ORIGINAL RESEARCH

Negative Affect and Risk of Atrial Fibrillation: MESA

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Background—Current literature examining the prospective relationship between depression and other measures of negative affect with atrial fibrillation (AF) are limited. We determined the relationships of depression, anger, anxiety, and chronic stress with incident AF in a multiethnic cohort of middle- and older-aged adults.

Methods and Results—This analysis included 6644 MESA (Multi-Ethnic Study of Atherosclerosis) study participants who were free of AF at baseline. Depressive symptoms were assessed at baseline and defined as either a 20-item Center for Epidemiologic Studies Depression Scale score ≥16 or use of antidepressant medications. The Spielberger Trait Anger Scale, Spielberger Trait Anxiety Scale, and Chronic Burden Scale were also administered at baseline to assess anger, anxiety, and chronic stress, respectively. The primary outcome was incident AF, identified by follow-up study visit ECGs, hospital discharge diagnoses, or Medicare claims data. A total of 875 (13%) incident AF cases were detected over a median follow-up of nearly 13 years. A Center for Epidemiologic Studies Depression Scale score ≥16 (referent, Center for Epidemiologic Studies Depression Scale score <2) and antidepressant use were associated with a 34% and 36% higher risk of AF, respectively, in separate adjusted Cox proportional hazards analyses (hazard ratio, 1.34; 95% CI 1.04–1.74 for Center for Epidemiologic Studies Depression Scale ≥16; hazard ratio, 1.36; 95% CI, 1.04–1.77 for antidepressant use). No significant associations were observed for anger, anxiety, or chronic stress with development of AF.

Conclusions—Depressive symptoms are associated with an increased risk of incident AF. Further study into whether improving depressive symptoms reduces AF incidence is important. **(*J Am Heart Assoc.* 2019;8:e010603. DOI: 10.1161/JAHA.118.010603.)**

Key Words: arrhythmia • atrial fibrillation • depression

Although prior research into atrial fibrillation (AF) risk factors has allowed for a better understanding of its causation and prediction, over 40% of the risk attributed to AF still remains unexplained after accounting for established risk factors.[1] Continued investigation into identifying additional risk factors is important to improve our understanding of the mechanisms that cause AF.

Emotional distress has been suggested as a potential risk factor for AF via mechanisms involving increased inflammation and increased activation of the autonomous nervous system (ANS), hypothalamus-pituitary-adrenal axis, and renin-angiotensin-aldosterone system (RAAS).[2–4] Current epidemiologic literature examining the prospective relationship between depression and incident AF is sparse and consists of a single study of predominantly white females.[5] Prospective literature evaluating associations of other measures of emotional distress with AF are similarly limited.[6–8] In these studies, chronic psychological stress were not associated with AF while anger, hostility, and tension were, but only in men.

Therefore, the purpose of our study was to examine the association of baseline measures of negative affect, including depressive symptoms, anger, anxiety, and chronic stress, with incident AF in a well-characterized cohort. The MESA (Multi-Ethnic Study of Atherosclerosis) includes repeat assessments of these measures as well as a broad array of risk factor data, allowing us to control for important confounding variables and examine potential underlying mechanisms.

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010603

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Received August 8, 2018; accepted November 21, 2018.

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Clinical Perspective

What Is New?

- This is the first study to report that depressive symptoms, as defined by either an elevated Center for Epidemiology Studies Depression Scale or self-reported use of antidepressants, are associated with a higher risk of incident atrial fibrillation.

What Are the Clinical Implications?

- Our findings identify a large portion of Americans who may be at an increased risk for developing atrial fibrillation and who may benefit from more targeted efforts to prevent this arrhythmia.
- If findings are confirmed in future studies, particularly those with formal assessment of clinical depression, then studies will be needed to see whether treating depression may lower the risk for atrial fibrillation.

Methods

Study Population

MESA is a National Heart, Lung, and Blood Institute–funded multicenter longitudinal community-based study. Participants were followed longitudinally for incident cardiovascular disease events and cause-specific mortality. The study recruited 6814 adults aged 45 to 84 years and free of clinically recognized cardiovascular disease from 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St Paul, Minnesota) to undergo baseline examination between 2000 and 2002.[9] The study participants self-identified with 1 of 4 race/ethnic groups: non-Hispanic white (38%), black (28%), Hispanic (22%), and Chinese (12%). Follow-up visits 2, 3, 4, and 5 were done in 2002–2004, 2004–2005, 2005–2007, and 2010–2012, respectively. Institutional review boards at each site approved the study, and all participants gave informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Depressive Symptom, Anger, Anxiety, and Chronic Stress Measures

Depressive symptoms were assessed by the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) at Visits 1, 3, 4, and 5.[10] CES-D scores were scored on a continuous scale, with higher scores indicating more depressive symptomatology. Five CES-D groups were created based on the score distribution in approximate quartiles, with the top quartile split into 2 such that the top group represent people with a score ≥16, a value commonly used to identify clinically relevant symptoms.[10] Participants reporting use of antidepressant medications were also considered to have depressive symptoms. Trained staff reviewed most medications, including pill-bottle review. Antidepressant use was coded as a yes/no variable based on current use of tricyclic antidepressants, monoamine oxidase inhibitors, and other nontricyclic antidepressants.

Anger, anxiety, and chronic stress were measured at visits 1 and 3. Anger was measured by the Spielberger Trait Anger scale, which includes 10 items assessing extent and frequency of experiencing anger.[11] Anxiety was measured by the Spielberger Trait Anxiety scale, which also consisted of 10 items and measured feelings of apprehension, tension, worry, and nervousness.[12] Items on each scale had a 4-point response from "almost never" (1) to "almost always (4) and scores were summed across items to create a Trait Anger score and Trait Anxiety score (range, 10–40). Total scores were modeled categorically into approximate quartiles, based on the distribution of scores, to evaluate potential threshold effects.

Chronic stress was assessed by the Chronic Burden Scale, which assesses presence and severity of ongoing stress in 5 domains: (1) health problems of oneself; (2) health problems of close others; (3) job or ability to work; (4) relationships; and (5) finances.[13] Participants were coded as experiencing stress for each domain in which they indicated an ongoing problem as moderately or very stressful. The chronic stress score was the number of domains for which a participant had ongoing difficulties (range, 0–5). Three stress groups were created based on scores of 0, 1, and ≥2.

Atrial Fibrillation

AF identified by either self-report or study visit ECG was an exclusion criterion for enrollment in MESA. Incident AF was identified from study ECGs verified for AF at visit 5, *International Classification of Diseases, Ninth Revision* (*ICD-9*) hospital discharge diagnoses consistent with AF (427.31 or 427.32), and, for participants enrolled in fee-for-service Medicare, inpatient and outpatient AF claims data.[14] Among participants 55 years of age or older at baseline, 86% were enrolled in fee-for-service Medicare at some point during follow-up. Follow-up consisted of phone calls or field center visits every 9 to 12 months to identify hospitalizations and medical records, including discharge diagnoses. ECGs in MESA were read at a centralized ECG reading center, Epidemiological Cardiology Research Center, at Wake Forest University. The time to AF was set as the time of study visit if AF was identified from a study ECG; otherwise, it was set as

time of hospital or physician claim if it was identified through hospitalizations and medical records.

Covariates

Standardized questionnaires were used at baseline to obtain demographic information, level of education, annual household income, physical activity, alcohol consumption, smoking history, and medication usage, including statin, antihypertensive, or antidiabetic use. Education was categorized into "high school or less," "some college," or "college or more." Annual household income was dichotomized at <$20 000, ≥$20 000 but less than $50 000, ≥$50 000 but less than $75 000, or ≥$75 000. Body mass index was calculated as weight in kilograms divided by height in meters squared. Three separate systolic (SBP) and diastolic blood pressure measurements were taken in seated participants at rest, with the last 2 measurements being averaged for analysis. Physical activity was recorded as participant-reported number of intentional exercise metabolic equivalent-minutes per week. Current alcohol consumption was determined by self-report. Cigarette smoking was calculated in pack-years and also defined as current, former, or never. Total and high-density lipoprotein cholesterol and fasting glucose were measured from blood samples. Hypertension was defined as a self-report of physician diagnosis and use of an antihypertensive medication, or SBP ≥140 or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as a fasting glucose >125 mg/dL or use of antidiabetic medications.

Statistical Analysis

Individuals missing baseline measures for antidepressant use, CES-D, Spielberger Trait Anger, Spielberger Trait Anxiety, or the Chronic Burden Scale were excluded from the primary analysis (n=82). In addition, those with AF identified by Medicare claims data that occurred before enrollment (n=63) or missing AF follow-up data (n=5) were also excluded. Baseline characteristics were compared across CES-D score categories (<2, 2–5, 6–9, 10–15, ≥16) and according to development of AF. Categorical variables were reported as frequency and percentage while continuous variables were reported as mean±standard deviation. Statistical significance for categorical variables was tested using the chi-square method and the analysis of variance procedure for continuous variables.

Cox proportional hazards models were used to compute adjusted hazards ratios (HRs) and 95% CIs for incident AF across CES-D score categories (referent, CES-D <2) and antidepressant use (referent, no antidepressant use). The *P* trend was determined from modeling categories as either ordinal or continuous variables. Follow-up time was defined as the time from the baseline visit to AF development, death, loss to follow-up, or end of follow-up. Multivariable models were constructed to account for variables known to be associated with AF. Model 1 adjusted for age, sex, race, education, income, and clinic site; Model 2 adjusted for Model 1 covariates with the addition of cigarette smoking, body mass index, height, diabetes mellitus, glucose, SBP, moderate and vigorous physical activity, antihypertensive medication use, statin use, and current alcohol use. Similar analyses were performed to determine associations for Spielberger Trait Anger (referent, first quartile), Spielberger Trait Anxiety (referent, first quartile), and chronic burden scale (referent, 0) with incident AF. Associations between CES-D scores and incident AF in Model 2 were simultaneously adjusted for baseline Spielberger Trait Anger, Spielberger Trait Anxiety, and chronic burden scale scores. Associations between antidepressant use and incident AF in Model 2 were also additionally adjusted for all negative affect measures. We also performed an analysis of time-updated depressive symptoms measures with incident AF to determine if associations between depressive symptoms and incident AF are more strongly affected by more recent assessments (those occurring after the baseline visit). The most recent CES-D scale score and antidepressant use assessment was used for this analysis.

We evaluated for effect modification by sex and race/ethnicity, using stratification and interaction terms, for analyses involving depressive symptoms and incident AF. Due to limited sample size, the referent category for CES-D analyses was a score <16. Finally, we stratified participants according to CES-D score (<16 vs ≥16) and antidepressant use (yes versus no) determine if graded associations with incident AF existed across those meeting no, one, or both criteria for depressive symptoms (referent, CES-D <16 and no antidepressant use). Statistical significance for all comparisons including interactions was defined as $P<0.05$. SAS Version 9.4 (Cary, NC) was used for all analyses.

Results

A total of 6664 participants with baseline data on depressive symptoms and without previous AF were included in the final analysis (mean age=62±10 years; 53% female; 38% white, 28% black, 22% Hispanic, and 12% Chinese). The mean CES-D score was 7.6±7.6 and 423 (6.3%) participants reported antidepressant use at baseline. Eight hundred seventy-five (13.1%) participants developed AF (incidence rate per 1000 person-years=11.7; person-years of follow-up=74 759 years) over a median follow-up of 12.9 years (25th–75th percentiles=9.9–13.6 years).

Table 1 shows that participants with incident AF were older and more likely to be male, be white, be less educated, have a lower income, have a higher SBP, have a lower total cholesterol, have a higher serum glucose, have diabetes mellitus, have a smoking history, be less physically active, report using antihypertensive and statin medications, and have lower Spielberger Trait Anger scale and Chronic Burden scale scores. Both the CES-D scale and Spielberger Trait

Table 1. Baseline Characteristics of MESA Participants According to Presence or Absence of Incident Atrial Fibrillation*

Characteristic	Incident AF (n=875)	No AF (n=5789)	*P* Value†
Age, y	69 (7.9)	61 (10.0)	<0.001
Male, %	484 (55)	2659 (46)	<0.001
Race, %			<0.001
White	414 (47)	2138 (37)	
Chinese	107 (12)	690 (12)	
Black	192 (22)	1644 (28)	
Hispanic	162 (19)	1317 (23)	
Education, %			0.011
High school or less	348 (40)	2065 (36)	
Some college	216 (25)	1690 (29)	
College or more	311 (35)	2034 (35)	
Income, %			<0.001
<$20 000	295 (34)	1478 (26)	
$20 000–$49 999	293 (33)	2045 (35)	
$50 000–$74 999	115 (13)	979 (17)	
≥$75 000	172 (20)	1287 (22)	
Body mass index, kg/m^2	28 (5.5)	28 (5.5)	0.61
Systolic blood pressure, mm Hg	134 (22)	125 (21)	<0.001
Total cholesterol, mg/dL	191 (35)	195 (36)	0.007
HDL cholesterol, mg/dL	51 (15)	51 (15)	0.56
Glucose, mg/dL	101 (34)	97 (30)	<0.001
Diabetes mellitus, %	127 (15)	625 (11)	0.001
Smoking status, %			<0.001
Never	404 (46)	2948 (51)	
Former	372 (43)	2065 (36)	
Current	99 (11)	776 (13)	
Current alcohol use, %	471 (54)	3218 (56)	0.33
Moderate/vigorous physical activity, MET-min/week	4873 (5053)	5890 (5978)	<0.001
Antihypertensive use, %	443 (51)	2006 (35)	<0.001
Statin use, %	173 (20)	805 (14)	<0.001
Antidepressant use, %	63 (7)	360 (6)	0.26
CES-D Scale score	7.4 (7.4)	7.6 (7.6)	0.56
Spielberger Trait Anger Scale score	14 (3.4)	15 (3.7)	<0.001
Spielberger Trait Anxiety Scale score	16 (4.4)	16 (4.5)	0.083
Chronic Burden Scale score	1.1 (1.2)	1.2 (1.2)	0.018

AF indicates atrial fibrillation; CES-D, Center for Epidemiologic Studies Depression; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalents.
*Continuous variables are expressed as mean (SD). Categorical variables are N (%).
†Comparisons were made between incident AF and no AF. Fisher's exact test used to make statistical comparison.

Anxiety scale scores did not significantly differ between those with and without incident AF. Baseline characteristics are also compared across CES-D scale score categories in Table 2. Notably, younger age and female sex were associated with higher scores on the CES-D scale, while no significant trends were observed for SBP, serum glucose, diabetes mellitus, or antihypertensive use.

Table 3 shows the risk of incident AF by presence of baseline depressive symptoms. After adjustment for age, sex, race, education, income, clinic site, cigarette smoking, body mass index, height, diabetes mellitus, glucose, SBP, moderate and vigorous physical activity, antihypertensive medications, statins, and current alcohol use, higher CES-D scores were associated with an increased risk of AF (*P* trend=0.039). Participants with a CES-D score ≥16 had a higher risk of developing AF compared with those with a CES-D score <2 (HR=1.34; 95% CI, 1.04–1.74). Results remained significant with further adjustment for baseline anger, anxiety, or chronic

Table 2. Baseline Characteristics of MESA Participants According to Center for Epidemiologic Studies Depression Scale Score*

Characteristic	CES-D Scale Score					*P* Value†
	<2 (n=1322)	2 to 5 (n=2006)	6 to 9 (n=1444)	10 to 15 (n=1039)	≥16 (n=853)	
Age, y	63 (9.9)	62 (10)	62 (10)	62 (10)	61 (11)	<0.001
Male, %	725 (55)	1042 (52)	672 (47)	437 (42)	267 (31)	<0.001
Race, %						<0.001
White	488 (37)	868 (43)	538 (37)	391 (38)	267 (31)	
Chinese	202 (15)	251 (13)	162 (11)	116 (11)	66 (8)	
Black	387 (29)	521 (26)	438 (31)	274 (26)	216 (25)	
Hispanic	245 (19)	366 (18)	306 (21)	258 (25)	304 (36)	
Education, %						<0.001
High school or less	400 (30)	614 (31)	538 (37)	451 (43)	410 (48)	
Some college	359 (27)	600 (30)	426 (30)	287 (28)	234 (27)	
College or more	563 (43)	792 (39)	480 (33)	301 (29)	209 (25)	
Income, %						<0.001
<$20 000	329 (25)	425 (21)	357 (25)	324 (31)	338 (40)	
$20 000–$49 999	427 (32)	657 (33)	533 (37)	398 (38)	323 (38)	
$50 000–$74 999	198 (15)	392 (20)	256 (18)	146 (14)	102 (12)	
≥$75 000	368 (28)	532 (26)	298 (20)	171 (17)	90 (10)	
Body mass index, kg/m^2	29 (5.0)	28 (5.3)	28 (5.6)	29 (5.8)	29 (5.9)	<0.001
Systolic blood pressure, mm Hg	126 (20)	126 (21)	127 (22)	126 (21)	127 (23)	0.89
Total cholesterol, mg/dL	193 (35)	193 (34)	195 (35)	196 (39)	196 (37)	0.008
HDL cholesterol, mg/dL	50 (15)	50 (15)	52 (15)	51 (14)	52 (15)	<0.001
Glucose, mg/dL	98 (30)	96 (29)	97 (30)	97 (31)	100 (34)	0.097
Diabetes mellitus, %	138 (10)	206 (10)	169 (12)	124 (12)	115 (13)	0.099
Smoking status, %						<0.001
Never	666 (50)	1018 (51)	700 (48)	526 (51)	442 (52)	
Former	516 (39)	764 (38)	535 (37)	359 (34)	263 (31)	
Current	140 (11)	224 (11)	209 (15)	154 (15)	148 (17)	
Current alcohol use, %	745 (56)	1213 (60)	798 (55)	514 (50)	419 (49)	<0.001
Moderate/vigorous physical activity, MET-min/week	5348 (5647)	5736 (5522)	5878 (6155)	6157 (6150)	5745 (6159)	0.015
Antihypertensive use, %	490 (37)	697 (35)	521 (36)	413 (40)	328 (38)	0.064
Statin use, %	200 (15)	297 (15)	215 (15)	160 (15)	106 (12)	0.38
Antidepressant use, %	48 (4)	106 (5)	77 (5)	84 (8)	108 (13)	<0.001

CES-D indicates Center for Epidemiologic Studies Depression; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalents.
*Continuous variables are expressed as mean (SD). Categorical variables are N (%).
†Statistical significance for categorical variables tested using the chi-square method and for continuous variables the analysis of variance procedure was used.

Table 3. Associations of Baseline Depressive Symptoms With Incident AF*

	n AF/N at Risk	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
CES-D score			
<2	117/1322	1 (referent)	1 (referent)
2–5	275/2006	1.11 (0.91–1.35)	1.15 (0.94–1.39)
6–9	173/1444	1.07 (0.86–1.33)	1.07 (0.86–1.33)
10–15	140/1039	1.21 (0.96–1.53)	1.19 (0.94–1.50)
≥16	110/853	1.34 (1.04–1.73)	1.34 (1.04–1.74)
P trend		0.023	0.039
Antidepressant use			
No	812/6241	1 (referent)	1 (referent)
Yes	63/423	1.47 (1.13–1.91)	1.36 (1.04–1.77)

AF indicates atrial fibrillation; CES-D, Center for Epidemiologic Studies Depression; HR, hazard ratio.
*Results of multivariable Cox proportional hazards models.
†Model 1 adjusted for age, sex, race, education, income, and clinic site.
‡Model 2 adjusted for Model 1+cigarette smoking, body mass index, height, diabetes mellitus, glucose, systolic blood pressure, moderate and vigorous physical activity, statin use, antihypertensive use, and current alcohol use.

Table 4. Associations of Time-Dependent Depressive Symptoms With Incident AF*

	n AF/N at Risk	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
CES-D score			
<2	172/1413	1 (referent)	1 (referent)
2–5	212/1571	1.14 (0.93–1.40)	1.15 (0.94–1.42)
6–9	231/1708	1.14 (0.93–1.40)	1.09 (0.88–1.34)
10–15	143/1037	1.27 (1.01–1.60)	1.27 (1.00–1.60)
≥16	117/935	1.35 (1.05–1.73)	1.32 (1.02–1.69)
P trend		0.015	0.030
Antidepressant use			
No	796/6155	1 (referent)	1 (referent)
Yes	79/509	1.49 (1.17–1.89)	1.41 (1.11–1.79)

AF indicates atrial fibrillation; CES-D, Center for Epidemiologic Studies Depression; HR, hazard ratio.
*Results of multivariable Cox proportional hazards models with time-dependent CES-D measures and anti-depressant use.
†Model 1 adjusted for age, sex, race, education, income, and clinic site.
‡Model 2 adjusted for Model 1+cigarette smoking, body mass index, height, diabetes mellitus, glucose, systolic blood pressure, moderate and vigorous physical activity, statin use, antihypertensive use, and current alcohol use.

stress (HR, 1.50; 95% CI, 1.11–2.04). In a similarly adjusted model, participants reporting antidepressant also had a higher risk of developing AF compared with those reporting no antidepressant use (HR, 1.36; 95% CI, 1.04–1.77). Additional adjustment for baseline CES-D scores, anger, anxiety, or chronic stress did not attenuate associations between antidepressant use and incident AF (HR, 1.33; 95% CI, 1.02–1.74). When using the most recent CES-D score instead of the baseline measure, if one was available, participants with a CES-D score of 10 to 15 or ≥16 were both at an increased risk for incident AF compared with those with a CES-D score <2 (Table 4). CES-D assessments after the baseline visit were available for 5813 study participants (87%). When CES-D scores were dichotomized (≥16 vs <16), the risk of incident AF associated with a CES-D score ≥16 was not significantly increased (HR, 1.22; 95% CI, 0.98–1.51). No significant associations were observed for baseline measures of anger, anxiety, or chronic stress with development of AF (Table 5).

We used a test for interaction to assess the evidence for difference in the association of depressive symptoms with AF by sex. As shown in Table 6, the test for interaction was not significant (*P*=0.42 for CES-D; and *P*=0.44 for antidepressant use). Similarly, associations did not significantly differ across race/ethnicity (Table S1).

Stratifying participants according to both CES-D score ≥16 and antidepressant use, a progressive increase in AF risk in fully adjusted analyses across those meeting no, one, or both criteria for depressive symptoms was seen (*P* trend=0.005; Table 7).

Discussion

Higher CES-D scores were associated with an increased risk of incident AF in a multiethnic cohort with extended follow-up. Additionally, depressive symptoms as defined by either a CES-D score ≥16 or self-reported use of antidepressants were associated with a higher risk of incident AF compared with those with a CES-D score <2 and those reporting no antidepressant use, respectively. The risk of AF appeared to be greatest in those participants meeting both criteria for depressive symptoms. Anger, anxiety, and chronic stress were not associated with the development of AF in this same cohort.

Because the CES-D is a screening tool for depressive symptoms, our intention for including antidepressant use was to provide a proxy for previous diagnosis of depression. Interestingly, >75% of individuals on antidepressant therapy (315 of 423) had a baseline CES-D <16, suggesting that the CES-D is not necessarily capturing individuals with more severe depression at the time of enrollment, though it is possible they had a prior history of such symptoms. These individuals, therefore, represented a substantially different population than those with a high CES-D score. The risk of AF associated with receiving antidepressant treatment, however, was similar to that associated with a high CES-D score. Findings suggest that both tools are important but incomplete methods for identifying those individuals with a current or prior history of depressive symptoms who are at risk for developing AF. The findings also raise important questions

Table 5. Associations of Baseline Anger, Anxiety, and Chronic Stress With Incident AF*

	n AF/N at Risk	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
Spielberger Trait Anger score			
First quartile (<12)	204/1234	1 (referent)	1 (referent)
Second quartile (12–13)	191/1516	0.84 (0.69–1.03)	0.82 (0.67–1.00)
Third quartile (14–16)	288/2184	1.04 (0.86–1.25)	1.01 (0.83–1.22)
Fourth quartile (≥17)	192/1730	1.01 (0.82–1.25)	0.95 (0.77–1.17)
P-trend		0.53	0.97
Spielberger Trait Anxiety score			
First quartile (<12)	182/1227	1 (referent)	1 (referent)
Second quartile (12–14)	234/1751	1.03 (0.84–1.26)	1.03 (0.84–1.26)
Third quartile (15–18)	247/1933	1.05 (0.86–1.28)	1.05 (0.86–1.28)
Fourth quartile (≥19)	212/1753	0.99 (0.80–1.22)	0.97 (0.79–1.20)
P trend		0.89	0.74
Chronic Burden Scale score			
0	318/2276	1 (referent)	1 (referent)
1	301/2085	1.06 (0.90–1.25)	1.08 (0.92–1.28)
≥2	256/2303	1.13 (0.95–1.34)	1.06 (0.89–1.27)
P trend		0.78	0.47

AF indicates atrial fibrillation; HR, hazard ratio.
*Results of multivariable Cox proportional hazards models.
†Model 1 adjusted for age, sex, race, education, income, and clinic site.
‡Model 2 adjusted for Model 1+cigarette smoking, body mass index, height, diabetes mellitus, glucose, systolic blood pressure, moderate and vigorous physical activity, statin use, antihypertensive use, and current alcohol use.

regarding whether treatment of depression can help to actually lower the risk of AF or whether there may be proarrhythmic properties of antidepressants that mitigate any beneficial effect associated with improvement in depressive symptoms.[15,16]

Over one third of people with AF have depressive symptoms and mortality risk is increased in affected men.[17,18] Depressed mood is most prevalent among those with persistent AF subtype.[19] Prior cross-sectional study has found that rates of depressive symptoms are higher in individuals with AF

Table 6. Associations of Baseline Depressive Symptoms With Incident AF Stratified by Sex*

	Men		Women	
	n AF/N at Risk	HR (95% CI)†	n AF/N at Risk	HR (95% CI)†
CES-D score				
CES-D <16	445/2876	1 (referent)	320/2935	1 (referent)
CES-D ≥16	39/267	1.05 (0.74–1.49)	71/586	1.35 (1.02–1.78)
P interaction	0.42			
Antidepressant use				
No	464/3024	1 (referent)	348/3217	1 (referent)
Yes	20/119	1.16 (0.73–1.85)	43/304	1.50 (1.08–2.08)
P interaction	0.44			

AF indicates atrial fibrillation; CES-D, Center for Epidemiologic Studies Depression; HR, hazard ratio.
*Results of multivariable Cox proportional hazards models.
†Model adjusted for age, sex, race, education, income, clinic site, cigarette smoking, body mass index, height, diabetes mellitus, glucose, systolic blood pressure, moderate and vigorous physical activity, statin use, antihypertensive use, and current alcohol use.

Table 7. Associations of Baseline Depressive Symptoms Stratified by Baseline CES-D Score (≥16/<16) and Anti-Depressant Use (Yes/No) With Incident AF*

	n AF/N at Risk	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
CES-D <16+no antidepressant	717/5496	1 (referent)	1 (referent)
CES-D ≥16+no antidepressant	95/745	1.19 (0.94–1.49)	1.18 (0.94–1.49)
CES-D <16+antidepressant	48/315	1.43 (1.06–1.93)	1.32 (0.98–1.78)
CES-D ≥16+antidepressant	15/108	1.74 (1.03–2.93)	1.67 (0.99–2.81)
P-trend		0.001	0.005

AF indicates atrial fibrillation; CES-D, Center for Epidemiologic Studies Depression; HR, hazard ratio.
*Results of multivariable Cox proportional hazards models.
†Model 1 adjusted for age, sex, race, education, income, and clinic site.
‡Model 2 adjusted for Model 1+cigarette smoking, body mass index, height, diabetes mellitus, glucose, systolic blood pressure, moderate and vigorous physical activity, statin use, antihypertensive use, and current alcohol use.

compared with those without AF. In a large population-based study of over 10 000 individuals, the Gutenberg Health Study, individuals with AF were 21% more likely to have a history of depression than compared with those without AF.[20] These individuals also scored higher on the Patient Health Questionnaire-9, a measure of depressive symptoms.[20] In a study of nearly 100 individuals with either persistent or paroxysmal AF, arrhythmic episodes, as assessed by Holter monitor, were more likely to be preceded by negative emotions and less likely by happiness.[21] Sadness had the strongest odds of preceding an AF episode compared with the other negative emotions, including anger, stress, and anxiety.[21] Risk of recurrent AF is also higher in individuals with a depressed mood following cardioversion to sinus rhythm.[22]

Prospective studies evaluating the association of depressive symptoms and new onset AF are limited and no prior studies have used measures that are specific for the assessment of depressive symptoms.[5] In a large study of over 30 000 Women's Health Study participants, neither depressive symptoms nor antidepressant use were associated with incident AF over median follow-up over 10 years.[5] This study, however, had some important differences. Aside from including only women, this study was composed of a predominantly white population with a very low rate of incident AF (2.5%) over a similar follow-up period. Additionally, and most importantly, assessment of depression was with a short 5-item Mental Health Inventory and more detailed instruments to measure depression were not used.

Several mechanisms can be proposed to explain the findings observed in our study. Inflammation is associated with an increased risk of incident AF and depression intensifies the activation of the inflammatory response system.[23] Specifically, depression has been associated with lymphocyte proliferation, increased serum concentrations of acute-phase reactants such as C-reactive protein, decreased levels of negative acute-phase proteins, and enhanced cytokine secretion.[24] Depression may also increase AF risk through effects on the ANS, hypothalamic-pituitary-adrenal axis, and renin-angiotensin-aldosterone system. Catecholamine levels, primarily norepinephrine, are higher in depressed individuals compared with controls and may indicate increased sympathetic nervous activity.[25] Hypercortisolism and reduced feedback inhibition of the hypothalamic-pituitary-adrenal has also been observed in depression.[26] Finally, in a small study of 14 patients, nocturnal serum aldosterone levels were persistently elevated throughout the night in depressed patients compared with healthy controls, suggesting that mineralocorticoid sensitivity may be altered in depression.[27] Taken together, the increase in inflammation along with activation of the ANS, hypothalamic-pituitary-adrenal axis, and renin-angiotensin-aldosterone system seen in depression may increase AF susceptibility either directly by disrupting electrophysiologic properties of the atria as seen with ANS dysregulation or indirectly by promoting atrial fibrosis, increasing atrial pressure, and stretching the atria.[2] Finally, prior studies have reported the importance of behavioral mechanisms, including smoking, dietary adherence, stress reduction, physical inactivity, and medication nonadherence, in explaining associations between depression and risk of cardiovascular disease.[28,29] Considering that AF and cardiovascular disease share many common risk factors, it is possible that similar mechanisms may contribute to an increased incident AF risk as well. Dedicated research to more specifically evaluate the role of potential biological or behavioral mechanisms in the setting of depression and increased risk of AF will be important.

It is unclear why depressive symptoms were associated with incident AF, but other emotional distress measures had no association with AF. Anger, anxiety, and stress have also been suggested to elicit AF through similar mechanisms including activation of the ANS and hypothalamic-pituitary-adrenal axis as well as inducing direct electrophysiologic

changes in the heart.[3,4] Multiple prior studies, however, have also found no association between these negative emotions and incident AF.[5,6,8,30] While stress was found to be a common inciting factor in patients hospitalized with paroxysmal AF, 2 large prospective studies found no association between baseline stress levels and incident AF.[5,8,31] Similarly, while anxiety symptoms were associated with an increased likelihood of new-onset, postoperative AF among individuals undergoing cardiac surgery, in a prospective evaluation of over 3500 Framingham Offspring Study (FOS) participants baseline anxiety was not associated with incident AF.[6,30] Negative emotions of anger, hostility, and tension were all associated with the development of AF in men only, however, in this same population of FOS participants.[6,7] While overall associations, not stratified by sex, were not reported in these studies, our findings somewhat contrast those reported in the FOS. It is important to point out, however, that the FOS participants were significantly different from MESA participants. They were significantly younger (48 years vs 62 years), experiencing much lower cumulative incidence of AF (5% versus 13%). Rates of incident AF are high in older age, and the underlying substrate for its development is often age- and disease-related atrial remodeling.[32,33] AF presenting at an earlier age, as was the case in the FOS cohort, may be due to different substrates, more influenced by genetic predisposition and by other factors not related to remodeling.[33] Therefore, it is possible that certain negative emotions, such as anger, hostility, or tension, may play a more important role in early-onset AF but not in the later onset, more prevalent form.

The risk of AF associated with either CES-D scores $\geq$16 or antidepressant use was more pronounced among women compared with men. Although a statistically significant interaction for sex was not observed, we had limited power for the stratified analyses and the difference may have been significant with an adequate sample size. Prior literature has suggested that the presence of depression may influence cardiac electromechanical properties differently based on sex. In an analysis of nearly 400 individuals hospitalized with acute coronary syndrome, the corrected QT interval was nearly 30 ms longer in women with depressive symptoms compared with those without.[34] No significant differences in the corrected QT interval were observed, however, for men with and without depressive symptoms. Further study is needed in larger populations that definitely address whether a significant depression-sex interaction exists as it relates to AF risk as well the possible electromechanical changes underlying such an interaction.

An important strength of our study is the use of a large, well-characterized, multiethnic cohort with repeat assessment of depressive symptoms and long-term prospective follow-up. Our study also has some limitations. The CES-D scale measures depressive symptoms over a short time period. It does not allow one to assume chronicity of symptoms or make a clinical diagnosis of depression. However, the scale has been, validated for use in epidemiologic study and is the most widely used tool for assessing depressive symptoms for such research. Misclassification of participants on antidepressants may have occurred, as they may have been taking them for other indications. The method of AF detection used is not sensitive for cases of paroxysmal AF that were asymptomatic, and these cases may have been missed. Because no information regarding symptom presence or the paroxysmal versus permanent nature of AF is available, we cannot determine whether depression may have stronger associations with certain AF subtypes. Causality cannot be inferred on the basis of this observational study, and we cannot exclude the possibility that unmeasured or inadequately measured confounders may account for the observed associations.

AF accounts for nearly 15% of all US strokes, and annual costs for AF treatment alone exceed $6 billion. Considering that 20% of adults report prevalent depressive symptoms in representative US data samples, confirming that this large population is at increased risk for AF and, if so, whether targeted efforts to improve the identification and treatment of these individuals reduces AF incidence will be important.[35]

In conclusion, depressive symptoms, measured via a CES-D scale or antidepressant use, were associated with incident AF, and the risk appeared to be greatest in those participants both with a high CES-D score and using antidepressants. Further study in larger cohorts appropriately powered to detect significant interactions and with more comprehensive and clinically validated assessments of depression is needed. Additionally, once a diagnosis of depression is established, a better understanding of how antidepressant medication or other therapeutic interventions might then modify the risk of subsequent AF is also needed.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding

This research was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 and by grant R01-HL-127659 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from NCATS. O'Neal is supported by the National Heart, Lung, and Blood

Institute of the National Institutes of Health under award number F32HL134290. This work was additionally supported by American Heart Association grant 16EIA26410001 (Alonso).

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Associations of baseline depressive symptoms with incident atrial fibrillation stratified by race/ethnicity[*].

	White	Chinese	African-American	Hispanic
	HR (95% CI)[†]	HR (95% CI)[†]	HR (95% CI)[†]	HR (95% CI)[†]
CES-D score				
CES-D <16	1 (referent)	1 (referent)	1 (referent)	1 (referent)
CES-D ≥16	1.15 (0.81, 1.62)	0.90 (0.38, 2.13)	1.62 (1.05, 2.50)	1.26 (0.84, 1.91)
p-interaction	0.35			
Anti-depressant use				
No	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Yes	1.26 (0.89, 1.77)	0.75 (0.22, 2.54)	1.63 (0.71, 3.81)	1.84 (1.03, 3.29)
p-interaction	0.36			

AF=atrial fibrillation, CES-D=Center for Epidemiologic Studies Depression, HR=hazard ratio, CI=confidence interval

*Results of multivariable Cox proportional hazards models

†Model adjusted for age, sex, race, education, income, clinic site, cigarette smoking, body mass index, height, diabetes, glucose, systolic blood pressure, moderate and vigorous physical activity, statin use, antihypertensive use, and current alcohol use