European Journal of Preventive Cardiology

ESC European Society of Cardiology

Full research paper

European Journal of Preventive Cardiology
0(00) 1–9

DOI: 10.1177/2047487319897163
journals.sagepub.com/home/cpr

SAGE

Associations of anger, vital exhaustion, anti-depressant use, and poor social ties with incident atrial fibrillation: The Atherosclerosis Risk in Communities Study

Parveen K Garg[1], J'Neka S Claxton[2], Elsayed Z Soliman[3,4], Lin Y Chen[5], Tené T Lewis[2], Thomas Mosley Jr[6] and Alvaro Alonso[2]

Abstract

Background: We examined the relationships of anger, vital exhaustion, anti-depressant use, and poor social ties with incident atrial fibrillation in a biracial cohort of middle and older-aged adults.

Methods: This analysis included 11,445 Atherosclerosis Risk in Communities Study participants who were free of atrial fibrillation at baseline in 1990–1992. Vital exhaustion was assessed at baseline and defined as a score in the highest quartile on the 21-item Vital Exhaustion Questionnaire. Baseline anti-depressant use was self-reported. The Spielberger Trait Anger Scale to assess anger and both the Interpersonal Support Evaluation List and the Lubben Social Network Scale to assess social ties were also administered at baseline. The primary outcome was incident atrial fibrillation throughout 2016, identified by electrocardiogram, hospital discharge coding of atrial fibrillation, and death certificates.

Results: A total of 2220 incident atrial fibrillation cases were detected over a median follow-up of 23.4 years. After adjusting for age, race-center, sex, education, and height, participants in the 4th Vital Exhaustion Questionnaire quartile (referent = 1st Vital Exhaustion Questionnaire quartile) and those reporting anti-depressant use were at increased risk for atrial fibrillation (hazard ratio = 1.45, 95% confidence interval 1.29–1.64 for Vital Exhaustion Questionnaire; hazard ratio = 1.37, 95% confidence interval 1.11–1.69 for anti-depressant use). The increased atrial fibrillation risk observed for 4th Vital Exhaustion Questionnaire quartile participants remained significant after additional adjustment for relevant comorbidities (hazard ratio = 1.20; confidence interval 1.06–1.35). No significant associations were observed for anger or poor social ties with development of atrial fibrillation.

Conclusions: Vital exhaustion is associated with an increased risk of incident atrial fibrillation.

Keywords

Vital exhaustion, depression, atrial fibrillation, arrhythmia

Received 9 August 2019; accepted 5 December 2019

Introduction

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia in clinical practice, with an estimated prevalence of up to 17 m people in Europe by 2020.[1,2] After accounting for known modifiable risk factors, nearly half of the population attributable risk for AF development still remains unexplained.[3] Continued investigation into identifying additional risk factors is important to improve our understanding

[1]Division of Cardiology, University of Southern California Keck School of Medicine, USA
[2]Department of Epidemiology, Emory University, USA
[3]Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, USA
[4]Department of Medicine, Wake Forest School of Medicine, USA
[5]Division of Cardiology, University of Minnesota Medical School, USA
[6]MIND Center, University of Mississippi Medical Center, USA

Corresponding author:
Parveen K Garg, Division of Cardiology, University of Southern California Keck School of Medicine, 1510 San Pablo St, Suite 322, Los Angeles, CA 90033, USA.
Email: parveeng@med.usc.edu

of the mechanisms that cause AF. Psychological distress has been suggested as one such additional risk factor leading to AF development due to pathways involving the autonomic nervous system (ANS), hypothalamus-pituitary-adrenal (HPA) axis, and renin-angiotensin-aldosterone system, as well as through direct effects on the sinus and atrioventricular nodes.[4–6]

Studies in the literature examining the prospective relationship between psychosocial measures and incident AF have reported mixed results. Initial studies, performed in predominantly white populations, reported that depression and chronic stress were not associated with AF while anger, hostility, and tension were, but only in men.[7–10] More recently, a nationwide registry-based Danish study found that anti-depressant use was strongly associated with AF development.[11] In the Multi-Ethnic Study of Atherosclerosis, depressive symptoms were also associated with incident AF; however, there were no associations observed for anger, anxiety, or chronic stress.[12] Additionally, no studies have evaluated the associations of social support or social isolation with incident AF. We sought to build upon the current literature by examining the association of several psychosocial measures indicative of underlying distress with incident AF in the Atherosclerosis Risk in Communities (ARIC) study, a well-characterized cohort of predominantly whites and blacks.

Methods

Study population and design

The ARIC study included 15,792 men and women aged 45–64 years sampled from four US communities in 1987–1989.[13] Participants were re-examined in 1990–1992, 1993–1995, 1996–1998, 2011–2013, and 2016–2017, and were followed for cardiovascular events. Institutional review boards at each participating institution (University of Minnesota, Johns Hopkins University, University of North Carolina, and University of Mississippi Medical Center) approved the study and all participants gave written informed consent at each study visit.

ARIC participants attending Visit 2 (1990–1992) with exposure data on anger, vital exhaustion, anti-depressant use, and social support were eligible for this analysis. Visit 2 served as the baseline visit for this analysis. After excluding participants not attending Visit 2 ($n = 1444$), those with prevalent AF as defined below ($n = 245$), missing exposure data ($n = 51$), missing covariate information ($n = 2509$), those with no follow-up beyond visit 2 ($n = 6$), and, due to small numbers, race other than black or white and the few black participants from Minneapolis and Washington County ($n = 92$), the remaining sample size was 11,445. The current study is a prospective analysis of these participants to determine the relationships of psychosocial measures, assessed at Visit 2, and incident AF with follow-up through until 31 December 2016.

Psychosocial measures

Anger was measured by the Spielberger Trait Anger scale, which includes 10 items assessing extent and frequency of experiencing anger.[14] Each item has a four-point response from "almost never" ("1") to "almost always ("4") and scores are summed across items to create a Trait Anger score (range, 10–40). High trait anger was defined by scores of 22–40, moderate anger by scores of 15–21, and low anger by scores of 10–14.

Vital exhaustion was assessed via a 21-item Vital Exhaustion Questionnaire (VEQ).[15] The questions represented three categories: (a) vegetative depressive symptoms (fatigue, sleep pattern, energy, and concentration); (b) nonvegetative symptoms (crying spells, hopelessness, irritability, decreased libido, and suicidality); and (c) functional depressive symptoms (coping and productivity). Responses are summed to obtain an overall vital exhaustion score, which ranges from 0–42, with higher scores representing more depressive symptoms. The correlation of vital exhaustion and depressive scores measured by the Beck Depression Inventory is 0.62.[16] As established cut-offs do not exist, scores were stratified into approximate quartiles to evaluate potential threshold effects.

Use of anti-depressant medications served as a proxy for participants with mental disorders encompassing the affective and anxiety disorder spectrum. At each study visit, participants brought all medications, vitamins, and supplements taken over the previous two weeks. Trained staff transcribed and coded all medication names. Antidepressant use was coded as a yes/no variable based on current use of selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other antidepressants.

Social ties were assessed using the short form of the Interpersonal Support Evaluation List (ISEL-SF) and social network was assessed with the Lubben Social Network Scale (LSNS).[17,18] The 16-item ISEL-SF measures an individual's perception of his or her appraisal support, tangible assets, belonging support, and self-esteem support. Each question of the ISEL-SF is scored on a four-point rating scale (definitely true, probably true, probably false, and definitely false; scored 0–3). The total (summed) score is an aggregate index of social support, with higher scores indicating greater levels of perceived interpersonal support. As established cut-offs for ISEL-SF scores do not exist, scores were stratified into approximate quartiles to evaluate potential threshold effects.

The LSNS is a self-assessed measure of the size and availability of one's active social network of family, friends and peers, consisting of 10 questions on a 0–5 rating scale. Total scores range from 0–50 and are classified based on established levels of risk for social isolation: socially "isolated" (≤20), "high risk" for isolation (21–25), "moderate risk" for isolation (26–30) and "low risk" for isolation (≥31). Three groups were created based on scores of ≤25, 26–30, and ≥31. The "isolated" and "high risk" categories were collapsed because few participants score within the "isolated" range.

AF

Incident AF was defined as in previous ARIC analyses.[19] All electrocardiogram (ECG) recordings automatically coded as AF were visually re-checked by a trained cardiologist to confirm the diagnosis. A trained abstractor obtained and recorded all International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) hospital discharge diagnoses from each participant's hospitalizations reported in the annual follow-up interview. AF was defined as the presence of ICD-9-CM code 427.31 or 427.32 in the discharge codes (International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes I48.xx starting in 2015). AF hospitalization diagnoses occurring simultaneously with heart revascularization surgery or other cardiac surgery involving heart valves or septa, without evidence of AF in subsequent hospitalizations or study examinations were excluded. ARIC participants were also labeled as AF cases if the underlying cause of death was AF. The incidence date of AF was defined as the date for the first ECG showing AF or the first hospital discharge with an AF diagnosis. Individuals with ECG-diagnosed AF at either of the first two study visits or those with an AF hospitalization diagnosis prior to Visit 2 were considered to have baseline AF and excluded from this analysis.

Covariates

All covariates were assessed at Visit 2 and included age (years), sex, race, ARIC field center, education level (<high school degree, ≥high school degree; assessed only at visit 1), height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), cigarette smoking (never/former/current), alcohol consumption (never/former/current), physical activity (PA), medication use (anti-diabetic and anti-hypertensive), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, blood glucose, ECG-defined left ventricular hypertrophy (LVH), and cardiovascular disease (CVD).

The modified Baecke questionnaire was used to assess PA in sport activities during the past year.[20] Diabetes was defined as non-fasting blood glucose ≥200 mg/dl, eight-hour fasting blood glucose ≥125 mg/dl, self-reported history of physician-diagnosed diabetes, or use of anti-diabetic medications. CVD at baseline included the presence of coronary heart disease (CHD), heart failure (HF), or stroke. CHD was defined as a self-reported history of physician diagnosed myocardial infarction (MI), prior coronary revascularization, a previous MI by electrocardiogram. HF was defined as the reported use of HF medication or the presence of HF according to the Gothenburg criteria.[21] Stroke was defined as a self-reported history of physician diagnosed stroke. Prevalent CVD at Visit 2 also considered incident adjudicated events between Visits 1 and 2.

Statistical analysis

Baseline characteristics were compared across VEQ quartiles and according to the development of AF. Categorical variables were reported as frequency and percentage while continuous variables were reported as mean ± standard deviation.

Cox proportional hazards models were used to compute adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) for incident AF across VEQ score quartiles (referent = 1st quartile) and standard deviation increments as well as anti-depressant use (referent = no anti-depressant use). Follow-up time was defined as the time from Visit 2 to AF development, death, loss to follow-up, or censored at 31 December 2016. Multivariable models were constructed to account for variables known to be associated with AF. Model 1 adjusted for age, sex, race-center (whites, Washington County; whites, Minneapolis; blacks, Jackson; blacks, Forsyth County; or whites Forsyth County, education, and height; Model 2 adjusted for Model 1 covariates with the addition of weight, cigarette smoking, diabetes, SBP, DBP, antihypertensive medication use, TC, HDL, physical activity, current alcohol use, CHD, HF, LVH, and stroke. Similar analyses were performed to determine associations for Spielberger Trait Anger score (referent = low), overall and individual component ISEL-SF scores (referent = 1st quartile), and LSNS score (referent = low-risk) with incident AF.

We evaluated for effect modification by sex and race, using stratification and interaction terms, for analyses involving each of these psychosocial measures and incident AF. Due to the limited sample size, the referent categories were expanded to include the 2nd and 3rd quartiles for the VEQ and ISEL-SF measures and the moderate category for the Spielberger Trait Anger and LSNS measures. Finally, we stratified participants according to VEQ score (<4th quartile vs 4th quartile) and anti-depressant use (yes vs no) to determine associations with incident AF by joint categories of these

two variables. Statistical significance for all comparisons including interactions was defined as $p < 0.05$. SAS Version 9.4 (Cary, North Carolina, USA) was used for all analyses.

Results

A total of 11,445 participants with baseline data on psychosocial measures and without previous AF were included in the final analysis (mean age = 57 ± 5.7 years; 56% female; 74% white). The mean VEQ score was 10.3 ± 8.6 and 426 (3.7%) participants reported anti-depressant use at baseline. Two thousand two hundred and twenty (19.4%) participants developed AF (incidence rate per 1000 person-years = 9.8, 95% CI 9.5–10.2; person-years of follow-up = 225,502) over a median follow-up of 23.4 years (25th–75th percentiles = 15.0–25.3 years).

Baseline characteristics are compared according to development of AF (Table 1) and by level of vital exhaustion (Table 2). Female gender, black race, diabetes, cigarette smoking, CVD, LVH, anti-hypertensive and anti-depressant medication use were more common while alcohol consumption was less common among participants with higher VEQ scores. Participants with higher VEQ scores also were less educated, reported less PA, and had a higher BMI, lower height, higher SBP, lower DBP, higher TC, lower HDL cholesterol, and higher serum glucose.

Table 3 shows the risk of incident AF by presence of baseline psychosocial measures. After adjustment for age, sex, race-center, education, weight, cigarette smoking, diabetes mellitus (DM), SBP, DBP, anti-hypertensive medication, TC, HDL, physical activity, alcohol consumption, CHD, congestive HF, LVH, and stroke, higher VEQ scores were associated with an increased risk of AF (HR per SD increment = 1.08; 95% confidence interval (CI) 1.03–1.13). Participants with a VEQ score in the 4th quartile had a higher risk of developing AF compared to only those in the 1st quartile (HR = 1.20; 95% CI 1.06–1.35). Results were similar when AF risk for participants with a VEQ score in the 4th quartile were compared to all other participants (HR 1.13; 95% CI 1.02–1.25).

After adjusting for baseline demographics, participants reporting anti-depressant use also had a higher risk of developing AF compared to those reporting no anti-depressant use (HR 1.37; 95% CI 1.11–1.69); however, associations were considerably attenuated in the fully adjusted model (HR 1.21; 95% CI 0.98–1.50). The risk of developing AF did not differ across the various anti-depressant types (Supplemental Material Table 1). No significant associations were observed for baseline measures of anger, social support, or social network with development of AF (Table 3). Associations for each of the ISEL-SF sub-scales with incident AF were also not significant (Supplemental Material Table 2).

We conducted stratified analysis and used a test for interaction to assess the evidence for difference in the associations of vital exhaustion and anti-depressant use with AF by sex. As shown in Supplemental Material Table 3, the test for interaction was not significant ($p = 0.26$ for VEQ and $p = 0.79$ for anti-depressant use). Similarly, associations did not significantly differ across race (Supplemental Material Table 4). Risk of incident AF for participants stratified by both

Table 1. Baseline characteristics of Atherosclerosis Risk in Communities (ARIC) participants according to development of atrial fibrillation (AF).[a]

Characteristic	Incident AF ($n = 2220$)	No AF ($n = 9225$)
Age, years	58.8 (5.6)	56.5 (5.7)
Male, %	1133 (51)	3949 (43)
Race, %		
White	1796 (81)	6621 (72)
Black	424 (19)	2604 (28)
Education ≤ 12 years, %	1268 (57.1)	4785 (51.9)
Body mass index, kg/m^2	28.9 (5.7)	27.7 (5.3)
Height, cm	170.2 (9.5)	168.2 (9.2)
Systolic blood pressure, mm Hg	125.6 (19.9)	120.7 (18.4)
Diastolic blood pressure, mm Hg	72.6 (10.8)	72.2 (10.2)
Total cholesterol, mg/dl	208.8 (38.3)	209.9 (39.7)
HDL cholesterol, mg/dl	47.4 (15.5)	50.3 (16.9)
Glucose, mg/dl	118.0 (47.9)	113.4 (43.2)
Diabetes, %	402 (18.1)	1300 (14.1)
Smoking status, %		
Never	792 (35.7)	3761 (40.8)
Former	909 (41)	3406 (37)
Current	519 (23.4)	2058 (22.3)
Coronary heart disease, %	187 (8.4)	416 (4.5)
Heart failure, %	151 (6.8)	374 (4.1)
Stroke, %	54 (2.4)	151 (1.6)
Left ventricular hypertrophy, %	71 (3.2)	221 (2.4)
Sport activity, score	2.5 (0.8)	2.4 (0.8)
Current alcohol use, %	1275 (57.4)	5254 (57)
Anti-hypertensive use, %	779 (35.1)	2297 (25)
Anti-depressant use, %	90 (4.1)	336 (3.6)
Spielberger Trait Anger Scale score	16.2 (3.9)	16.0 (3.8)
Vital Exhaustion Questionnaire score	10.7 (8.8)	10.2 (8.6)
ISEL-SF score	36.7 (6.5)	37.0 (6.6)
LSNS score	35.1 (6.6)	35.1 (6.5)

HDL: high-density lipoprotein; ISEL-SF: Interpersonal Support Evaluation List; LSNS: Lubben Social Network Scale; SD: standard deviation.
[a]Continuous variables are expressed as mean (SD).

Table 2. Baseline characteristics of Atherosclerosis Risk in Communities (ARIC) participants by level of vital exhaustion ($n = 11{,}276$).[a]

	VEQ score			
Characteristic	Quartile 1 (≤4)	Quartile 2 (5–8)	Quartile 3 (9–15)	Quartile 4 (16–42)
Age, years	56.5 (5.6)	56.9 (5.7)	57.1 (5.8)	57.3 (5.8)
Male, %	2210 (60.1)	1033 (46.3)	1010 (37.9)	795 (29.4)
Black, %	721 (19.6)	548 (24.6)	774 (29.0)	934 (34.6)
Education ≤ 12 years, %	1552 (42.2)	1097 (49.2)	1490 (55.9)	1805 (66.9)
Body mass index, kg/m^2	27.3 (4.6)	27.7 (5.2)	28 (5.5)	29 (6.2)
Height, cm	171 (9.3)	168.8 (9.1)	167.8 (9.2)	166.2 (8.8)
Systolic blood pressure, mm Hg	120.3 (17.5)	122.2 (18.2)	121.9 (19)	122.6 (20.6)
Diastolic blood pressure, mm Hg	72.5 (9.8)	72.7 (10)	72 (10.5)	71.9 (10.9)
Total cholesterol, mg/dl	207.1 (37.4)	209.3 (37.9)	210.2 (39.7)	212.3 (42.1)
HDL cholesterol, mg/dl	48.1 (16.0)	50.1 (17.1)	50.4 (17.1)	50.8 (16.7)
Glucose, mg/dl	110.4 (36.7)	112.3 (39.9)	114.5 (43.5)	120.4 (55.6)
Diabetes, %	412 (11.2)	292 (13.1)	417 (15.6)	551 (20.4)
Smoking status, %				
Never	1444 (39.3)	899 (40.3)	1034 (38.8)	1092 (40.4)
Former	1547 (42.1)	858 (38.4)	980 (36.7)	882 (32.7)
Current	685 (18.6)	475 (21.3)	654 (24.5)	726 (26.9)
Coronary heart disease, %	159 (4.3)	109 (4.9)	145 (5.4)	183 (6.8)
Heart failure, %	70 (1.9)	71 (3.2)	133 (5)	242 (9)
Stroke, %	41 (1.1)	28 (1.3)	46 (1.7)	83 (3.1)
Left ventricular hypertrophy, %	55 (1.5)	38 (1.7)	84 (3.2)	110 (4.1)
Sport activity, score	2.6 (0.8)	2.5 (0.8)	2.4 (0.7)	2.2 (0.7)
Current alcohol use, %	2374 (64.6)	1346 (60.3)	1465 (54.9)	1275 (47.2)
Anti-hypertensive use, %	754 (20.5)	571 (25.6)	746 (28)	950 (35.2)
Anti-depressant use, %	54 (1.5)	58 (2.6)	108 (4.1)	200 (7.4)

HDL: high-density lipoprotein; SD: standard deviation; VEQ: Vital Exhaustion Questionnaire.
[a]Continuous variables are expressed as mean (SD). Categorical variables are *n* (percentage).

VEQ = 4th quartile and anti-depressant use is shown in Table 4. Only participants with VEQ = 4th quartile and without anti-depressant use were at a 13% statistically significant higher risk for developing AF (referent = VEQ < 4th quartile + no anti-depressant). Those using anti-depressant had a non-statistically significant 25–27% increased risk of AF.

Discussion

Vital exhaustion was associated with an increased risk of incident AF in a biracial cohort with extended follow-up. This relationship did not significantly differ across gender or race. Anti-depressant use showed an association of similar strength with development of AF; however, significance was lost with multi-variate adjustment. Anger and poor social ties were not associated with the development of AF in this same cohort.

Prior studies have reported on the prospective relationship of depressive symptoms and AF; however, none of these studies have specifically evaluated the relationship between the VEQ and AF.[9,11,12] Though multiple prior studies, performed predominantly in individuals with coronary artery disease, demonstrated the VEQ to be highly correlated with other depression screening measures, important differences between the constructs of vital exhaustion and depressive symptoms exist.[16,22,23] The VEQ assesses two symptom dimensions, fatigue and depression, and vital exhaustion itself is defined more broadly as excessive fatigue, feelings of demoralization, and increased irritability.[15,23] Guilt and low self-esteem – key features of depression – are largely absent among exhausted persons.[24] In a study of healthy individuals who were administered the VEQ, those with "exhaustion" predominantly suffered from loss of vigor and excess fatigue, while a depressed mood was almost absent.[25] In another study, although the correlation between vital exhaustion score and the Beck Depression Inventory was strong, clear differences in strength of association between depression, vital exhaustion, and several

Table 3. Baseline associations of vital exhaustion, anti-depressant use, anger, and social support with incident atrial fibrillation (AF) among Atherosclerosis Risk in Communities (ARIC) participants.[a]

	n AF/*n* at risk	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
VEQ score			
1st quartile (≤4)	671/3676	1 (referent)	1 (referent)
2nd quartile (5–8)	436/2232	1.17 (1.03–1.32)	1.09 (0.96–1.23)
3rd quartile (9–15)	510/2668	1.23 (1.10–1.39)	1.10 (0.98–1.24)
4th quartile (16–42)	560/2700	1.45 (1.29–1.64)	1.20 (1.06–1.35)
SD increment		1.16 (1.11–1.21)	1.08 (1.03–1.13)
Anti-depressant use			
No	2130/11,019	1 (referent)	1 (referent)
Yes	90/426	1.37 (1.11–1.69)	1.21 (0.98–1.50)
Spielberger Trait Anger score			
Low (10–14)	799/4223	1 (referent)	1 (referent)
Moderate (15–21)	1214/6254	1.08 (0.99–1.18)	1.02 (0.93–1.12)
High (22–40)	194/916	1.26 (1.08–1.48)	1.08 (0.92–1.27)
SD increment		1.08 (1.03–1.12)	1.02 (0.98–1.07)
LSNS score			
Low-risk (≥31)	1718/8750	1 (referent)	1 (referent)
Moderate-risk (26–30)	281/1569	0.95 (0.84–1.08)	0.93 (0.81–1.05)
High-risk/isolated (≤25)	183/926	1.13 (0.97–1.32)	1.09 (0.94–1.27)
SD increment		0.99 (0.95–1.03)	1.01 (0.97–1.05)
ISEL-SF score			
1st quartile (2–33)	636/3167	1 (referent)	1 (referent)
2nd quartile (34–38)	585/2906	0.92 (0.82–1.03)	0.97 (0.87–1.09)
3rd quartile (39–42)	513/2718	0.89 (0.79–1.00)	0.97 (0.86–1.09)
4th quartile (43–48)	447/2479	0.87 (0.77–0.99)	0.97 (0.86–1.10)
SD increment		0.94 (0.90–0.98)	0.98 (0.94–1.02)

CI: confidence interval; DBP: diastolic blood pressure; DM: diabetes mellitus; HDL: high-density lipoprotein; HR: hazard ratio; ISEL-SF: Interpersonal Support Evaluation List; LSNS: Lubben Social Network Scale; SBP: systolic blood pressure; SD: standard deviation; TC: total cholesterol; VEQ: Vital Exhaustion Questionnaire.

[a]Results of multivariable Cox proportional hazards models. SD increments were as follows: VEQ = 8.62, Spielberger Trait Anger = 3.77, LSNS = 6.55, and ISEL SF = 6.55

[b]Model 1 adjusted for age, sex, race-center, education, and height.

[c]Model 2 adjusted for Model 1 + weight, cigarette smoking, DM, SBP, DBP, anti-hypertensive medication, TC, HDL, physical activity, alcohol consumption, coronary heart disease, congestive heart failure, left ventricular hypertrophy, and stroke

Table 4. Associations of baseline Vital Exhaustion Questionnaire (VEQ) score (4th quartile/<4th quartile) and anti-depressant use (yes/no) with incident atrial fibrillation (AF).[a]

	n AF/*n* at risk	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
VEQ < 4th quartile + no anti-depressant	1569/8356	1 (ref)	1 (ref)
VEQ = 4th quartile + no anti-depressant	519/2500	1.29 (1.17–1.43)	1.13 (1.02–1.25)
VEQ < 4th quartile + anti-depressant	48/220	1.39 (1.05–1.86)	1.25 (0.94–1.67)
VEQ = 4th quartile + anti-depressant	41/200	1.58 (1.15–2.15)	1.27 (0.93–1.75)

CI: confidence interval; DBP: diastolic blood pressure; DM: diabetes mellitus; HDL: high-density lipoprotein; HR: hazard ratio; SBP: systolic blood pressure; TC: total cholesterol.

[a]Results of multivariable Cox proportional hazards models.

[b]Model 1 adjusted for age, sex, race-center, education, and height.

[c]Model 2 adjusted for Model 1 + weight, cigarette smoking, DM, SBP, DBP, anti-hypertensive medication, TC, HDL, physical activity, alcohol consumption, coronary heart disease, congestive heart failure, left ventricular hypertrophy, and stroke.

other variables were observed.[16] Cognitive and mood disturbances characteristic of depression occurred less frequently in the individuals with vital exhaustion whereas loss of energy was significantly more often associated with these individuals.

Despite these differences, however, the increased AF risk associated with higher levels of vital exhaustion observed in this study was consistent with those reported for studies evaluating the relationship between depressive symptoms and incident AF.[11,12] In the Multi-Ethnic Study of Atherosclerosis, depressive symptoms, as measured by the Center for Epidemiologic Studies Depression scale, and anti-depressant use were each associated with a 30% increased risk of incident AF.[12] In a large nationwide matched Danish cohort registry study spanning nearly 14 years, individuals initiating antidepressant medication were at a substantially higher risk of subsequent AF.[11] The risk was greatest in the 30 days before and after medication initiation, as much as 3–8 times higher during this time period compared to a randomly sampled background population without a history of antidepressant treatment. The risk remained increased following this time period but was substantially attenuated (37% and 11% higher in the 2–6 months and 6–12 months after antidepressant therapy initiation, respectively). This observed excess risk noted around the time of anti-depressant initiation may have been confounded by an improved recognition of prevalent AF identified in connection with the diagnosis of depression, either due to the intensification of AF symptoms or increased ECG screening prior to medication initiation.

In contrast to the two studies mentioned above, we found a weaker association of anti-depressant use with incident AF. The risk associated with anti-depressant use may reflect the presence of more severe depressive symptoms and not necessarily a lack of effectiveness of these agents. Antidepressant use, however, is indicated for a variety of conditions including both anxiety and affective disorders. Reported associations, therefore, more likely reflect a variety of underlying mental health conditions and not simply depressive symptoms. Additionally, there are many reports documenting the pro-arrhythmic effects of anti-depressants. Both selective serotonin reuptake inhibitors and tricyclic antidepressants have been associated with QT interval prolongation and a small but significant increased risk of sudden cardiac death.[24,26,27] While nearly all studies are focused on risks of ventricular arrhythmias, a very small study actually found that paroxetine reduces drug-resistant paroxysmal AF, potentially through its ability to modulate vagal tone.[28] Further study is still clearly needed to better understand the risk of AF associated with anti-depressant use.

Potential mechanisms linking vital exhaustion to the development of AF are similar to those for depression. Vital exhaustion is associated with an increased inflammatory response.[29,30] There is also evidence that vital exhaustion is associated with a decrease in activity of the hypothalamic-pituitary-adrenocortical axis, which is important in regulating the body's stress response.[31,32]

While some other psychosocial measures in this study were also associated with incident AF in bivariate analyses, the significance was lost after multivariate adjustment. Although it is unclear why vital exhaustion was associated with incident AF while anger and two distinct measures of social ties had no association, the findings are consistent with the previous literature.[8–10,12] Poor social support results in increased stress levels and, subsequently, increases the risk of unhealthy behaviors or adverse physiological conditions.[33–35] Both anger 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 electrophysiological changes in the heart.[36,37] While no prior studies have specifically looked at the risk of AF associated with poor social support or reduced social networks, multiple prospective studies found no association between baseline stress levels and incident AF.[9,10,12] In two prior studies, anger was associated with an increased AF risk in one study, but this was only observed in men.[8,12]

Our study has limitations. We had available only a single measure of psychosocial factors and this analysis does not account for fluctuations in these factors over time. Additionally, we cannot assess the impact of temporal relationships between the different psychosocial measures on AF risk. As mentioned above, the VEQ was not specifically developed to measure depressive symptoms and a commonly recognized cut-point for the presence of depressive symptoms based on this measure does not exist. The method of AF detection requiring either hospitalization or being present on routine ECG is not sensitive for cases of paroxysmal AF that were either asymptomatic or did not require hospitalization, and these cases were missed. Since no information regarding symptom presence or the paroxysmal vs permanent nature of AF is available, we cannot determine whether depression may have stronger associations with certain AF subtypes.

In conclusion, vital exhaustion was associated with an increased risk of incident AF. Considering the overall prevalence of depressive disorders in European nations is estimated at 8.5%, establishing whether vital exhaustion or anti-depressant use increase AF risk, even if only modestly, could have significant implications.[38] The effect size for the observed association between vital exhaustion and AF in this study was small and clinical relevance cannot be assumed. Further study in larger cohorts with more comprehensive and clinically validated assessments of depression is needed. Ultimately, determining whether targeted efforts to improve the

identification and treatment of these individuals actually reduces AF incidence and obtaining a better understanding of how these therapeutic interventions might modify risk will be most important.

Author contribution

PG, JC, and AA contributed to the conception or design of the work. All contributed to the acquisition, analysis, or interpretation of data for the work. PG and JC drafted the manuscript. All critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgements

The authors thank the staff and participants of the ARIC study for their important contributions.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN26820 1700005I, HHSN268201700004I). This work was additionally supported by the American Heart Association (grant number 16EIA26410001 to Alonso) and the NHLBI (grant number K24HL148521).

References

1. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union from 2000 to 2060. *Eur Heart J*. 2013; 34: 2746–2751.
2. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2013; 6: 213–220.
3. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: The Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011; 123: 1501–1508.
4. Chen PS and Tan AY. Autonomic nerve activity and atrial fibrillation. *Heart Rhythm* 2007; 4: S61–S64.
5. Brotman DJ, Golden SH and Wittstein IS. The cardiovascular toll of stress. *Lancet* 2007; 370: 1089–1100.
6. Insulander P, Juhlin-Dannfelt A, Freyschuss U, et al. Electrophysiologic effects of mental stress in healthy subjects: A comparison with epinephrine infusion. *J Electrocardiol* 2003; 36: 301–309.
7. Eaker ED, Sullivan LM, Kelly-Hayes M, et al. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: The Framingham Offspring Study. *Psychosomatic Medicine* 2005; 67: 692–696.
8. Eaker ED, Sullivan LM, Kelly-Hayes M, et al. Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. *Circulation* 2004; 109: 1267–1271.
9. Whang W, Davidson KW, Conen D, et al. Global psychological distress and risk of atrial fibrillation among women: The Women's Health Study. *J Am Heart Assoc* 2012; 1: e001107.
10. Svensson T, Kitlinski M, Engstrom G, et al. Psychological stress and risk of incident atrial fibrillation in men and women with known atrial fibrillation genetic risk scores. *Sci Rep* 2017; 7: 42613.
11. Fenger-Gron M, Vestergaard M, Pedersen HS, et al. Depression, antidepressants, and the risk of non-valvular atrial fibrillation: A nationwide Danish matched cohort study. *Eur J Prev Card* 2019; 26: 187–195.
12. Garg PK, O'Neal WT, Diez Roux A, et al. Depressive symptoms and risk of incident atrial fibrillation. *J Am Heart Ass* 2018; 8: e010603.
13. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: Design and objectives. *Am J Epidemiol* 1989; 129: 687–702.
14. Spielberger CD. *Preliminary manual for the State-Trait Personality Inventory*. Palo Alto, CA: Consulting Psychologist Press, 1980.
15. Appels A, Höppener P and Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. *Int J Cardiol* 1987; 17: 15–24.
16. Kopp MS, Falger PR, Appels A, et al. Depressive symptomatology and vital exhaustion are differentially related to behavioral risk factors for coronary artery disease. *Psychosom Med* 1998; 60: 752–758.
17. Cohen S, Mermelstein R, Kamarck T, et al. Measuring the functional components of social support. In: Sarason IG (Ed.) *Social support: Theory, research and applications*. Netherlands: Springer, 1985, pp.73–94.
18. Lubben JE. Assessing social networks among elderly populations. *Fam Community Health* 1988; 11: 42–52.
19. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2009; 158: 111–117.
20. Baecke JA, Burema J and Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982; 36: 936–942.
21. Eriksson H, Caidahl K, Larsson B, et al. Cardiac and pulmonary causes of dyspnoea: Validation of a scoring test for clinical-epidemiological use: The Study of Men Born in 1913. *Eur Heart J* 1987; 8: 1007–1014.
22. Wojciechowski FL, Strik JMH, Falger P, et al. The relationship between depressive and vital exhaustion symptomatology post-myocardial infarction. *Act Psychiatr Scand* 2000; 102: 359–365.

23. McGowan L, Dickens C, Percival C, et al. The relationship between vital exhaustion, depression and comorbid illnesses in patients following first myocardial infarction. *J Psychosom Res* 2004; 57: 183–188.
24. Castro VM, Murphy SN, Fava M, et al. QT interval and antidepressant use: A cross sectional study of electronic health records. *BMJ* 2013; 346: f288.
25. Diest Van R and Appels A. Vital exhaustion and depression: A conceptual study. *J Psychosom Res* 1991; 35: 535–544.
26. Qirjazi E, McArthur E, Nash DM, et al. Risk of ventricular arrhythmia with citalopram and escitalopram: A population-based study. *PLoS One* 2016; 11: e0160768.
27. Weeke P, Jensen A, Folke F, et al. Antidepressant use and risk of out-of-hospital cardiac arrest: A nationwide case-time control study. *Clin Pharmacol Ther* 2012; 92: 72–79.
28. Shirayama T, Sakamoto T, Sakatani T, et al. Usefulness of paroxetine in depressed men with paroxysmal atrial fibrillation. *Am J Cardiol* 2006; 97: 1749–1751.
29. Appels A, Bär FW, Bär J, et al. Inflammation, depressive symptomatology, and coronary artery disease. *Psychosom Med* 2000; 62: 601–605.
30. Kop WJ, Gottdiener JS, Tangen CM, et al. Inflammation and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia. *Am J Cardiol* 2002; 89: 419–424.
31. Bellingrath S, Weigl T and Kudielka BM. Cortisol dysregulation in school teachers in relation to burnout, vital exhaustion, and effort-reward imbalance. *Biol Psychol* 2008; 78: 104–113.
32. Nicolson NA and van Diest R. Salivary cortisol patterns in vital exhaustion. *J Psychosom Res* 2000; 49: 335–342.
33. Knox SS and Uvnas-Moberg K. Social isolation and cardiovascular disease: An atherosclerotic pathway? *Psychoneuroendocrinology* 1998; 23: 877–890.
34. Stuller KA, Jarrett B and DeVries AC. Stress and social isolation increase vulnerability to stroke. *Exp Neurol* 2012; 233: 33–39.
35. Loucks EB, Sullivan LM, D'Agostino RB Sr, et al. Social networks and inflammatory markers in the Framingham Heart Study. *J Biosoc Sci* 2006; 38: 835–842.
36. Peacock J and Whang W. Psychological distress and arrhythmia: Risk prediction and potential modifiers. *Prog Cardiovasc Dis* 2013; 55: 582–589.
37. Brotman DJ, Golden SH and Wittstein IS. The cardiovascular toll of stress. *Lancet* 2007; 370: 1089–1100.
38. Ayuso-Mateos JL, Vazques-Barquero JL, Dowrick C, et al. Depressive disorders in Europe: Prevalence figures from the ODIN study. *Br J Psychiatry* 2001; 179: 308–316.