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Hyperuricemia and Coronary Heart Disease: A Systematic Review and Meta-Analysis

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Abstract

BACKGROUND—The role of serum uric acid as an independent risk factor for cardiovascular disease remains unclear although hyperuricemia is associated with cardiovascular disease such as coronary heart disease (CHD), stroke and hypertension.

METHODS—A systematic review and meta-analysis using a random-effects model was conducted to determine the risk of CHD associated with hyperuricemia in adults. Studies of hyperuricemia and CHD were identified by searching major electronic databases using the Medical Subject Headings and keywords without language restriction (through February 2009). Only prospective cohort studies were included if they had data on CHD incidences or mortalities related to serum uric acid levels in adults.

RESULTS—26 eligible studies of 402,997 adults were identified. Hyperuricemia was associated with an increased risk of CHD incidence (unadjusted risk ratio (RR) 1.34; 95% confidence interval (CI) 1.19-1.49) and mortality (unadjusted RR 1.46; 95% CI 1.20-1.73). When adjusted for potential confounding, the pooled RR was 1.09 (95% CI: 1.03-1.16) for CHD incidence and 1.16 (95% CI: 1.01-1.30) for mortality. For each increase of 1 mg/dl in uric acid level, the pooled multivariate RR for CHD mortality was 1.12 (95% CI: 1.05-1.19). Subgroup analyses showed no

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significant association between hyperuricemia and CHD incidence/mortality in men, but an increased risk for CHD mortality in women (RR 1.67; 95% CI: 1.30-2.04).

CONCLUSION—Hyperuricemia may marginally increase the risk of CHD events, independently of traditional CHD risk factors. A more pronounced increased risk for CHD mortality in women should be investigated in future research.

Keywords

hyperuricemia; coronary heart disease; meta-analysis

INTRODUCTION

In humans, uric acid is the end product of purine metabolism due to the non-functioning uricase gene leading to elevated serum uric acid levels (1). Although the mechanism and biological reason for this mutation is still unknown, it has been hypothesized that the loss of uricase activity has evolutionary advantages related to protection from oxidative damage and the prolonged life span owing to the antioxidant properties of uric acid (1-3). However, this hypothesis is in conflict with many epidemiologic studies showing that hyperuricemia was frequently noted in patients either with cardiovascular disease or at a high risk of cardiovascular disease such as hypertension, coronary heart disease (CHD), peripheral vascular disease, heart failure, metabolic syndrome, and stroke (4-10). A recent meta-analysis of prospective observational studies (11) for hyperuricemia and risk of stroke demonstrated significantly increased risk for both stroke incidence [RR 1.47, 95% CI: 1.19-1.76] and mortality [RR 1.26, 95% CI: 1.12-1.39] based on studies that adjusted for traditional stroke risk factors such as age, gender, hypertension, hypercholesterolemia and serum glucose. Several patho-physiological mechanisms have been postulated including endothelial dysfunction, oxidative metabolism, and platelet adhesiveness and aggregation (12-14). However, the role of hyperuricemia as an independent risk factor for CHD remains controversial (15-20). It is perhaps related to the complex association between hyperuricemia and known CHD risk factors, resulting in methodological difficulties in some observational studies, particularly with a limited sample size, that elucidate its direct effect on CHD (21). The objective of this study was to systematically review published reports of prospective cohort studies to assess the risk of CHD incidence and mortality in hyperuricemia.

METHODS

LITERATURE SEARCH

We searched three major electronic databases — MEDLINE (through February 2009), EMBASE (1980- February 2009), and the Cochrane Library (through February 2009) — using the following heading MeSH terms and keywords: [*uric acid OR hyperuricemia OR urate] AND [coronary disease OR myocardial infarction OR coronary artery disease OR angina pectoris OR unstable angina OR cardiovascular disease OR coronary heart disease]* (See Appendix 1). We also searched bibliographies of identified reports and review articles for additional references. We followed the Meta-analysis of observational studies in epidemiology (MOOSE) study guidelines (22).

STUDY ELIGIBILITY

To be eligible for inclusion, we only considered 1) prospective cohort studies of adult patients, 2) with longer than one year of follow-up, 3) with a sample size of at least 100 subjects, and 4) an inception cohort free of CHD. No geographic or language restrictions

were applied. Studies reporting interventional and secondary prevention trials were excluded.

STUDY SELECTION

Two authors (S. Kim and K. Kim) independently screened each of the potential titles, abstracts, and/or full-texts to determine inclusion. Areas of disagreement or uncertainty were resolved by consensus. When multiple articles were published from a single study, we selected the reports that contained the most complete and relevant data on the association between hyperuricemia and CHD.

DATA ABSTRACTION AND QUALITY ASSESSMENT

All data were independently abstracted in duplicate by two authors (S. Kim and K. Kim) using a data abstraction form to retrieve information on study characteristics, participant information, cut-off levels for hyperuricemia, CHD outcome, analyses and adjustment. Discrepancies were resolved by consensus. When necessary, we attempted to contact the original authors for additional information, but we were unable to obtain unpublished data. We used the Newcastle–Ottawa Scale to assess the quality of studies (23). A quality score was calculated on the basis of three major components of cohort studies: selection of study groups (0–4 points), comparability of study groups (0–2 points) and ascertainment of the outcome of interest (0–3 points). A higher score represents better methodological quality. (Table 1)

DATA ANALYSIS

Some studies included in our meta-analysis used the International system (SI) of units (μmol per liter) to report levels of serum uric acid. We therefore converted those to the conventional units (milligram per deciliter), using a conversion rate of 16.81 (1 mg/dL = 59.48 μmol/L) (24). The category nearest to 6.8 mg/dl was considered as the hyperuricemia group for both genders (25).

Pooled estimates of both unadjusted and multivariate risk ratios (RRs) were calculated using the DerSimonian and Laird random-effects model (26, 27) for CHD incidence and mortality. This statistical technique weights individual studies by sample size and variance (both within- and between-study variance) and yields a pooled point estimate and a 95% confidence interval. The DerSimonian and Laird technique was considered an appropriate pooling technique because of the relative heterogeneity of the source population in each study. We evaluated the presence of heterogeneity across trials by using the I^2 statistic, which quantifies the percentage of variability that can be attributed to between-study differences (28). A stratified analysis by gender was conducted to evaluate gender-related heterogeneity in both unadjusted and multivariate risk ratios of CHD incidence and mortality. To investigate the impact of study characteristics, such as gender, publication year, ethnicity, study location, and cut-off level defining hyperuricemia, on the study estimates of RR, we performed a multivariate meta-regression analysis on the log-transformed scale of RR. To assess the potential for publication bias, we performed the Begg test and the Egger test and constructed funnel plots to visualize possible asymmetry (29). All the statistical analyses were done in Stata 10 (Stata Corp, College Station, TX).

RESULTS

DESCRIPTION OF THE STUDIES

The electronic database search identified 6557 references. Bibliographic lists of relevant review papers were manually searched and elicited 21 additional references. The title and abstract review of these references resulted in 310 original articles. A total of 26 prospective

cohort studies representing data from 402,997 participants were finally included in this review. Figure 1 shows the study flow.

The characteristics of the included studies and their participants are presented in Tables 1 and 2. A total of 26 studies (13 for CHD incidence and 13 for CHD mortality) were included. Nine (20, 30-37) studies were carried out in the United States, eleven (38-48) in Europe, and six (49-54) in Asia. All except one (38) were written in English. The lengths of follow-up in the included studies varied between 5 and 24.9 years. The definition of hyperuricemia ranged from 5.6 to 7.7 mg/dl in men and from 4.7 to 7.0 mg/dl in women. In most studies, CHD events were defined using the medical records and/or International Classification of Diseases (ICD) codes from the hospital records or death certificates. Results from 9 studies for CHD incidence and 8 studies for CHD mortality were fully adjusted for traditional CHD risk factors such as age, gender, hypertension, diabetes, smoking and hypercholesterolemia. The majority (85%) of included studies were of high quality.

HYPERURICEMIA AND CHD INCIDENCE

The pooled estimate of unadjusted RR for CHD incidence based on 13 studies (30-32, 37, 40, 42-45, 48-51) was 1.34 (95% CI: 1.19-1.49) (comparing hyperuricemic to normouricemic patients). A significant heterogeneity between studies was noted (I^2=64.4%, p=0.001). Based on 9 studies (30, 33, 37, 40, 42, 43, 48, 49, 51) that fully adjusted for traditional risk factors of CHD, the overall risk of incident CHD related to hyperuricemia had a pooled multivariate RR of 1.09 (95% CI: 1.03-1.16) with mild heterogeneity (I^2= 17.6%, p=0.27).

The pooled multivariate RR of incident CHD was 1.04 [N=7 (30, 33, 37, 42, 43, 48, 51) studies, 95% CI: 0.90-1.17] for men, and 1.07 [N=4 studies (30, 37, 48, 51), 95% CI: 0.82-1.32] for women. There was moderate heterogeneity between studies with respect to outcomes among men (I^2= 42%, p=0.11) but no heterogeneity between studies was noted among women (I^2=0.0%, p=0.76). The forest plot of multivariate RRs and 95% CIs for CHD incidence is shown in Figure 2 (Left).

HYPERURICEMIA AND CHD MORTALITY

The pooled unadjusted RR for CHD mortality based on 9 studies (20, 34, 36, 41, 46, 47, 52-54) was 1.46 (95% CI: 1.20-1.73). A significant heterogeneity between studies was noted (I^2 =77.6%, p=0.001). The RR based on 8 studies (20, 34, 38, 41, 46, 47, 50, 52, 53) that fully adjusted for traditional CHD risk factors was 1.16 (95% CI: 1.01-1.30), with mild heterogeneity (I^2= 29.4%, p=0.17).

The pooled multivariate RR for CHD mortality was 1.09 [N=7 studies (20, 34, 38, 41, 47, 50, 52, 53), 95% CI: 0.98-1.19] among men, and 1.67 [N=4 studies (20, 38, 46, 50, 52), 95% CI: 1.30-2.04] among women. There was no statistically significant heterogeneity between studies with respect to outcomes (I^2: 0.0% for both genders). The forest plot of multivariate RRs and 95% CIs for CHD mortality is shown in Figure 2 (Right).

For each increase of 1 mg/dl in uric acid level, the overall pooled multivariate RR for CHD mortality was 1.12 [N=4 studies (20, 35, 39, 50), 95% CI: 1.05-1.19] (Figure 3). The gender-specific relative risks for each increase of 1 mg/dl in serum uric level were similar, but no longer statistically significant.

PUBLICATION BIAS ASSESSMENT

Some evidence of publication bias for both CHD incidence and mortality was noted in the funnel plots (Figure 4), Begg's tests (p=0.06, 0.08 respectively) and Egger's tests (p=0.03, 0.12 respectively).

SENSITIVITY ANALYSES

A multivariate meta-regression analysis to investigate the impact of several covariates on the study estimates of RR found that none of the covariates – gender, year of publication, ethnicity (Asian versus non-Asian), study location and cut-off levels defining hyperuricemia — modified the association between hyperuricemia and CHD risk. On the other hand, earlier publication year (coefficient: 0.03, p= 0.002) and female gender (coefficient: 0.55, p<0.001) were significantly associated with a greater risk estimate for CHD mortality.

DISCUSSION

This systematic review and meta-analysis of prospective cohort studies shows a significant, modest association between hyperuricemia and CHD events, independent of traditional CHD risk factors. The overall risk of CHD death increased 12% for each increase of 1mg/dl of uric acid. In the subgroup analyses, hyperuricemia appeared to significantly increase risk of CHD deaths in women (approximately 70 %), but not in men. Although this gender differences require further research, our results support previous findings of a stronger association between hyperuricemia and cardiovascular disease in women (20, 31, 55, 56)

Our results are consistent with a previous meta-analysis of 16 observational studies that examined the association between hyperuricemia and coronary heart disease (48). It showed a pooled RR of 1.13 (95% CI: 1.07-1.20) with significant heterogeneity (p=0.02) (48). In their subgroup analyses, the RR for CHD was 1.12 (95% CI: 1.05–1.19) in men and 1.22 (95% CI: 1.05-1.40) in women. Eight of 16 studies used in the previous meta-analysis were not included in our review. Two (48, 57) were not prospective cohort studies and three (44, 58, 59) did not present the outcomes of our interest in their text. Unfortunately, we could not obtain the relevant, unpublished data from the authors of the original studies. Newer studies (32, 38, 41) were included in our meta-analysis, in place of 3 studies (60-62) that used the same cohorts.

Recent studies of losartan and atorvastatin showed that uric acid reduction contributes to attenuation of cardiovascular risk (63, 64). Fenofibrate has also shown a uricosuric effect in healthy and diabetic subjects (65, 66). These medications are useful for the management of patients with metabolic syndrome, identified as a multiplex risk factor for cardiovascular disease by the National Cholesterol Education Program's Adult Treatment Panel III report (67). In a small randomized clinical trial (68), allopurinol treatment in newly-diagnosed, hypertensive adolescents was associated with significant reductions in casual and 24-hour ambulatory blood pressure compared to placebo. Interestingly, a recent cohort study of hyperuricemic patients enrolled in Veterans Affairs medical centers in the Pacific Northwest reported that the use of allopurinol was associated with a 23% lower all-cause mortality rate (69). Several observational studies reported that gout was associated with multiple risk factors for cardiovascular disease and with cardiovascular morbidities and mortalities (70-73). Whether gout directly or indirectly through hyperuricemia increases the risk of cardiovascular disease remains uncertain, but current data suggest more aggressive cardiovascular risk management in patients with gout (9). Nevertheless, larger clinical trials with a longer follow-up period are still needed to determine the safety and efficacy of urate-lowering therapy such as allopurinol in cardiovascular disease.

Several potential limitations to this study are inherent to meta-analyses. First, even with our comprehensive search strategy and lack of language restriction, statistical assessment and a funnel plot examination did suggest the possibility of publication bias. Studies with null results are generally less likely to be published and, therefore, more likely to be missed in a database search. However, the majority of the included studies in our meta-analysis reported null results. Our study relied exclusively on published data. There were different definitions of hyperuricemia across the studies; therefore, we chose the category nearest to 6.8 mg/dl in each study for the hyperuricemia group. For men, the cut-off level to define hyperuricemia was between 6.5 and 7.0 mg/dl in 55% and 90% of the studies for CHD incidence and mortality, respectively. Most studies used a lower cut-off level to define hyperuricemia for women. However, different cut-off levels for hyperuricemia did not modify the study estimates of CHD risk based on our meta-regression analysis. Statistical methods and degree of adjustment differed slightly in each study. We utilized the best adjusted RR per individual study and performed separate analyses for unadjusted and multivariate RRs. Secondly, unmeasured confounding is also a common problem in observational studies, including prospective cohorts. In our review, use of concomitant medications such as diuretics and presence of medical comorbidities were not always adjusted for in the included studies. Thirdly, for the CHD outcome data, there is a possibility of misclassification bias because many of the included papers used death certificates or diagnostic codes to define their outcomes.

Our study has several important strengths. We selected only large prospective studies with inception cohort free of disease, which helped increase precision of estimates while minimizing heterogeneity. Assessment of the quality of individual studies is a necessary component for a systematic review of both randomized and observational studies. There has not been a consensus on which way is the best to measure the quality of observational studies. Indeed, a recent review identified more than 80 quality assessment tools and noted the lack of a single, best, generic tool for observational studies (74). We chose to use the Newcastle-Ottawa Scale (23) for quality assessment because this tool appropriately evaluates the three most important domains of prospective cohort studies: selection of study participants, measurement of exposures and outcomes, and control of confounding. We performed gender-specific subgroup analyses of the studies fully adjusting for traditional CHD risk factors. Multivariate meta-regression analysis further examined several potential sources of heterogeneity between the studies such as gender, ethnicity, study location, year of publication and cut-off level for hyperuricemia.

In conclusion, there is a modestly increased risk for CHD associated with hyperuricemia in our meta-analysis. A more pronounced increased risk for CHD mortality in women should be confirmed with future research. It would be particularly important to design further large, long-term studies that determine the effect of urate-lowering therapy on cardiovascular disease.

Appendix 1

Search strategy

MeSH term search	Direct keyword search
1. Uric Acid	9. urate
2. Hyperuricemia	10. hyperuric$
3. Coronary disease	11. coronary heart disease
4. Myocardial infarction	

MeSH term search	Direct keyword search
5. Coronary artery disease	
6. Angina pectoris	
7. Angina, unstable	
8. Cardiovascular Diseases	
12. “1 OR 2 OR 9 OR 10”	
13. “3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 11”	
14. “12 AND 13”	

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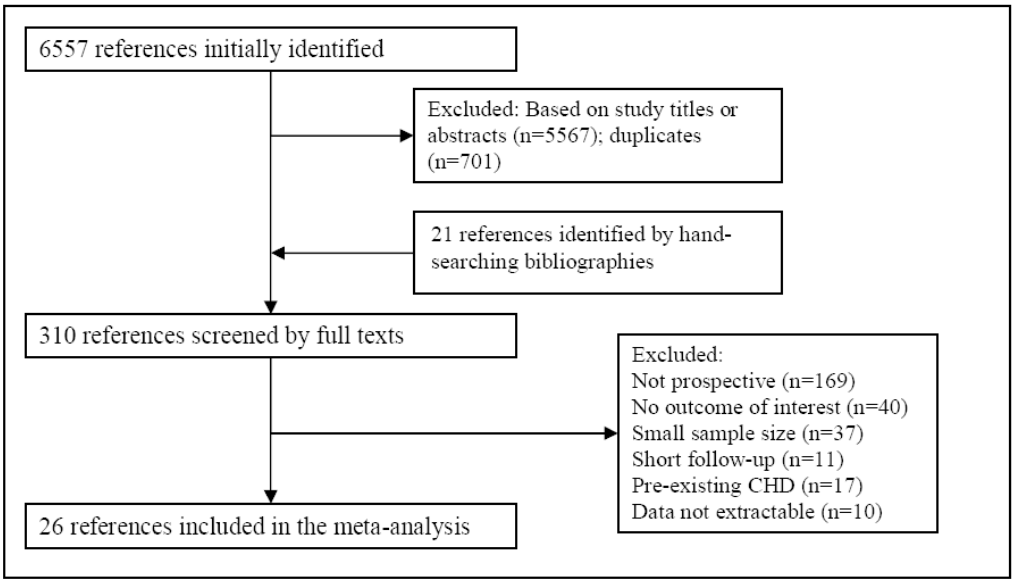

Figure 1.
Selection of studies included in the analysis.
CHD: coronary heart disease

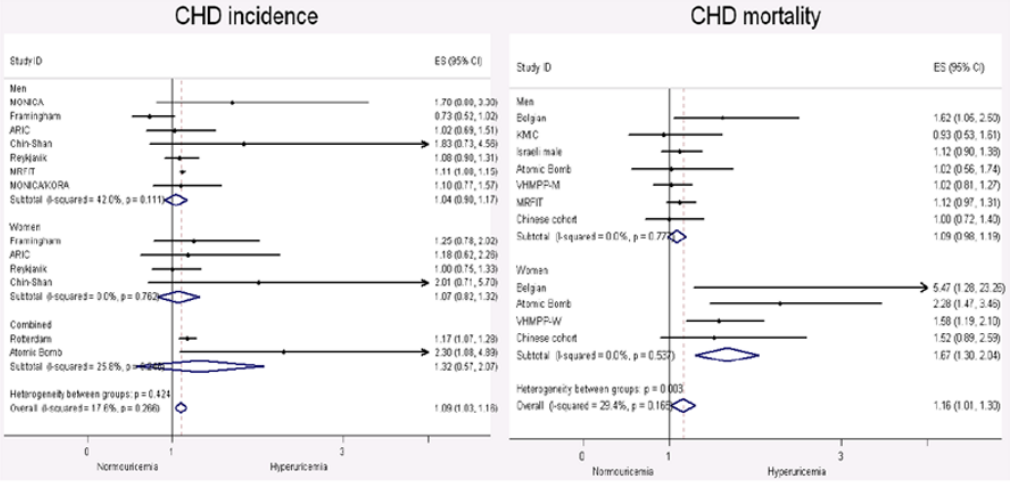

Figure 2.
Random effects analysis of multivariate risks of CHD associated with hyperuricemia
ES: Effect size, CI: confidence interval

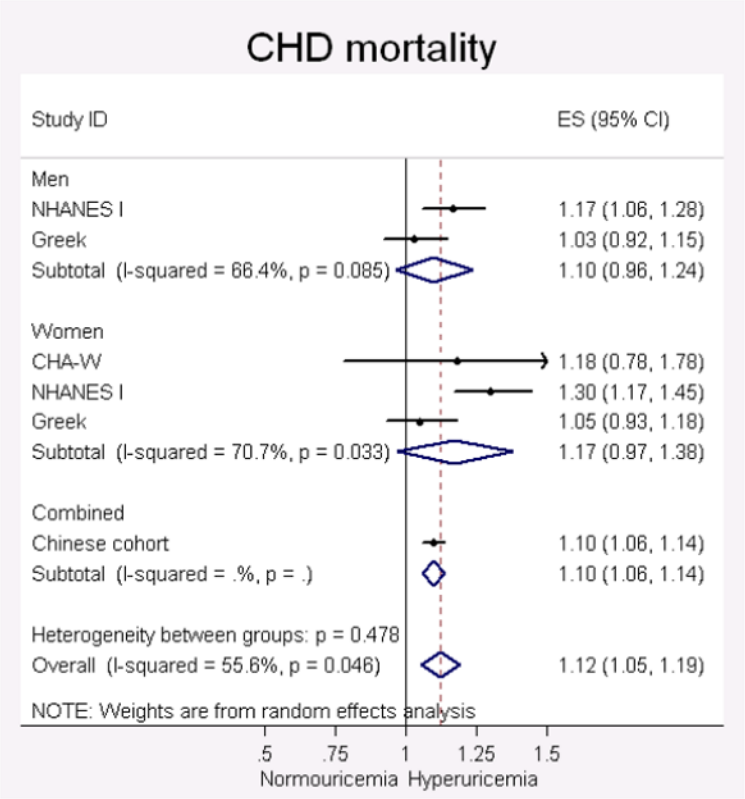

Figure 3.

Random effects analysis of multivariate risks of CHD mortality associated with an increase of 1mg/dl in serum uric acid level

ES: Effect size, CI: confidence interval

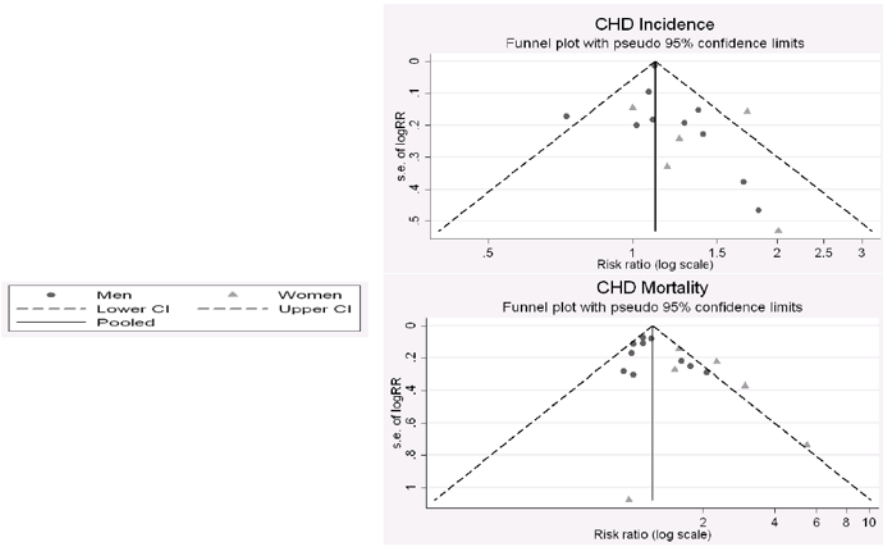

Figure 4.
Begg's funnel plot for publication bias in studies for CHD incidence and mortality

Table 1

Details of the cohort studies on incident coronary heart disease (CHD).

Study name, Year or publication,	Study population (% men)	Age (mean±SD)	Follow-up (yr)	Hyperuricemia definition (mg/dl)	No. of total CHD events	Outcome definition	Variables controlled	Quality assessment score§
GRIPS [44] 1994	5728 men free of atherosclerotic diseases in Germany	40-60	5	6.5 (M)	107 (M)	Based on clinical symptoms, EKGs, cardiac enzymes, angiography and CT	none	4/0/3
NHANES I [31] 1995	5421 (46) adults free of CHD at baseline in the U.S.	25-74	13.5	7 (C)	403 (M) 286 (W)	Based on hospital records and death certificates	Age, race, cholesterol, diastolic BP, smoking, alcohol, education level, and use of antihypertensive and diuretic meds	4/2/3
Honolulu Heart [32] 1995	2710 Japanese-American men free of cardiovascular disease in the U.S.	55-64	23	6.8 (M)	352 (M)	Based on autopsy reports and/or medical records such as EKGs and cardiac enzymes	Age	4/1/3
MONICA [42] 1999	960 heart attack-free, non-diabetic middle-aged men in Germany	45-64	8	6.3 (M)	55 (M)	Based on medical records such as clinical symptoms, EKGs, cardiac enzymes, and autopsy reports	Age, alcohol, cholesterol/HDL ratio, HTN, smoking, BMI, education, and use of diuretics	4/2/3
Framingham (30) 1999	6763 (45.5) adults free of cardiovascular disease in the U.S.	47±15	17.4	6.8 (M); 5.3 (W)	394 (M) 223 (W)	Based on medical records such as clinical symptoms, EKGs, and cardiac enzymes	Age, BMI, systolic BP, use of antihypertensive and diuretic meds, DM, cholesterol, alcohol, smoking, LVH, and menopausal status	4/2/3
ARIC [37] 2000	13504 (43.7) healthy middle-aged subjects in the U.S.	45-64	8	7.6 (M); 6.3 (W)	264 (M) 128 (W)	Based on medical records such as clinical symptoms, EKGs, and cardiac enzymes, and data on death certificates	Age, race, ARIC center, smoking, LDL, systolic BP, BMI, HDL, DM, waist/hip ratio, protein, triglycerides, alcohol, and antihypertensive meds	4/2/3
Gubbio study [45] 2001	2469 (45.2) adults free of cardiovascular disease at entry in Italy	35-74	6	7.3 (C)	68 (M) 41 (W)	Based on paper/phone questionnaires, EKGs, and medical records	Age, sex, systolic BP, cholesterol, glucose, smoking, and BMI	4/2/3
Chin-Shan [51] 2005	3602 adults free of cardiovascular disease in Taiwan	≥35	8.5	7.7 (M); 6.6 (W)	86	Based on death certificates and hospital records	Age, systolic BP, BMI, DM, cholesterol, smoking, and alcohol	4/2/3
Reykjavik study [48] 2005	6042 (70.3) adults without a history of MI in Iceland	(56±9)	17.5	5.7 (M) ; 4.7 (W)	2080	Based on questionnaires, EKGs, and medical records	Age, smoking, systolic BP, cholesterol, BMI, triglycerides, FEV1, and DM	4/2/3
Rotterdam study [40] 2006	4385 (35.4) adults free of CHD in the Netherlands	≥55	8.4	6.4 (M); 5.4 (W); 6.5 (C)	515	Based on ICD-9 codes on medical records	Age, sex, systolic BP, cholesterol, HDL, DM, smoking, diuretic use, and waist/hip ratio	4/2/3
MRFIT [33] 2006	12866 men free of cardiovascular disease at baseline in the U.S.	(46±6)	6.5	7.0 (M)	1108 (M)	Based on review of medical records such as EKGs and CABG surgery	Age, BP, cholesterol, serum creatinine, DM, smoking, BMI, family history of AMI, alcohol, aspirin and diuretic use	4/2/3
Atomic bomb study [49] 2007	2024 (38.3) atomic bomb survivors free of CHD at baseline in Japan	(62±9.9: M) (63.2±8.4: W)	8	7.0 (C)	49	Based on self-reports, EKGs, and medical records	Age, sex, smoking, alcohol, glucose, and fatty liver	4/2/3

Study name, Year or publication,	Study population (% men)	Age (mean±SD)	Follow-up (yr)	Hyperuricemia definition (mg/dl)	No. of total CHD events	Outcome definition	Variables controlled	Quality assessment score§
MONICA/KO RA [43] 2008	3424 men heart attack-free middle-aged men in German	45-74	11.7	6.6 (M)	297 (M)	Based on the population based data from MONICA/KORA Augsburg coronary event registry and death certificates	Age, smoking, alcohol, physical activity, HTN, BMI, DM, CRP dyslipidemia, creatinine, and diuretic use	4/2/3

GRIPS: Gottingen Risk Incidence and Prevalence Study, NHANES: National Health and Nutrition Examination Survey, MONICA: Monitoring trends and determinants on cardiovascular diseases, ARIC: Atherosclerosis Risk in Communities, MRFIT: Multiple Risk factor Intervention Trial, KORA: Cooperative Health Research in the Region of Augsburg, *: a nested case-control design M: men, W: women, C: combined, CT: computer tomography, BP: blood pressure, HTN: hypertension, DM: diabetes mellitus, BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein, AMI: acute myocardial infarction, FEV1: forced expiratory volume in one second LVH: left ventricular hypertrophy, EKG: electrocardiogram, CABG: coronary artery bypass graft, CRP: c-reactive protein

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Table 2

Details of the cohort studies on coronary heart disease (CHD) deaths.

Study name, Year of publication	Study population (% men)	Age (mean±SD)	Follow-up (yr)	Hyperuricemia definition (mg/dl)	No. of total CHD events	Outcome definition	Variables controlled	Quality assessment score§
CHA [36], 1979	7804 (54) white subjects free of CHD at baseline in the CHA Detection project in the U.S.	45-64	5	7.0 (M); 6.0 (W)	48 (M) 7 (W)	Based on ICD-8 codes on death certificates; autopsy and hospital reports if available	None	4/0/3
CHA-W [35] 1989	4825 white women in the CHA Detection project in the U.S.	45-64	11.5	Per 1 mg/dl	23 (W)	Based on ICD-8 codes on death certificates; autopsy and hospital reports if available	Age, weight, smoking, diastolic BP, cholesterol, and antihypertensive meds	4/2/3
NHANES I [20] 2000	5926 (45.6) non-institutionalized adults in the U.S.	25-74 (48.1)	16.4	7.0 (M); 5.6 (W); per 1 mg/dl increase	222 (M) 172 (W)	Based on ICD-9 codes on death certificates; hospital records if available	Age, cholesterol, race, BMI, smoking, alcohol, HTN, DM, and sex	4/2/3
Japanese male workers study [54] 2000	49413 Japanese male railroad workers	25-60	5.4	6.5 (M)	85 (M)	Based on ICD-9 codes on health and pension records	Age	4/1/3
Belgian study [38] 2001	9701 (53.9) adults in Belgium	25-74	10	7.0 (M); 5.4 (W)	150 (M) 51 (W)	Based on ICD-9 codes on hospital records	Age, diastolic BP, education level, smoking, and alcohol (M); age, cholesterol, systolic BP, smoking, BMI, alcohol and DM (W)	4/2/3
KMIC [53] 2004	22698 Korean men enrolled in the National Health Insurance Corporation	30-77	9	7.0 (M)	99 (M)	Based on ICD-9 and 10 codes from hospitalization records and death certificates	Age, HTN, DM, cholesterol, and smoking	4/2/3
Atomic Bomb study [52] 2005	10615 (36.4) Japanese atomic bomb survivors	(49±14. 8)	24.9	7.0 (M); 6.0(W)	177 (M) 250 (W)	Based on ICD-7 through 10 codes on death certificates	Age, BMI, smoking, alcohol, systolic BP, cholesterol, HTN, DM, kidney disease, malignant tumor, and estimated radiation dose from the atomic bombs	4/2/3
Israeli male study [41] 2005	9125 men free of CHD at baseline in Israel	(49±7)	23	5.6 (M)	830 (M)	Based on ICD-9 codes on death certificates and hospital records	Age, BMI, systolic BP, DM, cholesterol, smoking, and LVH on EKG	4/2/3
Greek study [39] 2005	1198 (42) adults in rural Greece	≥25	14	per 1mg/dl increase	34 (M) 33 (W)	Based on ICD-9 codes on death certificates	Age, body weight, smoking, alcohol, glucose, systolic BP, cholesterol, village, triglycerides, and educational level	4/2/3
MRFIT [34] 2008	9105 men free of cardiovascular disease at baseline in the U.S.	41-63	17	7.0 (M)	833 (M)	Based on ICD-9 and 10 codes on death certificates	Age, systolic/diastolic BP, cholesterol, BMI, triglycerides, serum creatinine, glucose, alcohol, smoking, family history of AMI, aspirin and diuretic use	4/2/3
VHMPP-M [47] 2008	83683 Austrian men	(41.6±14.6)	12.4	6.8 (M)	844 (M)	Based on ICD-9 and 10 codes on death certificates; autopsy records; if available	Age, BMI, cholesterol, systolic/ diastolic BP, triglycerides, GGT, smoking, and year of examinations	4/2/3

Study name, Year of publication	Study population (% men)	Age (mean±SD)	Follow-up (yr)	Hyperuricemia definition (mg/dl)	No. of total CHD events	Outcome definition	Variables controlled	Quality assessment score§
VHMPP-W [46] 2008	28613 elderly Austrian women	(62.3±8.8)	21	5.4 (W)	518 (W)	Based on ICD-9 and 10 codes on death certificates; autopsy records; if available	Age, BMI, cholesterol, systolic/ diastolic BP, triglycerides, GGT, smoking, glucose, occupational status, and year of examinations	4/2/3
Chinese cohort study [50] 2009	90393 (46.3) adults in Taiwan	(51.5±11.5)	8.2	7 (M, W); per 1 mg/dl increase	286	Based on ICD-9 codes on death certificates	Age, sex, BMI, cholesterol, DM, triglycerides, HTN, smoking, and alcohol	4/2/3

CHA: Chicago Heart Association, NHANES: National Health and Nutrition Examination Survey, KMIC: Korea Medical Insurance Corporation, MRFIT: Multiple Risk factor Intervention Trial, VHMPP: Vorarlberg Health Monitoring and Promotion Program M: men, W: women, BP, blood pressure, HTN: hypertension, DM: diabetes mellitus, BMI: body mass index, AMI: acute myocardial infarction, LVH: left ventricular hypertrophy, EKG: electrocardiogram, GGT: gamma-glutamyl transferase