Higher serum urate levels are associated with an increased risk for sudden cardiac death

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Word count main text: 3,219.

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Running head: Urate and sudden death.

Keywords [MeSH terms]: uric acid; sudden cardiac death; coronary heart disease; adults; primary prevention.

Funding

This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIA. Representatives of the NINDS were involved in the review of the manuscript but were not directly involved in the collection, management, analysis or interpretation of the data. Additional funding was provided by grants R01 HL080477 and K24 HL111154 from the National Heart, Lung,

and Blood Institute (NHLBI) and grant P50AR060772 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Representatives from the NHLBI or the NIMAS did not have any role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation or approval of the manuscript.

Conflict of interest

LDC receives research support from Amgen. AG receives research support from Amgen and honoraria from UpToDate. JAS receives consultant fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Medscape, WebMD, Clinical Care options, Clearview healthcare partners, Putnam associates, Spherix, Trio Health, Focus forward, Navigant consulting, Practice Point communications, Simply Speaking, the National Institutes of Health and the American College of Rheumatology, is member of the Executive Committee of Outcome Measures in Rheumatology (OMERACT), and is stockholder of Amarin pharmaceuticals and Viking therapeutics. MMS receives research support from Amgen. PM receives research support from Amgen and serves as a consultant for Amgen. KGS receives research support from Horizon, Takeda, Sobi, and Shanton, and serves as a consultant/advisor for Arthrosi, Atom Bioscience, LG Pharma, Mallinkrodt, Sobi, Horizon, and Takeda. The remaining authors have no disclosures.

Abstract (≤250 words)

Objective: Determine the association of serum urate levels with sudden cardiac death and incident coronary heart disease (CHD), separately, among adults without a history of CHD.

Methods: We conducted a case-cohort analysis of Black and White participants ≥45 years of age enrolled in the REason for Geographic And Racial Differences in Stroke (REGARDS) study without a history of CHD at baseline between 2003 and 2007. Participants were followed for sudden cardiac death or incident CHD (i.e., myocardial infarction or death from CHD excluding sudden cardiac death) through December 31, 2013. Baseline serum urate was measured in a random sample of participants (n=840) and among participants who experienced sudden cardiac death (n=235) or incident CHD (n=851) during follow-up.

Results: Participants with higher serum urate levels were older and more likely to be male or Black. The crude hazard ratio (95%CI) per 1 mg/dL higher serum urate level was 1.26 (1.14-1.40) for sudden cardiac death and 1.17 (1.09-1.26) for incident CHD. After adjustment for age, gender, race, and cardiovascular risk factors, the hazard ratio (95%CI) per 1 mg/dL higher serum urate level was 1.19 (1.03-1.37) for sudden cardiac death and 1.05 (0.96-1.15) for incident CHD. Hazard ratios for sudden cardiac death were numerically higher among participants 45-64 versus ≥65 years of age, without versus with diabetes, and among those of White versus Black race, although p-values for effect modification were all ≥0.05.

Conclusion: Higher serum urate levels were associated with an increased risk for sudden cardiac death but not with incident CHD.

Introduction

About 380,000 sudden cardiac deaths occur every year in the US, which represents 13.5% of all deaths (1). Coronary heart disease (CHD) is a frequent cause of sudden cardiac death (1, 2). However, other factors may also contribute to the occurrence of sudden cardiac death, including arrhythmias and respiratory and metabolic conditions (3).

High genetically-predicted serum urate levels were associated with an increased risk for sudden cardiac death in a Mendelian randomization analysis of White adults hospitalized for coronary angiography (4). About 80% of the study population had prevalent CHD at baseline (4). However, genetically-predicted serum urate levels were not associated with prevalent CHD, suggesting that the association with sudden cardiac death may be independent of the development of coronary atherosclerosis (4).

There are currently few data available on the risk for sudden cardiac death associated with serum urate levels in adults without a history of CHD, and in Black adults, a population with higher serum urate levels (5) and a higher risk for sudden cardiac death (2) compared to White adults. The objective of the current study was to determine the association of serum urate levels with sudden cardiac death and incident CHD (excluding sudden cardiac death), separately, among Black and White adults without a history of CHD in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study (6).

Materials and Methods

REGARDS study

The REGARDS study is a population-based cohort of 30,239 Black and White adults ≥45 years of age from all 48 contiguous US states and the District of Columbia who were enrolled between January 2003 and October 2007 (6). Black adults and residents in the Southeastern US states were oversampled by design. All REGARDS study participants completed a computer-assisted telephone interview and an in-home examination at baseline. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers (IRB-020925004, FWA00005960 - U Alabama Birmingham) and all participants provided written informed consent.

Baseline characteristics

Baseline characteristics of participants analyzed as part of the current analysis included age, gender, geographic region of residence, income, education, alcohol consumption, current smoking, body mass index (BMI), physical activity, chronic kidney disease (CKD), history of stroke, diabetes, atrial fibrillation, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), left ventricular hypertrophy (LVH), and use of antihypertensive medication, diuretics, statins and allopurinol.

We analyzed data on SLC2A9 single-nucleotide polymorphisms (SNP) rs12498742, rs1014290 and rs3733589, which were used in prior Mendelian randomization analyses

of serum urate (4, 7). We speculated that SLC2A9 SNPs may be confounders in an association between serum urate and sudden cardiac death. Specifically, SLC2A9 encodes the glucose transporter 9 (GLUT-9) which regulates the reabsorption of urate in the kidney, with SLC2A9 genetic variants explaining about 3% of the serum urate variation across individuals (4, 8). GLUT-9 is also expressed in the heart (9). Therefore, SLC2A9 SNPs could increase the risk for sudden cardiac death by affecting the transport of glucose and other hexoses in myocardial cells, independently from serum urate levels. We also analyzed data on QT interval corrected for heart rate as it has been proposed that high serum urate levels may lead to a prolonged QT interval and this may explain the higher risk for sudden cardiac death associated with serum urate (10).

Definitions of baseline characteristics are shown in **Supplemental Table 1**. History of CHD at baseline was defined by self-report of a prior diagnosis of myocardial infarction (MI), coronary bypass surgery, coronary angioplasty or stenting, or evidence of a previous MI on the baseline study electrocardiogram.

Sudden cardiac death and CHD events

Living participants or proxy respondents were contacted every six months via telephone to identify deaths and CHD-related hospitalizations (11). Two study clinicians independently reviewed medical records from CHD-related hospitalizations following published guidelines to determine whether the event was an MI based on signs, symptoms, electrocardiograms, and troponin and creatinine kinase-myocardial band

levels. When deaths were identified, trained study clinicians determined whether a sudden cardiac death or a CHD event was the main underlying cause of death based on interviews with next-of-kin, medical records, death certificates, and autopsy reports (12). Sudden cardiac death was defined by an unexpected death without an obvious extracardiac cause occurring with a rapid witnessed collapse (13). For unwitnessed deaths, sudden cardiac death was defined by a death that occurred within one hour after symptoms onset or an unexpected death without obvious extracardiac cause which occurred within the previous 24 hours (13). Death from CHD was defined as a death without evidence of non-coronary causes preceded by cardiac symptoms or signs, or in a participant with evidence of coronary atherosclerosis. For the current analysis, CHD events are defined by an MI or death from CHD excluding sudden cardiac deaths.

Serum urate measurements and study population

Baseline serum urate was measured using a colorimetric assay on a Cobas 311 analyzer (Roche, Basel, Switzerland) in a sample of REGARDS study participants following a case-cohort design (14). Specifically, serum urate was measured in a sample of 1,104 REGARDS study participants randomly selected using an age-sex-race-stratified sampling approach (i.e., the random sub-cohort), and in all participants who experienced sudden cardiac death without a prior CHD event (n=435) or a CHD event excluding sudden cardiac death (n=1,612) through December 31, 2013 (i.e., the cases). After excluding participants with a history of CHD and those with missing serum urate at baseline, the final analytic dataset for the current analysis included 840

REGARDS study participants from the random sub-cohort, 235 participants with sudden cardiac death, and 851 participants with incident CHD (**Figure 1**).

Statistical analysis

We calculated summary statistics for characteristics of participants in the random sub-cohort, and of those with sudden cardiac death and incident CHD, separately, stratified by serum urate levels (i.e., <5.0, 5.0 to <6.8 and ≥6.8 mg/dL). Cut-points of 5.0 and 6.8 mg/dL were selected because these are close to the tertiles of serum urate distribution among participants from the random sub-cohort, and because a value ≥6.8 mg/dL is clinically defined as hyperuricemia (15).

We used the Barlow's method to calculate hazard ratios (HR) and 95% confidence intervals (CI) for sudden cardiac death associated with serum urate levels (16). We used restricted cubic splines to plot the crude association between serum urate and sudden cardiac death. We also calculated the crude and multivariable-adjusted HR and 95% CI for sudden cardiac death associated with 1 mg/dL higher serum urate level. In addition to the crude model, four models with progressive adjustment for potential confounders were used. Model 1 included adjustment for age, gender and race. Model 2 included adjustment for age, gender, race, geographic region of residence, income and education. Model 3 included adjustment for variables in Model 2 and alcohol consumption, current smoking, BMI, and physical activity. Model 4 included adjustment for variables in Model 3 and CKD, history of stroke, diabetes, atrial fibrillation, SBP, total cholesterol, HDL-C, CRP, LVH, use of antihypertensive medication, diuretics, statin and

allopurinol, and SLC2A9 SNPs. In a separate model, we included adjustment for variables in Model 4 and QT interval as a possible mediator. The analyses described above were repeated to calculate HRs and 95% CIs for incident CHD associated with serum urate levels.

We calculated HRs and 95% CIs for sudden cardiac death and incident CHD per 1 mg/dL higher serum urate level within subgroups defined by age (i.e., 45-64 and ≥65 years of age), gender, race, CKD, diabetes, and use of diuretics including adjustment for variables in Model 4 described above, and for variables in Model 4 and QT interval. We used the approach described by Woodward to test whether HRs were different across subgroups (17). We also calculated HRs and 95% CIs for sudden cardiac death and incident CHD associated with serum urate levels of 5.0 to <6.8 and ≥6.8 mg/dL, separately, versus <5.0 mg/dL without adjustment, and with adjustment for variables in Models 1 through 4 described above, and for variables in Model 4 and QT interval. This analysis was repeated among men and women, separately, using gender-specific tertiles of serum urate distribution in the random sub-cohort to define serum urate categories. To test for linear trend across serum urate categories, we used the median serum urate level corresponding to each participant's category as the independent variable.

Analyses described above were weighted to extrapolate results to the full REGARDS study population. Chained equations were used to obtain 25 multiple imputed datasets in Stata 16.1 (Stata Corp, College Station, TX) to retain REGARDS study participants

with missing data in the regression models (**Supplemental Table 2**). All other analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Among participants in the random sub-cohort (n=840), those with higher serum urate levels were older and more likely to be male or Black, and have higher BMI, CKD, diabetes, higher SBP or CRP, and lower HDL-C (**Table 1**). The prevalence of the A-allele of rs12498742, the A-allele of rs1014290 and the G-allele of rs3733589 was higher among participants with higher serum urate levels. Participants with higher serum urate levels were also more likely to be taking antihypertensive medication, a diuretic or statin. Participants with sudden cardiac death (n=235) and incident CHD (n=851) were older and more likely to be men and have CKD, diabetes, higher SBP or CRP, or LVH versus those in the random sub-cohort (**Supplemental Tables 3, 4** and **5**).

Higher serum urate levels were associated with an increased risk for sudden cardiac death and incident CHD in crude models using splines, and these associations appeared to be linear (**Figure 2**). The crude HR for sudden cardiac death per 1 mg/dL higher serum urate level was 1.26 (95% CI 1.14, 1.40, **Table 2**). The HR for sudden cardiac death remained statistically significant after adjustment for variables in Model 4 (HR 1.19, 95% CI 1.03, 1.37) and for variables in Model 4 and QT interval (HR 1.18, 95% CI 1.02, 1.36). The crude HR for incident CHD per 1 mg/dL higher serum urate level was 1.17 (95% CI 1.09, 1.26). This association was not statistically significant after

adjustment for variables in Model 4 (HR 1.05, 95% CI 0.96, 1.15).

There was no statistically significant effect modification on the risk for sudden cardiac death or incident CHD per 1 mg/dL higher serum urate level in subgroup analyses by age, gender, race, CKD, diabetes and diuretic use (**Figure 3**). After adjustment for variables in Model 4, the HR for sudden cardiac death per 1 mg/dL higher serum urate level was 1.50 (95% CI 1.09, 2.07) and 1.10 (95% CI 0.92, 1.33) among participants 45-64 and ≥65 years of age, respectively, 1.30 (95% CI 1.00, 1.69) and 1.11 (95% CI 0.90, 1.35) among White and Black participants, respectively, and 1.29 (1.07, 1.56), and 0.84 (0.57, 1.24) among participants without and with diabetes, respectively. The increased risk for sudden cardiac death with higher serum urate levels among participants 45-64 years of age and in those of White race and without diabetes remained statistically significant after further adjustment for QT interval in addition to variables in Model 4.

The crude HR for sudden cardiac death associated with a serum urate ≥6.8 mg/dL versus <5.0 mg/dL was 2.14 (95% CI 1.40, 3.26, **Table 3**). The HR for sudden cardiac death associated with a serum urate level ≥6.8 mg/dL versus <5.0 mg/dL was 1.39 (95% CI 0.78, 2.49) after adjustment for variables in Model 4, and 1.37 (95% CI 0.76, 2.47) after adjustment for variables in Model 4 and QT interval. A serum urate level ≥6.8 mg/dL versus <5.0 mg/dL was associated with a higher risk for incident CHD in the crude model (HR 1.81, 95% CI 1.36, 2.42), but this association was attenuated and not statistically significant after adjustment for variables in Model 4 (HR 1.07, 95% CI 0.73, 1.58). Results on the risk for sudden cardiac death and incident CHD associated with

categories of serum urate levels defined using gender-specific tertiles among women and men, separately, are shown in **Supplemental Tables 6** and **7**, respectively.

Discussion

In the current analysis of a population-based cohort of US adults without a history of CHD, a higher serum urate level was associated with an increased risk for sudden cardiac death. However, there was no evidence of an association between serum urate levels and incident CHD. The current results suggest that a higher serum urate level is a risk factor for sudden cardiac death among adults without a history of CHD.

High serum urate levels were associated with an increased risk for sudden cardiac death in a prior Mendelian randomization analysis of White adults, most of whom had prevalent CHD (4). In the current study, a higher serum urate level was associated with an increased risk for sudden cardiac death in adults without CHD and after adjustment for known risk factors for sudden cardiac death and CHD. After multivariable adjustment, serum urate levels were not associated with incident CHD excluding sudden cardiac death. These results support that the association of serum urate with sudden cardiac death may be independent of the development of coronary atherosclerosis.

In the prior Mendelian randomization analysis, the multivariable-adjusted HR for sudden cardiac death per 1 mg/dL higher level of genetically-predicted serum urate was 2.41 (95% CI 1.16, 5.00) (4). However, the multivariable-adjusted HR for sudden cardiac

death per 1 mg/dL higher level of directly-measured serum urate found in the same study was 1.08 (95% CI 1.00, 1.17) (4). A possible explanation for the lower HR for sudden cardiac death associated with directly-measured versus genetically-predicted serum urate is that high serum urate levels may need to be present very early in life or over a very long period (which is captured by Mendelian randomization) in order to increase the risk for sudden cardiac death.

In a cross-sectional analysis conducted in China, high serum urate levels were associated with a prolonged QT interval, a risk factor for sudden cardiac death, among men (10). Therefore, the authors speculated that a prolonged QT interval may explain the increased risk for sudden cardiac death associated with high serum urate levels (10). In the current analysis, the association between serum urate levels and sudden cardiac death remained similar after adjustment for QT interval. This finding indicates that QT interval does not explain the increased risk for sudden cardiac death associated with high serum urate levels.

Cardiac arrhythmias are a frequent cause of sudden cardiac death in adults without CHD, and may mediate the association between serum urate levels and sudden cardiac death (18-21). Specifically, high serum urate levels may increase the risk for cardiac arrhythmias through an inflammatory-dependent mechanism in response to monosodium urate crystal deposition in the heart and other tissues over many years (21-23). Monosodium urate crystals increase proinflammatory cytokines, which have been shown to increase the susceptibility to develop potentially fatal paroxysmal

arrhythmias, including ventricular tachycardia and ventricular fibrillation, in animal models (24-26). Autonomic dysfunction is another factor associated with inflammation and sudden cardiac death, and may also mediate the association between serum urate levels and sudden cardiac death (27-29). It has also been suggested that urate overproduction may contribute to explain a substantial portion of the risk for cardiovascular events associated with serum urate (7). Therefore, future studies should investigate whether urate overproduction increases the risk for sudden cardiac death, for example by analyzing genetic variants that cause higher activity of xanthine oxidase. Understanding the mechanisms underlying the increased risk for sudden cardiac death associated with serum urate levels could contribute to identify high-risk subgroups and to develop preventive interventions in these populations.

In the current study, there was no statistically significant effect modification on the association of serum urate levels with sudden cardiac death by age, gender, race, CKD, diabetes, and diuretic use. However, the current study has limited statistical power to compare the risk for sudden cardiac death across subgroups. A 1 mg/dL higher serum urate level was associated with an increased risk for sudden cardiac death among participants 45 to 64 years of age, and those of White race or without diabetes, but not among those ≥65 years of age, of Black race or with diabetes. Older age, Black race, and diabetes are risk factors for sudden cardiac death (2, 30). Therefore, higher serum urate levels may not further increase the risk for sudden cardiac death in these high-risk populations. Given the number of comparisons performed, results from subgroups analyses need to be interpreted with caution and should be confirmed in future studies.

Some prior observational studies, but not all, have found an association between serum urate levels and incident CHD (31, 32). Many risk factors for incident CHD, including high SBP, BMI, and triglycerides, low HDL-C, and impaired glucose levels and renal function are associated with higher serum urate levels and may be confounders in observational studies (5, 33-35). Therefore, it has been speculated that differences in the adjustment for confounders may explain the heterogeneity in the association between serum urate and CHD across observational studies (31, 32). In the current study, HRs associated with serum urate levels were numerically higher for sudden cardiac deaths versus incident CHD excluding sudden cardiac deaths. Sudden cardiac death represents more than half of all fatal CHD events in adults without a prior history of CHD (2, 18, 36). Therefore, we speculate that sudden cardiac death may contribute to explain, at least in part, the heterogeneity of results on the association between serum urate and incident CHD across prior observational studies. Specifically, studies including a larger proportion of sudden cardiac deaths as part of the study outcome, for example those analyzing only CHD death or fatal MI (5, 37, 38), may be more likely to find an association between serum urate and CHD. In contrast, studies excluding sudden cardiac deaths from their CHD outcome definition, as the current study, may be less likely to find an association. This hypothesis is consistent with a prior systematic review which found that relative risks associated with hyperuricemia were numerically higher for incident CHD mortality (1.27, 95% CI 1.16, 1.39) versus fatal and nonfatal CHD (1.13, 95% CI 1.05, 1.21) (32).

The current analysis has several strengths. We used data from the REGARDS study, a large population-based cohort of Black and White adults who resided in all 48 contiguous US states and the District of Columbia which has a rigorous adjudication process for sudden cardiac death and incident CHD. We used a case-cohort design, an efficient approach that provides unbiased estimations of HRs for exposure-outcome associations (16, 39). Despite these strengths, the current study has known and potential limitations. The REGARDS study only included Black and White adults ≥45 years of age. Future studies should assess the association of serum urate levels with sudden cardiac death in other race groups and on adults <45 years of age. Data on whether participants had subclinical CHD, persistently elevated serum urate levels, gout, monosodium urate crystals deposited in joints or other tissues, or urate overproduction were not available.

In conclusion, a higher serum urate level was associated with an increased risk for sudden cardiac death but not for incident CHD excluding sudden cardiac death in a cohort of Black and White adults without a history of CHD. These results suggest that higher serum urate levels may be a risk factor for sudden cardiac death independently of the development of coronary atherosclerosis.

Acknowledgements

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at: https://www.uab.edu/soph/regardsstudy/.

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Figure legends

Figure 1. Flow-chart of REGARDS study participants included in the current analysis.

CHD: coronary heart disease; REGARDS: REasons for Geographic And Racial Differences in Stroke.

* The sub-cohort was randomly selected using a stratified sampling approach and is composed by 21 participants with sudden cardiac death without a CHD event, 54 participants with a CHD event (i.e., myocardial infarction or death from CHD excluding sudden cardiac death) and 1,029 participants without sudden cardiac death or a CHD event through December 31, 2013.

† Includes participants who had sudden cardiac death without a CHD event after their REGARDS in-home study visit through December 31, 2013.

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Figure 2. Crude association of serum urate levels with sudden cardiac death and incident CHD excluding sudden cardiac death.

CHD: coronary heart disease.

* Includes myocardial infarction or death from CHD excluding sudden cardiac death.

† Calculated among participants in the random sub-cohort (n=840).

Splines are unadjusted. The analysis includes 235 REGARDS study participants who experienced sudden cardiac death and 891 participants who experienced incident CHD through December 31, 2013.

P-values in the figure represent the p-value for the association between serum urate levels using splines and each outcome event. P-values assessing whether hazard ratios associated with serum urate using splines depart from a linear association were 0.21 for sudden cardiac death and 0.74 for incident coronary heart disease. These results support that the association of serum urate levels with sudden cardiac death and incident CHD is linear.

Figure 3. Risk for sudden cardiac death and incident CHD excluding sudden cardiac death associated with 1 mg/dL higher serum urate level within subgroups. CHD: coronary heart disease; CI: confidence interval; HR: hazard ratio. Model 4 includes age, gender, race, geographic region of residence, income, education, alcohol consumption, current smoking, body mass index, physical activity, chronic kidney disease, history of stroke, diabetes, atrial fibrillation, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, C-reactive protein, left ventricular hypertrophy, use of antihypertensive medication, diuretics, statin and allopurinol, and SLC2A9 single-nucleotide polymorphisms.

* QT interval is corrected for heart rate using the following equation: QT interval+154×(1−60/heart rate).

† Comparing hazard ratios across subgroups.

‡ A total of 9 participants in the random sub-cohort, and 6 participants with incident CHD had missing data on diabetes status at baseline and were excluded from the analysis.

§ A total of 4 participants in the random sub-cohort, and 1 participant with incident CHD had missing data on diuretic use at baseline and were excluded from the analysis.

‖ Includes myocardial infarction or death from CHD excluding sudden cardiac death.

Table 1. Baseline characteristics of REGARDS study participants in the random sub-cohort (n=840).

	Serum urate level		
Baseline characteristics*	**<5.0 mg/dL** (n=230)	**5.0 to <6.8 mg/dL** (n=361)	**≥6.8 mg/dL** (n=249)
Age, years, mean (SD)	63.5 (9.9)	64.0 (9.4)	65.5 (8.5)
Male, %	26.9	42.9	54.5
Black, %	40.9	38.6	50.9
Geographic region of residence, %†			
Stroke belt	39.9	38.5	28.3
Stroke buckle	16.5	15.9	22.0
Other US regions	43.6	45.7	49.8
<$25,000 annual household income, %	26.9	27.7	31.7
Less than high school education, %	10.7	9.3	14.0
Alcohol consumption, %			
None	64.8	59.3	62.0
Moderate	30.3	37.1	33.9
Heavy	4.9	3.6	4.2
Current smoking, %	15.7	13.3	11.6
Body mass index, %			
<25 Kg/m^2	43.1	24.1	11.5
25 to <30 Kg/m^2	31.6	38.2	35.8
≥30 Kg/m^2	25.3	37.7	52.7
Low physical activity, %‡	33.0	35.9	33.1
Chronic kidney disease, %	8.9	12.8	30.2
History of stroke, %	5.5	3.3	7.7
Diabetes, %	17.1	16.4	26.2

Atrial fibrillation, %	8.2	7.2	6.9
SBP, mm Hg, mean (SD)	124.2 (16.3)	126.7 (16.3)	130.5 (16.5)
Total cholesterol, mg/dL, mean (SD)	194.6 (41.0)	194.8 (37.2)	189.3 (40.1)
HDL cholesterol, mg/dL, mean (SD)	57.4 (17.6)	52.9 (17.1)	47.8 (14.2)
C-reactive protein >3 mg/dL, %	28.2	36.2	50.1
Left ventricular hypertrophy, %	3.8	3.6	5.8
QT interval, ms, mean (SD)§	404.6 (20.3)	405.0 (23.2)	405.8 (22.7)
SLC2A9 SNPs, %			
rs12498742: GG	21.6	8.2	12.5
rs12498742: GA	38.1	44.2	43.8
rs12498742: AA	40.2	47.5	43.7
rs1014290: GG	15.4	4.6	6.4
rs1014290: GA	37.5	38.4	33.1
rs1014290: AA	47.1	57.0	60.5
rs3733589: AA or GA	16.2	11.9	12.4
rs3733589: GG	83.8	88.1	87.6
Medication use, %			
Antihypertensive medication	36.4	47.8	64.0
Diuretics	19.2	25.7	48.4
Statin	22.2	24.9	36.1
Allopurinol	1.6	1.6	0.5

HDL: high-density lipoprotein; REGARDS: REasons for Geographic And Racial Differences in Stroke; SBP: systolic blood pressure; SD: standard deviation; SNP: single-nucleotide polymorphism; US: United States.

* Baseline characteristics are weighted to the full REGARDS study cohort to account for the stratified sampling design.

† Stroke buckle includes coastal North Carolina, South Carolina and Georgia. Stroke belt includes the remaining parts of North Carolina, South Carolina and Georgia, and Tennessee, Mississippi, Alabama, Louisiana and Arkansas. Other US regions includes the remaining 40 contiguous US states and the District of Columbia.

‡ Low physical activity is defined by self-reporting not engaging in any weekly activity intense enough to work up a sweat.

§ QT interval is corrected for heart rate using the following equation:

$$\text{QT interval} + 154 \times (1 - 60/\text{heart rate}).$$

Table 2. Association of 1 mg/dL higher serum urate level with sudden cardiac death and incident CHD.

	Sudden cardiac death	Incident CHD*
Random sub-cohort, n	840	840
Events	235	851
Hazard ratio (95% CI)		
Crude	1.26 (1.14, 1.40)	1.17 (1.09, 1.26)
Model 1	1.16 (1.05, 1.29)	1.11 (1.03, 1.19)
Model 2	1.18 (1.05, 1.31)	1.11 (1.03, 1.19)
Model 3	1.19 (1.06, 1.34)	1.10 (1.01, 1.19)
Model 4	1.19 (1.03, 1.37)	1.05 (0.96, 1.15)
Model 4 and QT interval‡	1.18 (1.02, 1.36)	1.04 (0.95, 1.14)

CHD: coronary heart disease.

Model 1 adjusts for age, gender and race.

Model 2 adjusts for age, gender, race, geographic region of residence, income and education.

Model 3 adjusts for variables in Model 2 and alcohol consumption, current smoking, body mass index, and physical activity.

Model 4 adjusts for variables in Model 3 and chronic kidney disease, history of stroke, diabetes, atrial fibrillation, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, C-reactive protein, left ventricular hypertrophy, use of

antihypertensive medication, diuretics, statin and allopurinol, and SLC2A9 single-nucleotide polymorphisms.

* Includes fatal and nonfatal myocardial infarction and death from CHD excluding sudden cardiac death.

‡ QT interval is corrected for heart rate using the following equation:

$$\text{QT interval} + 154 \times (1 - 60/\text{heart rate}).$$

Table 3. Association of categories of serum urate levels with sudden cardiac death and incident CHD excluding sudden cardiac death.

	Serum urate level			
	<5.0 mg/dL	5.0 to <6.8 mg/dL	≥6.8 mg/dL	p-trend‡
Random sub-cohort, n	230	361	249	
Sudden cardiac death				
Events	44	100	91	
Hazard ratio (95% CI)				
Crude	1 (reference)	1.53 (1.01, 2.29)	2.14 (1.40, 3.26)	<0.001
Model 1	1 (reference)	1.34 (0.88, 2.03)	1.57 (1.01, 2.42)	0.05
Model 2	1 (reference)	1.31 (0.85, 2.00)	1.58 (1.01, 2.46)	0.05
Model 3	1 (reference)	1.43 (0.91, 2.26)	1.73 (1.06, 2.85)	0.03
Model 4	1 (reference)	1.30 (0.78, 2.17)	1.39 (0.78, 2.49)	0.32
Model 4 and QT interval*	1 (reference)	1.30 (0.78, 2.18)	1.37 (0.76, 2.47)	0.35
Incident CHD†				
Events	174	372	305	
Hazard ratio (95% CI)				
Crude	1 (reference)	1.43 (1.09, 1.88)	1.81 (1.36, 2.42)	<0.001
Model 1	1 (reference)	1.32 (1.00, 1.73)	1.46 (1.08, 1.98)	0.02
Model 2	1 (reference)	1.27 (0.95, 1.68)	1.44 (1.06, 1.96)	0.03
Model 3	1 (reference)	1.25 (0.93, 1.69)	1.41 (1.01, 1.96)	0.06
Model 4	1 (reference)	1.16 (0.83, 1.62)	1.07 (0.73, 1.58)	0.84

Model 4 and QT interval*	1 (reference)	1.17 (0.83, 1.63)	1.07 (0.72, 1.57)	0.87

CHD: coronary heart disease.

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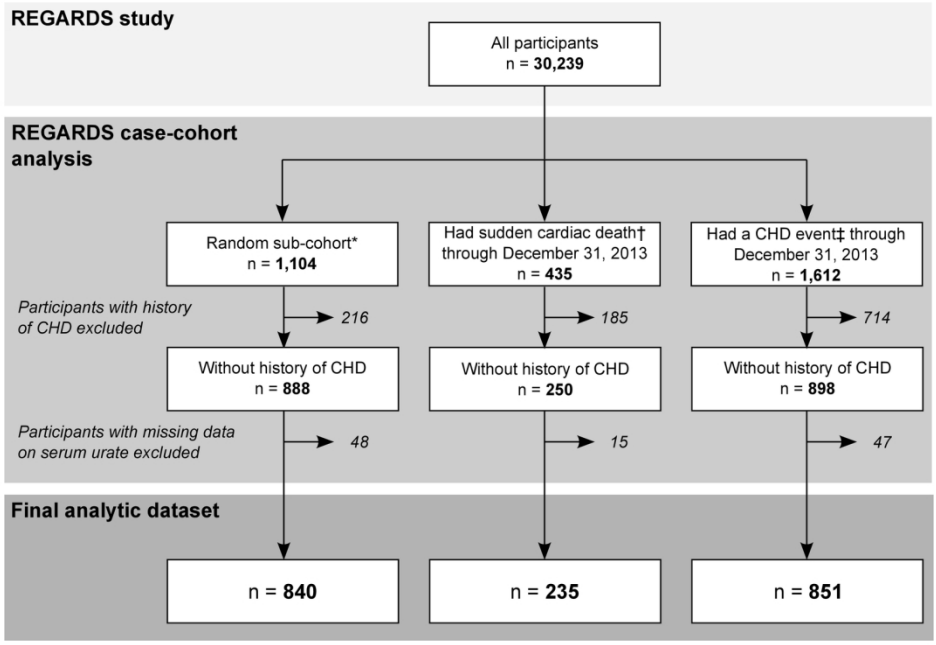
† Includes myocardial infarction or death from CHD excluding sudden cardiac death.

‡ Calculated using the median serum urate level corresponding to each participant's category as the independent variable.



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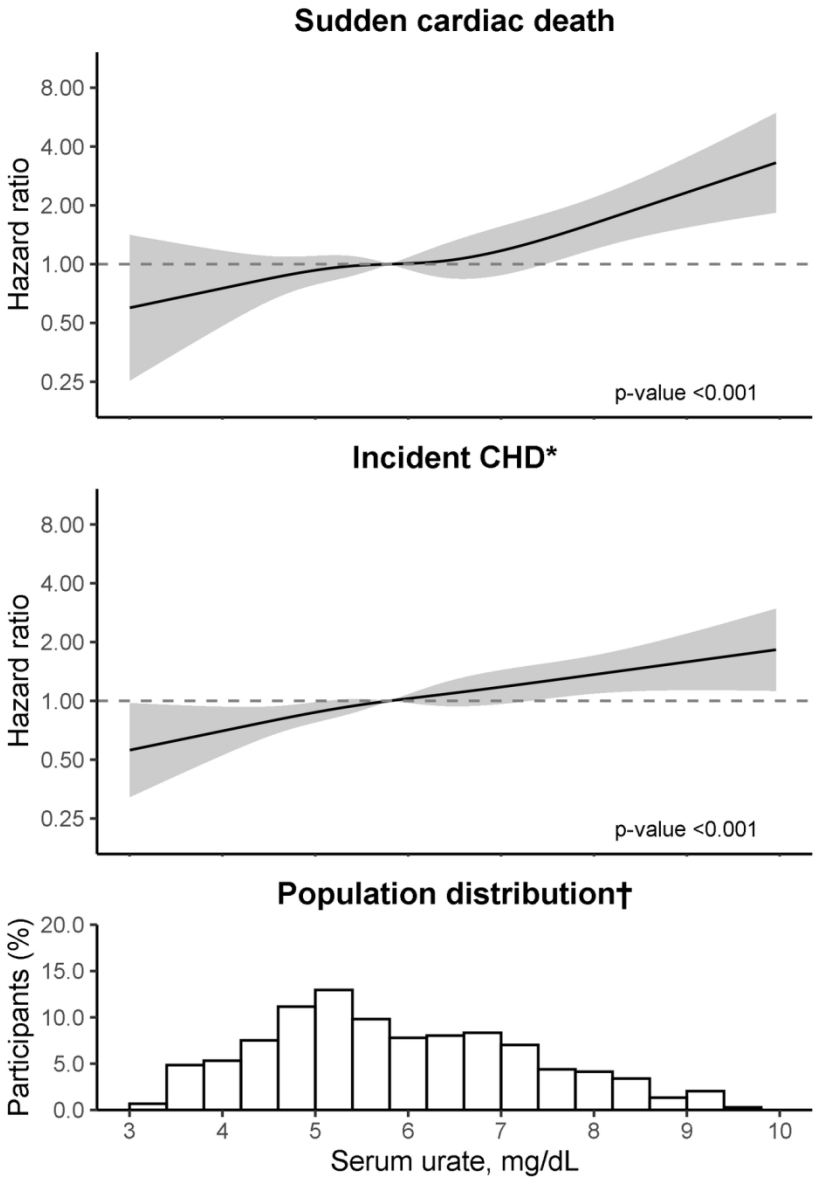

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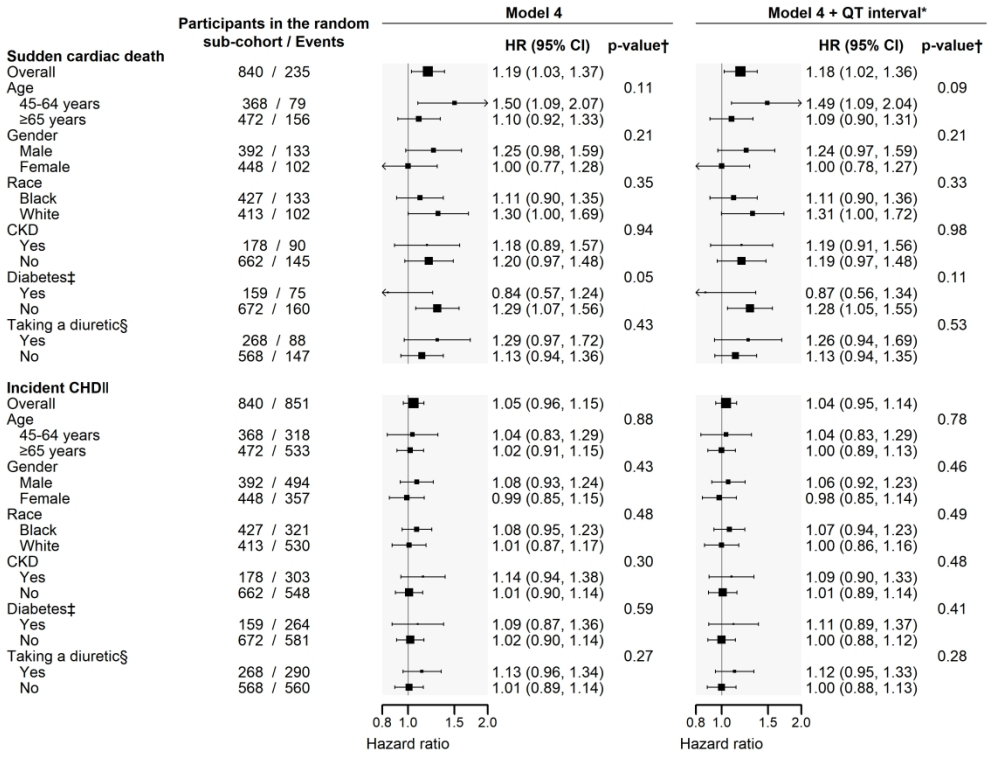

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