§P = .01 to .049.



Kaplan-Meier hazard curves for cardiovascular (A) and all-cause (B) death for serum uric acid categorized into thirds.

cause mortality. The serum uric acid concentration was associated with CVD mortality. Uric acid levels also tended to be associated with death from any cause during follow-up ($P = .06$).

The unadjusted Kaplan-Meier hazard curves for serum uric acid levels categorized into thirds (tertile limits, 5.04 and 5.88 mg/dL [299.78 and 349.74 μmol/L]) and CVD and all-cause mortality are shown in the **Figure**. In age-adjusted Cox proportional hazards analyses, serum uric acid levels in the 2 upper thirds were associated with 2.7-fold higher risk of death from CVD than uric acid levels in the lower third (**Table 2**). Taking into account cardiovascular risk factors and variables commonly associated with gout (model 2) increased the relative risk to 3.73 for the upper third vs the lower third. Further adjustment for factors related to the metabolic syndrome (dyslipidemia, insulin and glucose levels, leisure-time physical activity, and cardiorespiratory fitness) additionally strengthened the risk (relative risk for the upper third vs lower third, 4.77). Addition of white

Table 2. Risk of Death From CVD and Any Cause During the 11-Year Follow-up for Serum Uric Acid Levels Categorized Into Thirds in 1423 Middle-aged Men*

Tertile	Model 1	Model 2	Model 3
Relative Risks (95% CI) for Death From CVD			
1 (3.03-5.04 mg/dL)	1 (Reference)	1	1
2 (5.05-5.88 mg/dL)	2.69 (1.20-6.04)	3.29 (1.30-8.34)	4.98 (1.61-15.4)
3 (5.89-9.58 mg/dL)	2.69 (1.21-5.98)	3.73 (1.42-9.83)	4.77 (1.50-15.1)
Trend over tertiles, <i>P</i>	.02	.01	.01
Relative Risks (95% CI) for Death From Any Cause			
1 (3.03-5.04 mg/dL)	1 (Reference)	1	1
2 (5.05-5.88 mg/dL)	1.32 (0.85-2.03)	1.53 (0.96-2.45)	1.74 (1.05-2.88)
3 (5.89-9.58 mg/dL)	1.66 (1.10-3.08)	1.82 (1.12-2.97)	1.85 (1.08-3.17)
Trend over tertiles, <i>P</i>	.01	.02	.03

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.

SI conversion: To convert uric acid levels to micromoles per liter, multiply by 59.48.

*Model 1 was age-adjusted; model 2, adjusted for age, examination year, smoking (cigarettes per day), low-density lipoprotein cholesterol level, family history for coronary heart disease, systolic blood pressure, use of diuretics, use of β -blockers, use of other blood pressure medications, body mass index, alcohol intake, serum creatinine level, and adult socioeconomic class; model 3, adjusted for the covariates in model 2 and fasting serum insulin, triglyceride, and high-density lipoprotein cholesterol concentrations, fasting blood glucose levels, conditioning exercise (metabolic equivalents per week), and cardiorespiratory fitness.

blood cell count and serum fibrinogen concentrations to the models as measures of inflammation did not weaken the association (data not shown). Excluding the 53 men who were using diuretics at baseline had little effect on the results. Men with uric acid concentrations in the upper third were also more likely to die of coronary heart disease, but the association only tended to significance (32 deaths; relative risk, 3.12 [95% confidence interval, 0.92-10.6]; model 2). Likewise, men in the upper third had an increased risk of death from stroke (52 deaths; relative risk, 5.52 [95% confidence interval, 1.09-28.0]; model 2).

In Cox proportional hazards analyses adjusting only for age, men with serum uric acid levels in the upper third were 1.7-fold more likely to die of any cause than men with uric acid levels in the lower third (Table 2). Adjustment for further risk factors (models 2 and 3) strengthened the association somewhat. Addition of white blood cell count and fibrinogen to the models did not attenuate the association (not shown). Excluding the 53 men who used diuretics had little effect on the results.

COMMENT

In this prospective population-based study of healthy middle-aged men, we showed that the serum uric acid level was a strong independent risk marker for CVD death during 12 years of follow-up. Extensive adjustment for variables commonly associated with gout or metabolic syndrome did not attenuate this association, extending the large body of literature regarding the role of uric acid and CVDs. Moreover, uric acid was a marker of all-cause mortality.

Several prospective studies have shown elevated uric acid to be a predictor of cardiovascular mortality.^{4,7,10,12,13} Recent data from the Framingham Study found no independent association of hyperuricemia¹⁰ after adjustment for the use of diuretics. The large NHANES I follow-up data¹¹ nonetheless establish the role of serum uric acid level as an independent predictor of cardiovas-

cular mortality in subjects older than 45 years regardless of sex, menopausal status, diuretic use, presence of CVD, or race. The differences have been explained by the younger age and relatively lower risk of the Framingham population than those in NHANES I.¹² In NHANES I, the age- and race-adjusted risk of CVD and CHD mortality in white men with respect to hyperuricemia increased most markedly at the highest quartile (>6.98 mg/dL [$>415.17 \mu\text{mol/L}$]), but in multivariate Cox regression analyses controlling for age, race, body mass index, smoking, alcohol consumption, hypertension, diabetes, and use of diuretics, for each 1-mg/dL (59.48- $\mu\text{mol/L}$) increase in uric acid level, the risk of CVD and CHD death increased by 9% and 17%, respectively. In our population, the most marked increase for CVD death occurred at the second tertile, corresponding to a uric acid level of 5.21 mg/dL (309.89 $\mu\text{mol/L}$). In a previous population-based Finnish study,⁸ the risk of stroke in patients with type 2 diabetes increased steeply at the median value of 4.96 mg/dL (295.02 $\mu\text{mol/L}$). The relationship between uric acid and cardiovascular risk may therefore not be wholly linear, but whether this is so and at what point the curve steepens has yet to be established.

Elevated levels of serum uric acid may be due to increased dietary intake of purines, increase in uric acid production, or decrease in its excretion. Differences in alcohol consumption, exercise, or dietary purine intake may have caused transient hyperuricemia.⁴² Adjustment for alcohol consumption, leisure-time physical activity, or cardiorespiratory fitness did not attenuate the association of hyperuricemia with cardiovascular mortality. Dietary purines are also unlikely to explain the association.

The mechanisms by which hyperuricemia is associated with atherosclerotic vascular disease remain to be clarified. It is not even established whether hyperuricemia is a risk factor on its own, requiring treatment, or an innocent bystander in proximity to vascular accidents, merely reflecting an adverse risk factor pattern;

or even whether, as a major endogenous antioxidant, it could play a protective role in this respect.

With regard to the first possibility, there are no convincing data to show that treatment of hyperuricemia reduces cardiovascular events. Second, many associations of hyperuricemia have been reported, but during the past decade hyperuricemia has also been linked to reduced insulin sensitivity.¹⁶⁻¹⁹ In the study by Facchini et al,¹⁸ insulin-mediated glucose disposal was correlated with serum uric acid levels ($r=0.69$) and inversely with urinary uric acid clearance ($r=-0.49$); further, serum uric acid and urinary uric acid clearances were inversely related ($r=-0.61$). These findings suggest that serum uric acid level and hyperinsulinemia/insulin resistance interact at the level of the kidney. Acute hyperinsulinemia does not affect plasma uric acid levels, but it does cause a marked decrease in the urinary excretion of uric acid accompanied by decreased sodium and potassium excretion.⁴³ Furthermore, it has been demonstrated that high uric acid levels are independently associated with increased tubular sodium resorption in men.⁴⁴ This association is strikingly similar to the ability of insulin to promote renal sodium resorption, which may be one of the reasons for the high frequency of hypertension in the metabolic syndrome.⁴⁵ Serum uric acid levels are clearly an excellent surrogate marker of metabolic syndrome, which is also associated with cardiovascular mortality.⁴⁶ In our study, however, the adjustment for the components of metabolic syndrome including serum insulin levels did not weaken the predictive value of hyperuricemia with respect to cardiovascular outcome. This suggests that the serum uric acid concentration reflects or mediates processes beyond insulin resistance.

As to the third possibility, uric acid has strong antioxidant properties. Its serum concentrations in humans are much higher than in most animals, because the enzyme uricase, which catalyzes uric acid to allantoin, is not expressed in humans.^{1,2,47,48} Because atherosclerosis has been linked to increased oxidative stress,²² hyperuricemia could be a compensatory mechanism to protect the body from pro-oxidants. Uric acid may also protect nitric oxide from acute inactivation by the radical-generating xanthine oxidase.¹ If this is true, then hyperuricemia is indeed an early marker of cardiovascular risk, because the subjects in our study had no clinical symptoms of vascular disease, and diabetic subjects were excluded. Furthermore, a very early stage of evolving vascular disease is endothelial dysfunction.²³ Because one of the major sites of the production of uric acid in the cardiovascular system is the vessel wall and particularly the endothelium,¹ elevated serum uric acid may be a marker of endothelial dysfunction. Indeed, recently it has been shown that uric acid concentrations correlated inversely with flow-mediated brachial artery vasodilation,⁴⁹ an *in vivo* measurement of vascular nitric oxide reactivity. Moreover, in a controlled setting of dietary treatment with an arginine-enriched nutrient bar, which enhances nitric oxide activity, the increased flow-mediated dilation was associated with the reduction of uric acid levels.⁴⁹

The strengths of this study include its longitudinal population-based design, reliable assessment of causes

of death, detailed assessment and adjustment for metabolic and cardiovascular risk factors, and exclusion of diabetes, CVD, and cancer at baseline. A major limitation is the absence of women and elderly persons from the cohort. Furthermore, the study design does not allow generalization to other races.

To conclude, serum uric acid levels are a strong independent predictor of cardiovascular mortality in middle-aged men without clinical CVD, diabetes, or cancer. This association is not explained by the variables commonly associated with gout or the metabolic syndrome. Serum uric acid levels serve as an easily available and inexpensive risk marker, but whether it is an "innocent bystander," a "partner in crime," or even a protector in proximity to CVD cannot be answered based on observational studies.

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