Serum Uric Acid Concentration as a Risk Factor for Cardiovascular Mortality: A Longterm Cohort Study of Atomic Bomb Survivors

MASAYUKI HAKODA, NAOMI MASUNARI, MICHIKO YAMADA, SAEKO FUJIWARA, GEN SUZUKI, KAZUNORI KODAMA, and FUMIYOSHI KASAGI

ABSTRACT. ***Objective.*** To elucidate the association of serum uric acid concentration with cardiovascular mortality risk.

Methods. Serum uric acid level measured from 1966 through 1970 in 10,615 Japanese individuals from a cohort of atomic bomb survivors was analyzed for association with subsequent cardiovascular and all-cause mortality until 1999 using the Cox proportional hazard model.

Results. During an average followup of 24.9 years, 5225 deaths occurred, of which 1984 were ascribed to cardiovascular disease. In men, after adjustment for age, elevated serum uric acid level was associated with both cardiovascular and all-cause mortality. After additional adjustment for potential cardiovascular disease risk factors including body mass index, smoking status, alcohol consumption, systolic blood pressure, cholesterol level, and histories of hypertension, diabetes and cardiovascular disease, elevated serum uric acid level in men was associated with all-cause mortality but not with cardiovascular mortality. In women, even after these adjustments, elevated serum uric acid level was significantly associated with cardiovascular and all-cause mortality.

Conclusion. Increased serum uric acid level is a significant and independent risk factor for cardiovascular mortality in women and for all-cause mortality in both men and women. (J Rheumatol 2005;32:906–12)

Key Indexing Terms:
URIC ACID CARDIOVASCULAR DISEASE MORTALITY COHORT

Besides the well known causal relationship between uric acid and clinical manifestations of gout, an association of increased serum uric acid concentration with cardiovascular disease was first suggested about 50 years ago[1]. Since serum uric acid level is closely linked to other cardiovascular disease risk factors such as hypertension, hyperlipidemia, and obesity, numerous studies have debated whether the suggested association is independent from these other risk factors[2-14]. Among recent large-scale prospective studies, a report from the Framingham Heart Study noted that the apparent relationship of uric acid to cardiovascular or all-cause mortality did not remain significant after adjustments for other cardiovascular disease risk factors[9]. On the other hand, a report from the First National Health and Nutrition Examination Survey (NHANES I) showed a significant and independent association of uric acid concentration with cardiovascular and all-cause mortality in both men and women[11]. These 2 studies had similar population sizes and followup periods and therefore the source of the discrepancy in the results is unclear. Among individuals at higher risk for cardiovascular events, such as those with hypertension[15-17], prevalent cardiovascular disease[18], and diabetes[19], more consistent results have been obtained for the association of serum uric acid level with future risk for cardiovascular event and cardiovascular mortality.

To investigate this unresolved relationship between serum uric acid level and cardiovascular disease, we utilized a Japanese cohort that has been followed over many years. The Adult Health Study cohort was established in 1958 in the cities of Hiroshima and Nagasaki, Japan, to explore the longterm effects of ionizing radiation from the atomic bombs[20,21]. The participants of this cohort are invited to receive clinical examinations every 2 years, and nearly complete death information has been continuously obtained for this population. We analyzed the relationship between serum uric acid level, measured in more than 10,000 individuals from 1966 through 1970, and subsequent death until 1999, making it the longest and the largest of the studies on the association of uric acid level with subsequent risk for

From the Department of Clinical Studies and the Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan.

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M. Hakoda, MD, PhD, Chief, Division of Clinical Laboratories; N. Masunari, BSc, Pharmacist; M. Yamada, MD, PhD, Chief, Division of Health Examinations; S. Fujiwara, MD, PhD, Chief, Department of Clinical Studies; F. Kasagi, PhD, Assistant Chief, Department of Epidemiology; G. Suzuki, MD, PhD, Chief Scientist, Radiation Effects Research Foundation; K. Kodama, MD, PhD, Chief Scientist, Radiation Effects Research Foundation.

Address reprint requests to Dr. M. Hakoda, Department of Clinical Studies, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan. E-mail: hakoda@rerf.or.jp

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cardiovascular and all-cause mortality. We show here that serum uric acid level is significantly and independently associated with cardiovascular mortality in women and with all-cause mortality in both men and women.

MATERIALS AND METHODS

Subjects. The study population comprised the participants of biennial clinical examinations in the Adult Health Study, conducted since 1958 at the Radiation Effects Research Foundation in Hiroshima and Nagasaki, Japan, to evaluate the longterm effects of ionizing radiation from the atomic bombs on human health[20,21]. The original Adult Health Study cohort consisted of 19,961 individuals, about half of whom were exposed to the bomb proximally (< 2000 m from the hypocenter) and the other half who either were exposed distally (≥ 3000 m from the hypocenter) or were not in the city at the time of the bombings. The people making up this latter half were not substantially exposed to radiation from the bombs. The detailed study design of the Adult Health Study has been described[21]. Those persons selected underwent clinical examination at our institute only if they accepted our invitation to do so. The participation rate of subjects was actually about 75%. Serum uric acid level was measured in the examinations conducted from 1966 through 1970 (examination cycles 5–6). The number of participants during this period was 13,591, and the number of those who underwent serum uric acid measurement in this period was 13,559. Among this total, 10,615 participants (3860 men, 6755 women; mean age 48.6 yrs; age range 20–89 yrs) with available lifestyle information (smoking status and drinking habits), disease history, blood pressure, body mass index (BMI), and serum cholesterol level were the subjects for this analysis.

Baseline measurements. Participants were interviewed by nurses to obtain disease histories and lifestyle information including smoking status and drinking habits. Serum uric acid level was measured by a phosphotungstic acid procedure using an autoanalyzer (Technicon Instruments, Tarrytown, NY, USA). Total cholesterol and blood glucose were determined by the Abell-Kendall method and the Folin-Malmros microtechnique, respectively, with an autoanalyzer. Diagnosis of hypertension was based on a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or current treatment with antihypertensive drugs. Diabetes was defined on the basis of a fasting blood glucose level ≥ 140 mg/dl, a blood glucose level ≥ 180 mg/dl at the 2 h point of the 50 g glucose tolerance test, or the use of oral hypoglycemic agents or insulin.

Outcome measures. Primary outcome measures were death from cardiovascular disease (coronary heart disease, stroke, or other cardiovascular disease) and death from all causes. Deaths were identified through checks on the status of all surviving cohort members, using the Japanese family registration system (*koseki*). No individual was lost during the followup. Information on the underlying cause of death was obtained from death certificates, and was coded according to the *International Classification of Diseases* (ICD). Four ICD revisions were used depending on the time of death. Thus, ICD 7, ICD 8, ICD 9, and ICD 10 were used for deaths during 1966-67, 1968-78, 1979-97, and 1998-99, respectively (Table 1).

Table 1. International Classification of Diseases (ICD) codes for cause of death.

Period of Death	ICD Revision	ICD Codes: Total Cardiovascular Disease	ICD Codes: Coronary Heart Disease	ICD Codes: Stroke
1966–67	7th	400–468 330–334	420	330–334
1968–78	8th	390–458	410–414	430–438
1979–97	9th	390–459	410–414	430–438
1998–99	10th	100–199	120–125	160–169

Statistical analysis. Since uric acid level differs substantially between men and women, results of the 2 sex groups were analyzed separately. To evaluate uric acid level as a risk factor for cardiovascular and all-cause mortality, the subjects were stratified into 5 groups by sex depending on baseline serum uric acid level. For men, the dividing points were 5.0, 6.0, 7.0, and 8.0 mg/dl (297.4, 356.9, 416.4, 475.8 mmol/l, respectively), and for women, the points were 4.0, 5.0, 6.0, and 7.0 mg/dl (237.9, 297.4, 356.9, 416.4 mmol/l, respectively). Cox proportional hazard regression models were used to examine the relationship of serum uric acid level to death from all causes, total cardiovascular disease, coronary heart disease, or stroke. Mortality hazard ratio for each uric acid category was calculated using as reference the lowest uric acid categories, < 5.0 mg/dl (297.4 mmol/l) in men and < 4.0 mg/dl (237.9 mmol/l) in women. These analyses were adjusted for baseline characteristics, including age, BMI (kg/m^2), systolic blood pressure (mm Hg), total cholesterol level (mg/dl), smoking status (non-smoker, ex-smoker, or current smoker), alcohol consumption (g/week), histories (yes/no) of hypertension, coronary heart disease, stroke, diabetes, kidney disease and malignant tumor, and radiation dose (Gray) from the atomic bombings.

RESULTS

Mean (SD) age of the subjects at the time of uric acid measurement was 49.0 (14.8) years for men and 48.6 (13.5) years for women. Mean (SD) uric acid concentration was 5.4 (1.5) mg/dl [321.2 (89.2) µmol/l] in men and 4.2 (1.1) mg/dl [249.8 (65.4) µmol/l] in women, a statistically significant difference ($p < 0.001$). The 90th and 95th percentiles for uric acid distribution were 7.6 and 8.4 mg/dl for men and 5.6 and 6.3 mg/dl for women, respectively. Uric acid level was significantly and positively associated with other cardiovascular disease risk factors in both sexes including BMI, total cholesterol level, and presence of hypertension (Table 2). Uric acid level was also associated with alcohol use in both sexes (Table 2).

During an average followup of 24.9 years (22.9 yrs for men, 26.0 yrs for women), 5225 subjects (49.2%) of a total of 10,615 subjects died [2266 (58.7%) of 3860 men, 2959 (43.8%) of 6755 women]. Among these deaths, 1984 (38.0%) were attributed to cardiovascular disease (coronary heart disease, 427; stroke, 931; other cardiovascular disease, 626). Crude all-cause and cardiovascular mortality rates were 19.8 (25.6 for men, 16.8 for women) and 7.5 (8.5 for men, 7.0 for women) per 1000 person-years, respectively.

In men, age-adjusted hazard ratio for all-cause mortality was significantly increased in subjects with uric acid level ≥ 8.0 mg/dl compared with those in the lowest uric acid category (< 5.0 mg/dl; Table 3). This increase in risk for all-cause mortality remained significant after adjustment for other cardiovascular disease risk factors. In women, age-adjusted hazard ratio for all-cause mortality increased significantly in all uric acid categories compared with the lowest uric acid category (Table 3). After full adjustment, the hazard ratio for all-cause mortality remained significant in the uric acid categories 6.0–6.9 and ≥ 7.0 mg/dl, and a higher hazard ratio was observed for uric acid category ≥ 7.0 mg/dl compared with the 6.0–6.9 mg/dl category (Table 3).

The hazard ratio for cardiovascular mortality in men was

Table 2. Baseline characteristics by sex and uric acid level. Values are mean (SD).

Uric Acid Level, mg/dl	No. of Subjects	Age, yrs	Body Mass Index, kg/m^2	Total Cholesterol, mg/dl	Hypertension, %	Diabetes, %	Current Smoking, %	Alcohol Use, g[†]/wk	Radiation Dose, Gy
Men									
Total	3860	49.0 (14.8)	21.1 (2.8)	181.8 (38.7)	30.4	13.0	74.1	107 (140)	0.39 (0.82)
< 5.0	1184	51.8 (14.4)	20.5 (2.6)	178.1 (36.7)	27.8	14.4	75.4	92 (126)	0.38 (0.78)
5.0–5.9	1127	48.4 (14.5)	20.8 (2.8)	180.6 (37.0)	25.9	12.6	75.3	101 (144)	0.40 (0.83)
6.0–6.9	866	46.8 (14.8)	21.3 (2.8)	183.1 (39.7)	30.4	11.1	73.7	116 (141)	0.39 (0.85)
7.0–7.9	390	46.6 (15.1)	22.1 (3.1)	187.5 (41.8)	36.9	12.8	73.3	119 (143)	0.36 (0.77)
≥ 8.0	293	49.0 (15.2)	22.5 (3.0)	189.5 (43.3)	49.5	15.0	66.9	141 (156)	0.39 (0.84)
p for trend		< 0.001	< 0.001	< 0.001	< 0.001	> 0.5	0.007	< 0.001	> 0.5
Women									
Total	6755	48.6 (13.5)	22.1 (3.4)	191.8 (41.2)	26.4	6.6	14.4	8 (41)	0.36 (0.75)
< 4.0	3015	47.2 (13.0)	21.7 (3.0)	185.1 (39.6)	19.4	5.1	12.6	5 (26)	0.35 (0.70)
4.0–4.9	2261	48.6 (13.5)	22.1 (3.4)	191.9 (39.6)	27.1	5.9	14.6	9 (42)	0.36 (0.76)
5.0–5.9	1005	50.5 (14.0)	23.1 (3.7)	202.6 (42.3)	34.5	9.4	16.2	11 (50)	0.40 (0.86)
6.0–6.9	339	52.8 (14.1)	23.9 (4.0)	209.2 (46.2)	46.0	12.7	21.2	20 (78)	0.37 (0.78)
≥ 7.0	135	56.9 (13.8)	23.9 (4.0)	212.3 (45.1)	60.0	15.6	21.5	20 (60)	0.40 (0.76)
p for trend		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.07

[†] Ethanol weight.

Table 3. Relation of serum uric acid level to all-cause mortality.

Uric Acid Level, mg/dl	Person-yrs	No. of Deaths	Mortality Rate*	Age Adjusted Hazard Ratio	Age Adjusted 95% CI	Fully Adjusted[†] Hazard Ratio	Fully Adjusted[†] 95% CI
Men							
< 5.0	25,811	754	29.2	1.0		1.0	
5.0–5.9	26,259	649	24.7	1.00	0.90, 1.11	0.99	0.89, 1.10
6.0–6.9	20,871	461	22.1	0.95	0.85, 1.07	0.94	0.83, 1.06
7.0–7.9	9243	214	23.2	1.05	0.90, 1.22	1.05	0.90, 1.23
≥ 8.0	6182	188	30.4	1.38	1.17, 1.61	1.22	1.03, 1.44
Women							
< 4.0	81,405	1130	13.9	1.0		1.0	
4.0–4.9	58,786	980	16.7	1.10	1.01, 1.20	1.07	0.98, 1.16
5.0–5.9	25,226	525	21.0	1.14	1.02, 1.26	1.08	0.97, 1.20
6.0–6.9	7458	221	29.6	1.59	1.37, 1.84	1.44	1.24, 1.67
≥ 7.0	2538	103	40.6	1.90	1.54, 2.31	1.63	1.32, 2.00

* Values are expressed per 1000 person-years. [†] In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs.

significantly increased in the highest uric acid category (≥ 8.0 mg/dl) compared with subjects in the lowest uric acid category when adjustment was made only for age. However, this hazard ratio increase did not remain significant after full adjustment (Table 4). When cardiovascular disease was restricted to coronary heart disease, age-adjusted hazard ratio for mortality was significantly increased in the uric acid category ≥ 8.0 mg/dl, but it was no longer significant after full adjustment (Table 4). For stroke mortality, no significant increase in hazard ratio was observed in any of the uric acid categories in men.

In women, a significant increase in the hazard ratio for cardiovascular mortality was observed in the uric acid categories 6.0–6.9 and ≥ 7.0 mg/dl compared with the lowest uric acid category (< 4.0 mg/dl) even after full adjustment, and a higher hazard ratio was observed in the uric acid category ≥ 7.0 mg/dl compared with the 6.0–6.9 mg/dl category (Table 4). A significant increase in coronary heart disease mortality was observed for the 6.0–6.9 mg/dl category, but the increase was not significant in the ≥ 7.0 mg/dl category (Table 4). This may result from the small number of cases in this category (n = 12). For stroke mortality, a significant increase in hazard ratio was found for the ≥ 7.0 mg/dl category (Table 4).

Since menopausal status has substantial effects on both uric acid level and cardiovascular disease occurrence, the relation between uric acid level and mortality risk was examined in different age groups in women. Thus, women

Table 4. Relation of serum uric acid level to cardiovascular disease mortality.

	Uric Acid Level, mg/dl	No. of Deaths	Mortality Rate*	Age Adjusted Hazard Ratio	95% CI	Fully Adjusted† Hazard Ratio	95% CI
Cardiovascular disease mortality							
Men	< 5.0	266	10.3	1.0		1.0	
	5.0–5.9	201	7.7	0.89	0.74, 1.07	0.89	0.74, 1.07
	6.0–6.9	156	7.5	0.94	0.77, 1.14	0.83	0.67, 1.01
	7.0–7.9	65	7.0	0.94	0.71, 1.23	0.86	0.65, 1.13
	≥ 8.0	63	10.2	1.40	1.05, 1.83	1.08	0.81, 1.44
Women	< 4.0	457	5.6	1.0		1.0	
	4.0–4.9	382	6.5	1.06	0.92, 1.21	1.01	0.88, 1.15
	5.0–5.9	232	9.2	1.18	1.01, 1.38	1.08	0.91, 1.27
	6.0–6.9	111	14.9	1.91	1.54, 2.34	1.58	1.27, 1.96
	≥ 7.0	51	20.1	2.21	1.64, 2.93	1.79	1.31, 2.39
Coronary heart disease mortality							
Men	< 5.0	54	2.1	1.0		1.0	
	5.0–5.9	53	2.0	1.17	0.80, 1.71	1.14	0.78, 1.67
	6.0–6.9	33	1.6	0.99	0.63, 1.51	0.83	0.52, 1.28
	7.0–7.9	17	1.8	1.21	0.68, 2.04	1.02	0.56, 1.74
	≥ 8.0	20	3.2	2.14	1.25, 3.51	1.52	0.87, 2.58
Women	< 4.0	85	1.0	1.0		1.0	
	4.0–4.9	70	1.2	1.03	0.75, 1.42	0.96	0.69, 1.31
	5.0–5.9	49	1.9	1.33	0.93, 1.89	1.08	0.75, 1.55
	6.0–6.9	34	4.6	3.13	2.08, 4.62	2.28	1.47, 3.46
	≥ 7.0	12	4.7	2.67	1.38, 4.71	1.87	0.95, 3.38
Stroke mortality							
Men	< 5.0	139	5.4	1.0		1.0	
	5.0–5.9	96	3.7	0.83	0.64, 1.07	0.82	0.63, 1.07
	6.0–6.9	72	3.4	0.85	0.64, 1.13	0.76	0.56, 1.01
	7.0–7.9	30	3.2	0.85	0.56, 1.24	0.83	0.54, 1.22
	≥ 8.0	29	4.7	1.25	0.82, 1.84	0.95	0.61, 1.42
Women	< 4.0	216	2.7	1.0		1.0	
	4.0–4.9	175	3.0	1.01	0.83, 1.23	0.96	0.79, 1.18
	5.0–5.9	103	4.1	1.10	0.87, 1.39	1.01	0.79, 1.28
	6.0–6.9	48	6.4	1.71	1.23, 2.32	1.39	0.99, 1.91
	≥ 7.0	23	9.1	2.01	1.27, 3.03	1.67	1.05, 2.55

* Values are expressed per 1000 person-years. † In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs.

subjects were divided into 3 groups depending on baseline age: < 45, 45–54, and ≥ 55 years. As shown in Table 5, in the age groups < 45 years (most subjects likely to be premenopausal) and ≥ 55 years (most subjects likely to be postmenopausal), a significant increase in hazard ratio for all-cause and cardiovascular mortality was observed with increasing uric acid levels. In the age group 45–54 years, which includes both menstrual and postmenopausal women, the association of uric acid level with mortality was not significant.

Since information about diuretic use was not available in our study, and since most users of diuretics are patients with hypertension, those individuals were excluded, and association of uric acid level with subsequent mortality was analyzed in women. As shown in Table 6, exclusion of hypertensive individuals (n = 1781) did not affect the association of uric acid level with all-cause and cardiovascular mortality in women. Similarly, when the subjects were restricted to those without baseline cardiovascular disease, non-diabetics, non-smokers, and those with low total cholesterol (< 200 mg/dl), association of uric acid level with mortality did not substantially change except for cardiovascular mortality for those without baseline cardiovascular disease in the uric acid category ≥ 7.0 mg/dl (Table 6).

DISCUSSION

This large prospective study found that serum uric acid concentration is independently associated with cardiovascular mortality in women and with all-cause mortality in both men and women. Association of serum uric acid level with cardiovascular disease or mortality has been described in women in several other cohort studies[2,6,7,11], whereas the results in men are more inconsistent[2-4,7-14]. Among 2 large prospective studies conducted recently in the United States,

Table 5. Relation of serum uric acid level to all-cause and cardiovascular mortality stratified by age among women (fully adjusted*).

	Baseline Age Category, yrs†					
	< 45		45–54		≥ 55	
Uric Acid Level, mg/dl	Hazard Ratio	95% CI	Hazard Ratio	95 % CI	Hazard Ratio	95% CI
All-cause mortality						
< 4.0	1.0		1.0		1.0	
4.0–4.9	1.15	0.92, 1.44	0.77	0.62, 0.95	1.13	1.02, 1.26
5.0–5.9	1.27	0.93, 1.70	0.96	0.74, 1.24	1.04	0.92, 1.19
6.0–6.9	2.11	1.32, 3.22	1.01	0.68, 1.47	1.45	1.21, 1.73
≥ 7.0	2.32	0.90, 4.86	1.28	0.67, 2.20	1.72	1.35, 2.16
Cardiovascular disease mortality						
< 4.0	1.0		1.0		1.0	
4.0–4.9	1.26	0.76, 2.07	0.78	0.54, 1.11	1.00	0.86, 1.17
5.0–5.9	1.55	0.80, 2.85	1.09	0.72, 1.63	1.00	0.82, 1.20
6.0–6.9	2.14	0.72, 5.11	1.23	0.66, 2.16	1.57	1.22, 1.99
≥ 7.0	5.88	1.36, 17.5	1.83	0.63, 4.27	1.74	1.23, 2.39

* In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs. † The number of deaths due to all causes was 414, 509, and 2036 for the age categories < 45, 45–54, and ≥ 55 years, respectively. The number of deaths due to cardiovascular disease was 88, 193, and 952 for the same age categories, respectively.

Table 6. Relation of serum uric acid level to all-cause and cardiovascular mortality in women stratified by cardiovascular risk profiles (fully adjusted*).

		All-Cause		Cardiovascular	
	Uric Acid Level, mg/dl	Hazard Ratio†	95% CI	Hazard Ratio	95 % CI
Non-hypertensives					
	6.0–6.9	1.68	1.33, 2.09	1.88	1.25, 2.72
	≥ 7.0	1.67	1.12, 2.38	1.99	1.00, 3.55
No cardiovascular disease					
	6.0–6.9	1.42	1.21, 1.66	1.76	1.13, 2.63
	≥ 7.0	1.62	1.28, 2.02	1.95	0.86, 3.81
Non-diabetics					
	6.0–6.9	1.43	1.21, 1.67	1.52	1.19, 1.91
	≥ 7.0	1.64	1.30, 2.06	1.79	1.28, 2.45
Non-smokers	6.0–6.9	1.51	1.27, 1.78	1.71	1.32, 2.17
	≥ 7.0	1.81	1.41, 2.29	2.02	1.41, 2.82
Low total cholesterol (< 200 mg/dl)					
	6.0–6.9	1.51	1.18, 1.89	1.72	1.21, 2.40
	≥ 7.0	1.80	1.28, 2.45	1.96	1.17, 3.11

* In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, stroke, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs. † Hazard ratio for only 2 categories with high uric acid levels is presented.

the Framingham Heart Study showed no significant association of uric acid level with cardiovascular or all-cause mortality in either men or women[9]. The First National Health and Nutrition Examination Survey (NHANES I), on the other hand, showed a significant and independent association of uric acid level with cardiovascular and all-cause mortality in both sexes[11]. Since both studies are population-based and their adjusted confounders are similar, the source for the difference in the results is unclear. Our study utilized the largest cohort with the longest followup period among the cohorts so far analyzed, and adds further evidence for the association of uric acid level with cardiovascular mortality in women. Our population consisted entirely of Japanese subjects, and as shown in the baseline characteristics (Table 1), they are generally slimmer and have lower cholesterol levels compared with people in Western countries. Although such baseline factors were all adjusted in the analysis, ethnic differences existing in the study population might also have

played a role in the differences in results between our study and previous studies.

The strengths of our study are its large population size, long followup period, complete coverage of mortality during the followup period, and large number of subjects reaching the endpoint. Limitations include unavailability of information regarding diuretic use. Culleton, *et al* concluded that diuretic use was the major confounding factor in the apparent association of uric acid level with cardiovascular events among women in the Framingham Heart Study population[9]. On the other hand, several other studies including the NHANES I study have shown that the association of uric acid level with cardiovascular events or mortality remained significant even after adjustment for diuretic use[5,11,15-18]. We performed an analysis excluding hypertensive individuals, the major users of diuretics, and obtained nearly identical results. Therefore, it seems unlikely that diuretic use was the source for the association of uric acid level with cardiovascular mortality in our study. Unavailability of information on serum creatinine level is one more limitation of our study. It has also been reported in other studies, however, that adjustment for serum creatinine level did not render the association of serum uric acid level with cardiovascular or total mortality insignificant[5,11,15,16]. Other limitations may include misclassification of causes of death due to inaccuracy of diagnoses coded on death certificates.

Insulin resistance may be a plausible explanation for the association of uric acid level with cardiovascular disease risk since insulin resistance has been reported to be associated with both increased risk for cardiovascular events and increased serum uric acid levels[22,23]. Several other mechanisms have also been suggested, including activation of platelets and cytokine production[24-26]. Oxygen free radicals are generated when xanthine oxidase produces uric acid, and this xanthine oxidase activity in vascular endothelial cells may be associated with impaired endothelial cell function, which may in turn lead to the development of atherosclerosis[27-29]. It has also been suggested that elevated serum uric acid level may be a compensatory mechanism to counteract oxidative damage related to atherosclerosis[30,31]. In animal models, direct association of increased uric acid level with hypertension and uric acid-induced proliferation of vascular smooth muscle cells have been suggested[32,33].

The source for the difference in association of uric acid level with cardiovascular mortality between men and women in our study is unclear. A stronger association of uric acid level with cardiovascular disease in women than in men has also been reported in previous studies[2,7]. In men, serum uric acid level is generally higher than in women, a phenomenon also observed in our study. The sex difference in serum uric acid level is largely due to the difference in renal clearance rate of uric acid: men have a lower clearance rate than women[34]. Such physiological differences controlling serum uric acid level may be functioning in men in a way that obscures the association of serum uric acid level with cardiovascular risk. It may not be the case that female hormones alone contributed to the closer association of uric acid level with mortality risk in women, because the analysis stratified by age in our study suggested that the association is significant in both premenopausal and postmenopausal women.

Our study showed that serum uric acid concentration is associated with cardiovascular mortality risk in women. Although the causal mechanism for such an association remains unknown, it can be inferred that serum uric acid level may be used in both clinical and healthcare settings as a marker reflecting cardiovascular disease risk especially for women.

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