Higher Serum Urate Levels Are Associated With an Increased Risk for Sudden Cardiac Death

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ABSTRACT. **Objective.** To determine the association of serum urate (SU) 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 aged ≥ 45 years 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 [MI] or death from CHD excluding sudden cardiac death) through December 31, 2013. Baseline SU 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 SU levels were older and more likely to be male or Black. The crude HR (95% CI) per 1 mg/dL higher SU 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, sex, race, and cardiovascular risk factors, the HR (95% CI) per 1 mg/dL higher SU level was 1.19 (1.03–1.37) for sudden cardiac death and 1.05 (0.96–1.15) for incident CHD. HRs for sudden cardiac death were numerically higher among participants aged 45–64 vs ≥ 65 years, without vs with diabetes, and among those of White vs Black race, although P values for effect modification were all ≥ 0.05.

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

Key Indexing Terms: adults, coronary heart disease, primary prevention, sudden cardiac death, uric acid

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Approximately 380,000 sudden cardiac deaths occur every year in the US, representing 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 as well as respiratory and metabolic conditions.[3]

High genetically predicted serum urate (SU) levels were associated with an increased risk for sudden cardiac death in a Mendelian randomization analysis of White adults hospitalized for coronary angiography.[4] Approximately 80% of the study population had prevalent CHD at baseline.[4] However, genetically predicted SU 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 SU levels in adults without a history of CHD, and in Black adults, a population with higher SU 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 SU 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]

METHODS

REGARDS study. The REGARDS study is a population-based cohort of 30,239 Black and White adults aged ≥ 45 years 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 – University of Alabama at Birmingham), and all participants provided written informed consent.

Baseline characteristics. Baseline participant characteristics analyzed included age, sex, geographic region of residence, income, education, alcohol consumption, current smoking, 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

(SNPs) rs12498742, rs1014290, and rs3733589, which were used in prior Mendelian randomization analyses of SU.[4,7] We speculated that SLC2A9 SNPs may be confounders in an association between SU 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 SU 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 SU levels. We also analyzed data on QT interval corrected for heart rate, as it has been proposed that high SU levels may lead to a prolonged QT interval, and this may explain the higher risk for sudden cardiac death associated with SU.[10]

Definitions of baseline characteristics are shown in Supplementary Table 1 (available with the online version of this article). 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 6 months by 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 1 hour after symptom onset or an unexpected death without obvious extracardiac cause that occurred within the previous 24 hours.[13] Death from CHD was defined as a death without evidence of noncoronary 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.

SU measurements and study population. Baseline SU was measured using a colorimetric assay on a Cobas 311 analyzer (Roche) in a sample of REGARDS study participants following a case-cohort design.[14] Specifically, SU was measured in a sample of 1104 REGARDS study participants randomly selected using an age-/sex-/race-stratified sampling approach (i.e., the random subcohort), 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 = 1612) through December 31, 2013 (i.e., the cases). After excluding participants with a history of CHD and those with missing SU at baseline, the final analytic dataset for the current analysis included 840 REGARDS study participants from the random subcohort, 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 subcohort, and of those with sudden cardiac death and incident CHD, separately, stratified by SU levels (i.e., < 5.0, 5.0 to < 6.8, and ≥ 6.8 mg/dL). Cutpoints of 5.0 and 6.8 mg/dL were selected because these are close to the tertiles of SU distribution among participants from the random subcohort, and because a value ≥ 6.8 mg/dL is clinically defined as hyperuricemia.[15]

We used the Barlow method to calculate HRs and 95% CI for sudden cardiac death associated with SU levels.[16] We used restricted cubic splines to plot the crude association between SU 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 SU level. In addition to the crude model, 4 models with progressive adjustment for potential confounders were used. Model 1 included adjustment for age, sex, and
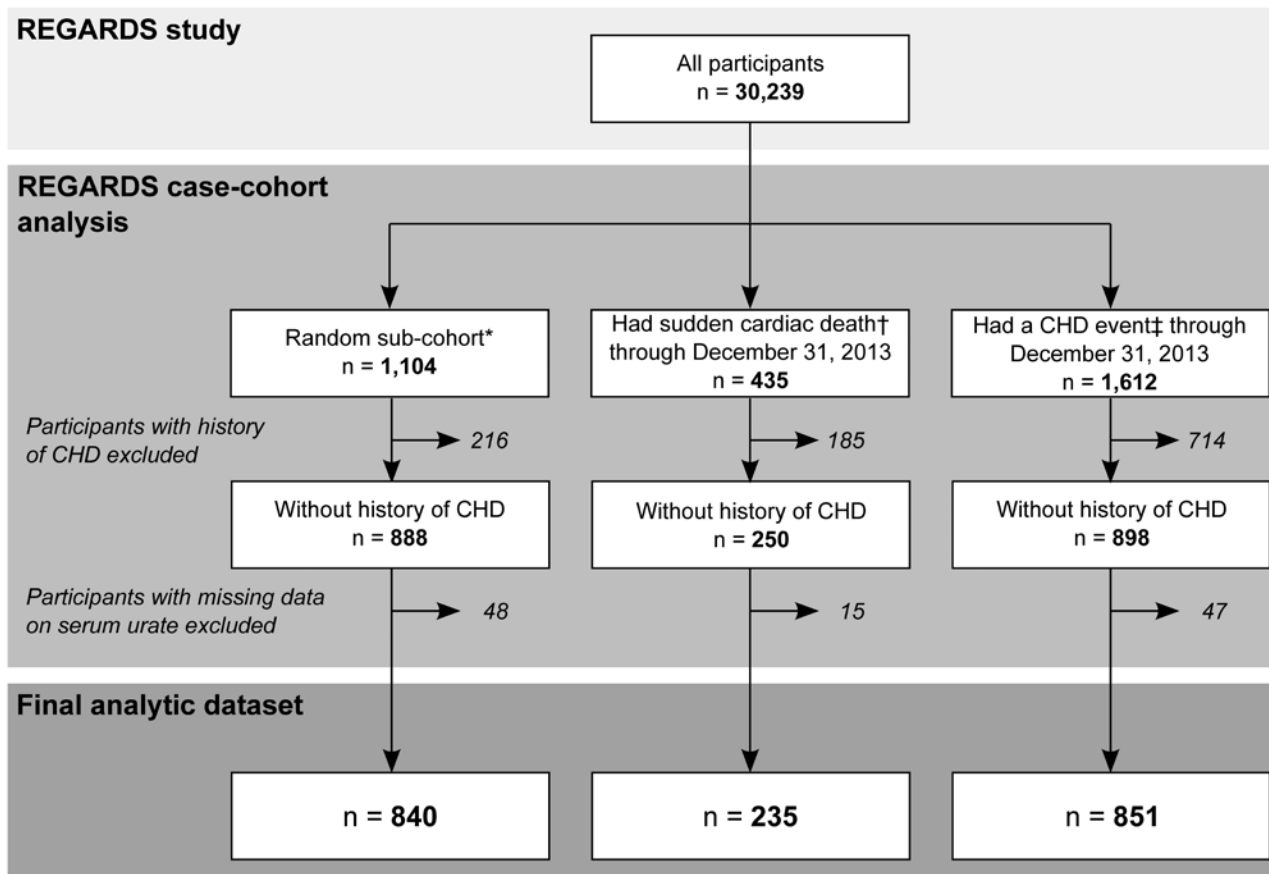
Figure 1. Flowchart of REGARDS study participants included in the current analysis. * The subcohort was randomly selected using a stratified sampling approach and is composed of 21 participants with sudden cardiac death without a CHD event, 54 participants with a CHD event (i.e., MI or death from CHD excluding sudden cardiac death), and 1029 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. ‡ CHD events include MI or death from CHD excluding sudden cardiac death. CHD: coronary heart disease; MI: myocardial infarction; REGARDS: REasons for Geographic And Racial Differences in Stroke.

race. Model 2 included adjustment for age, sex, 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, SLC2A9 SNPs, and use of antihypertensive medication, diuretic, statin, and allopurinol. 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 SU levels.

We calculated HRs and 95% CIs for sudden cardiac death and incident CHD per 1 mg/dL higher SU level within subgroups defined by age (i.e., 45–64 and ≥ 65 yrs), sex, 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 SU levels of 5.0 to < 6.8 and ≥ 6.8 mg/dL, separately, vs < 5.0 mg/dL without adjustment, and with adjustment for variables in Models 1 through 4 described above, as well as for variables in Model 4 and QT interval. This analysis was repeated among men and women, separately, using sex-specific tertiles of SU distribution in the random subcohort to define SU categories. To test for linear trend across SU categories, we used the median SU 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 (StataCorp.) to retain REGARDS study participants with missing data in the regression models (Supplementary Table 2, available with the online version of this article). All other analyses were conducted using SAS 9.4 (SAS Institute).

RESULTS

Among participants in the random subcohort (n = 840), those with higher SU 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 SU levels. Participants with higher SU 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 vs those in the random subcohort (Supplementary Tables 3–5, available with the online version of this article).

Higher SU levels were associated with an increased risk for

Table 1. Baseline characteristics[a] of REGARDS study participants in the random subcohort (n = 840).

	Serum Urate Level		
	< 5.0 mg/dL, n = 230	5.0 to < 6.8 mg/dL, n = 361	≥ 6.8 mg/dL, n = 249
Age, yrs, 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[b], %			
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
BMI, kg/m^2, %			
< 25	43.1	24.1	11.5
25 to < 30	31.6	38.2	35.8
≥ 30	25.3	37.7	52.7
Low physical activity[c], %	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, mmHg, 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[d], 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, %			
Antihypertensives	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

[a] Baseline characteristics are weighted to the full REGARDS study cohort to account for the stratified sampling design. [b] 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 include the remaining 40 contiguous US states and the District of Columbia. [c] Low physical activity is defined by self-reporting not engaging in any weekly activity intense enough to work up a sweat. [d] QT interval is corrected for heart rate using the following equation: QT interval + 154 × (1 − 60/heart rate). HDL: high-density lipoprotein; REGARDS: REasons for Geographic And Racial Differences in Stroke; SBP: systolic blood pressure; SNP: single-nucleotide polymorphism.

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 SU 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 SU 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

Sudden cardiac death

Incident CHD*

Population distribution†
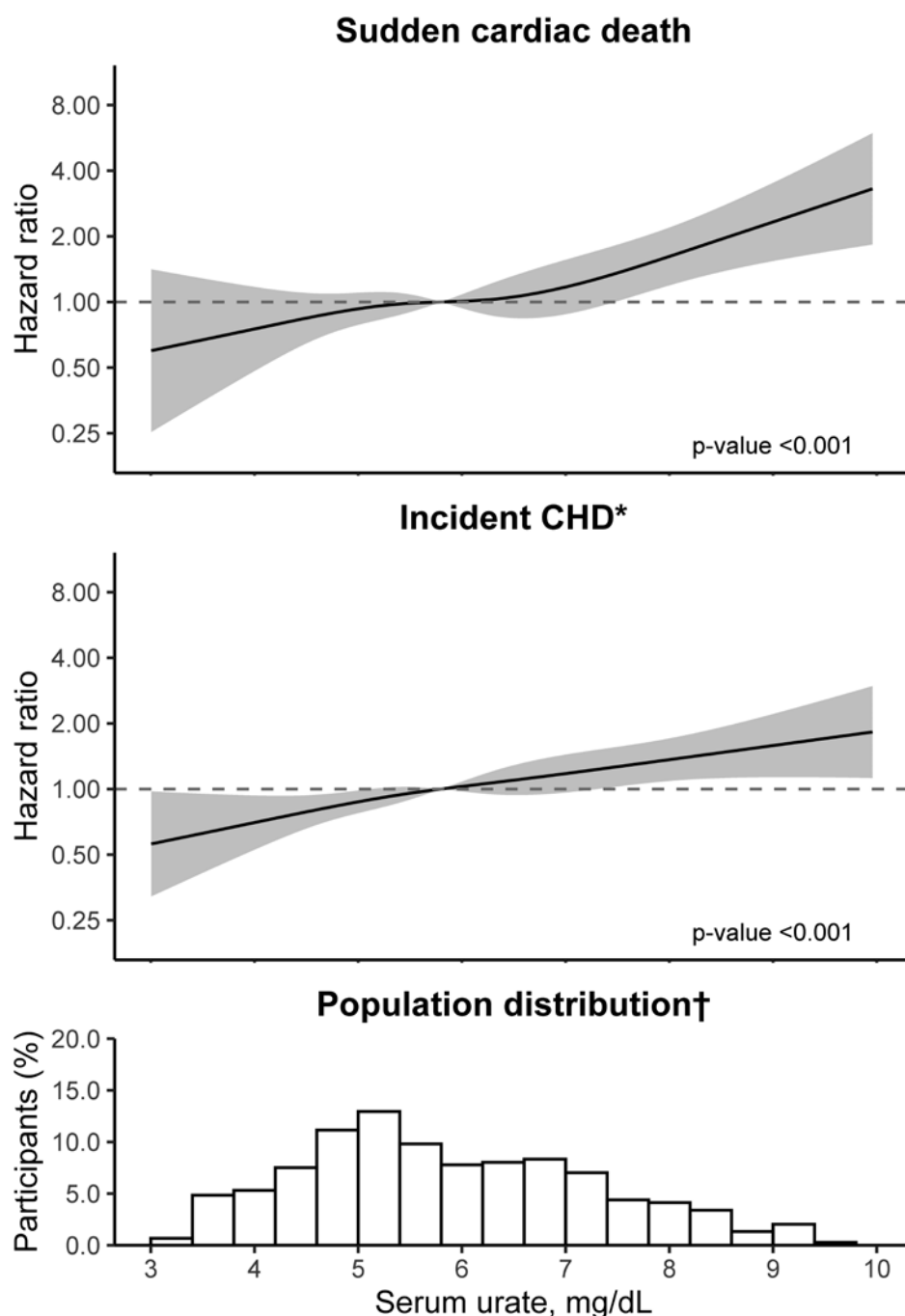
Figure 2. Crude association of SU levels with sudden cardiac death and incident CHD excluding sudden cardiac death. * Includes myocardial infarction or death from CHD excluding sudden cardiac death. † Calculated among participants in the random subcohort (n = 840). Splines are unadjusted. The analysis 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 SU levels using splines and each outcome event. *P* values assessing whether HRs associated with SU using splines depart from a linear association were 0.21 for sudden cardiac death and 0.74 for incident CHD. These results support that the association of SU levels with sudden cardiac death and incident CHD is linear. CHD: coronary heart disease; REGARDS: REasons for Geographic And Racial Differences in Stroke; SU: serum urate.

the risk for sudden cardiac death or incident CHD per 1 mg/ dL higher SU level in subgroup analyses by age, sex, 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 SU level was 1.50 (95% CI 1.09–2.07) and 1.10 (95% CI 0.92–1.33) among participants aged 45–64 and ≥ 65

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

	Sudden Cardiac Death	Incident CHD[a]
Random subcohort, n	840	840
Events	235	851
HR (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[b]	1.18 (1.02–1.36)	1.04 (0.95–1.14)

Model 1 adjusts for age, sex, and race. Model 2 adjusts for age, sex, race, geographic region of residence, income, and education. Model 3 adjusts for variables in Model 2 and alcohol consumption, current smoking, BMI, 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, SLC2A9 single-nucleotide polymorphisms, and use of antihypertensive medication, diuretics, statin, and allopurinol. [a] Includes fatal and nonfatal myocardial infarction and death from CHD excluding sudden cardiac death. [b] QT interval is corrected for heart rate using the following equation: QT interval + $154 \times (1 - 60/\text{heart rate})$. CHD: coronary heart disease.

years, 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 (95% CI 1.07–1.56) and 0.84 (95% CI 0.57–1.24) among participants without and with diabetes, respectively. The increased risk for sudden cardiac death with higher SU levels among participants aged 45–64 years 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 SU ≥ 6.8 mg/dL vs < 5.0 mg/dL was 2.14 (95% CI 1.40–3.26) (Table 3). The HR for sudden cardiac death associated with a SU level ≥ 6.8 mg/dL vs < 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. An SU level ≥ 6.8 mg/dL vs < 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 SU levels defined using sex-specific tertiles among women and men, separately, are shown in Supplementary Tables 6 and 7 (available with the online version of this article), respectively.

DISCUSSION

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

High SU 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 SU 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, SU levels were not associated with incident CHD excluding sudden cardiac death. These results support the possibility that the association of SU with sudden cardiac death is 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 SU 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 SU 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 vs genetically predicted SU is that high SU levels may need to be present very early in life or over a very long period (captured by Mendelian randomization) in order to increase the risk for sudden cardiac death.

In a cross-sectional analysis conducted in China, high SU levels were associated with a prolonged QT interval, which is 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 SU levels.[10] In the current analysis, the association between SU 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 SU levels.

Cardiac arrhythmias are a frequent cause of sudden cardiac death in adults without CHD, and may mediate the association between SU levels and sudden cardiac death.[18,19,20,21] Specifically, high SU 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.[21,22,23] 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.[24,25,26] Autonomic dysfunction is another factor associated with inflammation and sudden cardiac death, and may also mediate the association between SU levels and sudden cardiac death.[27,28,29] It has also been suggested that urate overproduction may explain a substantial portion of the risk for cardiovascular events associated with SU.[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 SU levels could contribute to identifying
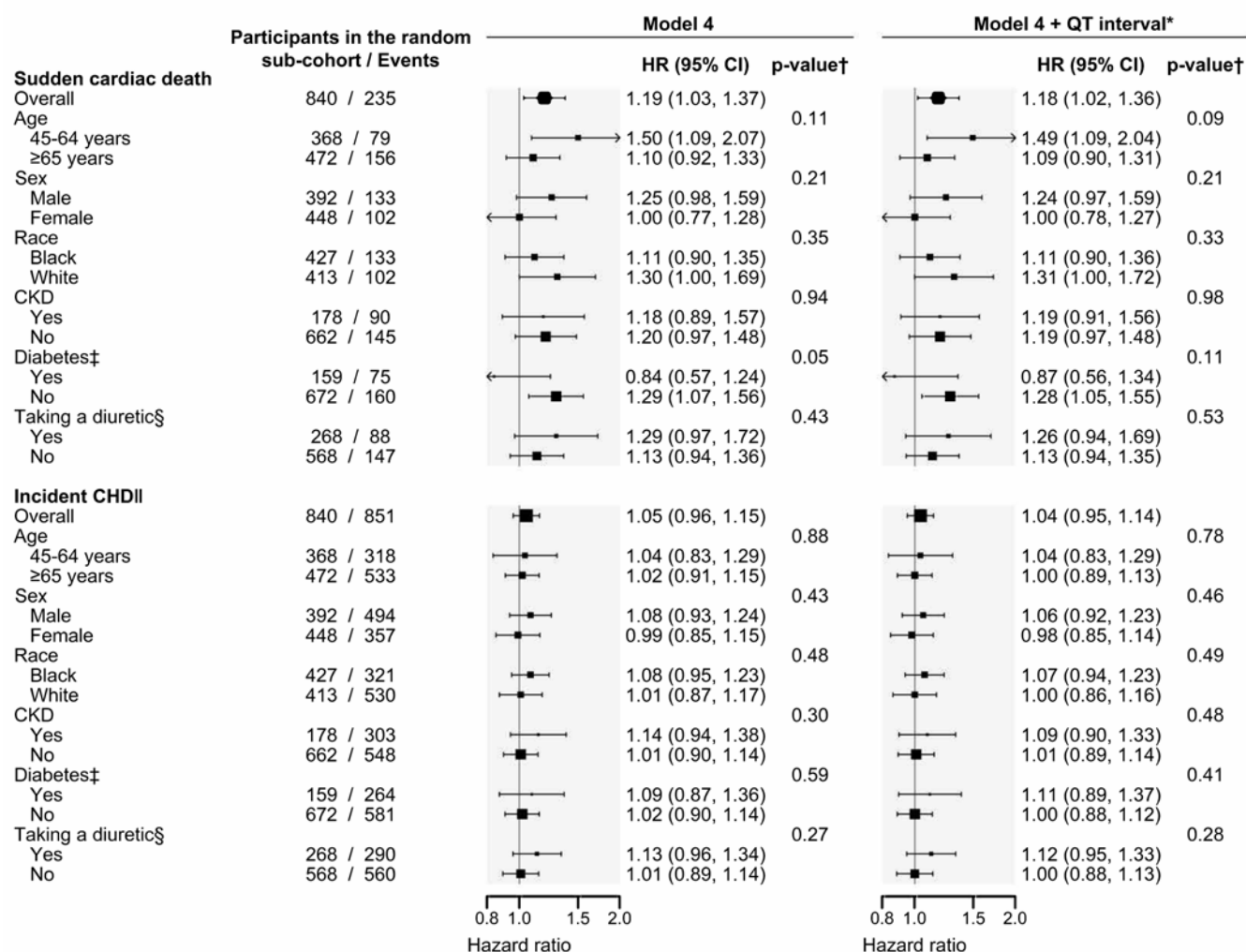
	Participants in the random sub-cohort / Events	Model 4		Model 4 + QT interval*	
		HR (95% CI)	p-value†	HR (95% CI)	p-value†
Sudden cardiac death					
Overall	840 / 235	1.19 (1.03, 1.37)		1.18 (1.02, 1.36)	
Age			0.11		0.09
45-64 years	368 / 79	1.50 (1.09, 2.07)		1.49 (1.09, 2.04)	
≥65 years	472 / 156	1.10 (0.92, 1.33)		1.09 (0.90, 1.31)	
Sex			0.21		0.21
Male	392 / 133	1.25 (0.98, 1.59)		1.24 (0.97, 1.59)	
Female	448 / 102	1.00 (0.77, 1.28)		1.00 (0.78, 1.27)	
Race			0.35		0.33
Black	427 / 133	1.11 (0.90, 1.35)		1.11 (0.90, 1.36)	
White	413 / 102	1.30 (1.00, 1.69)		1.31 (1.00, 1.72)	
CKD			0.94		0.98
Yes	178 / 90	1.18 (0.89, 1.57)		1.19 (0.91, 1.56)	
No	662 / 145	1.20 (0.97, 1.48)		1.19 (0.97, 1.48)	
Diabetes‡			0.05		0.11
Yes	159 / 75	0.84 (0.57, 1.24)		0.87 (0.56, 1.34)	
No	672 / 160	1.29 (1.07, 1.56)		1.28 (1.05, 1.55)	
Taking a diuretic§			0.43		0.53
Yes	268 / 88	1.29 (0.97, 1.72)		1.26 (0.94, 1.69)	
No	568 / 147	1.13 (0.94, 1.36)		1.13 (0.94, 1.35)	
Incident CHD‖					
Overall	840 / 851	1.05 (0.96, 1.15)		1.04 (0.95, 1.14)	
Age			0.88		0.78
45-64 years	368 / 318	1.04 (0.83, 1.29)		1.04 (0.83, 1.29)	
≥65 years	472 / 533	1.02 (0.91, 1.15)		1.00 (0.89, 1.13)	
Sex			0.43		0.46
Male	392 / 494	1.08 (0.93, 1.24)		1.06 (0.92, 1.23)	
Female	448 / 357	0.99 (0.85, 1.15)		0.98 (0.85, 1.14)	
Race			0.48		0.49
Black	427 / 321	1.08 (0.95, 1.23)		1.07 (0.94, 1.23)	
White	413 / 530	1.01 (0.87, 1.17)		1.00 (0.86, 1.16)	
CKD			0.30		0.48
Yes	178 / 303	1.14 (0.94, 1.38)		1.09 (0.90, 1.33)	
No	662 / 548	1.01 (0.90, 1.14)		1.01 (0.89, 1.14)	
Diabetes‡			0.59		0.41
Yes	159 / 264	1.09 (0.87, 1.36)		1.11 (0.89, 1.37)	
No	672 / 581	1.02 (0.90, 1.14)		1.00 (0.88, 1.12)	
Taking a diuretic§			0.27		0.28
Yes	268 / 290	1.13 (0.96, 1.34)		1.12 (0.95, 1.33)	
No	568 / 560	1.01 (0.89, 1.14)		1.00 (0.88, 1.13)	

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. Model 4 includes age, sex, race, geographic region of residence, income, education, alcohol consumption, current smoking, BMI, 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, SLC2A9 single-nucleotide polymorphisms, and use of antihypertensive medication, diuretics, statin, and allopurinol. * QT interval is corrected for heart rate using the following equation: QT interval + 154 × (1 − 60/heart rate). † Comparing HRs across subgroups. ‡ A total of 9 participants in the random subcohort 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 subcohort and 1 participant with incident CHD had missing data on diuretic use at baseline and were excluded from the analysis. ‖ Incident CHD includes myocardial infarction or death from CHD excluding sudden cardiac death. CHD: coronary heart disease; CKD: chronic kidney disease.

high-risk subgroups and developing preventive interventions in these populations.

In the current study, there was no statistically significant effect modification on the association of SU levels with sudden cardiac death by age, sex, 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 SU level was associated with an increased risk for sudden cardiac death among participants aged 45–64 years, and those of White race or without diabetes, but not among those aged ≥ 65 years, of Black race, or with diabetes. Older age, Black race, and diabetes are risk factors for sudden cardiac death.[2,30] Therefore, higher SU 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 SU 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 SU levels and may be confounders in observational studies.[5,33,34,35] Therefore, it has been speculated that differences in the adjustment for confounders may explain the heterogeneity in the association between SU and CHD across observational studies.[31,32] In the current study, HRs associated with SU levels were numerically higher for sudden cardiac deaths vs incident CHD excluding

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[a]
Random subcohort, n	230	361	249	
Sudden cardiac death				
Events	44	100	91	
HR (95% CI)				
Crude	1 (ref)	1.53 (1.01–2.29)	2.14 (1.40–3.26)	< 0.001
Model 1	1 (ref)	1.34 (0.88–2.03)	1.57 (1.01–2.42)	0.05
Model 2	1 (ref)	1.31 (0.85–2.00)	1.58 (1.01–2.46)	0.05
Model 3	1 (ref)	1.43 (0.91–2.26)	1.73 (1.06–2.85)	0.03
Model 4	1 (ref)	1.30 (0.78–2.17)	1.39 (0.78–2.49)	0.32
Model 4 and QT interval[b]	1 (ref)	1.30 (0.78–2.18)	1.37 (0.76–2.47)	0.35
Incident CHD[c]				
Events	174	372	305	
HR (95% CI)				
Crude	1 (ref)	1.43 (1.09–1.88)	1.81 (1.36–2.42)	< 0.001
Model 1	1 (ref)	1.32 (1.00–1.73)	1.46 (1.08–1.98)	0.02
Model 2	1 (ref)	1.27 (0.95–1.68)	1.44 (1.06–1.96)	0.03
Model 3	1 (ref)	1.25 (0.93–1.69)	1.41 (1.01–1.96)	0.06
Model 4	1 (ref)	1.16 (0.83–1.62)	1.07 (0.73–1.58)	0.84
Model 4 and QT interval[b]	1 (ref)	1.17 (0.83–1.63)	1.07 (0.72–1.57)	0.87

Model 1 adjusts for age, sex, and race. Model 2 adjusts for age, sex, race, geographic region of residence, income, and education. Model 3 adjusts for variables in Model 2 and alcohol consumption, current smoking, BMI, 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, SLC2A9 single-nucleotide polymorphisms, and use of antihypertensive medication, diuretics, statin, and allopurinol. [a] Calculated using the median serum urate level corresponding to each participant's category as the independent variable. [b] QT interval is corrected for heart rate using the following equation: QT interval + 154 × (1 − 60/heart rate). [c] Includes myocardial infarction or death from CHD excluding sudden cardiac death. CHD: coronary heart disease.

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 explain, at least in part, the heterogeneity of results in the association between SU 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 SU and CHD. In contrast, studies excluding sudden cardiac deaths from their CHD outcome definition, such 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) vs 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 residing 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, which is 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 aged ≥ 45 years. Future studies should assess the association of SU levels with sudden cardiac death in other race groups and on adults aged < 45 years. Data on

whether participants had subclinical CHD, persistently elevated SU levels, gout, monosodium urate crystals deposited in joints or other tissues, or urate overproduction were not available.

In conclusion, a higher SU 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 SU levels may be a risk factor for sudden cardiac death independently of the development of coronary atherosclerosis.

ONLINE SUPPLEMENT
Supplementary material accompanies the online version of this article.

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