

# Elucidating the Association Between Depressive Symptoms, Coronary Heart Disease, and Stroke in Black and White Adults: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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**Background**—Depression is a relapsing and remitting disease. Prior studies on the association between depressive symptoms and incident cardiovascular disease (CVD) have been limited by single measurements, and few if any have examined both incident coronary heart disease and stroke in a large biracial national cohort. We aimed to assess whether time-dependent depressive symptoms conferred increased risk of incident CVD.

**Methods and Results**—Between 2003 to 2007, 22 666 black and white participants (aged  $\geq 45$  years) without baseline CVD in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study were recruited. Cox proportional hazards regression analyses assessed the association between up to 3 measurements of elevated depressive symptoms (4-item Center for Epidemiologic Studies Depression Scale score  $\geq 4$ ) and incident coronary heart disease, stroke, and CVD death adjusting for age, sex, region, income, health insurance, education, blood pressure, cholesterol, medication, obesity, diabetes mellitus, kidney disease, C-reactive protein, corrected QT interval, atrial fibrillation, left ventricular hypertrophy, smoking, alcohol, physical inactivity, medication adherence, and antidepressant use. The participants' average age was 63.4 years, 58.8% were female, and 41.7% black. Time-varying depressive symptoms were significantly associated with CVD death (adjusted hazard ratio 1.30, 95% CI 1.04–1.63), with a trend toward significance for fatal and nonfatal stroke (adjusted hazard ratio 1.26, 95% CI 0.99–1.60) but not fatal and nonfatal coronary heart disease (adjusted hazard ratio 1.11, 95% CI 0.89–1.38). Race did not moderate the association between depressive symptoms and CVD.

**Conclusions**—Proximal depressive symptoms were associated with incident fatal and nonfatal stroke and CVD death even after controlling for multiple explanatory factors, further supporting the urgent need for timely management of depressive symptoms. (*J Am Heart Assoc.* 2016;5:e003767 doi: 10.1161/JAHA.116.003767)

**Key Words:** cardiovascular disease • depression • epidemiology

A growing body of evidence suggests that depressive symptoms may confer an increased risk for incident cardiovascular disease (CVD).<sup>1–4</sup> Nevertheless, few if any previous studies have analyzed both coronary heart disease (CHD) and stroke simultaneously in a large biracial national sample, and almost all studies have been limited to single

measurements of depressive symptoms.<sup>5</sup> Single measurements do not account for the fact that depression is a relapsing and remitting disease, and cumulative measurements may be limited by selection bias through differential loss to follow-up.

The mechanisms underlying the association between depressive symptoms and CVD have proven difficult to fully elucidate.<sup>4</sup> Although successive meta-analyses have shown that depressive symptoms increase the risk of incident CHD and CHD death, with pooled hazard ratios (HRs) estimated at 1.6 and 1.8,<sup>2,3,6</sup> there has been concern about incomplete risk factor adjustment in the majority of studies included in prior meta-analyses and limited use of time-dependent variables.<sup>2</sup> Similarly, although depressive symptoms have been considered an inconsistent risk factor for incident cerebrovascular disease,<sup>7–9</sup> a recent meta-analysis found pooled HRs of 1.5 and 1.6 for total and fatal stroke; again, only 6 of 28 studies simultaneously controlled for alcohol, body mass index, and smoking status, and 1 controlled for

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medication adherence.<sup>10</sup> In addition to unmeasured confounders, research also remains inconsistent as to whether race truly moderates the association between depressive symptoms and incident CVD.<sup>11–14</sup> Prior studies suggest that racial and ethnic minorities face unique barriers to depression treatment in the United States,<sup>15</sup> and as such, it is unclear how race and time-dependent depressive symptoms interact to influence CVD events.

Given that time-varying analyses may better elucidate the timing of the association between depressive symptoms and CVD, the aim of this study was to assess whether time-varying depressive symptoms confer increased risk of stroke and CHD, adjusting for potential explanatory factors in a large national diverse cohort. We secondarily sought to assess whether depressive symptoms differentially predicted incident stroke and CHD in black and white participants.

## Methods

### Study Procedures

Details of the REasons for Geographic And Racial Differences in Stroke (REGARDS) study have been described previously.<sup>16</sup> In brief, REGARDS is a national cohort study of stroke incidence and cognitive decline in black and white patients aged  $\geq 45$  years living in the United States and stratified to reflect specific race, sex, and geographic strata. CHD outcomes were ascertained from a REGARDS ancillary study. Participants were recruited by mail using commercially available lists of US residents, followed by a telephone call and a subsequent home visit at which time patients gave consent and were enrolled. Between January 2003 and October 2007, 30 183 black and white adults were enrolled. Of these, 484 (1.6%) were lost to follow-up, and 171 (0.6%) were missing baseline depressive symptom measurements (Figure 1). Our current analysis was limited to 22 666 participants without existing CVD at baseline (6862 had stroke, CHD, peripheral vascular disease, or aneurysm). The REGARDS study protocol was approved by the institutional review boards of the participating centers.

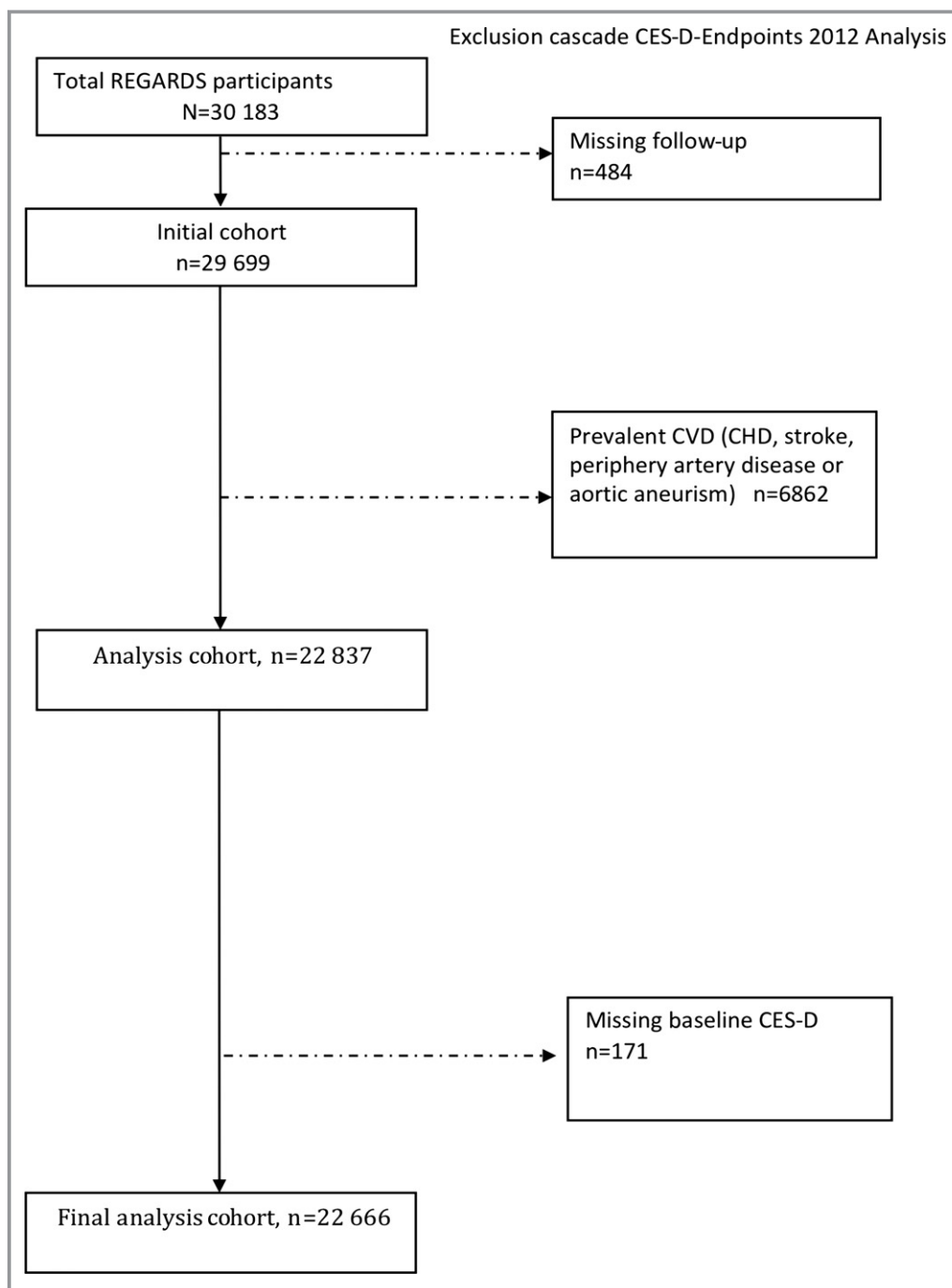
Baseline data were collected through computer-assisted telephone interviews, an in-home examination, and self-administered questionnaires. Trained research staff conducted telephone interviews to collect demographic data and education. Following telephone interview, patients had an in-home visit during which physical measurements, a resting electrocardiogram, medication inventory, phlebotomy, and urine were collected. Medication use was measured by self-report or pill bottle review during the in-home visit.

### Primary Outcomes

The primary outcomes for these analyses were (1) incident CHD events, defined as definite or probable nonfatal or fatal myocardial infarction or acute CHD death events; (2) incident stroke events, defined as probable nonfatal or fatal stroke; (3) incident CVD death, defined as death from CHD, stroke, heart failure, sudden cardiac death, vascular pathology, and other CVD causes. Living participants or their proxies were followed up every 6 months by telephone, with retrieval of medical records for reported hospitalizations or physician visits. Data were collected on suspected stroke events that required hospitalization and on physician evaluations for stroke-like symptoms detected using the Questionnaire for Verifying Stroke-Free Status.<sup>17</sup> The adjudication process validated stroke occurrence and classified events by stroke “subtype” and severity using the National Institutes of Health Stroke Scale. Stroke was defined as rapid onset of a persistent neurological deficit attributable to an obstruction or rupture of the arterial system (including stroke occurring during a procedure such as angiograph or surgery) that causes a deficit not known to be secondary to brain trauma; that lasts  $>24$  hours, unless death supervenes; and that has a demonstrable lesion compatible with acute stroke on computed tomography or magnetic resonance imaging.<sup>16,18</sup> For CHD events, medical records were examined for the presence of signs and symptoms of ischemia, cardiac enzymes, electrocardiogram changes consistent with ischemia, or myocardial infarction based on the Minnesota code; myocardial infarctions were adjudicated as being definite or probable, based on published guidelines.<sup>19,20</sup> Deaths were detected by report of next of kin or through online services (eg, Social Security Death Index) or the National Death Index.<sup>16</sup> Death certificates, medical records, and autopsy reports were obtained to adjudicate cause of death and cardiovascular outcomes.

### Depressive Symptoms

The primary predictor was time-varying depressive symptoms. The 4-item Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess the presence of depressive symptoms. This scale asks participants to rate the number of days over the past week in which they (1) felt depressed, (2) felt lonely, (3) had crying spells, and (4) felt sad. Response options included  $<1$  day (no points), 1 to 2 days (1 point), 3 to 4 days (2 points), and 5 to 7 days (3 points). Cronbach's  $\alpha$  for the CES-D in the total sample was 0.80 and among black and white participants was 0.81 and 0.79, respectively. Elevated depressive symptoms were defined as a summed score of  $\geq 4$ .<sup>21</sup> The reliability and validity of the 4-item CES-D is similar to the original 20-item



**Figure 1.** Cohort flow diagram. Numbers of participants originally recruited for the REGARDS study, lost to follow-up, missing baseline depressive symptoms, excluded from the analysis due to existing baseline CVD, and in the final analysis. CES-D indicates Center for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; CVD, cardiovascular disease; REGARDS, REasons for Geographic And Racial Differences in Stroke.

instrument.<sup>22</sup> The CES-D was administered 3 times: (1) during the initial telephone interview, (2) at 5 years after baseline measurement, and (3) at 2 years after the second measurement. CES-D scores measured after an end point or after the end of follow-up were not eligible to be included in the time-varying analysis.

### Covariates

Demographic data included self-reported age, sex, race (black or white), education (less than high school, high school graduate, some college, and college graduate and higher), annual income (less than \$20 000, \$20 000–\$34 999,

\$35 000–\$74 999, \$75 000 and above), insurance status (yes or no), and stroke region (“stroke belt,” defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee, and the noncoastal regions within the states of North Carolina, South Carolina, and Georgia; “stroke buckle,” defined as coastal regions within the states of North Carolina, South Carolina, and Georgia). Clinical CHD risk factors included diabetes mellitus, defined as fasting blood glucose  $\geq 126$  mL/dL, random glucose  $>200$  mL/dL, or oral hypoglycemic or insulin use; systolic and diastolic blood pressures based on the average of 2 standardized blood pressure measurements (continuous variables in mm Hg); body mass index based on measured height and weight; albumin:creatinine ratio; and high-density lipoprotein and total cholesterol. We also assessed use of aspirin (yes or no), statins (yes or no), and antihypertensive medications (yes or no). Behavioral risk factors included (1) smoking status, based on self-reported pack-years of cigarette smoking; (2) physical inactivity, ascertained by asking, “How many times per week do you engage in intense physical activity, enough to work up a sweat?” with response options of “none,” “1 to 3 times per week,” or “4 or more times per week”; (3) alcohol use, ascertained by asking, “How many alcoholic beverages do you drink?” and use based on National Institute on Alcohol Abuse and Alcoholism classifications (none, moderate [1 drink per day for women or 2 drinks per day for men], and heavy [ $>1$  drink per day for women and  $>2$  drinks per day for men])<sup>16</sup>; and (4) medication nonadherence, assessed with the 4-item Morisky Medication Adherence Scale (ranging from 0–4, with a score  $\geq 1$  indicating medication nonadherence).<sup>23</sup> Potential mediators included high-sensitivity C-reactive protein, QT intervals corrected for heart rate using the formula  $QT+(154 \times [1-(60/\text{heart rate})])$ , and antidepressant use (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants; yes or no).

## Statistical Analyses

Baseline characteristics of participants with and without elevated depressive symptoms at baseline were compared using chi-square tests, Student *t* tests, and Kruskal–Wallis tests, as appropriate.

Cox proportional hazards regression models were constructed to separately analyze the association between depressive symptoms (CES-D score  $\geq 4$ ) and incident CHD, incident stroke, and CVD death. The end date of follow-up for this analysis was December 31, 2012. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of the first CHD or stroke event, death, the last telephone follow-up, or the end of follow-up. Depressive symptoms were measured with the CES-D at

baseline and again at 5- and 7-year follow-up. In the analyses, we considered depressive symptoms as a time-varying exposure, with updates of exposure at 5- and 7-year follow-up. Consequently, each participant contributed up to 3 measures of CES-D over follow-up. Adjusted modeling proceeded in stages, with each model including additional covariates. Model 1 adjusted for demographic factors, including age, sex, region, income, health insurance, education, and traditional CVD risk factors (systolic blood pressure; total cholesterol; high-density lipoprotein-cholesterol; use of aspirin, statins, or antihypertensives; body mass index; logarithmically transformed albumin:creatinine ratio; and diabetes status). Model 2 additionally adjusted for behavioral CVD risk factors (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication nonadherence). Model 3 adjusted for other physiological explanatory factors including logarithmically transformed high-sensitivity C-reactive protein, antidepressant use, and QT interval corrected for heart rate. Model 3 for stroke was additionally adjusted for atrial fibrillation and left ventricular hypertrophy. The analyses were conducted overall and were stratified by race. We also conducted a formal test for interaction with depressive symptoms by race in the fully adjusted models. The proportionality assumption was tested by assessing depressive symptoms by log of follow-up time interactions and was satisfied for all end points.

Missing data in covariates were imputed using chained equations, and final estimates were derived by bootstrapping across the 5 imputed data sets. Among the 22 666 participants, the following data were missing: 2768 (12%), income; 9 (0.03%), education; 22 (0.09%), health insurance; 831 (4%), diabetes mellitus; 13 (0.06%), aspirin use; 61 (0.3%), statin use; 61 (0.3%), antidepressant use; 242 (1%), antihypertension medication use; 326 (1%), physical activity; 2415 (11%), medication adherence; 146 (0.6%), body mass index; 908 (4%), cholesterol; 1027 (5%), high-density lipoprotein; 659 (3%), pack-years smoked; 60 (0.3%), systolic blood pressure; 1000 (4%), albumin:creatinine ratio; 296 (1%), corrected QT interval; 1379 (6%), C-reactive protein. Analyses were conducted using SAS software version 9.4 (SAS Institute) and Stata version 12 (StataCorp).

## Results

### Participant Characteristics

Of the 22 666 eligible participants, 2267 (10.0%) had elevated depressive symptoms at baseline (CES-D score  $\geq 4$ ). Overall, 73.7% of participants completed a second measurement, and 59.9% completed a third measurement. Of patients with elevated depressive symptoms at baseline, 39.2% and 37.5% had elevated depressive symptoms at the

**Table 1.** Baseline Characteristics of REGARDS Cohort Members Who Were Free of CVD, \* by Baseline Depressive Symptoms (CES-D)

Characteristics	Overall (n=22 666)	CES-D Score ≥4 (n=2267)	CES-D Score <4 (n=20 399)	P Value†
<b>Sociodemographics</b>				
Age, y, mean±SD	63.9±9.3	62.2±9.7	64.1±9.2	<0.001
Sex, n (%)				<0.001
Female	13 321 (58.8)	1675 (73.9)	11 646 (57.1)	
Race, n (%)				<0.001
Black	9444 (41.7)	1183 (52.2)	8261 (40.5)	
Education, n (%)				<0.001
Less than high school	2466 (10.9)	484 (21.4)	1982 (9.7)	
High school graduate	5718 (25.2)	692 (30.5)	5026 (24.7)	
Some college	6127 (27.0)	592 (26.1)	5535 (27.1)	
College graduate and higher	8343 (36.8)	498 (22.0)	7845 (38.5)	
Annual household income, n (%)				<0.001
Less than \$20 000	3705 (16.3)	768 (33.9)	2937 (14.4)	
\$20 000 to \$34 999	5314 (23.4)	573 (25.3)	4741 (23.2)	
\$35 000 to \$74 999	6965 (30.7)	443 (19.5)	6522 (32.0)	
\$75 000 and above	3908 (17.2)	168 (7.4)	3740 (18.3)	
Declined to report	2771 (12.2)	315 (13.9)	2456 (12.0)	
No health insurance, n (%)	1642 (7.3)	307 (13.5)	1335 (6.6)	<0.001
Region,‡ n (%)				<0.001
Stroke belt	7832 (34.6)	850 (37.5)	6982 (34.2)	
Stroke buckle	4776 (21.1)	533 (23.5)	4243 (20.8)	
Not stroke belt or buckle	10 055 (44.4)	884 (39.0)	9171 (45.0)	
<b>Physiological risk factors</b>				
Body mass index, kg/m <sup>2</sup> , mean±SD	29.3±6.2	30.5±7.0	29.2±6.1	<0.001
Diabetes mellitus,§ n (%)	4051 (18.6)	560 (25.6)	3491 (17.8)	<0.001
Systolic blood pressure, mm Hg, mean±SD	126.8±16.3	127.5±17.4	126.7±16.2	0.0370
Total cholesterol, mg/dL, mean±SD	195.7±39.0	198.2±41.0	195.4±38.8	0.0014
High-density lipoprotein, mg/dL, mean±SD	53.0±16.3	54.0±16.3	52.9±16.3	0.0027
QT interval, corrected for heart rate, ms, mean±SD	406.0±22.2	408.0±21.8	405.8±22.2	<0.001
High-sensitivity C-reactive protein, mg/L, median (IQR)	2.2 [0.9–4.9]	2.9 [1.2–6.6]	2.1 [0.9–4.7]	<0.001
Albumin to creatinine ratio, mg/g, median (IQR)	7.0 [4.5–13.9]	7.4 [4.8–15.4]	7.0 [4.5–13.8]	<0.001
<b>Medications</b>				
Antihypertensive medication use, n (%)	10 589 (47.2)	1184 (52.9)	9405 (46.6)	<0.001
Statin use, n (%)	5626 (24.9)	571 (25.3)	5055 (24.8)	0.6555
Aspirin use, n (%)	8282 (36.6)	800 (35.3)	7482 (36.7)	0.1947
Antidepressant use, n (%)	2913 (12.9)	600 (26.6)	2313 (11.4)	<0.001
<b>Behavioral risk factors</b>				
Self-reported smoking, pack years, mean±SD	11.3±20.3	12.5±22.0	11.2±20.1	0.0031
Alcohol use, n (%)				<0.001
Heavy	964 (4.3)	97 (4.4)	867 (4.3)	
Moderate	7595 (34.2)	617 (28.0)	6978 (34.8)	
None	13 676 (61.5)	1490 (67.6)	12 186 (60.8)	

Continued

Table 1. Continued

Characteristics	Overall (n=22 666)	CES-D Score ≥4 (n=2267)	CES-D Score <4 (n=20 399)	P Value <sup>†</sup>
Physical inactivity, n (%)	7303 (32.7)	997 (44.5)	6306 (31.4)	<0.001
Medication nonadherence, n (%)	5916 (29.2)	773 (37.5)	5143 (28.3)	<0.001

CES-D indicates Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; IQR, interquartile range; REGARDS, REasons for Geographic And Racial Differences in Stroke.

\*CVD defined as baseline coronary heart disease, stroke, peripheral artery disease, or aortic aneurysm.

<sup>†</sup>P values from chi-square or student *t* tests.

<sup>‡</sup>“Stroke belt” is defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee, and the noncoastal regions within the states of North Carolina, South Carolina, and Georgia. “Stroke buckle” is defined as coastal regions within the states of North Carolina, South Carolina, and Georgia.

<sup>§</sup>Diabetes is defined as fasting blood glucose ≥126 mL/dL, random glucose >200 mL/dL, or oral hypoglycemic or insulin use.

second and third measurements, respectively. The participants' average age was 63.4 years, 58.8% were female, 41.7% were black, 18.6% had diabetes, 32.7% were physically inactive, and 29.2% were nonadherent to their medication regimens. Of the participants who completed the initial baseline scale, patients with elevated depressive symptoms were more likely to be younger, female, and black; have less than a high school education; have an income below \$20 000 (39.9% versus 14.4%); be uninsured; have higher systolic blood pressure and total cholesterol; have high-density lipoprotein; be obese; have diabetes mellitus; have higher self-reported pack-years; be physically inactive; report medication nonadherence; have higher C-reactive protein levels; use antihypertensive medications; and, finally, have a prolonged corrected QT interval at baseline (Table 1).

### Incident Cardiovascular Events

The median follow-up time was 6.9 years. Among participants with elevated depressive symptoms at any of the 3 assessments, there were 96 (10.7%) CHD events, 81 (12.2%) strokes, and 94 (13.4%) CVD deaths. In the unadjusted analyses, the HR for CHD associated with time-varying depressive symptoms was 1.15 (95% CI 0.93–1.42), which remained similar after adjusting for demographics, traditional CVD, and other explanatory behavioral and physiological factors (Table 2). The unadjusted HR for fatal and nonfatal stroke with depressive symptoms was 1.35 (95% CI 1.07–1.70). The adjusted HR (aHR) for fatal and nonfatal stroke was 1.31 (95% CI 1.04–1.67) after controlling for demographic and traditional CVD risk factors, 1.30 (1.02–1.65) after adjusting for behavioral factors, and 1.26 (0.99–1.60) after additionally adjusting for other physiological factors. Time-varying depressive symptoms were significantly associated with CVD death in the unadjusted analysis (HR 1.49, 95% CI 1.20–1.85) and remained so after adjusting for demographics and traditional CVD risk factors (aHR 1.36, 95% CI 1.09–1.70), behavioral risk factors (aHR 1.35, 95% CI 1.08–1.68),

and other explanatory physiological factors (aHR 1.30, 95% CI 1.04–1.63) (Figure 2).

### Assessment of the Potential for Effect Modification by Race

In additional analyses, we further assessed whether race moderated the association between depressive symptoms and CVD. We found that there was no significant interaction between depressive symptoms and race for any of the aforementioned outcomes (Table 2). In Model 1, the *P* value for the depressive symptoms by race interaction term was 0.21 for CHD, 0.89 for stroke, and 0.77 for CVD death in the overall models adjusted for all covariates. In the race-stratified analyses, the HRs for depressive symptoms and CHD in black and white participants were 1.32 (95% CI 0.99–1.75; aHR 1.17, 95% CI 0.87–1.57) and 0.97 (95% CI 0.70–1.34; aHR 0.98, 95% CI 0.70–1.36), respectively.

### Discussion

In this large biracial cohort of participants free of CVD and enrolled in the REGARDS study, we found that proximate depressive symptoms were associated with a 26% increased risk of incident stroke and a 30% increased risk of incident CVD death. Interestingly, depressive symptoms did not confer increased risk for the outcome of incident CHD. This is one of few large cohort studies to use multiple measurements of depressive symptoms and to more definitively clarify that race does not appear to moderate the relationship between depressive symptoms and CVD, which was shown inconsistently in the previous literature.

Our study is consistent with prior studies demonstrating that depressive symptoms confer an increased risk of stroke,<sup>2,10,24</sup> including prior meta-analyses (aHR 1.34, 95% CI 1.17–1.54)<sup>10,25</sup> and a prospective study of stroke risk in middle-aged women with time-varying covariates (adjusted odds ratio 1.94, 95% CI 1.37–2.74).<sup>26</sup> We expanded on prior

**Table 2.** Incident Cardiovascular Events and Death Associated With Time-Varying CES-D Scores\*

	Time-Varying Categorical CES-D (Score ≥4 vs <4), HR (95% CI)		
	Overall	Black	White
<b>CHD</b>	n=895	n=377	n=518
Unadjusted	1.15 (0.93–1.42)	1.32 (0.99–1.75)	0.97 (0.70–1.34)
Model 1 <sup>†</sup>	1.16 (0.93–1.43)	1.24 (0.93–1.66)	1.02 (0.74–1.42)
Model 2 <sup>‡</sup>	1.14 (0.92–1.42)	1.22 (0.91–1.64)	1.00 (0.72–1.39)
Model 3 <sup>§</sup>	1.11 (0.89–1.38)	1.17 (0.87–1.57)	0.98 (0.70–1.36)
<b>Stroke<sup>  </sup></b>	n=663	n=299	n=364
Unadjusted	1.35 (1.07–1.70) <sup>¶</sup>	1.34 (0.97–1.84)	1.29 (0.91–1.82)
Model 1 <sup>†</sup>	1.31 (1.04–1.67) <sup>¶</sup>	1.28 (0.93–1.77)	1.30 (0.91–1.85)
Model 2 <sup>‡</sup>	1.30 (1.02–1.65) <sup>¶</sup>	1.28 (0.95–1.77)	1.29 (0.91–1.84)
Model 3 <sup>§</sup>	1.26 (0.99–1.60) <sup>¶</sup>	1.28 (0.92–1.78)	1.23 (0.86–1.76)
<b>CVD death</b>	n=702	n=376	n=326
Unadjusted	1.49 (1.20–1.85) <sup>¶</sup>	1.41 (1.08–1.86) <sup>¶</sup>	1.40 (0.98–1.98)
Model 1 <sup>†</sup>	1.36 (1.09–1.70) <sup>¶</sup>	1.35 (1.02–1.80) <sup>¶</sup>	1.29 (0.90–1.86)
Model 2 <sup>‡</sup>	1.35 (1.08–1.68) <sup>¶</sup>	1.35 (1.01–1.79) <sup>¶</sup>	1.29 (0.90–1.85)
Model 3 <sup>§</sup>	1.30 (1.04–1.63) <sup>¶</sup>	1.28 (0.96–1.71)	1.25 (0.83–1.80)

HR and 95% CI were estimated by Cox proportional hazards regression models. CES-D indicates Center for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio.

\*Excludes participants with baseline CVD (history of CHD, stroke, peripheral artery disease, aortic aneurism). All participants' follow-up time ended at the time of the end point, death, or last follow-up. End of follow-up was December 31, 2012. CES-D measurements taken after an end point or end of follow-up were not considered. Missing data in covariates were imputed.

<sup>†</sup>Adjusted for demographics: age, sex, region, income, health insurance, education, and traditional CHD risk factors (systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and medication use [aspirin, statins, any antihypertensive medications], body mass index, log of albumin:creatinine ratio, diabetes mellitus).

<sup>‡</sup>Adjusted for model 1 covariates and behavioral risk factors: pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication adherence. All-cause mortality models also adjusted for self-reported physical health (Short Form 12, Physical Component Summary).

<sup>§</sup>Adjusted for model 2 covariates and other physiological factors: log of high-sensitivity C-reactive protein, antidepressant use, QT interval corrected for heart rate.

<sup>||</sup>Models of stroke also adjusted for atrial fibrillation and left ventricular hypertrophy.

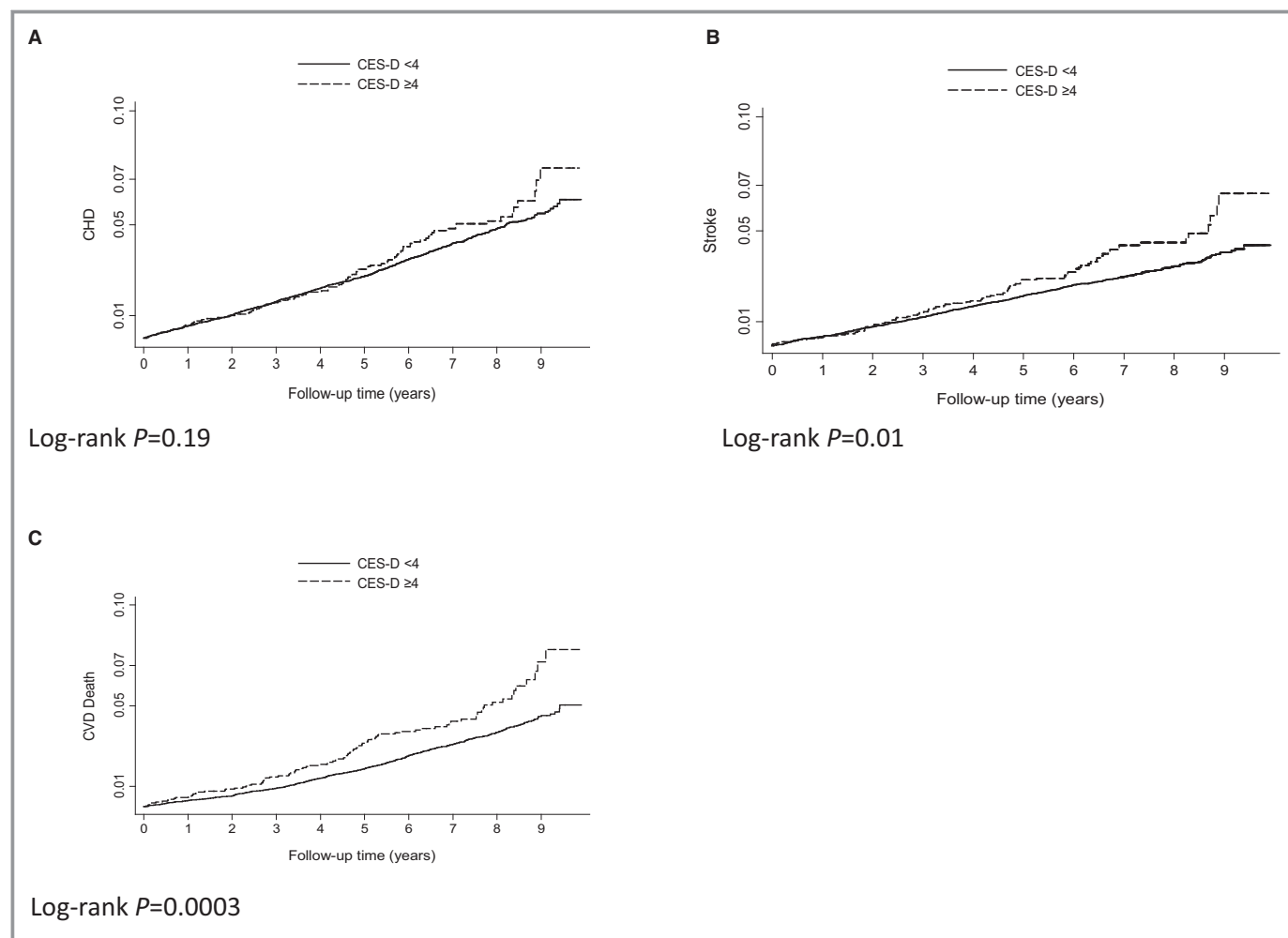
<sup>¶</sup>P<0.05.

literature by accounting for factors such as atrial fibrillation and left ventricular hypertrophy as well as behavioral factors such as medication adherence and physical activity, which were rarely included in prior studies.<sup>2,10</sup> In addition, few studies simultaneously examined the association between depressive symptoms and both stroke and CHD among participants free from underlying CVD. A prior European study of predominantly white men did not adjust for behavioral risk factors or explore physiological factors and found that baseline depressive symptoms increased the risk of stroke over 0 to 5 years only (aHR 1.60, 95% CI 1.1–2.3), whereas only cumulative depressive symptoms led to CHD incidence (1–2 times per case: aHR 1.12, 95% CI 0.7–1.7; 3–4 times: aHR 2.06, 95% CI 1.2–3.7).<sup>27</sup> Another study, also conducted in Europe, found that baseline depressive symptoms conferred an increased risk of CHD (aHR 1.47, 95% CI 1.08–1.99) but not stroke (aHR 0.87, 95% CI 0.57–1.32) in a predominantly young (aged 20–55 years) nondiverse group of women.<sup>7</sup> Our study of diverse middle-aged to older participants living in the continental United States adds to the literature by suggesting that elevated depressive symptoms may be an independent proximal risk factor for

stroke and CVD death but not for CHD, even after controlling for traditional, behavioral, and other physiological explanatory factors.

Depressive symptoms have been shown to be associated with smoking,<sup>28</sup> medication noncompliance,<sup>29</sup> and physical inactivity<sup>30</sup> as well as diabetes,<sup>31</sup> obesity,<sup>32</sup> hypertension,<sup>33</sup> and inflammation.<sup>34</sup> We added to the literature by demonstrating that these factors and others such as antidepressant use<sup>35</sup> and corrected QT interval<sup>36</sup> do not appear to fully explain the association between depressive symptoms and incident CVD death and stroke in otherwise healthy persons. Other unmeasured mediating factors such as heart rate variability, platelet activation, neurohormonal activation, and endothelial interaction may play a greater role and explain the proximate effects on CVD death.<sup>37</sup>

Our study supports prior literature showing a proximal association between depressive symptoms and stroke, which has not been shown to be associated with lifetime or prior history of depressive symptoms,<sup>9</sup> and highlights the urgent need for early intervention in patients with depressive symptoms. A recent study showed that collaborative



**Figure 2.** Kaplan–Meier graphs of depression and CVD events and deaths on or before December 31, 2012. Kaplan–Meier curves and log-rank  $P$  values for the relationship between depressive symptoms and fatal and nonfatal CHD (A), fatal and nonfatal stroke (B), and CVD death (C). CES-D indicates Center for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; CVD, cardiovascular disease.

depression care in the primary care setting might lead to decreased risk of incident CVD events in older patients<sup>38</sup>; however, depressive symptoms continue to be suboptimally recognized, diagnosed, and treated in primary care.<sup>39,40</sup> Further research is needed to examine the moderating effect of depression treatment on incident CVD and to improve treatment rates in primary care settings.

We did not find an association between depressive symptoms and our composite outcome of probable myocardial infarction or fatal CHD, although the directionality is concordant with prior literature.<sup>2,3,6,41</sup> Nonetheless, time-dependent analyses may afford more robust findings (aHR 1.15) compared with the previously published null relationship between baseline depressive symptoms and incident CHD in the REGARDS cohort (aHR 0.99, 95% CI 0.66–1.48).<sup>42</sup> Prior research has suggested that cumulative depressive symptoms over  $\geq 2$  occasions, although subject to selection bias, are better associated with increased risk of CHD as a

dose-response effect than baseline or proximate symptoms.<sup>27</sup> Nonetheless, depressive symptoms may be a better marker of CHD prognosis in patients with existing heart disease than of CHD incidence.<sup>43</sup>

Racial disparities exist for depressive symptom severity, recognition, and treatment<sup>15,44,45</sup> and CVD outcomes.<sup>46</sup> Nevertheless, we found that race did not appear to moderate the association between depressive symptoms and CVD. REGARDS is a large biracial prospective cohort with expert adjudication of outcomes, and that may explain why we were able to better elucidate the potential moderating effect of race shown in prior studies.<sup>11–14</sup> In addition, prior research has suggested that income may mediate the relationship between race and CVD outcomes<sup>47</sup> and that stress confers increased CVD events among low-income persons.<sup>48</sup> In our analyses, income did not appear to fully explain the relationship between depressive symptoms and CVD for either black or white participants. Further research is needed to better define the relationship



among race, income, depression, and CVD. Nonetheless, we demonstrated that early depressive symptom recognition and treatment should be emphasized, regardless of race.

Our study had several limitations. We were unable to assess other time-varying covariates, limiting conclusions regarding mediating effects of behavioral and physiological conditions. In addition, the use of self-reported covariates may have led to misclassification and reporting biases, which may have overestimated our results. In addition, our findings for this biracial US cohort may not be generalizable to other races and nationalities. We were unable to confirm whether depressive symptoms were simply a marker of preclinical CVD, which in turn contributed to CVD death and stroke.<sup>27</sup> Finally, we used the short CES-D measurement for depressive symptoms, but it does not fully measure the breadth of cognitive and somatic symptoms of depression. Research has shown that cognitive symptoms are better recognized by providers but are less likely to predict mortality than somatic symptoms.<sup>49</sup> This may have contributed to the nonsignificant association between depressive symptoms and CHD, although the 4-item CES-D has been shown to have adequate sensitivity and specificity compared with depressive symptoms on the 20-item CES-D and has been used to assess depressive symptoms in prior CVD studies.

In conclusion, time-varying depressive symptoms were independently associated with incident stroke and CVD death but not with incident CHD in a large cohort of black and white adults living in the continental United States, with no indication that associations were moderated by race. These findings lend support to the belief that depressive symptomatology is an early modifiable risk factor for CVD. Improving depressive symptom screening and treatment has the potential to reduce the burden of incident CVD in the United States.

## Author Contributions

Drs Khodneva and Richman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Moise, Khodneva, Safford; *Acquisition of data:* Khodneva, Safford; *Analysis and interpretation of data:* Khodneva, Moise, Richman, Safford; *Drafting of the manuscript:* Moise, Khodneva *Critical revision of manuscript for important intellectual content:* Moise, Khodneva, Richman, Shimbo, Kronish, Safford; *Statistical analysis:* Khodneva; *Obtained funding:* Safford; *Study supervision:* Safford.

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## Disclosures

None.

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**Elucidating the Association Between Depressive Symptoms, Coronary Heart Disease, and Stroke in Black and White Adults: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study**

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