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Investigation of selection bias in the association of race with prevalent atrial fibrillation in a national cohort study: REasons for Geographic And Racial Differences in Stroke (REGARDS)

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Abstract

PURPOSE—Atrial fibrillation (AF) is diagnosed more commonly in whites than blacks in the US. In epidemiologic studies, selection bias could induce a non-causal positive association of white race with prevalent AF if voluntary enrollment were influenced by *both* race and AF status. We investigated whether non-random enrollment biased the association of race with prevalent self-reported AF in the US-based REasons for Geographic And Racial Differences in Stroke Study (REGARDS).

METHODS—REGARDS had a two-stage enrollment process, allowing us to compare 30,183 fully enrolled REGARDS participants with 12,828 people who completed the first-stage telephone survey but did not complete the second-stage in-home visit to finalize their REGARDS enrollment (telephone-only participants).

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RESULTS—REGARDS enrollment was higher among whites (77.1%) than among blacks (62.3%), but did not differ by self-reported AF status. The age-, sex-, income-, education, and health-adjusted prevalence of AF was 8.45% in whites and 5.86% in blacks. The adjusted white/black prevalence ratio of self-reported AF was 1.43 (95% confidence interval: 1.32, 1.56) among REGARDS participants and 1.38 (1.22, 1.55) among telephone-only participants.

CONCLUSIONS—These findings suggest that selection bias is not a viable explanation for the higher prevalence of self-reported AF among whites in population studies such as REGARDS.

Keywords

selection bias; cohort study; atrial fibrillation; race

INTRODUCTION

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia, becomes increasingly common with age, and carries increased risks for heart failure, stroke, cognitive decline, hospitalization, and death (1). Unlike most cardiovascular conditions, which occur more commonly in blacks than in whites in the United States, AF is diagnosed more commonly in whites than in blacks (2–5). This occurs in a variety of settings including integrated health systems (6–8) and population-based or community-based epidemiologic studies (9–14). AF occurring more in whites is considered paradoxical because blacks have higher prevalence of many risk factors for AF including hypertension, diabetes, obesity, chronic kidney disease, heart failure, and cigarette smoking (14,15). Some evidence suggests that higher occurrence of AF in whites may have a biological basis, for example whites tend to have larger left atria than blacks (16), and among blacks AF risk is associated with genetically-defined European ancestry (17). However, the association of white race with higher occurrence of AF could also potentially reflect biases arising from racial differences in data collection (information bias) or racial differences in study participation (selection bias).

Information bias could induce a non-causal positive association of white race with AF if whites were more frequently or more carefully examined for AF, leading to more complete detection and diagnosis of AF among whites (4). However, information bias is unlikely to explain the association of white race with AF in studies conducted in integrated health systems or in population-based or community-based epidemiologic studies. In integrated health systems, information bias is unlikely because health system enrollees would all have, at least in principle, equal access to the same clinical care and diagnostic services (6–8). Evidence from the Veterans Health Administration suggests these resources are *not* disproportionately accessed by whites compared with blacks (7). In epidemiologic studies, information bias may occur when AF is determined by self-report, if whites are more likely than blacks to correctly recall and report their physician diagnosis of AF (18). This could occur if, for example, whites had higher health literacy or better relationships with their physicians than blacks. However, other data collection methods to determine AF status in epidemiologic studies are standardized for all study participants, including electrocardiography, medical record review, and health insurance database linkage. These

methods also yield higher AF prevalence among whites, making information bias an unlikely explanation (9–14).

Selection bias could induce a non-causal positive association of white race with AF if selection of participants into studies was a function of race and, simultaneously, a function of AF status. As described in the causal inference literature, two factors that each separately strongly influence selection of participants into research studies will tend to be associated among study participants, even if they are not associated in the underlying population from which participants were selected (19–21). For example, if whites were more likely than blacks to agree to participate in a study, and independently, people with prevalent AF were *less* likely than people without prevalent AF to agree to participate in that same study, then the association of white race with prevalent AF observed among the study participants could be biased in a positive direction.

In studies conducted in integrated health systems, selection bias is unlikely because individuals eligible for enrollment in the health system would decide whether to enroll without regard to their own AF status (6–8). For example, evidence from the Kaiser system indicates that history of hypertension and diabetes among enrollees is fairly similar to that of non-enrollees, which suggests that other chronic diseases like AF would be unlikely to influence enrollment (22). Health system enrollment decisions among eligible individuals could differ by race due to racial differences in trusting health care or doctors. However, Kaiser data also show that whites are *not* over-represented among enrollees compared with blacks, relative to the underlying population (22,23). This makes selection bias an unlikely explanation for the association of white race with AF observed in integrated health systems.

However, selection bias *is* a concern in population-based or community-based epidemiologic studies with voluntary enrollment, because whites tend to enroll in such studies more readily than blacks (24,25), *and* people free of chronic diseases tend to enroll more readily than people with a history of chronic diseases (25,26). If study participation was non-random with respect to race, and simultaneously, non-random with respect to chronic disease status, the observed associations of race with chronic conditions, including prevalent AF, could be biased among enrolled participants (19–21). Because voluntary epidemiologic studies play an important role in identifying associations of social, psychosocial, and behavioral factors with AF, this potential selection bias warrants investigation.

The purpose of the present study was to investigate whether non-random study enrollment biased the association of white race with prevalent self-reported AF observed at baseline among participants in a population-based epidemiologic study in the United States, REasons for Geographic And Racial Difference in Stroke (REGARDS) (27). As previously reported, baseline prevalence of self-reported physician diagnosis of AF in REGARDS participants was significantly higher in whites than in blacks (10). To determine whether non-random study enrollment influenced this observed racial difference in prevalence, ideally we would compare the distributions of race and prevalent self-reported AF in REGARDS participants versus the underlying population of people eligible to participate in REGARDS. However, race and AF status are not available from the underlying population, rendering a direct comparison impossible. Instead, we compared REGARDS participants with a group of

people who were invited to join REGARDS and initially agreed to participate and reported their race and medical history by telephone, but who ultimately did not participate in REGARDS. During REGARDS enrollment, In-home assessments were required to be performed on Monday through Thursday mornings, to allow fasting blood samples to be collected and shipped to the central lab during weekdays. Due to these scheduling constraints and perhaps other reasons, not all who completed the telephone survey were able to complete the in-home component of the study. As such, those who failed to complete the required in-home study visit never finalized their enrollment in REGARDS. These people are referred to hereafter as “telephone-only participants.” In contrast, those who completed the in-home study visit are referred to as “REGARDS participants.” We considered REGARDS participants a more-selected group and telephone-only participants a less-selected group, relative to the underlying population. We compared the distributions of race and prevalent self-reported AF in REGARDS participants versus telephone-only participants to investigate selection bias due to non-random study enrollment following completion of the telephone survey.

MATERIALS AND METHODS

Study design, setting, and participants

This is a cross-sectional analysis of baseline data from REGARDS. From 2003–2007, REGARDS enrolled black and white men and women aged 45 and older from all 48 contiguous United States using a two-stage baseline data collection design (27). A nationwide list stratified by age, sex, race, and geographic region was obtained from a commercially available source (Gensys, Inc.). Potentially eligible households were contacted first by letter, then by phone. When a household was contacted by phone, household members were enumerated, and one eligible member of the household was selected to participate in the study. In the first stage, an eligible participant completed the telephone survey in which they answered questions about their demographic characteristics and medical history. In the second stage, after the telephone survey, a participant finalized enrollment in REGARDS by completing the in-home visit, which included various physical measurements and additional questionnaires. Telephone-only participants completed the first stage but not the second stage. Institutional review boards of the collaborating institutions approved the REGARDS study protocol. Verbal informed consent was obtained during the telephone survey and written informed consent during the in-home visit. Analyzing differences in the characteristics of in-home visit completers vs telephone-only participants was anticipated when the REGARDS study was designed (27).

Data collection

In the telephone survey, participants self-reported their demographic characteristics including age, sex, race, annual household income, and education; their perceived general health; and their medical history including AF, stroke, myocardial infarction, heart failure symptoms, hypertension, dyslipidemia, diabetes, and kidney disease. History of AF was determined by the question “has a doctor or other health professional ever told you that you had atrial fibrillation?” Participants who answered “I don’t know” to a medical history question were coded as having a missing response to that question.

Statistical analysis

The goal of the analysis was to determine whether in-home visit completion differed by both race and AF status reported in the telephone survey, such that the apparent association of race with prevalent self-reported AF among REGARDS participants would be biased. We tabulated participant characteristics overall, by in-home visit completion status, by self-reported AF status, and by race. We calculated race-specific prevalence of self-reported AF among all participants, among REGARDS participants, and among telephone-only participants, using predicted probabilities from logistic regression, unadjusted and adjusted for age, sex, income, education, and perceived general health (Stata *adjprop* command). We calculated prevalence ratios and 95% confidence intervals of self-reported AF for whites vs. blacks among all participants, among REGARDS participants, and among telephone-only participants, using generalized linear models with a log link for the binomial family, unadjusted and adjusted for age, sex, income, education, and perceived general health (Stata *binreg* command with *rr* option). We tested for equality of prevalence ratios in REGARDS participants vs. telephone-only participants by including in-home visit completion status and a multiplicative interaction of in-home visit completion status with race in the model and testing whether the interaction term's coefficient was significantly different from zero. Variables in our analysis had missing values in 1% of participants, except income, which had missing values in 14%. To address these missing data we used multiple imputation by chained equations to create five imputed datasets, analyzed the imputed datasets, and combined the results using Rubin's rules (28,29).

RESULTS

Of 43,067 eligible people who completed the REGARDS baseline telephone survey, 30,239 (70%) went on to complete the REGARDS baseline in-home visit, thereby finalizing their enrollment as REGARDS participants. The remaining 12,828 (30%) did not complete the in-home visit and became telephone-only participants. We excluded 56 REGARDS participants due to anomalous data, retaining 30,183 REGARDS participants and 43,011 total participants for analyses.

Participant characteristics are shown in Table 1. Compared with telephone-only participants, REGARDS participants tended to be younger, men, and white, with higher income, education, and perceived general health, and similar prevalence of several self-reported cardiovascular diseases. There were a few differences in cardiovascular disease risk factors, with hypertension, diabetes, and kidney disease being more common among telephone-only participants, and dyslipidemia being more common among REGARDS participants. Compared with participants who did not self-report AF, participants who self-reported AF tended to be older, women, white, with lower income, education, and perceived general health, and higher prevalence of cardiovascular diseases and risk factors. Compared with black participants, white participants tended to be older, men, with higher income, education, and perceived general health, and lower prevalence of cardiovascular diseases and risk factors, except for atrial fibrillation, myocardial infarction, and dyslipidemia.

Our results of study participation by self-reported AF status and by race, and of the association of race with prevalent AF, are shown in Table 2. In-home visit completion was

70.2% overall, and was higher among whites (77.1%) than among blacks (62.3%), but was similar among participants who self-reported AF (70.6%) and participants who did not self-report AF (70.1%). Age-, sex-, income-, education-, and health-adjusted prevalence of self-reported AF was about 2.7 percentage points higher in whites than in blacks among REGARDS participants, and about 2.3 percentage points higher in whites than in blacks among telephone-only participants. White/black prevalence ratios and 95% confidence intervals of self-reported AF calculated among REGARDS participants were similar to those calculated among telephone-only participants. Among REGARDS participants, adjusted AF prevalence was about 43% higher in whites than in blacks (95% CI: 32% to 56% higher). Among telephone-only participants, adjusted AF prevalence was about 38% higher in whites than in blacks (95% CI: 22% to 55% higher). Additional adjustment for cardiovascular diseases and risk factors did not substantially alter the results (data not shown).

DISCUSSION

In REGARDS, a nationwide study of white and black adults, we observed higher prevalence of self-reported AF in whites compared with blacks. For selection bias to have influenced this observed association, study participation would have to have been a function of *both* race and self-reported AF status (19–21). We found that whites who completed the telephone survey were much more likely to participate in REGARDS than blacks who completed the telephone survey, indicating that the first condition necessary for selection bias was present. However, we also found that self-reported AF status was *not* related to REGARDS participation among those who completed the telephone survey, indicating that the second condition necessary for selection bias was absent. Therefore, we conclude that participant self-selection, inherent in the process of enrolling volunteers for epidemiologic cohort studies, is not a viable explanation for the higher prevalence of self-reported AF observed among whites in REGARDS.

The two-stage baseline data collection design of REGARDS was a key feature that made our analysis of selection bias possible, by enabling a comparison of REGARDS participants with telephone-only participants – people who were eligible to join REGARDS and reported their race and AF status. In the past, a similar strategy was used in the Atherosclerosis Risk in Communities (ARIC) study to assess racial differences in study participation and baseline cardiovascular health and disease status, by comparing ARIC participants with people who were eligible to join ARIC (25). In ARIC, participation appeared to be jointly affected by race *and* cardiovascular disease status. Whites were more likely to participate in ARIC than blacks. Among whites, self-reported history of myocardial infarction, stroke, or diabetes was associated with *lower* ARIC participation; but among blacks, self-reported history of those diseases was associated with *higher* ARIC participation. Thus there was some evidence in ARIC that the association of race with baseline myocardial infarction, stroke, or diabetes could have been influenced by selection bias (25). Unfortunately, the ARIC report did not include AF, whereas we focused specifically on AF. In our study, the prevalence of self-reported AF, myocardial infarction, stroke, and heart failure symptoms were all similar for REGARDS participants and telephone-only participants within each race. Thus, in contrast to ARIC, the REGARDS data did not indicate evidence for selection bias. To our knowledge we are the first to use data from a two-stage enrollment and data collection process in a

population-based epidemiologic study to assess whether selection bias might influence the association of white race with higher prevalence of AF, so consistently observed in epidemiologic studies.

Strengths of our study include the large national sample and high proportion of blacks. Our study also has limitations. First, we compared REGARDS participants with telephone-only participants, rather than comparing REGARDS participants with the underlying eligible population, which was blacks and whites aged 45 and above in the United States. However, we believe characteristics of the underlying eligible population may be more accurately represented by telephone-only participants than by REGARDS participants who completed the in-home visit. The reason we are willing to make this assumption is that completing the telephone survey would require less disruption of day-to-day activities than completing the in-home visit, and thus would not likely be as prone to self-selection as the in-home visit. We lack data to empirically verify our assumption. Using telephone-only participants may have limited our ability to rule out selection bias, relative to using the ideal comparison group, a random sample of the underlying population. However, comparing a more-selected group (REGARDS participants) with a less-selected group (telephone-only participants) yielded results suggesting that selection bias is unlikely. Second, we did not verify self-reported AF by medical record review. An analysis of the validity of self-reported AF would enrich our investigation, but the necessary medical records were not available for REGARDS participants or for telephone-only participants. However, prior work in REGARDS has shown self-reported AF to be strongly associated with incident stroke, and stroke risk prediction models function equally well with inputs of self-reported AF or electrocardiogram-detected AF (30). The observed association of self-reported AF with stroke risk mitigates concerns about the validity of self-reported AF, but does not rule out the possibility of misclassified AF status. Although our study is subject to the limitations described above, which are not remediable, we have used the available information in REGARDS to the best of our ability to investigate the possibility of selection bias, finding no support for such bias.

White-black racial differences in AF have been observed not only in REGARDS (10,18), but also in other biracial epidemiologic cohort studies including ARIC (11,31), the Cardiovascular Health Study (14,32,33), the Southern Community Cohort Study (13), and others (9,12). Like REGARDS, these other studies enrolled volunteer participants and have a potential for selection bias due to non-random study enrollment. Because whites are more likely to participate than blacks (24,25), if AF status were also a strong determinant of participation in these cohorts, observations of racial differences in AF could be biased. Fortunately, we found no evidence of such a bias in REGARDS, which is reassuring and may apply to the other cohorts as well. Our results pertain to prevalent AF at baseline, but may not apply to incident AF ascertained during cohort follow-up. Selection bias in the association of race with incident AF could occur if loss to follow-up were a function of both AF incidence and race, but this was beyond the scope of our present study.

AF is more prevalent in whites than in blacks, not only in voluntary epidemiologic studies and integrated health systems that cover large general populations, but also in studies based on national health care utilization and cause of death statistics (34–36), health care claims

data from Medicare beneficiaries (37), and numerous studies of specific clinical populations (38–45). The consistency of this finding across many different types of studies and populations suggests that the association is unlikely to be an artifact of methodological limitations, and points us toward the likelihood that biological explanations may eventually resolve the race and AF paradox.

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ABBREVIATIONS

AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities Study
REGARDS	REasons for Geographic And Racial Difference in Stroke Study

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Table 1

Baseline Characteristics of REGARDS Participants, United States, 2004–2007.

Characteristic ^a	All N = 43,011	REGARDS participants N = 30,183	Telephone-only participants N = 12,828	Self-reporting AF N = 3,512	Not self-reporting AF N = 39,499	White N = 22,920	Black N = 20,091
Age, y	65.0 (9.8)	64.8 (9.4)	65.2 (10.5)	67.3 (9.8)	64.8 (9.7)	65.4 (9.8)	64.4 (9.7)
Male	18,589 (43.2)	13,551 (44.9)	5,038 (39.3)	1,464 (41.7)	17,125 (43.4)	11,061 (48.3)	7,528 (37.5)
White	22,920 (53.3)	17,669 (58.5)	5,251 (40.9)	2,038 (58.0)	20,882 (52.9)	22,920 (100.0)	0 (0.0)
Income							
<\$20,000/y	10,359 (24.1)	6,517 (21.6)	3,842 (29.9)	1,040 (29.6)	9,319 (23.6)	3,515 (15.3)	6,844 (34.1)
\$20,000–\$34,999/y	12,129 (28.2)	8,388 (27.8)	3,740 (29.2)	1,048 (29.8)	11,081 (28.1)	6,045 (26.4)	6,084 (30.3)
\$35,000–\$74,999/y	13,655 (31.7)	10,019 (33.2)	3,637 (28.4)	1,010 (28.7)	12,646 (32.0)	8,347 (36.4)	5,308 (26.4)
\$75,000/y	6,868 (16.0)	5,259 (17.4)	1,609 (12.5)	415 (11.8)	6,543 (16.3)	5,012 (21.9)	1,856 (9.2)
Education							
< High school	6,602 (15.3)	3,797 (12.6)	2,805 (21.9)	608 (17.3)	5,994 (15.2)	1,966 (8.6)	4,635 (23.1)
High school graduate	11,559 (26.9)	7,813 (25.9)	3,746 (29.2)	980 (27.9)	10,580 (26.8)	5,904 (25.8)	5,655 (28.1)
Some college	11,201 (26.0)	8,096 (26.8)	3,105 (24.2)	914 (26.0)	10,288 (26.0)	6,185 (27.0)	5,017 (25.0)
College graduate	13,649 (31.7)	10,477 (34.7)	3,172 (24.7)	1,011 (28.8)	12,638 (32.0)	8,865 (38.7)	4,784 (23.8)
Perceived general health							
Excellent	6,457 (15.0)	4,813 (15.9)	1,644 (12.8)	236 (6.7)	6,221 (15.7)	4,489 (19.6)	1,968 (9.8)
Very good	12,601 (29.3)	9,183 (30.4)	3,418 (26.6)	741 (21.1)	11,861 (30.0)	7,914 (34.5)	4,687 (23.3)
Good	15,333 (35.6)	10,600 (35.1)	4,733 (36.9)	1,255 (35.7)	14,078 (35.6)	7,248 (31.6)	8,085 (40.2)
Fair	6,933 (16.1)	4,521 (15.0)	2,412 (18.8)	893 (25.4)	6,039 (15.3)	2,523 (11.0)	4,410 (21.9)
Poor	1,687 (3.9)	1,066 (3.5)	621 (4.8)	387 (11.0)	1,300 (3.3)	746 (3.3)	941 (4.7)
Self-reported medical history							
AF	3,512 (8.2)	2,478 (8.2)	1,034 (8.1)	3,512 (100.0)	0 (0.0)	2,038 (8.9)	1,474 (7.3)
Stroke	2,834 (6.6)	1,941 (6.4)	893 (7.0)	423 (12.1)	2,410 (6.1)	1,248 (5.4)	1,586 (7.9)
Myocardial infarction	3,658 (8.5)	2,573 (8.5)	1,085 (8.5)	740 (21.1)	2,919 (7.4)	2,132 (9.3)	1,526 (7.6)
Heart failure symptoms							
Orthopnea	5,086 (11.8)	3,526 (11.7)	1,561 (12.2)	934 (26.6)	4,152 (10.5)	2,335 (10.2)	2,751 (13.7)
Paroxysmal nocturnal dyspnea	4,029 (9.4)	2,823 (9.4)	1,206 (9.4)	742 (21.1)	3,287 (8.3)	2,016 (8.8)	2,013 (10.0)
Hypertension	25,537 (59.4)	17,652 (58.5)	7,885 (61.5)	2,545 (72.5)	22,992 (58.2)	11,561 (50.4)	13,976 (69.6)
Dyslipidemia	21,864 (50.8)	15,844 (52.5)	6,019 (46.9)	2,126 (60.5)	19,738 (50.0)	12,250 (53.4)	9,614 (47.9)

Characteristic ^a	All N = 43,011	REGARDS participants N = 30,183	Telephone-only participants N = 12,828	Self-reporting AF N = 3,512	Not self-reporting AF N = 39,499	White N = 22,920	Black N = 20,091
Diabetes	10,136 (23.6)	6,840 (22.7)	3,296 (25.7)	1,031 (29.3)	9,105 (23.1)	3,944 (17.2)	6,191 (30.8)
Kidney disease	845 (2.0)	552 (1.8)	293 (2.3)	141 (4.0)	704 (1.8)	340 (1.5)	505 (2.5)

Abbreviation: AF, atrial fibrillation; REGARDS, REasons for Geographic And Racial Differences in Stroke Study.

^aStatistics are N (column %) except for age statistics which are mean (standard deviation). Due to rounding, sums of subgroup counts may differ slightly from totals and percentages may differ slightly from subgroup counts divided by totals.

Table 2
Race-specific prevalence of self-reported AF and white/black prevalence ratios, REGARDS, United States, 2004–2007.

Participant status and race	N (%) ^a			Unadjusted		Adjusted ^b	
	All	Self-reporting AF	Not self-reporting AF	Prevalence of self-reported AF	White/black prevalence ratio ^c	Prevalence of self-reported AF	White/black prevalence ratio ^c
All participants							
All	43,011	3,512	39,499				
White	22,920	2,038	20,882	8.89%	1.21	8.45%	1.42
Black	20,091	1,474	18,617	7.34%		5.86%	
REGARDS participants							
All	30,183 (70.2)	2,478 (70.6)	27,705 (70.1)				
White	17,669 (77.1)	1,561 (76.6)	16,108 (77.1)	8.83%	1.21	8.58%	1.43
Black	12,514 (62.3)	917 (62.2)	11,597 (62.3)	7.33%		5.92%	
Telephone-only participants							
All	12,828 (29.8)	1,034 (29.4)	11,794 (29.9)				
White	5,251 (22.9)	477 (23.4)	4,774 (22.9)	9.08%	1.23	8.02%	1.38
Black	7,577 (37.7)	558 (37.8)	7,019 (37.7)	7.35%		5.74%	

Abbreviations: AF, atrial fibrillation; CI, confidence interval; REGARDS, REasons for Geographic And Racial Differences in Stroke Study.

^aPercentage in each participant status, race, and self-reported AF category is [NREGARDS participants/Nall participants] or [Ntelephone-only participants/Nall participants]. Due to rounding, sums of subgroup counts may differ slightly from totals and percentages may differ slightly from subgroup counts divided by totals.

^bAdjusted for age, sex, income category, education category, and perceived general health.

^cTests for equality of prevalence ratios in REGARDS participants vs. telephone-only participants: Unadjusted: P = 0.76; Adjusted: P = 0.57.