



## Association of sickle cell trait with atrial fibrillation: The REGARDS cohort

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### ABSTRACT

**Background:** Sickle cell trait (SCT), sickle cell disease's (SCD) carrier status, has been recently associated with worse cardiovascular and renal outcomes. An increased prevalence of atrial fibrillation (AF) is documented in SCD patients; however, studies in individuals with SCT are lacking.

**Objectives:** To determine the association of SCT with AF.

**Methods:** Among African-American participants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study we assessed the association of SCT (by ECG or medical history) with prevalent AF using logistic regression adjusting for age, sex, income, education, history of stroke, myocardial infarction, diabetes, hypertension, and chronic kidney disease. A second evaluation was performed a mean of 9.2 years later among available participants, and the same model was used to test the association of SCT with incident AF.

**Results:** In 10,409 participants with baseline ECG data and genotyping, 778 (7.5%) had SCT and 811 (7.8%) had prevalent AF. After adjusting for age, sex, education and income, SCT was associated with AF, OR 1.32 (95% CI 1.03–1.70). The association with incident AF assessed at the second in-home visit with the same adjustments was similar; OR 1.25 (95% CI 0.77–2.03).

**Conclusions:** SCT was associated with a higher prevalence of AF and a non-significantly higher incident AF over a 9.2 year period independent of AF risk factors. SCT remained associated with prevalent AF after adjusting for potential factors on the causal pathway such as hypertension and chronic kidney disease suggesting alternate mechanisms for the increased risk.

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### Introduction

Sickle cell trait (SCT) is the heterozygous, purportedly asymptomatic carrier state for sickle cell disease (SCD) and is present in approximately 8% of African-Americans [1]. SCD profoundly affects individuals' quality of life and leads to painful vaso-occlusive crises and progressive disability leading to early death. Once thought to be a benign condition [2], SCT is associated with an increased risk of chronic kidney disease (CKD) [3,4], and other medical conditions [5–9]. Previous studies have shown no evidence to date that SCT leads to a lower life expectancy

[10,11], or stroke [12], and there are mixed data on the association with coronary artery disease [13–15]. Prior studies have not examined associations between arrhythmias such as atrial fibrillation (AF) and SCT.

AF has been documented in SCD patients in multiple studies [16–19]. In contrast to SCD, there are no similar studies documenting AF in SCT carriers. Cardiac problems in people with SCT have focused on athletes and sudden cardiac death [5,20]. We evaluated the association with SCT and AF as AF is a common condition with an increasing prevalence [21] especially as the population ages and is a risk factor for ischemic stroke and heart failure [22].

Naik et al. demonstrated an association of SCT with an increased risk of CKD in several cohorts, including the REasons for Geographic and Racial Differences in Stroke (REGARDS) study [3,4]. CKD and hypertension

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are known risk factors for AF [23], and SCT may be associated with AF by other poorly defined mechanisms beyond simply exacerbating other known risk factors. Thus we hypothesized that SCT would be associated with an increased risk of prevalent and incident AF in African-Americans.

## Methods

### Study cohort

REGARDS recruited 30,239 black and white men and women over 45 years old from 2003 to 2007, with the principal aim of identifying causes of racial and regional disparities in stroke incidence and mortality in the United States. The detailed study design has been published [24]. REGARDS recruited individuals from a commercially available list of U.S. residents. Participants were excluded if they could not speak English, had a self-reported race other than black or white, were on a waiting list for a nursing home, or had active cancer in the past year. Using a computer-assisted telephone interview, interviewers obtained demographic information and a cardiovascular medical history, including a physician diagnosis of AF. Consent was obtained initially on the telephone and subsequently in writing during an in-person evaluation 3–4 weeks later. During the visit, staff obtained blood and urine samples, medication history, and performed a resting ECG. ECGs were centrally interpreted for factors including prevalent AF. Participants were followed every 6 months by telephone for possible stroke and other outcomes [25]. A second in-home visit was performed an average of 9.2 years later among available REGARDS participants, where participants gave their health history and a second ECG was performed, and similarly interpreted for AF.

SCT status was determined by direct genotyping for rs334 using TaqMan® [26,27].

Genotyping for SCT was not performed on participants who self-reported as white. For this analysis, REGARDS participants were excluded if they did not self-identify as black, did not have stored DNA or consent for genetics research, or hemoglobin SS (SCD) or hemoglobin SC disease (a related sickling hemoglobinopathy). REGARDS was approved by the institutional review boards of all participating institutions and was conducted according to the provisions of the Declaration of Helsinki.

### Outcomes

For the cross-sectional analysis, as previously reported [28], AF was defined at baseline as ECG evidence of AF at the time of the in-home

physical exam or as a self-reported physician diagnosis of AF. For the incident AF analysis, Incident AF was defined as a self-reported physician diagnosis of AF or ECG evidence of AF in those free of AF by ECG or self-report at baseline.

### Definitions

Age was specified as age at the time of entry into the REGARDS cohort. Income was categorized as <\$20,000, \$20,000–34,999, \$35,000–74,999, or ≥\$75,000 annually, and education as less than high-school, high-school graduate, some college, and college and above. Cardiovascular disease (CVD) was defined as a self-reported physician diagnosis of prior myocardial infarction or stroke. Hypertension was defined as the use of antihypertensive medications, or a resting in-home systolic blood pressure reading of ≥140 mm Hg. Diabetes was defined as a prior self-reported physician diagnosis of diabetes, or the use of oral medications or insulin, excluding gestational diabetes. CKD was stratified into four groups (stage 0–1, 2, 3, 4+) according to the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guidelines [29] incorporating estimated glomerular filtration rate from the CKD-EPI equation [30] and urine albumin concentration.

### Statistical analysis

Baseline characteristics were compared by SCT status using chi-square analysis and *t*-tests for continuous variables. Staged logistic regression models were used to calculate odds ratios (ORs) of AF by presence of SCT. Covariates were added in three steps:

Model 1: adjusted for age, sex, income, and education

Model 2: Model 1 + body mass index, history of CVD, and diabetes

Model 3: Model 2 + CKD and hypertension

The purpose of Model 3 was to test for possible mediation of the association by CKD and hypertension, given the known association of SCT with CKD [3]. In addition to model 3, to control for population substructure, 10 principal components (PC) of genetic ancestry were generated in Eigenstrat [31] and added to Model 3. PC of genetic ancestry was measured in a case-control study and available in 67% of African-Americans. As these were not available in all individuals, we assessed the association of SCT with AF in those with PC of ancestry available. Additionally, a sensitivity analysis using electrocardiogram documented AF only was performed. Unadjusted baseline associations were also compared using Chi square analysis. All two-sided *p* values <0.05 were considered significant.

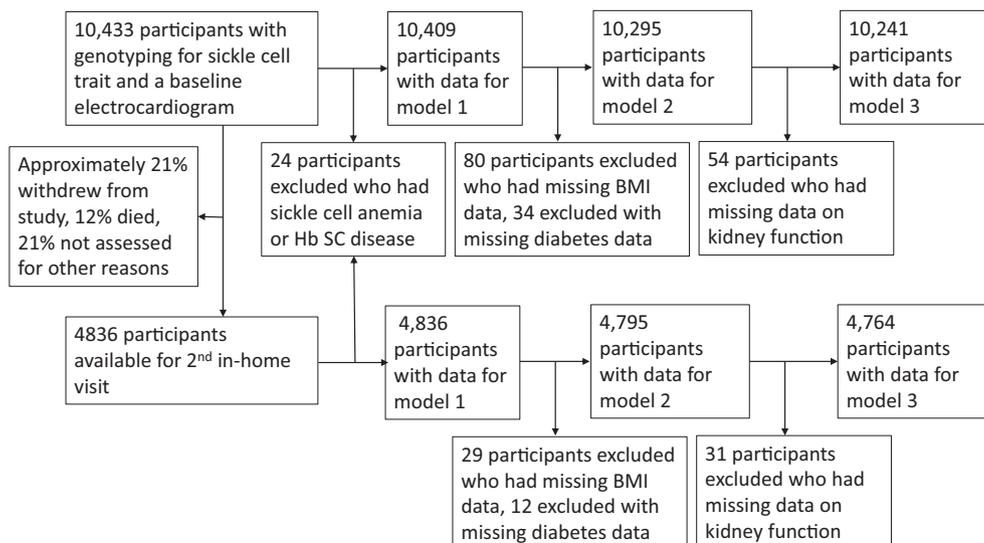


Fig. 1. Summary of participant exclusions and missing data.

The above analyses were repeated in those who had a 2nd home visit by REGARDS investigators who were free of AF at the initial visit to determine the OR of incident AF based on AF status at the second examination. Given that it is not possible to estimate the precise timing of developing AF based on ECG evidence seen on the 2nd home visit, cox proportional hazard models could not be used.

All analysis was performed using STATA v 14.1 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.)

## Results

There were 10,433 African-American REGARDS participants who had genotyping for SCT as well as ECG and complete medical history (83% of the 12,514 African Americans in the study). Ten individuals homozygous for hemoglobin SS (sickle cell anemia) (0.09%) and 14 (0.13%) with Hemoglobin SC disease were excluded from the analysis. There were 778 participants with SCT (7.5%). Fig. 1 outlines how many participants were excluded or had missing data at each stage of the analysis. Overall, 811 (7.8%) of these participants had either a medical history and/or ECG evidence of AF at baseline. Table 1 summarizes the baseline characteristics of participants with and without SCT. The mean baseline age was 64 years (range 45–96). Twice as many participants with SCT had stage 4 kidney disease by KDIGO criteria (2.9% vs 1.4% for people with and without SCT respectively,  $p = 0.001$ ).

Table 2 outlines the main results of the cross sectional analysis. Overall, SCT was associated with an approximately 1.3-fold increased odds of AF in all models (lower limit of the 95% CI >1.0). In Model 1 (the demographic model) the OR (95% CI) was 1.32 (1.03–1.70). Further adjustment for AF risk factors (Model 2) or for CKD and hypertension (Model 3) did not attenuate or strengthen the association of SCT with AF.

At the second in-home visit, an average 9.2 years after baseline, 4836 participants with baseline known AF status and genotyping had an ECG. There was a similar association with incident AF and SCT as seen in prevalent AF with the OR in model 3 being 1.25 but the 95% confidence intervals were wider and crossed 1 (0.77, 2.03) (Table 3). In a sensitivity analysis classifying prevalent AF as AF present at either REGARDS exam, the association of SCT with AF was stronger than in analysis from the baseline visit, with an OR of 1.39 (1.01, 1.92) for model 3 (Table 4). In this analysis, the total prevalence of ever having reported a history of AF or ever having ECG evidence of AF in the participants available for a 2nd in-home visit was slightly higher than the main cohort, at 10.1%.

In an additional sensitivity analysis of the odds of prevalence of ECG evidence of AF, the association of SCT with AF was greater, with ORs of 1.7–1.8 in all three models, while the association was weaker for AF defined by history alone (OR of 1.26 in all three models), but in both instances the 95% CIs included 1.0. When we restricted the analysis to individuals with PCs of genetic ancestry available, there was no association of SCT with AF in this subset (OR 1.01; 95% CI 0.71, 1.44), as such we

**Table 1**

Baseline characteristics of African American REGARDS participants by sickle cell trait status.

	No sickle cell trait	Sickle cell trait	p-Value
Mean age (SD)	64 (9)	63.5 (9)	0.14
Female	61%	64%	0.10
Income < \$20,00/year	38.9%	40.9%	0.28
Less than high school education	19.7%	19.2%	0.84
Mean BMI (SD)	30.8 (6.7)	30.7 (6.8)	0.72
History of cardiovascular disease	13.7%	13.5%	0.85
Diabetes	30.3%	32.2%	0.25
Stage 4 or higher chronic kidney disease	1.4%	2.9%	0.001
Hypertension	66%	63%	0.07
Mean systolic blood pressure (SD)	131 (17)	132 (17.7)	0.26
Atrial fibrillation	7.3%	9.5%	0.02

SD = standard deviation.

**Table 2**

Odds ratios (ORs) and 95% confidence intervals (CIs) of prevalent atrial fibrillation with sickle cell trait.

	N	N with prevalent AF	OR (95% CI)
Model 1	10,409	811	1.32 (1.03, 1.70)
Model 2	10,295	797	1.33 (1.03, 1.71)
Model 3	10,241	793	1.32 (1.02, 1.70)

Model 1: adjustment for age, sex, income and education. Model 2: Model 1 + adjustment for body mass index, cardiovascular disease history, diabetes. Model 3: Model 2 + adjustment for chronic kidney disease and hypertension.

did not further pursue adjusting for PC of genetic ancestry in additional models.

## Discussion

The main findings of this study were a 32% higher odds of prevalent AF in African Americans with SCT after adjusting for age, gender, education, income, cardiovascular disease. Additional adjustment for CKD or hypertension did not attenuate this association. There was also a 26% higher odds of incident AF, though this finding was not statistically significant.

To our knowledge, the association of SCT with AF has not been reported before. We had hypothesized that SCT could be associated with AF by acting through the intermediaries of CKD [23] which in turn may be associated with hypertension [32]. Arguing against CKD and hypertension mediating the association of SCT with AF is that after adjusting for CKD, hypertension, and known cardiovascular disease, the association of SCT with AF did not meaningfully change. These data are confusing but consistent with the surprising but robust recent epidemiological research demonstrating that SCT was not independently associated with risk of ischemic stroke among African Americans in the United States [12], even though ischemic stroke is associated with CKD and SCT is associated with risk of CKD.

While we have previously shown the substantial accuracy of self-reported AF [28], a strength of this study include the ability to capture AF data by both medical history and ECG. Medical history reported by REGARDS participants has also been validated by comparing it with Medicare claims data in other cardiovascular diseases [33] and it provides a better capture of paroxysmal or persistent AF, conditions which are still associated with thromboembolism and that require anticoagulation [34] as well as rhythm-controlled AF, and reported history of AF has been found to be a significant risk factor in developing ischemic stroke [28]. Furthermore, when a more strict definition of AF by ECG criteria alone was used, the direction of the association was similar with a greater magnitude. Additionally, the fact that there was a similar prevalent and incident association is helpful in that it provides an internal replication of results.

This study has several limitations. While data on prevalent AF at the time of entry into the study is robust, but the data on incident AF was less so: medical histories and a second in-home ECG were available from only about half of the participants, with approximately 12% dying between visits, 21% withdrawing from the study, and 21% not assessed for other reasons. The number of participants with incident AF was relatively small so our power was limited. Finally, when we

**Table 3**

Odds ratios (ORs) and 95% confidence intervals (CIs) of incident AF over 9.2 years by sickle cell trait.

	N	N with incident AF	OR (95% CI)
Model 1	4836	208	1.25 (0.77, 2.03)
Model 2	4795	206	1.27 (0.78, 2.07)
Model 3	4764	206	1.28 (0.78, 2.08)

Model 1: adjustment for age, sex, income and education. Model 2: Model 1 + adjustment for body mass index, cardiovascular disease history, diabetes. Model 3: Model 2 + adjustment for chronic kidney disease and hypertension.

**Table 4**

Odds ratios (ORs) and 95% confidence intervals (CIs) of cross-sectional analysis of all prevalent AF noted at 2nd in-home visit by sickle cell trait.

	N	N with prevalent AF	OR (95% CI)
Model 1	4836	490	1.43 (1.05, 1.97)
Model 2	4795	483	1.41 (1.03, 1.94)
Model 3	4764	482	1.39 (1.01, 1.92)

Model 1: adjustment for age, sex, income and education. Model 2: Model 1 + adjustment for body mass index, cardiovascular disease history, diabetes. Model 3: Model 2 + adjustment for chronic kidney disease and hypertension.

looked at the subset of participants with PC of genetic ancestry available there was no association between SCT and AF. PC data was available in only a subset of the cohort, and as there were significantly more participants with AF in the subset that did not have PC data available, it appeared to be non-random, rather than a simple loss of power. In theory, SCT could be a marker of another nearby mutation and adjusting for population substructure may have attenuated this association. While possible, this would be unlikely due to the known pathologic implications of SCT and SCD as well as lack of attenuation of SCT with adverse outcomes after adjusting for PC of genetic ancestry for other diseases in other populations [3,12]. Finally, as genotyping for SCT was limited to African American participants in REGARDS, these findings may not be generalizable to people of other races or living in other regions.

## Conclusions

SCT was associated with AF independent of risk factors for AF. The mechanism does not appear to act through CKD and hypertension, known risk factors for AF and conclusions regarding a proposed mechanism cannot be drawn from the data. Given the association of HTN and CKD with AF, these data support the need to better understand the clinical consequences of SCT as well as other polymorphisms which may impact the association of SCT with cardiovascular diseases. These data add AF to the potential diseases associated with SCT and demonstrate the keen need to understand the health consequences of SCT as it seems less and less to be an asymptomatic carrier state of a common genetic disease.

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## Disclosures

No relevant disclosures.

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