Relationship between psychological factors and atrial fibrillation
A meta-analysis and systematic review
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Abstract
Background: Although several studies have investigated the role of psychological factors in atrial fibrillation (AF), the results are still under debate. Therefore, we performed a meta-analysis to examine the relationship between psychological factors and the risk of incident AF.

Methods: We systematically searched the PubMed and EMBASE databases from inception to December 2019 to identify eligible studies. The hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled by using a random-effects model.

Results: A total of 11 cohort studies were included in this meta-analysis. There were 5, 2, 4, and 5 studies examining the association of anxiety, anger, depression, and psychological stress with AF, respectively. In the pooled analysis by a random-effects model, anxiety (HR = 1.10, 95%CI 0.97–1.24; \(P = .14\)), anger (HR = 1.08, 95%CI 0.95–1.23; \(P = .21\)), depression (HR = 1.15, 95%CI 0.98–1.35; \(P = .08\)), and work stress (HR = 1.14, 95%CI 0.96–1.34; \(P = .09\)) were not associated with the risk of AF. These results were not changed when we re-performed the analysis using a fixed-effects model.

Conclusions: Based on current evidence, no associations were observed for anger, anxiety, and work stress with the risk of AF.

Abbreviations: AF = atrial fibrillation, CES-D = catchment-area epidemiology survey-depression, CI = confidence interval, HR = hazard ratio, MHI-5 = 5-item mental health inventory.

Keywords: anger, anxiety, atrial fibrillation, depression, stress

1. Introduction
Atrial fibrillation (AF) is the most common arrhythmia with an incidence that increases with age. AF is associated with higher risks of stroke, death, cardiac events, and heart failure. Thus, it is important to early identify high-risk AF patients and suppress AF-related adverse outcomes. Prior studies have identified a series of established risk factors for AF, improving the understanding of its causation and prediction. However, over 40% of the risk attributed to AF is still unexplained; and therefore, additional risk factors for AF such as smoking\textsuperscript{[1]} cardio-metabolic factors (e.g., hypertension and metabolic syndrome\textsuperscript{[2]}) and psychological factors need further investigations.

More recently, several basic and epidemiological studies have gradually recognized psychological factors as the potential risk factors for AF\textsuperscript{[3–5]} However, different studies have provided conflicting findings. Composition of evidence is a method capable of combing a collection of existing data.\textsuperscript{[6]} Depressive symptoms could increase the risk of AF in the general population\textsuperscript{[7]} or in patients with psoriasis.\textsuperscript{[8]} In addition, depression impairs the perception of mental and physical health status in AF.\textsuperscript{[9]} However, no significant associations were observed for depression with the risk of AF in the other 2 studies.\textsuperscript{[9,10]} Similar contradictory results may exist in other psychological factors including anger, anxiety, and psychological stress.\textsuperscript{[7,10–18]}

Although a prior systematic review on this issue has been performed, a clear-cut conclusion on the role of psychological factors in AF could not be drawn from this qualitative investigation. In this study, 6 of 8 included studies were cross-sectional studies with no data for quantitative synthesis; and the other 2 studies also had substantial limitations: Whang et al\textsuperscript{[10]} only included women, whereas Graff et al\textsuperscript{[19]} reported a specific and severe psychological stress (i.e., partner bereavement). As such, the association of psychological factors with AF remains unknown. We herein aimed to conduct a meta-analysis by including more studies on the association between psychological factors and the risk of incident AF.
2. Methods
The ethical approval was not provided because this study was performed by including the published studies. The data that support the findings of this meta-analysis will be available from the corresponding author on reasonable requests.

2.1. Search strategy
The PubMed, and EMBASE electronic databases were searched (from inception to December 15, 2019) by 2 independent reviewers (YH-F and WF-H) to identify potentially eligible studies that reported the relationship between psychological factors and the risk of AF. We did not apply language restrictions in the search. The following search terms were used and limited to retrieval in the titles and abstracts: (atrial fibrillation OR atrial flutter) AND (psychological factors OR psychological distress OR emotional distress OR anxiety OR depression OR stress OR anger). The literature search strategy is presented in Supplemental Table 1, http://links.lww.com/MD/E49. The reference lists of the included studies and review articles were searched to identify additional studies.

2.2. Eligibility criteria
Studies were included if they met the following criteria:

1. studies that reported the relationship between psychological factors and AF;
2. observational cohort studies with both comparison and control groups;
3. studies applying validated instruments to assess psychological factors including depression, anger, anxiety, and psychological stress.

We excluded studies that did not adjust for any potential confounders. Reviews, letters to the editor, case reports, book chapters, editorials and meeting abstracts were excluded. Studies with insufficient or duplicate data were also excluded.

2.3. Data extraction
Study selection was performed by 2 independent authors (YH-F and WF-H) by using the predefined criteria. The first phase of study selection was based on the titles and abstracts of each study. In the second phase, the full-texts were evaluated to detect whether they met the inclusion criteria. All discrepancies were resolved through discussion or by a third researcher (B-W). The general characteristics were recorded for each study, including the first author, publication year, geographic location, information of participants (sample size, age, and sex), instruments of psychological factors, adjusted confounders, and follow-up duration. If one study reported the adjusted RRs by using multiple models, we included the mostly adjusted study in this meta-analysis.

2.4. Risk of bias assessment
The methodological quality of the included studies was assessed independently by 2 researchers (YH-F and WF-H) by using the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale involved 3 domains ranging from 0 to 9 stars: the selection of cohorts (0–4 stars), the comparability of cohorts (0–2 stars), and the assessment of the outcome (0–3 stars). The certain study was considered a moderate to high quality if its score was more than 6 stars.[20–21]

2.5. Statistical analysis
The presentations of this meta-analysis were based on the preferred reporting items for reporting systematic reviews and meta-analyses.[22] The statistical analyses were performed using the Review Manager version 5.3 software (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark).

The statistical statistic and the Q-test were used to measure the statistical heterogeneity. Either $P<.1$ or $I^2>50\%$ indicated a substantial heterogeneity. Maximally adjusted measures of hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted. The studies that reported multiple categories of psychological factors (e.g., high, moderate, low, or no symptoms of depression), HR in the most severe category was used. For each study, the corresponding natural logarithm (Ln[RR]) and standard error (SE) were calculated. Given the heterogeneity inherent across the included studies, the inverse-variance weighted random-effects model was applied to pool the Ln [RR] and its SE. The sensitivity analysis or subgroup analysis was not performed due to the limiting data. According to the Cochrane handbook, it was unsuitable to perform the publication bias for the reported effect estimates when the number of included studies was less than 10. A $P$ value of less than .05 indicated statistical significance.

3. Results
3.1. Study selection
Figure 1 shows the flow diagram used to identify the relevant studies. We identified 5560 studies from our initial database search. After excluding duplicates, the titles/abstracts of 5000 remaining studies were reviewed in detail. Thereinto, 4966 studies did not meet the objectives of this study. After reviewing the full texts of the remaining 34 articles, 12 studies[7–18] were potentially available. In addition, we further excluded the study of Schnabel et al[9] because it was a cross-sectional study. Finally, 11 cohort studies[7,8,10–18] were included in this meta-analysis. The general characteristics of the included studies are shown in Table 1. All of the included studies were acceptable using the Newcastle-Ottawa scale.

3.2. Relationship between psychological factors and AF
3.2.1. Anxiety. A total of 5 included studies examined the association of anxiety with the AF risk. The only included study of Cheng et al[12] reported that panic disorder was associated with an increased rate of AF even after adjusting for potential confounders. In the study of Eaker et al[13] anxiety was not a risk factor for AF in both men and women. As presented in Figure 1, there was no significant association of anxiety with AF (HR=1.10, 95%CI 0.97–1.24; $P=.14$) with an acceptable heterogeneity across the included studies ($I^2=52\%$).

3.2.2. Anger. Two included studies assessed the relationship between anger and the development of AF. Eaker et al[13] demonstrated that anger was related to the risk of AF in men but not in women. As shown in Figure 2, the pooled analysis suggested no association of anger with AF (HR=1.08, 95%CI
0.95–1.23; \( P = .21 \). There was no heterogeneity across the included studies (\( I^2 = 0\% \)).

3.2.3. Depression. As shown in Figure 2, 4 studies were included with regard to depression and the risk of AF. Overall, depression was not associated with an increased risk of AF (HR = 1.15, 95%CI 0.98–1.35; \( P = .08 \)) with an acceptable heterogeneity across the included studies (\( I^2 = 49\% \)).

3.2.4. Psychological stress. As shown in Figure 2, work stress was not significantly associated with an elevated risk of AF (HR = 1.14, 95%CI 0.98–1.34; \( P = .09 \)) with a potential heterogeneity across the included studies (\( I^2 = 59\% \)). The included study by Svensson et al[16] also found no association of non-occupational stress with the risk of AF (HR = 1.07, 95%CI 0.96–1.19; \( P > .05 \))

4. Discussion

To our knowledge, we first comprehensively conducted a meta-analysis to determine the role of psychological factors including depression, anger, anxiety, and psychological stress in AF. With the use of data from 11 included studies, our present meta-analysis suggested that no associations were observed for depression, anger, anxiety, or psychological stress with AF after adjustment for confounders.

It has been reported that AF patients (regardless of the AF subtypes) have high levels of depression symptoms[23,24]; and persistent AF patients may have a more severe depressed mood[25] Two prior studies reviewing the relationship of AF with depression suggested a condition of comorbidity[26,27]. However, it is not that simple for the link of AF with depression. Recent pieces of evidence have enlarged our perspective that
Table 1

General characteristics of the 11 included studies for this meta-analysis.

| Included Studies | Study Design | Source of Participant | Number of Participants (N) | Mean Age (yr) | Sex | Psychological Factors | Instruments | Maximally Adjusted Confounders | Follow-up Period (yr) | NOS Items |
|------------------|-------------|-----------------------|-----------------------------|---------------|-----|-----------------------|-------------|-------------------------------|---------------------|----------|
| Eaker, 2004 Cohort | United States | 3873 | 48.5 | Both | Anger | Framingham Scales | Age, diabetes, hypertension, history of myocardial infarction or history of congestive heart failure, and pulmonary heart disease | 10.0 | 8 |
| Eaker, 2005 Cohort | United States | 3682 | 49.0 | Both | Anxiety | Framingham Scales | Age, diabetes, hypertension, history of myocardial infarction or history of congestive heart failure, and pulmonary heart disease | 10.0 | 8 |
| Whang, 2012 Cohort | United States | 30,746 | 59.0 | Female | Depression; anxiety | Subset of MHI-5 questionnaire | Age, race, body mass index, hypertension, diabetes, hypercholesterolemia, smoking, alcohol intake, kilocalories from exercise, and randomized treatment assignment | 10.4 | 8 |
| Cheng, 2013 Cohort | China | 42,768 | 46.0 | Both | Panic Disorder | ICD-9-CM | Antidepressant use | 7.0 | 7 |
| Egeberg, 2015 Cohort | Denmark | 67,853 | 42.9 | Both | Depression | Age, sex, socioeconomic status, comorbidities and use of concomitant medication | 5.1 | 7 |
| Fransson, 2015 Cohort [WOLF] | Sweden | 13,200 | 47.4 | Both | Work stress | Job demand-control model | Age, smoking, socioeconomic status, hypertension, body mass index and diabetes | 16.8 | 8 |
| Torén, 2015 Cohort | Sweden | 6035 | 55.3 | Male | Work stress | Job-exposure matrix | Age, gender, education, socioeconomic index, smoking, alcohol consumption, prevalent diabetes mellitus, coronary event, heart failure, Body Mass Index, and hypertension | 14.7 | 8 |
| Svensson, 2017 Cohort | Sweden | 22,308 | 57.9 | Both | Psychological stress | Work stress; Job demand-control model; Non-occupational stress; Non-occupational stress | 13.6 | 8 |
| Fransson, 2018 Cohort [SLOSH] | Sweden | 10,121 | 42.5 | Both | Work stress | Job demand-control model | Age, sex, education, smoking, physical activity, body mass index and hypertension | 12.9 | 8 |
| Garg, 2019 Cohort | United States | 6644 | 62 | Both | Depression, anger, anxiety, and chronic stress | Antidepressant use, CES-D, Spielberger Trait Anger, Spielberger Trait Anxiety, or the Chronic Burden Scale | 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, anti-hypertensive use, and current alcohol use | 8.1 | 8 |
| Feng, 2019 Cohort | Norway | 37,402 | 53.4 | Both | Depression, anxiety | The Norwegian version of the Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety (HADS-A) and depression (HADS-D) | Age, sex, weight, height, smoking status, occupation, marital status, physical activity, alcohol consumption, chronic disorders, metabolite components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins, and C-reactive protein.) | 8.1 | 8 |

CES-D = Center for Epidemiologic Studies Depression Scale; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; MHI-5 = 5-item mental health inventory; NOS = Newcastle-Ottawa Scale; SLOSH = Swedish Longitudinal Occupational Survey of Health; WOLF = work, lipids, and fibrinogen.
depression may affect the onset, severity, and prognosis of AF. Compared to AF patients without depression, the risks of death\cite{28,29} and combined ischemic stroke and intracranial hemorrhage\cite{30} are higher and health-related quality of life\cite{31} is poor in patients with depression. In addition, depressive symptoms may predict recurrent AF after cardioversion\cite{32} or postoperative AF.\cite{33}

A prior meta-analysis has indicated that depression is associated with increased risks of sudden cardiac death, ventricular tachycardia/ventricular fibrillation, and AF recurrence, but not incident AF.\cite{34} With regard to depression and incident AF, this meta-analysis only included 2 studies, and both of them had large limitations. In the first study by Whang et al.\cite{10} aside from including only women, is composed of a predominantly white population known to have a lower risk of AF. The second study by Tully et al.\cite{33} explored a potential association of depression with postoperative AF; and thus, this study should not be included for analysis. In light of these limitations, our current meta-analysis included more appropriate researches and found a positive association of depression with incident AF. Moreover, the findings were stable after we excluded the study of Whang et al.\cite{10} It could be explained by several mechanisms why depressive symptoms were associated with AF. Depression may lead to an increase in inflammation and the activation of the autonomous nervous system, hypothalamus-pituitary-adrenal axis, and renin-angiotensin-aldosterone system, which finally increases susceptibility of AF.\cite{7} An increased risk of AF among individuals with depression would support a greater screening and more aggressive measures to prevent AF. Further study is needed to confirm if the reported association is causal.

Studying the role of depression in AF is methodologically challenging. The assessment of psychological factors different methods might lead to the different results. With regard to the measurement of depression symptoms, the current studies applied to different methods. The individuals in the study of Schnabel et al.\cite{9} scored higher on the Patient Health Questionnaire-9. Egeberg et al.\cite{8} included antidepressant use to provide a proxy for a history of depression. The remaining 2 included
studies used both the screening score (the 5-item Mental Health Inventory [MHI-5] score by Whang et al.\textsuperscript{[10]}) and the CES-D (Cheatcape-area Epidemiology Survey-Depression) score by Garg et al.\textsuperscript{[7]} and antidepressant use to create a proxy variable for depression. The risk of AF associated with antidepressant use was similar to that associated with a high MHI-5 or CES-D score.\textsuperscript{[7,10]} In addition, among the users of antidepressants, it is still a controversial issue whether treatment of depression could actually reduce the AF risk\textsuperscript{[13,15,36]} or whether there could be pro-arrhythmic properties of antidepressants that mediate the development of AF.\textsuperscript{[37]} Future studies should include comprehensive and clinically validated assessments of depression to test for its association with AF. The involvement of clinical psychologists in medical research protocols of this field might overcome some methodological problems.

Negative emotions such as anger, anxiety, and psychological stress have been linked to AF in basic researches, which may involve similar biological pathways with depression including activation of the autonomous nervous system and hypothalamus-pituitary-adrenal axis. However, multiple studies found no associations between anger, anxiety, or psychological stress and risk of AF. Also, negative emotions of hostility\textsuperscript{[11]} and tension\textsuperscript{[13]} were associated with AF risk only in men. Further study should confirm the associations between anger, anxiety, or psychological stress and risk of AF. As we know, second-generation cryoballoon is an effective method for the treatment of paroxysmal and persistent AF.\textsuperscript{[38–39]} Whether psychological intervention could reduce the occurrence of AF needs further research.

4.1. Limitations

Several limitations would be acknowledged in this meta-analysis. First, instruments to measure psychological factors across the included studies were inconsistent and had certain disadvantages. For example, the CES-D score was used to measure depressive symptoms over a short time period; and thus, chronicity of symptoms could not be assessed and a clinical diagnosis of psychological disorders might not be made.\textsuperscript{[11]} More comprehensive and clinically validated assessments of depression are needed in the future. Second, some of the included studies did not have medical records to verify psychiatric diagnoses, such that misclassification of psychological symptoms may bias the findings toward no associations. Third, given the nature of observational data, residual confounders might exist although we only included multivariate-adjusted HRs. Fourth, the potential heterogeneity among studies existed and may have resulted from the differences in sample size, analytic strategies, and participant characteristics; however, the subgroup analysis based on these factors could not be performed due to the limited data. Finally, sex differences in the association of depression with AF might exist, but the subgroup analysis based on sex could not be performed due to the limiting data.

5. Conclusions

Based on current publications, no associations were observed for depression, anger, anxiety, and psychological stress with AF. Further study was needed to confirm our findings.

Author contributions

Bo Wei was in charge of the entire project and revised the draft; Yonghui Fu and Wenfeng He performed the literature search, study selection, data extraction, quality assessment, and statistical analysis. Yonghui Fu drafted the first version of the manuscript.

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