Relationship Between Psychosocial Stressors and Atrial Fibrillation in Women >45 Years of Age

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Negative emotions have been linked to the development of atrial fibrillation (AF), and positive effect may be protective. However, there are few large-scale studies examining the association between psychosocial stressors that may provoke these emotions and the occurrence of AF. We examined the cross-sectional relation between psychosocial stress and AF in 24,809 women participating in the Women's Health Study. Participants answered questions about work stress (e.g., excessive work, conflicting demands), work-family spillover stress (e.g., too stressed after work to participate in activities with family), financial stress (e.g., difficulty paying monthly bills), traumatic life events (e.g., death of a child), everyday discrimination (e.g., less respect, poor service), intimate partner stress (e.g., how judgmental is your spouse/partner), neighborhood stress (e.g., neighborhood safety, trust), negative life events within 5 years (e.g., life threatening illness, legal problems), and cumulative stress (a weighted measure of the stress domains). The prevalence of confirmed AF was 3.84% (N = 953) and risk factor profiles differed by AF status. Women with AF reported significantly higher financial stress, traumatic life events, and neighborhood stress ($p_{each} < 0.05$). Only traumatic life events (odds ratio 1.37, 95% confidence interval 1.19 to 1.59) was significantly associated with AF after adjustment for cardiovascular risk factors, socioeconomic and psychosocial status. These large-scale cross-sectional data thus indicate a potential relationship between traumatic life events and AF in older women. Published by Elsevier Inc. (Am J Cardiol 2018;122:1684−1687)

Atrial fibrillation (AF) is a common arrhythmia that disproportionately affects older patients.[1] It is important to understand the determinants of AF in older women as women generally live longer than men and constitute a potentially high-risk group for AF.[1] The pathophysiology of AF is complex and incompletely understood. Numerous cardiac and extra-cardiac factors interact to alter the structural and electrophysiological properties of the atria leading to the arrhythmia.[2−3] Established risk factors for AF such as older age, hypertension, alcohol use, European ancestry, and heart failure do not fully explain AF risk.[2−3] Emerging studies show that psychosocial factors, including anxiety and job stress are related to AF in men.[4−5] Psychosocial factors potentially impact AF through inflammatory, autonomic, and neuro-hormonal mechanisms.[3,6−7] Data about psychosocial factors and AF are largely limited to evaluation of mood or to a small number of individual stressors, and information in women remains sparse. Therefore, we investigated the relationship between multiple individual domains of psychosocial stress, as well as the combination of domain-specific acute and chronic stressors and AF in older women participating in the follow-up cohort of the Women's Health Study (WHS).

Methods

The participants in this study were drawn from the WHS follow-up cohort.[8] WHS was a randomized controlled clinical trial of aspirin and Vitamin E in the primary prevention of cancer and cardiovascular disease (CVD) in 39, 876 female health professionals ≥45 years old at study inception in 1991.[8] At the conclusion of the trial in 2004, women were invited to participate in continued observational follow-up; 4,324 women declined participation. Since 2005, 33,796 consented women have been followed yearly by mailed questionnaires to update demographic and clinical data. Morbidity and mortality follow-up is over 95%.

The WHS Stress Study was initiated in 2012 and 24,809 women without known CVD or AF at baseline completed a

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supplemental cumulative stress questionnaire and comprises this analysis.[9] All WHS participants in the ongoing follow-up cohort were invited to complete the stress questionnaire. These 24,809 women represent >90% of the follow-up cohort and reflects low natural attrition as is generally noted in this cohort. Details of the WHS Stress Study have been previously published.[9] The questionnaire contains a combination of acute and chronic stressors, as well as lifetime stressors using psychometric scales adapted from the Chicago Community Health and Aging and the Americans Changing Lives studies.[9] Eight stress domains are evaluated as follows: (1) work (e.g., unable to make decisions, excessive work); (2) work−family spillover (e.g., too stressed to participate in after work activities); (3) financial; (4) traumatic life events (e.g., death of a child, life threating illness, or accident to family member); (5) everyday discrimination (e.g., less respect, poor service, treated as unintelligent, or dangerous); (6) Intimate partner stress (e.g., happiness with relation, satisfaction with conflict resolution); (7) neighborhood stress (e.g., neighborhood safety); and (8) negative life events within past 5 years (e.g., life-threatening illness, accidental injury, or death to someone close, unemployment, moved to a worse neighborhood, robbery victim). A cumulative stress score was calculated that includes the aforementioned 8 domains. Specifically, this cumulative stress score utilizes weighting that captures the relative number of questions in each stress domain and then all 8 domains were summed (score range 16 to 394).

Ascertainment of AF has been previously described.[10] WHS participants who reported incident AF on their yearly follow-up questionnaire or family members of deceased participants who reported AF before death submitted an additional questionnaire about AF. Medical record review including electrocardiographic review for AF or a documented personal history of AF was performed by an end point committee of physicians. If a subject died within the duration of the study, the next of kin was contacted to obtain informed consent.

Baseline characteristics of the sample were reported in those who had confirmed cases of AF, and those without AF as means or frequencies. Comparisons between the 2 groups were assessed by Chi-Square or Wilcoxon rank sums tests. Logistic regression models were used to assess odds of AF associated with different stress domains computing odds ratios (ORs) and corresponding 95% confidence intervals (CIs). We computed an age adjusted model and a fully adjusted model that included age, race/ethnicity, cardiovascular disease risk factors (i.e., hypertension, hypercholesterolemia, body mass index, diabetes, family history of myocardial infarction, physical activity, smoking, and alcohol use), household income, highest education level, and depressive (i.e., feeling down in the dumps, feeling downhearted/blue, perceived level of happiness), and anxiety symptoms (e.g., level of nervousness or calmness/peacefulness). We used the Benjamini-Hochberg test procedure to control the False Discovery Rate to the alpha = 0.05 level.[11] All p values are 2-tailed and statistical analyses were performed on SAS (version 9.4). All WHS Stress Study participants provided written informed consent. Internal Review Board approval was obtained from the Brigham and Women's Hospital, Boston, Massachusetts and University of California at San Francisco.

Results

In the 24,809 women without known CVD and AF at baseline participating in the WHS Stress Study, 953 had confirmed cases of AF. Table 1 shows the baseline characteristics of participants. Table 2 demonstrates individual stressor domain mean scores based on AF status. Women with AF tended to have higher levels of financial, traumatic life event, neighborhood stress, and lower everyday discrimination stress scores than women without AF. Cumulative stress score was significantly lower in women with AF versus women without AF. Table 3 shows the likelihood of AF in the highest quartile of various psychosocial stress domains compared to the lower 3 quartiles. Only traumatic life event stress continued to be significantly associated with odds of AF in age-adjusted models (OR 1.37, CI [1.19 to 1.59], $p < 0.0001$), as well as in fully adjusted models (OR 1.32, CI [1.12 to 1.52], $p < 0.0007$).

Discussion

In this cross-sectional analysis using the WHS Stress Cohort, traumatic life event stress was significantly associated with higher odds of AF even after adjustment for a number of cardiovascular disease risk factors. The other examined domains of stress showed no significant association with AF. The reason for the lack of association of other domains such as work stress with AF is unknown. However, traumatic life events are generally defining and permanent fixtures of a patient's personal history and may confer sustained health

Table 1
Baseline characteristics in women with and without atrial fibrillation (AF), women's health N = 24,809

Variable	Atrial fibrillation		
	No (N = 23,856)	Yes (N = 953)	p value*
Age (years) (mean, SD)†	72.0 ± 5.95	75.5 ± 6.88	<0.0001
White*	22,641 (95.50%)	929 (98.3%)	<0.0001
Education*			
≥ BS degree	11,220 (47.76%)	392 (41.75%)	0.0003
Household income*			
>$40,000	17,282 (76.58%)	622 (68.13%)	<0.0001
Family history of MI*	3,367 (14.29%)	128 (13.73%)	0.63
Hypertension*	16,497 (69.07%)	872 (91.50%)	<0.0001
Hypercholesterolemia*	17,559(73.52%)	723(75.87%)	0.11
Diabetes mellitus*	2,419 (10.13%)	129(13.54%)	0.0007
Body mass index(kg/m^2) (mean, SD)†	26.8 ± 5.40	27.6 ± 6.23	0.0008
Physical activity*			
>=7.5 (mets/hour)	15,613 (65.37%)	518 (54.35%)	<0.0001
Alcohol use*			
1+ alcoholic (drink/day)	3580 (14.99%)	131 (13.75%)	<0.0001
Current smoker	1145 (4.79%)	30 (3.15%)	0.015
Depression score (mean, SD)†	5.51 ± 2.10	5.65 ± 2.14	0.030
Anxiety score (mean, SD)†	4.38 ± 1.61	4.44 ± 1.66	0.29

SD = Standard Deviation.

* Chi-square test was used to compute p values for race and/or ethnicity, socioeconomic characteristics, and CVD risk factors (categorical variables).

† SD denotes standard deviation, and Wilcoxon rank sums tests for continuous variables were used for significance testing.

Table 2
Baseline stress domain scores*,† in women with and without atrial fibrillation (AF)

Stress Score (Mean ± SD)	No AF (N = 23856)	AF (N = 953)	p value
Work stress*	13.29 ± 3.45	13.24 ± 3.17	0.91
Work-family spillover stress*	4.26 ± 1.87	4.32 ± 1.85	0.42
Financial stress*	3.02 ± 1.13	3.13 ± 1.16	0.0007
Traumatic life event*	0.86 ± 0.88	1.05 ± 0.93	<0.0001
Everyday discrimination*	7.44 ± 2.55	7.23 ± 2.46	0.015
Intimate partner stress*	8.41 ± 2.93	8.23 ± 2.98	0.11
Neighborhood stress*	4.95 ± 1.45	5.03 ± 1.52	0.044
Negative life event within 5 years*	2.22 ± 1.69	2.13 ± 1.45	0.17
Cumulative stress†	163.10 ± 50.74	152.83 ± 49.41	<0.0001

* Stress domains are comprised of the following: work stress (e.g., being able to express creativity at work, having the ability to make decisions at work, having a variety of things to do at work, excessive work, having the time to accomplish responsibilities at work, conflicting demands, job security), work−family conflict (e.g., too stressed after work to participate in activities with family, friends, or community members), financial stress (e.g., having enough money to meet personal or family needs, difficulty paying monthly bills), traumatic life events (e.g., death of a child, victim of assault, life threating illness, or accident to family member), everyday discrimination (e.g., less respect, poor service, feeling as being treated as unintelligent or dangerous, feeling threatened, or harassed), intimate partner stress (e.g., level of happiness with relation, level of demands requested by partner, how judgmental is partner, level of satisfaction with conflict resolution), neighborhood stress (e.g., neighborhood safety during the day and night, ability to trust community members while calling on them in times of need), and negative life event within 5 years stress (e.g., life-threatening illness, accidental injury, or death to someone close, fired from job, >3 months unemployment, household member unemployed or looking for work, moved to a worse residence or neighborhood, robbed or burglarized, serious financial issues, romantic partner infidelity, legal problems, upsetting events that happened to the participant or someone close to the participant).

† Cumulative stress is a weighted measure of the following stress domains: work stress, work-family spillover stress, financial stress, lifetime traumatic life events, negative life events within last 5 years, perceived discrimination, relation stress, and neighborhood stress.

effects. Work stress, intimate partner stress, and work family spillover stress, for instance, may be modified by purposeful change in circumstances. While subsequent counseling and treatment may help a patient cope with the aftermath of a traumatic life event, the fixed nature of the insult itself may account at least in part for the association of this particular domain of stress with increased AF odds. Certainly, traumatic life events can have potent, prolonged effects on mental and physical health.[12]

Our findings support previous work examining the association of individual psychosocial stressors with AF. Previous studies have shown that psychosocial stress is the most common patient identified factor triggering episodes of paroxysmal AF and that negative emotions are more likely than positive emotions to precede these episodes.[13−14] In support of the latter are data showing an association between anxiety with development of postoperative AF, and depressive symptoms with higher failure rates of electrical cardioversion for AF.[15−16] Prospective data from the Framingham Offspring cohort found that psychosocial tension was an independent risk factor for the development of AF in men but not women.[4] Previous research in the WHS also found no association between global psychosocial distress, depressive symptoms, or anxious symptoms with AF.[17] In contrast to our study, these previous studies focused their examination on a few, limited domains of stress or symptoms of stress.[4,17] Additionally, they focused primarily on negative emotions.[4,17] Our study evaluated multiple specific domains of stress encompassing a broad range of acute and chronic psychosocial stressors known to have good psychometric properties and association with physical and mental health outcomes.[6,12,18,19]

Mechanistically, psychosocial stress might lead to sustained increases in autonomic tone, hormonal dysregulation, and inflammation that may, in turn, facilitate atrial fibrosis and AF.[6,20−23] Modulation of the body's inflammatory milieu by psychosocial stressors includes upregulation of interulekin-6 and high-sensitivity CRP, circulating inflammatory markers that have numerous downstream, end-organ effects.[7] In these are the cardiac consequences of accelerated atherosclerosis and, as mounting evidence suggests, a predisposition toward the development of AF.[24−25] Previous studies of both animal models and humans suggest a relationship between psychosocial stress and ventricular tachycardia, which is driven in part by upregulation of the sympathetic nervous system.[26−28] Canine models, in particular, have demonstrated an increased susceptibility to ventricular tachycardia with psychosocial stress, a susceptibility that resolves after β-blocker treatment.[26] Our own group's previous work and a previous Finnish study further demonstrated a relationship between psychosocial stress and sudden cardiac death.[27−28]

Table 3
Odds ratio of atrial fibrillation in each psychosocial stress domain in highest quartile compared to lower 3 quartiles

	Age adjusted			Fully adjusted*		
Stress domain	OR	CI (95%)	p value	OR	CI (95%)	p value
Work stress	0.91	0.71-1.15	0.43	0.79	0.61-1.03	0.07
Work family spillover stress	1.14	0.83-1.56	0.40	1.02	0.73-1.43	0.90
Financial stress	1.20	0.97-1.49	0.10	1.04	0.82-1.32	0.74
Traumatic life event stress	1.37	1.19-1.59	<0.0001	1.32	1.12-1.52	0.0007
Discrimination stress	0.92	0.77-1.10	0.36	0.91	0.75-1.10	0.30
Intimate partner stress	0.97	0.78-1.20	0.76	0.96	0.75-1.22	0.74
Neighborhood stress	1.01	0.87-1.17	0.93	0.91	0.78-1.08	0.29
Negative life events within 5 years	1.01	0.86-1.20	0.87	0.95	0.80-1.14	0.60
Cumulative stress	0.98	0.82-1.17	0.81	0.90	0.74-1.09	0.29

* Adjusted for age, race, cardiovascular disease risk factors, socioeconomic status, and psychosocial status (depression and anxiety).

This study has several limitations. First, the analysis was cross-sectional. As such, no conclusion can be drawn about the temporal or causal relationship between the evaluated psychosocial stressors and AF. Second, as the WHS is comprised primarily of white, although socioeconomically diverse female health professionals, our results may not be generalizable to women of other races or ethnicities. Thus, similar analyses in other populations are warranted. Additionally, asymptomatic AF was not captured. Should asymptomatic AF cluster in groups with particular stress profiles, then our inability to capture it may have altered the results of our study. Finally, perceived stress was self-reported by participants. However, psychosocial stress by definition is primarily inherently perceived by a patient. Indeed, its effect on health is intrinsically dependent on the reaction of individual physiologic systems to this perception. Furthermore, previous research has demonstrated that particularly high perceived stress scores correlate with unfavorable health behaviors.[29] Although the possibility of bias related to nonresponse to the stress questionnaire exists, the likelihood is very low given that over 90% of WHS participants in the follow-up cohort completed the WHS stress questionnaire representing low attrition given participant dropout largely due to death in this cohort of older women, and restriction of the questionnaire to women without known CVD.

In summary, these data indicate a potential relationship between traumatic life events and AF in older women. Further investigation is necessary to confirm whether or not this association is longitudinal. If prospective work establishes an association between AF and traumatic life events, evaluation of stress relieving interventions once an event has occurred is warranted because the impact of the event on health outcomes such as AF might be modifiable although the event itself is typically unmodifiable.

Declarations of interest

None.

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