



Global epidemiology of mental disorder in atrial fibrillation between 1998-2021: A systematic review and meta-analysis

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Abstract

BACKGROUND

As the burden of mental disorders among patients with atrial fibrillation (AF) increases, researchers are beginning to pay close attention to the risk and prevalence of these comorbidities. Although studies have independently analyzed the risk of comorbidity with depression and anxiety in patients with AF, no study has systematically focused on the global epidemiology of these two mental disorders.

AIM

To explore the prevalence of depression and anxiety in patients with AF.

METHODS

Five databases were searched from their date of establishment until January 2023. Observational studies reporting the comorbidity of AF with depression and anxiety, were included in this study. Basic information, such as the first author/publication year, study year, study type, and prevalence of depression and anxiety, were extracted. STATA SE 15.1 was used to analyze the data. Subgroup, meta-regression, and sensitivity analyses were performed to estimate study heterogeneity.

RESULTS

After a thorough search, 26 studies were identified and included in this meta-analysis. The prevalence rates of depression and anxiety in adults with AF were 24.3% and 14.5%, respectively. Among adult males with AF, the prevalence was 11.7% and 8.7%, respectively, whereas in females it was 19.8% and 10.1%,

respectively. In older adults with AF, the prevalence rates of depression and anxiety were 40.3% and 33.6%, respectively. The highest regional prevalence of depression and anxiety was observed in European (30.2%) and North American (19.8%) patients with AF.

CONCLUSION

In this study, we found that the prevalence of depression and anxiety among patients with AF varies with sex, region, and evaluation scales, suggesting the need for psychological interventions for patients with AF in clinical practice.

Key Words: Atrial fibrillation; Depression; Anxiety; Prevalence

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Core Tip: Mental disorders are risk factors for the development of atrial fibrillation (AF). The global prevalence of AF comorbidity with depression and anxiety is not clear. This is the first study to evaluate the global prevalence of two types of psychiatric disorders (depression and anxiety) in patients with AF from the aspects of age, sex, country, and evaluation scale for depression and anxiety.

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INTRODUCTION

Atrial fibrillation (AF), an irregular and rapid heart rate, is one of the most common cardiac arrhythmias[1,2]. The prevalence of AF has increased steadily over the past three decades, with approximately 60 million people worldwide currently suffering from it[3]. It has been demonstrated that age, gender, smoking, alcohol consumption, hypertension, diabetes, and genetic predisposition are all recognized risk factors for the development and progression of AF[4,5]. The continued increase in AF prevalence and mortality adversely affects patients' quality of life with a significant burden on health and economic development[6].

Recently, mental disorders have become a serious concern worldwide. As reported by WHO in 2019, 970 million people worldwide have mental disorders, with anxiety and depression being the two most common categories[7]. Emerging evidence has shown that patients with acute and chronic cardiovascular diseases are at a higher risk of developing mental disorders[8]. Mental disorders are also on the agenda for patients with AF. Studies have shown that patients with AF have a poorer quality of life than patients with other cardiovascular diseases, regardless of disease symptoms[9], which directly affects their psychological well-being. In another study, several factors affecting Health-related quality of life in patients with AF included depression and anxiety[10]. Although studies have independently analyzed the risk of comorbidity with depression and anxiety in patients with AF[11], no study has systematically focused on the global epidemiology of these two mental disorders. Therefore, we aimed to analyze the epidemiology of AF's co-morbidity with depression and anxiety.

MATERIALS AND METHODS

This study was conducted according to the PRISMA 2009 statement and Meta-analysis of Observational Studies in Epidemiology guidelines (Supplementary Table 1). This study was registered in the PROSPERO (No. CRD42023405975) database.

Search strategy

Two researchers (Zhang S and Zhang N) independently searched the PubMed, Embase, CNKI, Wanfang, and Sinomed databases from their construction date to January 2023 using a combination of subject and free words. The primary search terms were: "AF", "mental health", "depression", "anxiety", "affective symptoms", "psychological distress", "epidemiology", "prevalence", and "incidence". The details are shown in Supplementary Tables 2-6.

Inclusion and exclusion criteria

The criteria for inclusion in this study were as follows: (1) Epidemiological studies reporting co-morbidity of AF with depression and anxiety; (2) observational studies, including cohort studies and cross-sectional studies; (3) studies

published in Chinese or English; and (4) no restrictions for age, gender, and country.

The exclusion criteria were as follows: (1) Literature not relevant to the topic of the study; (2) duplicate studies; (3) case-control studies and non-observational studies; and (4) unavailability of full texts.

Data extraction

Two investigators (Zheng W and Ma ZL) separately extracted the key constituents for inclusion in the study. The following information was retrieved: first author/publication year, study year, study type, age, region (country), type of mental health, diagnostic criteria for mental health, generation, number of cases of AF, and prevalence of comorbidities. If the prevalence was not stated in the study or if the study was cross-sectional, we used the following formula: Cases/total number of subjects in the observational group $\times 100\%$.

Study quality

Two researchers (Zhao YL and Qiao SY) evaluated the quality of the pooled research. The Agency for Healthcare Research and Quality tool was used to estimate the risk of bias in cross-sectional studies. Additionally, the Newcastle-Ottawa Scale was used to assess the cohort studies. The researchers graded each study based on the entries of the scale and classified them as high (8-11), moderate (4-7), and low (0-3) quality.

Statistical analysis

We used STATA SE 15.1 for data analysis, and the I^2 test was used to evaluate heterogeneity. A fixed-effects model was used if the I^2 value was $< 50\%$; otherwise, a random-effects model was applied. Heterogeneity was assessed by subgroup, meta-regression, and sensitivity analyses. Publication bias was determined using Egger's and Begg's linear tests. If there was a publication bias, the trim-and-fill method was used to estimate the number of missing studies to rectify it. We used the R 4.2.2 software to visualize world maps for the prevalence of depression and anxiety in patients with AF.

RESULTS

Characteristics of the included studies

We identified 2681 studies. A total of 2391 studies remained after removing duplicates, of which 1851 were thematic discrepancies, 370 were reviews, and 29 were duplicates. Subsequently, 141 full-text articles were assessed for eligibility. From these, 115 studies were removed due to irrelevant topics, missing data, or other study types. Finally, 26 studies[12-37] were used in the meta-analysis (Figure 1).

Of the included studies, 25 and 14 analyzed the prevalence of depression and anxiety in patients with AF, respectively. One study reported the prevalence of AF in patients with depression[14]. Details were shown in Table 1.

Study quality

After evaluating and scoring the studies, we found that they had scores ranging from 4 to 7, all of which were of moderate quality. The details are listed in Supplementary Tables 7 and 8.

Outcomes

Depression: The aggregated prevalence of depression in patients with AF was 22.0% (95%CI: 0.207-0.233). the prevalence was 24.3% (95%CI: 0.228-0.257) in adults and 40.3% (95%CI: 0.264-0.541) in patients ≥ 60 years. Additionally, the prevalence of depression in patients with AF differed between men [11.7% (95%CI: 0.088-0.147)] and women [19.8% (95%CI: 0.1494-0.252)] (Table 2, Supplementary Figures 1-4). We found in the study that evaluated the prevalence of AF in patients with depression that 46.37% of 6055 patients with depression had AF (Supplementary Table 9).

In terms of continents, the prevalence of AF co-morbidity with depression in Europe, Asia, North America, and Oceania was 30.2% (95%CI: 0.274-0.330), 8.6% (95%CI: 0.072-0.100), 28.8% (95%CI: 0.145-0.431), and 29.0% (95%CI: 0.242-0.341), respectively (Table 2, Supplementary Figure 5). European countries such as Poland, Greece, Russia, United Kingdom, Germany, Norway, Sweden and Denmark had a prevalence of 54.5% (95%CI: 0.390-0.700), 35.3% (95%CI: 0.281-0.430), 43.8% (95%CI: 0.295-0.588), 38.6% (95%CI: 0.291-0.488), 37.9% (95%CI: 0.356-0.401), 2.2% (95%CI: 0.021-0.024), 4.0% (95%CI: 0.039-0.040), and 12.0% (95%CI: 0.118-0.122), respectively. Similarly, in Asia, countries such China and Korea had a prevalence of 27.8% (95%CI: 0.143-0.412) and 3.0% (95%CI: 0.030-0.030), respectively. The prevalence rates in Oceania and North America were consistent with those in Australia and the United States (Table 2, Supplementary Figure 6). The worldwide prevalence of depression among patients with AF is shown in Figure 2.

We analyzed the impact of different study types on prevalence and found a 58.2% (95%CI: 0.468-0.695) prevalence in cross-sectional, 15.3% (95%CI: 0.124-0.182) in cohort and 24.4% (95%CI: 0.217-0.271) in other studies (Table 2, Supplementary Figure 7). We subsequently analyzed the comorbidity rate of depression in patients with AF using various depression evaluation scales such as beck depression inventory, hospital anxiety and depression scale (HADS), patient health questionnaire (PHQ-9), the major depression inventory, center for epidemiological studies depression scale, international classification of diseases (ICD), and the geriatric depression scale with rates of 43.4% (95%CI: 0.370-0.499), 32.3% (95%CI: 0.187-0.459), 34.4% (95%CI: 0.225-0.463), 72.8% (95%CI: 0.693-0.761), 29.0% (95%CI: 0.242-0.341), 6.3% (95%CI: 0.039-0.087), and 44.1% (95%CI: 0.380-0.503), respectively (Table 2, Supplementary Figure 8).

Anxiety: In estimating the prevalence of anxiety in patients with AF, the meta-analysis identified an overall prevalence of

Table 1 Characteristic of included studies

| Ref. | Study year | Study type | Region (country) | Type of MH | Diagnostic criteria of MH | Age (mean \pm SD) (yr) [†] | Generation (yr) | AF (n) | P (MH in AF); Total (M/F) (%) |
|---------------------------------------|------------|--|---------------------------------|------------|------------------------------------|---------------------------------------|----------------------|-------------------|---|
| Thrall <i>et al</i> [20] | - | - | Europe (United Kingdom) | D and A | Depression-BDI; anxiety-STAI | 66.30 11 | Adult (\geq 18 y) | 101 | D (38.00); A (28.00/38.00) |
| Ariansen <i>et al</i> [35] | - | - | Europe (Norway) | D | HADS | - | Adult (\geq 75 y) | 27 | 11.10 |
| Gehi <i>et al</i> [32] | 2008-2011 | Cohort study | North America (United States) | D and A | Depression-PHQ-9; anxiety-HADS | 61.70 13.50 | Adult (\geq 18 y) | 300 | D (50.00); A (17.00) |
| Ball <i>et al</i> [31] | | SAFETY | Oceania (Austria) | D | CES-D | 75 13 | Adult (\geq 45 y) | 335 | 29.00 |
| Schnabel <i>et al</i> [30] | 2007 | Population-based Gutenberg Health Study | Europe (Germany) | D | PHQ-9 | 64.8 8.2 | Adult (35-74 y) | 309 | 8.00 |
| Thompson <i>et al</i> [19] | 2009-2012 | Cohort study | North America (United States) | D and A | Anxiety-HADS-A Depression-PHQ-9 | 61.60 13.30 | Adult (\geq 18 y) | 378 | D (39.40/16.9); A (17.72) |
| von Eisenhart Rothe <i>et al</i> [21] | 2005-2008 | Cross-sectional study | Europe (Germany) | D | MDI scale | - | Adult (\geq 18 y) | 702 | 73.00 |
| Hsu <i>et al</i> [29] | - | Population based community health survey | Asia (China) | D and A | HADS | 74.90 6.90 | Adult (\geq 65 y) | 1732 | D (14.00); A (36.00) |
| Wändell <i>et al</i> [28] | 2001-2007 | Cohort study | Europe (Sweden) | D and A | ICD-10 | - | Adult (\geq 45 y) | 12283 (6702/5750) | D (8.50) (6.10/10.90); A (4.03) (2.70/5.40) |
| Hu <i>et al</i> [12] | 2000-2010 | Cohort study | Asia (China) | D and A | ICD-9-CM | 72.70 13.40 | Adult (\geq 18 y) | 88259 | D (1.57); A (1.06) |
| Rewiuk <i>et al</i> [13] | 2007-2012 | Population-based, multicenter study | Europe (The Republic of Poland) | D | GDS | 78.0 7.7 | Adult (65-104) | 788 | 41.24 |
| Polikandrioti <i>et al</i> [15] | - | - | Europe (Greece) | D and A | HADS | - | Adult (\geq 18 y) | 170 | Anxiety-low (38.25) (39.80/35.30); anxiety-moderate (26.47) (31.40/15.70); anxiety-high (34.71) (28.80/49.00); depression-low (63.53) (65.80/60.80); depression-moderate (15.29) (14.50/17.60); depression-high (20.00) (19.70/21.60) |
| Hagengaard <i>et al</i> [16] | 2005-2014 | Cohort study | Europe (Denmark) | D and A | ICD-10 | - | - | 146377 | D (0.29); A (0.07) |
| Uchmanowicz <i>et al</i> [17] | 2019 | Cross-sectional study | Europe (The Republic of Poland) | D | HADS GDS | 70.27 3.48 | Adult (\geq 65y) | 100 | Anxiety (HADS 8-10) (22.00); anxiety (HADS 11-21) (20.00); depression (HADS 8-10) (26.00); depression (HADS 11-21) (28.00); depression (GDS 6-15) (51.00) |
| Krupenin <i>et al</i> [18] | 2017-2018 | - | Europe (Russia) | D and A | GDS | 78 ² | Adult (\geq 65 y) | 48 | 41.67 |
| Wang <i>et al</i> [22] | - | SAGE-AF Study | North America (United States) | D and A | Anxiety-GAD Depression-PHQ-9 | 76.00 7.00 | Adult (\geq 65 y) | 1244 | D (29.00); A (24.00) |
| Kim <i>et al</i> [23] | 2009-2018 | Cohort study | Asia (Korea) | D | ICD-10 | 46.99 14.06 | Adult (\geq 20 y) | 5031222 | 3.00 (1.04/1.92) |

| | | | | | | | | | |
|--------------------------------------|-----------|-----------------------|---------------------------------|---------|--------------|------------|------------------|------------------------|--|
| Jankowska-Polańska <i>et al</i> [24] | - | Cohort study | Europe (The Republic of Poland) | D and A | HADS | 70.7 | Adult (≥ 60 y) | 158 | Depression (8-10) (37.97); depression (11-21) (37.87); anxiety (8-10) (32.91); anxiety (11-21) (48.10) |
| Feng <i>et al</i> [25] | 2006-2008 | HUNT study | Europe (Germany) | D and A | HADS | 53.4 15.2 | Adult (≥ 20y) | 37402 | D (2.20); A (4.90) |
| Wändell <i>et al</i> [28] | 1998-2012 | Cohort study | Europe (Sweden) | D and A | ICD-10 | - | Adult (≥ 45 y) | 537513 (287959/249554) | D (3.91) (3.46/4.44); A (2.70) (2.23/3.25) |
| Piwoński <i>et al</i> [27] | - | Cross-sectional study | Europe (The Republic of Poland) | D | BDI | - | Adult (18-79 y) | 124 (57/67) | 47.58 (43.86/50.75) |
| Wu <i>et al</i> [33] | 2020-2021 | - | Asia (China) | D | PHQ-9 | - | Adult (≥ 18 y) | 329 | 35.56 |
| Fenger-Grøn <i>et al</i> [34] | 2005-2016 | - | Europe (Denmark) | D | ICD-8/ICD-10 | 78.7 10.1 | Adult (18-100 y) | 147162 | 12.16 |
| Rosman <i>et al</i> [36] | - | Cohort study | North America (USA) | D and A | ICD-9 | 30.29 9.19 | Adult (18-60 y) | 988090 | 9.04 |
| Zhang <i>et al</i> [37] | 2012-2013 | Cross-sectional study | Asia (China) | D | PHQ-9 | 63.3 9.5 | Adult (≥ 35 y) | 134 | 63.00 |

¹Ages in atrial fibrillation patients.

²Median age.

A: Anxiety; AF: Atrial fibrillation; BDI: Beck depression inventory; CES-D: Centre for epidemiological studies depression scale; D: Depression; GAD-7: 7-item generalized anxiety disorder-7 scale; GDS: Geriatric depression scale; HADS: Hospital anxiety and depression scale; HUNT study: The trøndelag health study; ICD: International classification of diseases; MDI: Major depression inventory; MH: Mental health; PHQ: Patient health questionnaire; SAFETY: Standard versus atrial fibrillation specific management study; SAGE-AF: Systematic assessment of geriatric elements in atrial fibrillation; STAI: State-trait anxiety inventory.

13.0% (95%CI: 0.117-0.142); 14.5% (95%CI: 0.132-0.158) in adults, 33.6% (95%CI: 0.246-0.425) in older adults ≥ 60 years old, 8.7% (95%CI: 0.063-0.111) in males, and 10.1% (95%CI: 0.069-0.133) in females (Table 2, Supplementary Figures 9-12).

Only three continents, Asia, Europe, and North America, reported a prevalence of anxiety in patients with AF. These were 1.10% (95%CI: 0.010-0.012), 13.9% (95%CI: 0.118-0.159), and 19.8% (95%CI: 0.149-0.248), respectively (Table 2, Supplementary Figure 13). Five studies reported the prevalence in five individual European countries, including Greece, 61.8% (95%CI: 0.540-0.691); Poland, 45.7% (95%CI: 0.396-0.518); United Kingdom, 33.3% (95%CI: 0.268-0.398); Norway, 4.9% (95%CI: 0.047-0.051); and Sweden, 2.7% (95%CI: 0.027-0.028). In Asia and North America, the prevalence of comorbidity of anxiety with AF was reported only in China and the United States at 1.10% (95%CI: 0.010-0.012) and 19.8% (95%CI: 0.149-0.248), respectively (Table 2, Supplementary Figure 14). The worldwide prevalence of anxiety among patients with AF is shown in Figure 3.

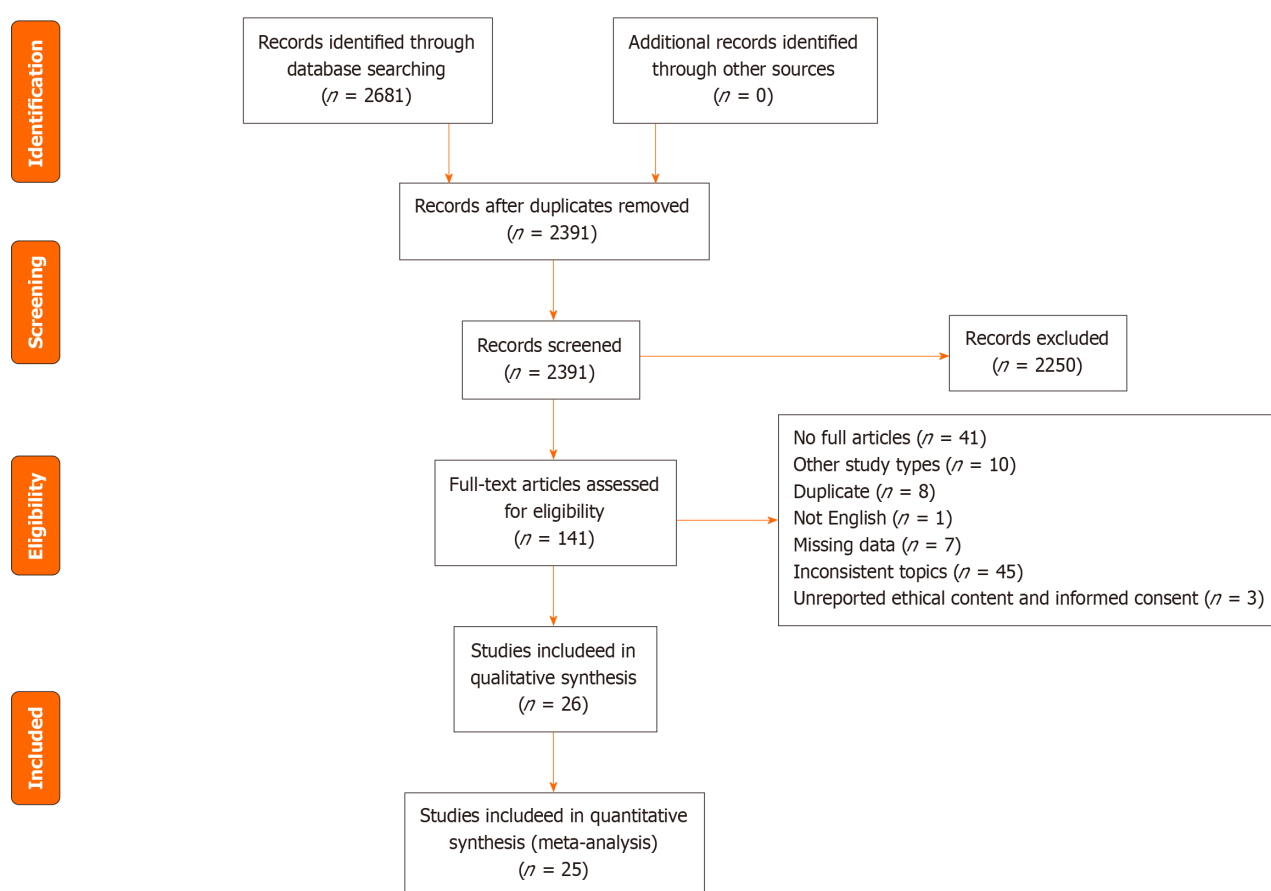
A comparison of the occurrence of anxiety in patients with AF among different observational study types showed a prevalence of 42.0% (95%CI: 0.322-0.523), 8.1% (95%CI: 0.053-0.109), and 24.8% (95%CI: 0.218-0.277) in cross-sectional, cohort and other studies, respectively (Table 2, Supplementary Figure 15). Four criteria were used to diagnose anxiety. The prevalence rate using the state-trait anxiety inventory, HADS, ICD, and generalized anxiety disorder scale was 28.7% (95%CI: 0.201-0.386), 31.2% (95%CI: 0.174-0.449), 2.6% (95%CI: 0.013-0.039), 24.0% (95%CI: 0.217-0.265), respectively (Table 2, Supplementary Figure 16).

Table 2 Prevalence of mental health in atrial fibrillation patients

| Study or subgroup | Prevalence (95%CI) | I ² (%) | P value |
|-----------------------|---------------------|--------------------|---------|
| Depression | | | |
| Overall prevalence | 22.0 (0.207, 0.233) | 100 | < 0.001 |
| Prevalence in adults | 24.3 (0.228, 0.257) | 100 | < 0.001 |
| Gender | | | |
| Male | 11.7 (0.088, 0.147) | 97.3 | < 0.001 |
| Female | 19.8 (0.144, 0.252) | 98.7 | < 0.001 |
| Age group | | | |
| ≥ 60 yr | 40.3 (0.264, 0.541) | 100 | < 0.001 |
| Other ages | 20.4 (0.188, 0.221) | 100.0 | < 0.001 |
| Study design | | | |
| Cross-sectional study | 58.2 (0.468, 0.695) | 91.7 | < 0.001 |
| Cohort study | 15.3 (0.124, 0.182) | 100 | < 0.001 |
| Others | 24.4 (0.217, 0.271) | 99.9 | < 0.001 |
| Region | | | |
| Asia | 8.6 (0.072, 0.100) | 100 | < 0.001 |
| Europe | 30.2 (0.274, 0.330) | 99.9 | < 0.001 |
| North America | 28.8 (0.145, 0.431) | 99.3 | < 0.001 |
| Oceania | 29.0 (0.242, 0.341) | 0 | - |
| Diagnostic criteria | | | |
| BDI | 43.4 (0.370, 0.499) | 0 | - |
| HADS | 32.3 (0.187, 0.459) | 99.5 | < 0.001 |
| PHQ-9 | 34.4 (0.225, 0.463) | 98.3 | < 0.001 |
| MDI | 72.8 (0.693, 0.761) | 0 | - |
| CES-D | 29.0 (0.242, 0.341) | 0 | - |
| ICD | 6.3 (0.039, 0.087) | 100 | < 0.001 |
| GDS | 44.1 (0.380, 0.503) | 41.2 | 0.183 |
| Anxiety | | | |
| Overall prevalence | 13.0 (0.117, 0.142) | 99.9 | < 0.001 |
| Prevalence in adults | 14.5 (0.132, 0.158) | 99.7 | < 0.001 |
| Gender | | | |
| Male | 8.7 (0.063, 0.111) | 97.9 | < 0.001 |
| Female | 10.1 (0.069, 0.133) | 97.3 | < 0.001 |
| Age group | | | |
| ≥ 60yr | 33.6 (0.246, 0.425) | 95.2 | < 0.001 |
| Other ages | 7.6 (0.063, 0.088) | 99.7 | < 0.001 |
| Region | | | |
| Asia | 1.1 (0.010, 0.012) | - | - |
| Europe | 13.9 (0.118, 0.159) | 99.2 | < 0.001 |
| North America | 19.8 (0.149, 0.248) | - | - |
| Study design | | | |
| Cross-sectional study | 42.0 (0.322, 0.523) | 0 | - |

| | | | |
|---------------------|---------------------|------|---------|
| Cohort study | 8.1 (0.053, 0.109) | 99.2 | < 0.001 |
| Other | 24.8 (0.218, 0.277) | 99.6 | < 0.001 |
| Diagnostic criteria | | | |
| STAI | 28.7 (0.201, 0.386) | - | - |
| HADS | 31.2 (0.174, 0.449) | 99.4 | < 0.001 |
| ICD | 2.6 (0.013, 0.039) | - | - |
| GAD | 24.0 (0.217, 0.265) | - | - |

BDI: Beck depression inventory; CES-D: Centre for Epidemiological Studies Depression Scale; GAD: Generalized anxiety disorder scale; GDS: Geriatric depression scale; HADS: Hospital anxiety and depression scale; ICD: International classification of diseases; MDI: Major depression inventory; PHQ-9: Patient health questionnaire; STAI: Stait-trait anxiety inventory.



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Figure 1 Flow chart of search strategy according to PRISMA 2009 guidelines.

Meta-regression analysis

A meta-regression analysis was conducted to examine the sources of heterogeneity in the prevalence of anxiety and depression among patients with AF. We found that the diverse study types, diagnostic criteria, and age groups were sources of heterogeneity in the prevalence of AF comorbidity with anxiety (Table 3).

Sensitivity analyses

We performed a sensitivity analysis of the prevalence of depression and anxiety in patients with AF and found that the results were robust after applying the respective exclusions (Supplementary Figures 17 and 18).

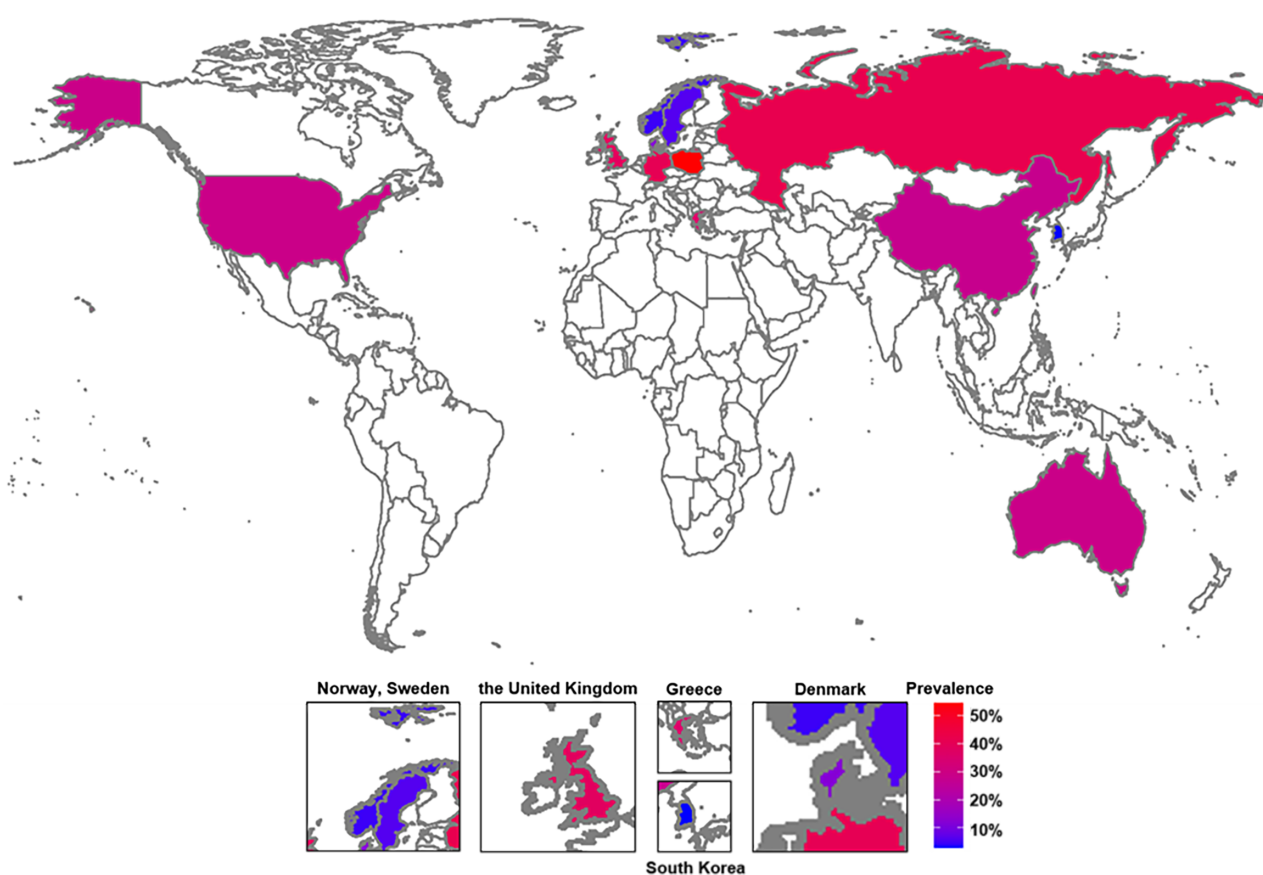
Publication bias

We analyzed the publication bias for the prevalence of depression and anxiety in adults with AF using Egger's and Begg's linear tests. We found the publication bias for these two disorders (Supplementary Figures 19-22). These parameters were then evaluated using the trim-and-fill method. We discovered an increase of 34 and 20 studies on depression and anxiety,

Table 3 Meta-regression analysis of prevalence of mental health in atrial fibrillation

| Possible source of heterogeneity | Number of studies | Coef (95%CI) | P value |
|----------------------------------|-------------------|----------------------|---------|
| Depression | | | |
| Study design | 24 | 0.40 (-0.18, 0.98) | 0.18 |
| Cross-sectional study | 4 | 1.34 (0.21, 2.47) | 0.02 |
| Cohort study | 6 | -1.76 (-3.03, -0.49) | 0.01 |
| Others | 14 | -1.11 (-2.28, 0.05) | 0.06 |
| Region | 24 | 0.46 (-0.12, 1.04) | 0.11 |
| Asia | 5 | -0.82 (-2.29, 0.64) | 0.27 |
| Europe | 14 | -0.12 (-1.33, 1.10) | 0.85 |
| North America | 4 | 0.29 (-0.87, 1.44) | 0.63 |
| Oceania | 1 | 0.16(-2.38, 2.70) | 0.90 |
| Age group | 24 | -0.67(-1.67, 0.33) | 0.19 |
| ≥ 60 | 7 | 0.33 (-0.70, 1.36) | 0.53 |
| Other ages | 17 | -0.33 (-1.36, 0.70) | 0.53 |
| Diagnostic criteria | 24 | -0.22(0.45, 0.02) | 0.07 |
| BDI | 2 | 0.28 (-2.22, 2.78) | 0.83 |
| HADS | 6 | -2.96 (-2.23, 1.64) | 0.76 |
| PHQ-9 | 6 | 0.02 (-1.86, 1.91) | 0.98 |
| MDI | 1 | 0.93 (-1.56, 3.42) | 0.47 |
| CES-D | 1 | 0.40 (-1.95, 2.76) | 0.74 |
| ICD | 6 | -1.73 (-3.64, 0.17) | 0.07 |
| GDS | 2 | 0.44 (-1.60, 2.48) | 0.67 |
| Anxiety | | | |
| Region | 13 | -0.24 (-1.01, 0.52) | 0.53 |
| Asia | 2 | -1.03 (-2.87, 0.81) | 0.27 |
| Europe | 8 | 1.00 (-0.98, 2.97) | 0.32 |
| North America | 3 | 1.14 (-1.16,3.43) | 0.32 |
| Study design | 13 | -0.21 (-1.07, 0.65) | 0.63 |
| Cross-sectional study | 1 | 1.95 (-0.59, 4.50) | 0.13 |
| Cohort study | 4 | -1.30 (-2.61, 0.01) | 0.05 |
| Others | 8 | 1.22 (-0.15, 2.60) | 0.08 |
| Age group | 13 | -1.38 (-2.53, -0.24) | 0.02 |
| ≥ 60 | 5 | 1.15 (-0.13, 2.43) | 0.08 |
| Other ages | 8 | -1.15 (-2.43, 0.13) | 0.08 |
| Diagnostic criteria | 14 | -0.84 (-1.63, -0.05) | 0.04 |
| STAI | 1 | 0.15 (-2.01, 2.32) | 0.89 |
| HADS | 9 | 0.07 (-1.54, 1.67) | 0.94 |
| ICD | 3 | -2.36 (-4.11, -0.61) | 0.01 |
| GAD | 1 | 0.51 (-2.10, 3.13) | 0.70 |

BDI: Beck depression inventory; CES-D: Centre for Epidemiological Studies Depression Scale; GAD: Generalized anxiety disorder scale; GDS: Geriatric depression scale; HADS: Hospital anxiety and depression scale; ICD: International classification of diseases; MDI: Major depression inventory; PHQ-9: Patient health questionnaire; STAI: Stait-trait anxiety inventory.



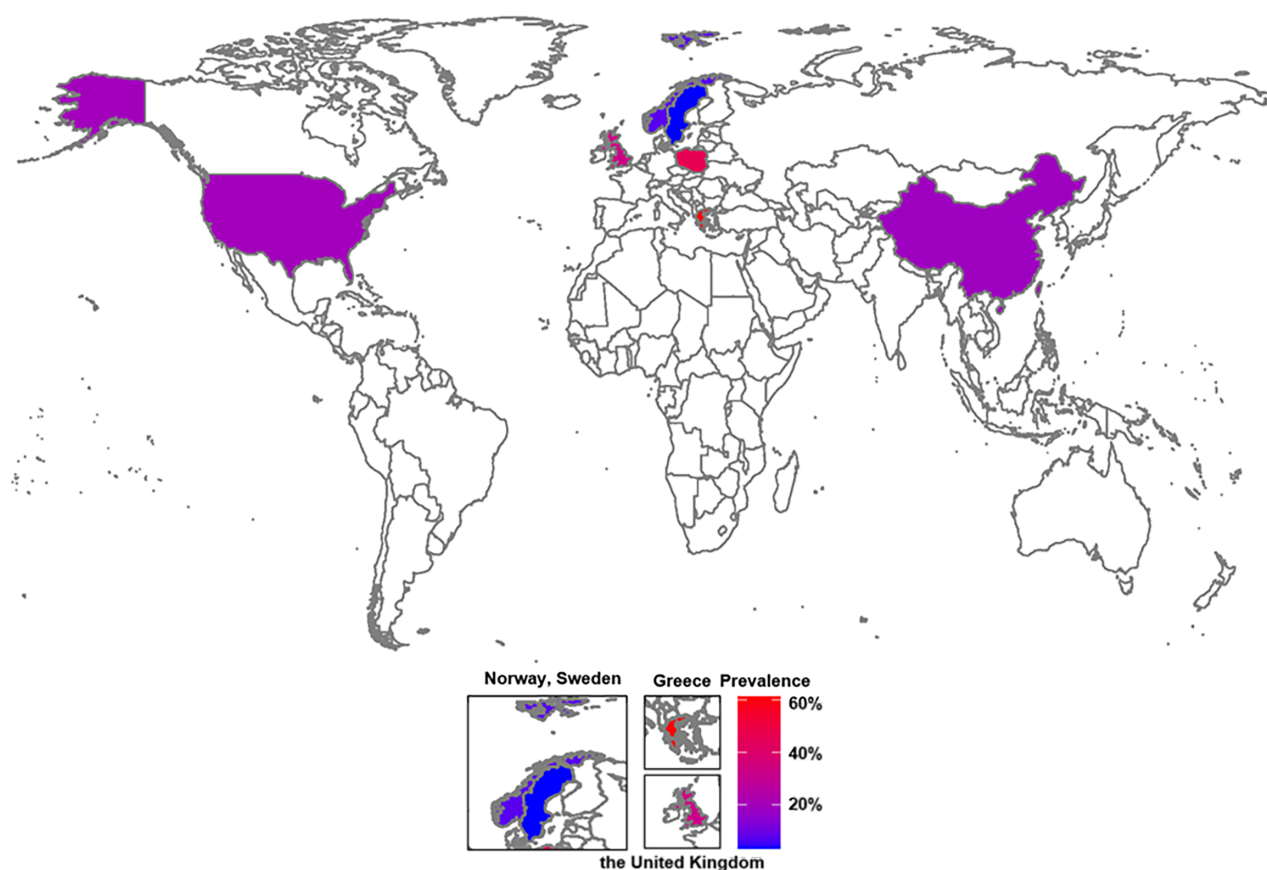
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Figure 2 Global prevalence of depression among adult patients with atrial fibrillation.

respectively, among patients with AF after five iterations. The prevalence of depression and anxiety in patients with AF decreased to 15.8% (95%CI: 0.14-0.17) and 7.9% (95%CI: 0.066-0.091), respectively.

DISCUSSION

To our knowledge, this is the first study to present the global prevalence of depression and anxiety in patients with AF. After a systematic and holistic evaluation, we identified a 22.0% and 13.0% prevalence of depression and anxiety, respectively, in patients with AF and 24.3% and 14.5% in adults. Furthermore, the prevalence of depression and anxiety in patients with AF was 11.7% and 8.7%, 19.8% and 10.1%, 40.3% and 33.6% in males, females and the elderly, respectively. This prevalence varied in regional distribution. A higher percentage of European (30.2%) and North American (19.8%) patients with AF experienced depression and anxiety, respectively, than those in other continents. Furthermore, the highest percentage of patients with AF and depression and anxiety were found in Poland (54.5%) and Greece (61.8%), respectively. Cardiovascular diseases remain the primary cause of morbidity worldwide, with the total disability-adjusted life years caused by AF and atrial flutter at 8.39 million in 2019[38]. Anxiety, inflammation, and left atrial dilation are significant predictors of the quality of life in patients with AF[39]. Another study indicated that as the severity of AF-specific symptoms increases, there is a positive correlation between the levels of anxiety and depression [19]. Furthermore, one-third of patients with AF were reported to have persistent levels of depression and anxiety at a 6-month follow-up[20]. These findings underscore the importance of identifying and increasing interventions for psychological factors in patients with AF. Our study demonstrated that depression and anxiety in patients with AF exhibit sex and regional differences. The prevalence of AF comorbidity with both depression and anxiety appears to be higher in females than males. This may be linked to sex differences, as studies have shown that women are more likely to develop AF than men[40]. The differences in biological factors between men and women, such as sex hormones, X and Y chromosomes, reactions to stimuli, and body fats, contribute to the sex differences[40]. Age is a crucial risk factor for AF, and its prevalence increases with age. We found that patients with AF aged > 60 years had a higher probability of comorbidity with depression and anxiety. Furthermore, the high prevalence of depression among patients with AF in Poland may be related to the inclusion of older populations in the reported studies. Additionally, the increasing disease burden due to the aging population in developed countries may contribute to the increasing prevalence of AF[41], the higher prevalence of depression and anxiety in Europe and North America in our study may be related to this aspect. Pathogenic links exist between AF and psychiatric disorders. Autonomic nerves innervate the heart, and AF can be



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Figure 3 Global prevalence of anxiety among adult patients with atrial fibrillation.

induced when the cardiac action potential receives a rapid discharge stimulus[42]. Previous studies have shown that in states of depression and anxiety, sympathetic nerves are overexcited, and catecholamine secretion increases. High concentrations of catecholamines can damage vascular endothelial cells and cause palpitations on the one hand, leading to the formation of arrhythmic substrates; on the other hand, they accelerate the heart rate, shorten the atrioventricular node's refractory period, depolarize the atrial ectopic pacing point, trigger the feedback mechanism, resulting in AF. In addition, catecholamines can overstimulate β -adrenergic receptors, affect calmodulin expression, impair calcium handling systems, and lead to atrial remodeling[43-45]. Inflammation is another important link between AF and depression or anxiety. Studies have shown that patients with AF have significantly higher serum levels of ultrasensitive C-reactive protein and interleukin 6, and anxiety and depression are strongly associated with these two inflammatory mediators[46,47]. The renin-angiotensin-aldosterone system (RAAS) is also implicated in AF and mental disorders. Anxiety and depression contribute to an active RAAS, which is accompanied by an increase in angiotensin secretion. Elevated levels of angiotensin II promote cardiac fibrosis, slow down cardiomyocyte signaling, and damage the myocardium, leading to myocardial remodeling and an increase in the number of folds, which provides a favorable environment for the development of AF[48-51]. Additionally, it has been demonstrated that chronic stimulation of a rat depression model with sigma-1 receptors with antidepressant effects attenuates atrial electrical remodeling, fibrosis, and AF susceptibility [52]. Furthermore, patients with significant depression share the *ZHX3* and *ADI1P1* genes with AF patients[53]. Overall, there are few studies on the co-morbidity mechanisms of AF and psychiatric disorders, which could be a direction for future research.

AF treatment involves using antiarrhythmic drugs, direct-current cardioversion, catheter ablation, or surgical ablation to restore and maintain sinus rhythm[54]. A recent randomized controlled trial showed that symptoms of depression and anxiety significantly improved in patients who underwent catheter ablation of AF[55]. In addition, there is evidence of significant improvement in depression and anxiety in patients with AF after treatment with newer anticoagulants, such as rivaroxaban and dabigatran, compared with oral warfarin[56,57]. Some antidepressants protect the body from cardiovascular damage. However, the use of antidepressants in the treatment of AF has been poorly studied[58]. Paroxetine is an antidepressant that reduces the number of episodes of paroxysmal AF and may exert its therapeutic effect by modulating the vagal tone in the brain and inhibiting vasovagal reflexes[59]. In addition, exercise therapy, such as yoga, is an effective option for managing depression and anxiety in patients with AF[60].

Few studies have reported the prevalence of depression and anxiety in patients with AF. Zhuo *et al*[61] elucidated the correlation between preoperative depression in patients with AF and recurrence after catheter ablation. Three studies analyzed the prevalence and risk index of depression and anxiety in patients with AF[10,11,62]. This study not only presents an analysis of the rate of depression and anxiety in patients with AF but also highlights regional discrepancies in

their prevalence by country, allowing for a more visual representation of the data.

Although we tried to be as rigorous as possible, this study had a few limitations. First, the studies we included were published in English or Chinese, which may have resulted in language bias. Second, the prevalence of anxiety in patients with AF was reduced after the trim-and-fill method. This might result from the inclusion of only observational studies in our analysis and our inability to find the “gray literature” in our study. However, after sensitivity analyses, the conclusions were robust. Third, although AF is divided into various types, such as paroxysmal and persistent AF, our study did not address this aspect because no previous study has analyzed the prevalence of diverse types of AF. Additionally, the scales and diagnostic criteria used to evaluate anxiety and depression differed in the included studies, leading to significant differences in prevalence. In the meta-regression, we also found that different scales were a source of heterogeneity and then divided them into subgroups for analysis. Further studies are needed to analyze the prevalence of depression and anxiety in patients with different types of AF and standardize the evaluation criteria for anxiety and depression as much as possible. The mechanism of AF comorbidity with depression and anxiety can be elucidated using molecular biology and cellular immunology, which is another direction for future research. Moreover, large-scale observational epidemiological studies are needed to analyze its prevalence and provide a basis for clinical diagnosis and treatment.

CONCLUSION

We integrated and systematically analyzed the prevalence of two psychiatric disorders, depression and anxiety, in patients with AF. We found that the prevalence of comorbid psychiatric disorders in patients with AF was associated with sex and region. These facts underscore the need for clinicians to actively engage in mental health interventions in managing patients with AF.

ARTICLE HIGHLIGHTS

Research background

Atrial fibrillation (AF), an irregular and rapid heart rate, is one of the most common types of cardiac arrhythmias. Research has shown that patients with AF are more prone to psychological problems than the general population. These problems increase the recurrence rate of AF while seriously affecting the quality of life, morbidity, and mortality rate of patients.

Research motivation

Anxiety and depression are the two most common mental health disorders worldwide. Studies have independently analyzed the risk of comorbidity with depression and anxiety in patients with AF. No study has systematically focused on the global epidemiology of these two mental disorders in patients with AF. A deeper understanding of the prevalence of comorbid depression and anxiety in these patients is essential in guiding clinical management.

Research objectives

To explore the prevalence of depression and anxiety in patients with AF.

Research methods

Five databases were searched from their establishment until January 2023. Observational studies reporting the comorbidity of AF with depression and anxiety were included. STATA SE 15.1 was applied to analyze the data. Subgroup, meta-regression, and sensitivity analyses were performed to estimate study heterogeneity.

Research results

The prevalence rates of depression and anxiety in adults with AF were 24.3% and 14.5%, respectively. Among adult males with AF, the prevalence of depression and anxiety were 11.7% and 8.7%, respectively. This prevalence varied with sex, age and region; in females, it was 19.8% and 10.1%, and 40.3% and 33.6% in the older adults, respectively. The highest prevalence rate of depression and anxiety was observed in European (30.2%) and North American (19.8%) patients with AF. Furthermore, the prevalence varied according to the different evaluation scales.

Research conclusions

We found that the prevalence of depression and anxiety among patients with AF was differentially distributed according to sex, region, and evaluation scales, suggesting the need for psychological interventions for patients with AF in clinical practice.

Research perspectives

To explore this association further, future studies should focus on assessing the prevalence of depression and anxiety in patients with different types of AF, delineating the mechanisms of AF comorbidity with depression and anxiety using molecular biology and cellular immunology, and carrying out a large-scale observational epidemiological study to

analyze its prevalence and provide a basis for clinical diagnosis and treatment.

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FOOTNOTES

Co-first authors: Shuai Zhang and Na Zhang.

Co-corresponding authors: Shuai Zhang and Lin Shen.

Author contributions: Zhang S and Shen L were co-corresponding authors who proposed the concept, designed the study and raised fundings; Zhang S and Zhang N were co-first authors for they contributed equally in this research. Additionally, Zhang S, Liu L and Zhang N were responsible for literature search, screening and writing drafts; Zheng W and Ma ZL extracted data; Zhang YL and Qiao SY assessed the quality of studies; Wei YH, Wu G, Yu QT and Deng B analyzed the data. All the authors read and approved the final manuscript. The reasons for designating Zhang S and Zhang N as co-first authors are twofold: Firstly, they made equal contributions to the writing and revision of the manuscript. Secondly, this study was conducted collaboratively, and appointing Zhang S and Zhang N as co-first authors facilitate effective communication in addressing issues related to research design, writing, and data analysis, thereby ensuring smooth progress in the research. The rationale behind selecting Zhang S and Shen L as co-corresponding authors lies in their equal contributions to formulating, conceptualizing, and executing the study, as well as providing funding support. In summary, the co-first and co-corresponding authors in this study not only ensured its seamless execution but also enhanced the rationality and depth of the research topic.

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