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Abhishek Bose, *Wake Forest School of Medicine*
Wesley T. O'Neal, *Emory University*
Aleena Bennett, *University of Alabama Birmingham*
Suzanne Judd, *Emory University*
Waqas T. Qureshi, *Wake Forest School of Medicine*
Xuemei Sui, *University of South Carolina*
Virginia J. Howard, *University of Alabama Birmingham*
George Howard, *University of Alabama Birmingham*
Elsayed Z. Soliman, *Wake Forest School of Medicine*

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Relation between Estimated Cardiorespiratory Fitness and Atrial Fibrillation (from the REasons for Geographic And Racial Differences in Stroke Study)

Abhishek Bose, MD1, Wesley T. O’Neal, MD2, Aleena Bennett, MS3, Suzanne E. Judd, PhD3, Waqas T. Qureshi, MD MS4, Xuemei Sui, MD, PhD5, Virginia J. Howard, PhD5, George Howard, DrPH3, Elsayed Z. Soliman, MD4,7

1Department of Medicine, Section on Hospital Medicine, Wake Forest School of Medicine, Winston-Salem, NC
2Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA
3Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, AL
4Department of Medicine, Section on Cardiology, Wake Forest School of Medicine, Winston-Salem, NC
5Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC
6Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL
7Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC

Abstract

Estimated cardiorespiratory fitness (e-CRF) based on readily available clinical and self-reported data is a promising alternative to the costly traditional assessment of CRF using exercise equipment but its role as a predictor for incident atrial fibrillation (AF) is unclear. This study included 10,126 participants (54.5% women, 35% African American, mean age 63.2 years) from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study who were free of AF at baseline. Baseline (2003–2007) e-CRF was determined using a previously validated non-exercise algorithm. Incident AF cases were identified at a follow-up examination by electrocardiogram and self-reported medical history of prior physician diagnosis. After a median follow-up of 9.4 years, 906 (8.9%) participants developed AF. In a multivariable logistic regression model adjusted for socio-demographics and baseline cardiovascular disease (CVD) risk

Corresponding Author: Elsayed Z Soliman MD, MSc, MS, Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, esoliman@wakehealth.edu, Phone: (336)716-8632; Fax: (336)716-0834.

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factors as well as incident coronary heart disease, heart failure, and stroke, each 1-MET increase in e-CRF was associated with a 5% lower risk of AF development (OR (95% CI) 0.95 (0.92, 0.99); p=0.0129). This association was stronger in women (OR (95% CI) 0.85 (0.79, 0.92) than men (OR (95% CI) 0.88 (0.84, 0.93), interaction p-value=0.05. No significant interactions by age, race, history of CVD, or physical limitations were observed. In conclusion, e-CRF using a non-exercise algorithm is a useful predictor of incident AF, which is consistent with prior reports using traditional CRF. This suggests that e-CRF using non-exercise algorithms may serve as a useful alternative to CRF measured by costly and time consuming exercise testing.

Keywords
Estimated Cardiorespiratory Fitness; Atrial Fibrillation; REGARDS Study

Introduction
Poor cardiorespiratory fitness (CRF) measured in metabolic equivalent of task (MET) is a strong predictor of cardiovascular disease (CVD) including AF. (1–5) However the need for specialized exercise equipment and trained personnel have been obstacles for wide use of CRF in risk stratification and identifying individuals at risk for poor outcomes. A novel method for estimating CRF using readily available clinical and self-reported data including age, sex, body mass index, heart rate, physical activity, waist circumference and smoking status has recently been developed (6). Estimated CRF (e-CRF) is a promising alternative to the need for expensive exercise testing but its role as a predictor of incident AF is unclear. Therefore, we examined the association between e-CRF and AF in the REasons for Geographic And Racial Differences in Stroke (REGARDS), one of the largest biracial population studies in the United States.

Methods
The methods and design for the REGARDS study have been published previously.(7) The primary aim of the REGARDS study was to elucidate the mechanisms behind black-white and regional differences in stroke mortality. Participants were recruited from the continental US with oversampling from blacks and the stroke belt (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) between January 2003 to October 2007 using commercially available postal and telephone records. Following verbal consent, the initial assessment involved computer assisted telephone interview (CATI) followed by an in-home physical examination. During the telephone interview demographic information and medical history was obtained, while during the in-home exam, blood and urine sample collection, an electrocardiogram, medication information, height and weight measurements, and blood pressure recording were performed. All participants provided written informed consent and the study was approved by the Institutional Review Boards of all participating universities.

The final cohort included 30,239 participants with baseline data. Approximately 10 years after the baseline assessment, 15,521 participants completed a 2nd examination similar to the baseline visit. Of those who completed the 2nd assessment visit, we excluded participants
with baseline AF, body mass index (BMI) <18.5 and missing variables for e-CRF calculation or covariates leaving a final sample of 10,126 participants.

A non-exercise based sex-specific algorithm was used to calculate e-CRF as follows: e-CRF (women) = 14.17873 + (Age × 0.1159) – (Age² × 0.0017) – (Body mass index × 0.1534) – (Waist circumference × 0.0085) – (Resting heart rate × 0.0364) + (Active × 0.5987) – (Smoker × 0.2994) or e-CRF (men) = 21.2870 + (Age × 0.1654) – (Age² × 0.0023) – (Body mass index × 0.2318) – (Waist circumference × 0.0337) – (Resting heart rate × 0.0390) + (Active × 0.6351) – (Smoker × 0.4263). (6) Active was defined as someone who exercises 4 times or more per week based on a prior REGARDS paper. (8) Smoker was defined based on self-reported current use of cigarettes.

Details regarding the identification of AF have been previously published. (9) Incident AF was identified by the study electrocardiogram and also from a self-reported medical history of a physician diagnosis during the CATI surveys. The electrocardiograms were read and coded at a central reading center (Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, NC, USA) by analysts who were masked to other REGARDS data. Self-reported AF was defined as an affirmative response to the following question: “Has a physician or a health professional ever told you that you had atrial fibrillation?”

Age, sex, race, education, household income and smoking status were self-reported. Physical limitation was defined as self-reported inability to climb stairs or to perform moderate physical activities. Fasting blood samples were obtained and assayed for total cholesterol, high-density lipoprotein, and serum glucose. Hyperlipidemia was defined as total cholesterol \( \geq 240 \) mg/dL or LDL \( \geq 160 \) mg/dL or HDL \( \leq 40 \) mg/dL or on cholesterol lowering medication. Diabetes was defined as a fasting glucose \( \geq 126 \) mg/dL (or a non-fasting glucose \( \geq 200 \) mg/dL among those failing to fast) or self-reported diabetes medication use. The current use of antihypertensive medications was self-reported. After the participant rested for 5 minutes in a seated position, blood pressure was measured using a sphygmomanometer. Two values were obtained following a standardized protocol and averaged. Hypertension was defined as systolic blood pressure \( \geq 140 \) mmHg or a diastolic blood pressure \( \geq 90 \) mmHg, or by the self-reported use of antihypertensive medications. Coronary heart disease was ascertained by self-reported history of myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, or if evidence of prior myocardial infarction was present on the baseline electrocardiogram. Prior stroke was ascertained by participant self-reported history. History of CVD was defined as the composite of coronary heart disease, stroke, peripheral vascular disease or aortic aneurysm. BMI was calculated using the height and weight collected during the in-home visit. Coronary heart disease, heart failure and stroke events that occurred during follow up were ascertained from medical records by an adjudication committee.

Baseline characteristics were compared between those who developed and did not develop AF. Categorical variables were reported as frequency and percentage while continuous variables were reported as mean ± standard deviation (SD). Statistical significance for categorical variables was tested using the chi-square method and the student’s t-test.
procedure for continuous variables. Multivariable logistic regression was used to calculate the odds ratio (ORs) and 95% confidence intervals (CIs) for the association between baseline e-CRF (per 1-MET increase) and incident AF. The multivariable models were adjusted as follows. Model 1: baseline race, region, education and income; Model 2 further adjusted for systolic blood pressure, blood pressure lowering medications, diabetes, hypercholesterolemia, history of CVD and presence of physical limitations, Model 3: further adjustment for coronary heart disease, stroke, and heart failure occurring during follow-up. To test for the consistency of the results across, we conducted subgroup analysis stratified by age (median), sex, and race/ethnicity and examined interactions. Statistically significant results were defined by a p-value of < 0.05. Statistical analysis for this study was performed by SAS version 9.3 (SAS, Cary, NC).

Results

A total of 10,126 (54% women, 35% African American, mean age 63.2 years) were included in the final analysis. The baseline e-CRF was 8.7 ± 2.1 METs. After a median follow-up of 9.4 years, 906 (8.9%) participants developed AF. Table 1 shows the baseline characteristics of the participants stratified by occurrence of AF during follow-up. As shown, baseline e-CRF was lower in those who developed AF vs those who did not (p<0.01). Also, study participants who developed AF were more likely to have risk factors such as hypertension, diabetes, and history of CVD (Table 1).

In multivariable analysis adjusted for socio-demographics, every 1-MET increase in e-CRF decreased the risk of AF by 9% (p < 0.001). On further adjusting for CVD risk factors and presence of physical limitations the risk of AF was still reduced by 5% (p < 0.007), which did not change after further adjustment for incident coronary heart disease, heart failure, and stroke (Table 2). This association was stronger in women than men (interaction p-value=0.05), but no differences were observed in the participant subgroups stratified by age, race, history of CVD, or physical limitations (Figure 1).

Discussion

In this analysis from the REGARDS study we showed that better e-CRF, estimated from readily available clinical and self-reported data, is associated with lower risk of AF. This suggests that e-CRF using non-exercise algorithms may serve as a useful alternative to CRF measured by costly and time consuming exercise testing.

Poor CRF is known to be associated with CVD morbidity and mortality.(2, 3, 10) The relationship between development of AF and lifetime physical activity was evaluated by a few observational studies based on self-reported questionnaires (11, 12) while other studies have utilized maximal oxygen uptake during exercise as a measure of CRF.(5) There also has been an interest in correlating METs achieved during exercise stress testing as a measure of CRF with results suggesting that higher CRF leads to lower occurrence of AF.(4, 13, 14) Nevertheless the wide utilization of CRF in predicting AF is challenged by the need for costly equipment and trained personnel. A simple estimation of e-CRF through non-exercise algorithms based on easily available clinical and self-reported variables, as demonstrated in
this analysis, could serve as a promising alternative that overcomes the practical issues of directly measured CRF in healthcare settings.

We observed a stronger association with better e-CRF and lower risk of AF in women than men. Although we cannot provide an explanation for this finding, it may have an important implication in prevention of AF complication in women. Compared to men, women have worse prognosis after stroke. (15, 16) Similarly, women with AF have a higher risk to develop myocardial infarction. (17) This higher risk of AF-related complications necessitates more aggressive AF prevention strategies in women than men. Observing a more favorable effect of better CRF on AF in women than men suggests that improving cardiorespiratory fitness could be one of these strategies.

Our study is not without limitations. We relied on self-reported questionnaires to obtain some of the baseline characteristics which subjected our study to recall bias. Since we utilized resting ECG and self-reported history of AF, it is possible we missed cases of paroxysmal AF. Although we adjusted for several risk factors, residual confounding remains a possibility. Despite these limitations, to our knowledge this is the first study to examine the role of e-CRF in predicting incident AF. The key strengths of our study include the large cohort of participants with representation of women and men, blacks and whites, well-ascertained covariates and centrally read ECG data, and long follow-up duration.

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References


Figure 1:
Association between Estimated-Cardiorespiratory Fitness and Atrial Fibrillation in Subgroups of REGARDS Participants
*Model adjusted for baseline race, region, and education and income, systolic blood pressure, blood pressure lowering medications, diabetes, Hyperlipidemia, prior cardiovascular disease and presence of physical limitations as well as coronary heart disease, stroke, and heart failure occurring during follow-up. Age and sex are already included in the calculation of e-CRF)
Table 1:
Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total cohort (n=10,126)</th>
<th>With AF YES (n=906)</th>
<th>NO (n=9,220)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.2 ± 8.3</td>
<td>67.1 ± 8.0</td>
<td>62.9 ± 8.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Women</td>
<td>5514 (54.5%)</td>
<td>381 (42.1%)</td>
<td>5133 (55.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black</td>
<td>3543 (35.0%)</td>
<td>195 (21.5%)</td>
<td>3348 (36.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td>.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>707 (7.0%)</td>
<td>60 (6.6%)</td>
<td>647 (7.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High school graduate</td>
<td>2346 (23.2%)</td>
<td>211 (23.3%)</td>
<td>2135 (23.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Some college</td>
<td>2646 (26.1%)</td>
<td>253 (27.9%)</td>
<td>2393 (26.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥College graduate</td>
<td>4427 (43.7%)</td>
<td>382 (42.2%)</td>
<td>4045 (43.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td>.039</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $20k</td>
<td>1164 (11.5%)</td>
<td>102 (11.3%)</td>
<td>1062 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>$20k-$34k</td>
<td>2212 (21.8%)</td>
<td>207 (22.9%)</td>
<td>2005 (21.8%)</td>
<td></td>
</tr>
<tr>
<td>$35k-$74k</td>
<td>3484 (34.4%)</td>
<td>329 (36.3%)</td>
<td>3155 (34.2%)</td>
<td></td>
</tr>
<tr>
<td>≥$75k</td>
<td>2231 (22.0%)</td>
<td>164 (18.1%)</td>
<td>2067 (22.4%)</td>
<td></td>
</tr>
<tr>
<td>Refused</td>
<td>1035 (10.2%)</td>
<td>104 (11.5%)</td>
<td>931 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5465 (54.0%)</td>
<td>588 (64.9%)</td>
<td>4876 (52.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>5772 (57.0%)</td>
<td>575 (63.5%)</td>
<td>5197 (56.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1631 (16.1%)</td>
<td>182 (20.1%)</td>
<td>1449 (15.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1466 (14.5%)</td>
<td>250 (27.6%)</td>
<td>1216 (13.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1069 (10.6%)</td>
<td>80 (8.8%)</td>
<td>989 (10.7%)</td>
<td>.076</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>29.2 ± 5.7</td>
<td>29.8 ± 5.8</td>
<td>29.1 ± 5.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>95.2 ± 14.8</td>
<td>99.5 ± 17.6</td>
<td>94.7 ± 14.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.4 ± 18.1</td>
<td>88.9 ± 19.0</td>
<td>83.9 ± 18.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>125.4 ± 15.4</td>
<td>128.3 ± 15.6</td>
<td>125.1 ± 15.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.2 ± 9.2</td>
<td>75.6 ± 9.4</td>
<td>76.2 ± 9.2</td>
<td>.072</td>
</tr>
<tr>
<td>Use of BP medications</td>
<td>4839 (47.8%)</td>
<td>530 (58.5%)</td>
<td>4309 (46.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resting heart rate (beats/minute)</td>
<td>65.5 ± 16.9</td>
<td>63.7 ± 11.3</td>
<td>65.7 ± 17.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>physical limitations</td>
<td>4368 (43.1%)</td>
<td>467 (51.6%)</td>
<td>3901 (42.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Estimated cardiorespiratory fitness</td>
<td>8.7 ± 2.1</td>
<td>8.4 ± 2.1</td>
<td>8.7 ± 2.1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Values expressed as Mean ± SD or n (%)

Hyperlipidemia was defined as total cholesterol ≥240 mg/dL or LDL≥160 mg/dL or HDL≤40 mg/dL or on cholesterol lowering medication.
Diabetes was defined as a fasting glucose ≥26 mg/dL (or a non-fasting glucose ≥200 mg/dL among those failing to fast) or self-reported diabetes medication use. Hypertension was defined as systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, or by the self-reported use of antihypertensive medications.
Table 2:
Association between Estimated Cardiorespiratory Fitness and Incident Atrial Fibrillation

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds ratio per 1-MET increase in e-CRF</th>
<th>95% Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
<td>0.91</td>
<td>0.88, 0.94</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Model 2†</td>
<td>0.95</td>
<td>0.92, 0.99</td>
<td>0.0066</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>0.95</td>
<td>0.92, 0.99</td>
<td>0.0129</td>
</tr>
</tbody>
</table>

e-CRF = Estimated Cardiorespiratory Fitness
* Model 1: Race, region, and education and income (age and sex are already included in the calculation of e-CRF)
† Model 2: further adjusted for systolic blood pressure, blood pressure lowering medications, diabetes, Hyperlipidemia, prior cardiovascular disease and presence of physical limitations,
‡ Model 3: further adjustment for coronary heart disease, stroke, and heart failure occurring during follow-up.