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Depression or anxiety and all-cause mortality in adults with atrial fibrillation – A cohort study in Swedish primary care

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Abstract

Objective—Our aim was to study depression and anxiety in atrial fibrillation (AF) patients as risk factors for all-cause mortality in a primary care setting.

Methods—The study population included adults (n = 12 283) of 45 years and older diagnosed with AF in 75 primary care centres in Sweden. The association between depression or anxiety and all-cause mortality was explored using Cox regression analysis, with hazard ratios (HRs) and 95% confidence intervals (95% CIs). Analyses were conducted in men and women, adjusted for age, educational level, marital status, neighborhood socio-economic status (SES), change of neighborhood status and anxiety or depression, respectively, and cardiovascular co-morbidities. As a secondary analysis, background factors and their association with depression or anxiety were explored.

Results—The risk of all-cause mortality was higher among men with depression compared to their counterparts without depression even after full adjustment (HR = 1.28, 95% CI 1.08–1.53). For anxiety among men and anxiety or depression among women with AF, no associations were found. Cerebrovascular disease was more common among depressed AF patients.

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Declaration of interest

The authors have no conflict of interest to disclose.

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Conclusions—Increased awareness of the higher mortality among men with AF and subsequent depression is called for. We suggest a tight follow-up and treatment of both ailments in clinical practice.

Keywords

Anticoagulants; anxiety; atrial fibrillation; co-morbidity; depression; follow-up; gender; mortality

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia, and, based on the health care records, about 2% of the adult population in Sweden is diagnosed with atrial fibrillation (1). Many AF patients in Sweden receive medical care at primary health care centres, and in Stockholm County 64% of the AF patients had an AF diagnosis registered in primary care (1).

There are substantial sex differences in the epidemiology of atrial fibrillation. Men develop atrial fibrillation around five years earlier than women do (2); and it has been reported that men have a 1.5-fold higher risk of developing atrial fibrillation compared to women after adjustment for age and predisposing conditions (3). Moreover, both men and women with atrial fibrillation have a higher age-adjusted mortality than individuals without atrial fibrillation (4); however, women with AF have been shown to have worse outcomes than their male counterparts. Indeed, based on the Framingham Heart Study cohort data, AF was found to be associated with a 50% increase in death in men and a 90% increase in death in women after adjusting for age and comorbid conditions (5). This may partly explain the higher risk of stroke among women with AF compared to that among men with AF (6).

Psychological distress is often present among patients diagnosed with AF (7). Symptoms of depression and/or anxiety are associated with greater symptom severity of AF (8–10), and with recurrence of AF (7). Furthermore, depressive mood has been shown to be more common among patients with persistent AF than paroxysmal AF (11). In addition, depression is more common among female than male AF patients (12), which is in line with the general population, with a female preponderance for both depression and anxiety (13).

As regards to the association between depression and mortality in patients with heart disease, an increased mortality has been found in patients with heart disease in general (14), and among patients with coronary heart disease (CHD) (15). In addition, anxiety is also a risk factor for total mortality in men and women (16). However, as far as we know, the impact of anxiety or depression on mortality among men and women with AF has not been explored earlier, with the exception of a study in AF patients with comorbid heart failure, where elevated depression symptoms were associated with a higher risk of both all-cause and cardiovascular mortality (17).

The main aim of this study was to explore the potential effect of depression and anxiety on all-cause mortality in men and women diagnosed with AF; and whether this effect is independent of factors known to influence mortality in patients with AF, such as age, cardiovascular co-morbidities, as well as marital status, educational level and

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neighbourhood socio-economic status. We hypothesize that all-cause mortality among patients with atrial fibrillation is higher in patients with depression or anxiety, and that this is independent of potential confounders. As there are differences among men and women both as regards to the presence of depression and anxiety, and as regards to the epidemiology of AF, analyses for men and women were performed separately. In addition, and as a secondary analysis, we also aimed to explore background factors for depression and anxiety among men and women with AF.

Methods

Design

This study was performed using individual-level patient data from 75 Swedish primary health care centres (PHCC) in an open cohort study. The majority of the centres were located in Stockholm County (n = 48). Men and women visiting any of the participating PHCCs between 2001 and 2007 were included in the study. We used *Extractor* software (http://www.slso.sll.se/SLPOtemplates/SLPOPage1____10400.aspx; accessed September 19, 2010) to collect individual files from the electronic patient records (EPR) at the PHCCs. Individual identification numbers were replaced by serial numbers to ensure anonymity. The EPR files were linked to a database constructed using Swedish national registers (18). The registers used were: The Total Population register (which contains data on, e.g., age and education for the entire population of Sweden); The Inpatient Register (hospital admissions); and The Cause of Death Register. These registers contain individual-level population data for all residents registered in Sweden. Thus, a new research database was created, containing individual clinical patient data from a total of 1,098,420 subjects registered at these 75 PHCCs, linked to national demographic and socioeconomic data. A follow-up was performed using the Swedish Cause of Death Register, which has been shown to be almost complete, 99.8%, and lacking data only for a few emigrants from Sweden to other countries and thus lost to follow-up (19).

Study population and co-morbidities

The study included all patients with diagnosed AF, and also identified diagnoses of depression or anxiety among them. Atrial fibrillation was identified by the presence of the ICD-10 code (10th version of the WHO's International Classification of Diseases) for atrial fibrillation (I48) in patients' medical records. Depression included depressive episodes, recurrent depressive disorder, persistent mood disorders, including cyclothymia and dysthymia, and other or unspecified mood disorders (F32–F34, F38–F39); and anxiety included anxiety disorders (including phobias) (F40–F41). The following related cardiovascular disorders were used as covariates: hypertension (I10–15), coronary heart disease (CHD; I20–25), cardiac heart failure (CHF; I50 and I110), cerebrovascular diseases (CVD; I60–69), and diabetes mellitus (E10–14). Any patient being diagnosed with AF at any of the 75 primary healthcare centres during 2001–2007 was included in the study. Thus, in total 6646 men and 5637 women aged 45 years or older at the time of AF diagnosis, were included in the study (20).

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Outcome variables

Time to death during the assessment period was obtained (from registration of the AF diagnosis to 31 December 2010) from the National Cause of death register. In secondary analysis, subsequent depression and anxiety diagnoses were obtained from electronic patient records in primary health care, and were used as outcomes in logistic regression models.

Individual demographic and socio-economic variables

Sex: Men and women.

Age was categorized as follows: 45–54, 55–64, 65–74, 75–84 and ≥85 years. Individuals younger than 45 years were excluded (AF was rare in individuals below 45 years of age and non-representative of AF patients in general).

Educational attainment was categorized as ≤9 years (partial or complete compulsory schooling), 10–12 years (partial or complete secondary schooling) and >12 years (attendance at college and/or university).

Marital status was characterized as married, unmarried, divorced or widowed.

Neighbourhood level SES

Neighbourhood socio-economic status was derived from Small Area Market Statistics (SAMS), which were originally created for commercial purposes and pertain to small geographic areas with boundaries defined by homogenous types of buildings. The average population in each SAMS neighbourhood is approximately 2000 persons for Stockholm and 1000 persons for the rest of Sweden. Neighbourhood status was classified as high, middle or low SES, or as low, middle and high deprivation index (21). The index was based on the following four variables: low educational status (<10 years of formal education), low income (<50% of the median individual income from all sources), unemployment and receipt of social welfare. The index was categorized into three groups: more than one standard deviation (SD) below the mean (high SES or low deprivation level), more than one SD above the mean (low SES or high deprivation level), and within one SD of the mean (middle SES or deprivation level).

Statistical analysis

Baseline subject characteristics for men and women with or without depression or anxiety were presented as mean (SD) if continuous, and as frequencies if categorical. The potential effects of depression or anxiety on mortality in adults diagnosed with atrial fibrillation were evaluated using Cox-proportional hazards modelling. Cox regression was used to calculate total risk time between inclusion in the study, i.e. at time of diagnosis of AF, until the end of the follow-up in 31 December 31 2010. Before running the regression models, variables were tested for interactions, and significant ones were included in the models. The following four models were created: (1) Model 1: depression or anxiety; (2) Model 2: Model 1 and inclusion of educational attainment, marital status, neighbourhood SES and change of residence according to neighbourhood status; (3) Model 3: Model 2 and inclusion of comorbidities (depression or anxiety; hypertension, coronary heart disease, heart failure,

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cerebrovascular disease and diabetes) and age × comorbidity interaction terms (CHD and diabetes among men, and CHD and CVS among women). Analyses were performed separately for men and women. p-Values of <0.05 were considered statistically significant.

In secondary analysis, the association between background factors, i.e. age, socio-economic factors and cardiovascular co-morbidity, and depression or anxiety in men and women with AF was explored using logistic regression. The main model (Model 1) included the following risk factors: age-group, neighborhood SES with change of neighborhood SES during follow-up, marital status, educational level and cardiovascular co-morbidities. Model 2 contained all risk factors from Model 1, and it was adjusted for anxiety (model with depression as an outcome) or depression (model with anxiety as an outcome). Relevant and significant interactions were also included in the model. The study was approved by the regional ethics boards at Karolinska Institutet and Lund University.

Results

Table 1 presents the characteristics of the 6646 men and 5637 women included in the study. Data on women and men with depression or anxiety are also shown. Among men, a total of 412 (6.2%) were diagnosed with depression, and 183 (2.8%) with anxiety, while 627 (11.1%) women were diagnosed with depression and 313 (5.6%) with anxiety. A total of 1983 men and 1971 women died during the follow-up, 29.8% vs. 35.0% ($p < 0.001$). The calculated hazard ratios were based on a total of 71 602 person-years at risk, 39 154 person-years among men and 32 448 among women. The mean follow-up time was 5.8 years (standard deviation 2.4 years).

Tables 2 and 3 show background factors associated with depression and anxiety among the AF male and female patients separately. Among men (Table 2), the odds of depression were significantly lower among men aged 65–74 years, and aged 85 years or older; while the odds were higher among divorced and widowed men, and among men with cerebrovascular diseases. These associations persisted after including anxiety in the model, which otherwise was significantly associated with higher odds for depression. Furthermore, the odds of anxiety were lower among men living in high SES neighbourhoods; these odds remained significant after the inclusion of depression in the model. Higher odds for anxiety among men with CHD were no longer significant after adjusting the model for depression. Depression was also associated with higher odds for anxiety.

For women (Table 3), the odds of depression were consistently higher for widowed, as for the presence of CHD and cerebrovascular disease; the odds were higher for CHD and lower for diabetes only in models without adjustment for co-present anxiety, which also showed higher odds for depression. The odds for anxiety were consistently higher for hypertension. Higher odds for unmarried and widowed women and also for CHD were only present when not adjusting for co-morbid depression, which showed higher odds for anxiety.

The effects of depression and anxiety on all-cause mortality among men and women separately are presented in Table 4 (Cox proportional-hazards regression models). The results of the Cox regression analyses showed a significantly higher risk of mortality among

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men with depression compared to their counterparts without depression: crude model HR 1.31 (95% 1.11–1.54) and fully adjusted model HR 1.28 (95% 1.08–1.53). We did not observe any significant association between anxiety and mortality in men. Similarly, being diagnosed with depression or anxiety was not significantly associated with mortality among women with AF.

Discussion

This study explored the effects of depression and anxiety on all-cause mortality in patients with AF. We observed a 30% increased mortality risk in men with AF and concomitant depression compared to their counterparts without depression. Among women, the association between depression or anxiety and all-cause mortality was weaker and statistically non-significant.

An increased risk of all-cause mortality was hypothesized for both depression and anxiety, based on results from earlier studies (14,16,17). This was to some extent confirmed by the increased risk estimate for all-cause mortality for depression among men in the present study, but the lack of an excess mortality in women with either depression or anxiety compared to those without these conditions is notable. Both depression and anxiety are more common among women (13), but our data are not sufficient to explain why the mortality risk was not significantly increased in contrast to the findings among men. However, several factors may contribute to the observed sex difference in the association between AF and mortality in people with depression. Men, in comparison to women, tend to disregard health professional's advice and are less likely to ask for help (22). Men have in comparison to women smaller and less intimate social networks (23), a well-known vulnerability factor for morbidity (24). In addition, it has been proposed that men's depression symptoms are different from women's (25). Rather than asking for help, men tend to externalize their emotions in the form of irritability and anger or self-destructive behaviour such as substance use or "workaholism" (26). The observed sex difference could thus partly be a result of insufficiently treated and poorly followed up depression among males.

As regards to socio-economic factors, we included both neighbourhood and individual levels, as they are not completely overlapping, and thus give complementary information, and identify partly different risks. Low neighbourhood SES has been shown to be associated with increased mortality among men with AF (21). Individuals living in low SES neighbourhoods have a lower awareness of healthy life-style changes than individuals in high SES neighbourhoods (27), and have been shown to have an earlier onset of multi-morbidities (28). Moreover, they receive less optimal pharmacotherapy for their AF (29). Yet, the present results of a higher mortality in men with AF and subsequent depression remained significant after adjustments for neighbourhood SES, indicating that the neighbourhood SES does not explain the excess mortality.

Marital status is also of importance, as unmarried, divorced and widowed men and women have a higher mortality than married men and women (30). We found that men who were divorced or widowed were more likely to be diagnosed with depression. Furthermore, married men had half the risk of dying compared to unmarried men (31). Being divorced or

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widowed must be regarded as a risk factor especially for men; a fact that needs more attention in the clinical setting.

Furthermore, we observed that men were more likely to be depressed if diagnosed with cerebrovascular disease; while women were more likely to be depressed if diagnosed with cerebrovascular disease, CHD and heart failure. The association between cerebrovascular disease and depression in our study was rather expected, and in fact, post-stroke depression is a well-known concept (32–34). Depression is also a risk for incident stroke (35) translating into a vicious cycle of the depression-stroke relationship. Similarly, both depression and anxiety are known to be associated with various cardiovascular conditions (36). We also observed a higher likelihood of an anxiety diagnosis among men and women with CHD, which is in congruence with previous reports (37). Although depression and anxiety are highly related, the association between anxiety and mortality was not significant in the present cohort of AF patients in primary care.

This study has certain limitations. As this is an observational study, we can only show results on associations, not on causality between AF and concomitant cardiovascular diseases and depression or anxiety. Data were extracted from primary health care electronic patient records, and some data may be missing from those records. We only had access to clinical diagnoses of anxiety and depression in the electronic patient records, and there might be both underdiagnoses and overdiagnoses. Furthermore, we did not have access to prescriptions of anti-depressive medication. In addition, listings of diagnoses may be incomplete. However, diagnoses of common diseases such as cardiovascular diseases and diabetes could be expected to be more accurate and complete than many other diagnoses (38). Furthermore, data on disease severity, e.g. NYHA classification of CHF, were not available. We also had no data available on the type of atrial fibrillation (paroxysmal, persistent, or permanent) and rhythm (sinus rhythm, fibrillation). Furthermore, we had no information on catheter ablation procedures or Cox–Maze operations. Given that our predominant focus was on cardiovascular co-morbidity and whether the relationship between depression or anxiety and all-cause mortality was independent of cardiovascular comorbidity, we did not include other diagnoses potentially associated with mortality such as presence of cancers, or other noncardiovascular conditions. On the other hand, since the variables available in the present study were obtained from primary health care electronic patient records they may be assumed to mirror the information available for the clinician. In addition, we did not have access to multiple measures of individual SES. However, we adjusted our analyses for level of formal education, which is a commonly used proxy for individual SES (39).

Despite the limitations, one of the key strengths of this study is the linkage of clinical data from individual patients to national demographic and socioeconomic data with less than 1% missing data. The clinical data were also highly complete; less than 2% of the total number of diagnoses were missing (38). The comprehensive nature of our data made it possible to analyze men and women from all educational backgrounds and marital statuses. Another strength is the sample size of the study, i.e. 6646 men and 5637 women, and almost 72 000 person-years at risk analyzed. We also had access to data on change of place of residence, and consequently neighborhood SES, which is important in this sample in which the

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majority was older and almost 40% changed their neighborhood SES. Finally, many previous follow-up studies of atrial fibrillation have used data from hospital samples, which could display higher rates of all-cause morbidity and mortality than our sample from primary care.

Significant outcomes

Men diagnosed with both AF and depression are at greater risk of death compared to their male counterparts.

Cerebrovascular disease was linked to depression among both men and women.

No increased mortality was found in women with depression or anxiety.

Limitations

Being an observational study, results can only show associations between AF with depression and mortality, and no conclusions on causality can be drawn.

Data were extracted solely from primary health care electronic patient records, why some hospital data may be missing.

Data on the type of atrial fibrillation and rhythm, as well as the severity of cardiovascular co-morbidity were not available.

Conclusions

This study found a higher mortality among men with AF and co-morbid depression. This should urge general practitioners and cardiologists to screen for depression and to pay special attention to men with depression in whom we found an increased risk for death.

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Table 1

Data on subjects aged 45+ years (n = 12 283) with a diagnosis of atrial fibrillation in primary care from 1 January 2001 to 31 December 2007, by the presence or absence of a psychiatric disease (diagnosis of depression or anxiety).

	Men			Women		
	With depression n = 412	**With anxiety n = 183**	**Without psychiatric disease n = 6107**	**With depression n = 627**	**With anxiety n = 313**	**Without psychiatric disease n = 4810**
Age (years), mean (SD)	71.9 (10.6)	71.9 (10.8)	72.2 (10.1)	76.7 (9.2)	76.5 (9.3)	77.2 (9.3)
Age group (years)						
n (%)						
45–54	32 (7.7)	12 (6.6)	330 (5.4)	12 (1.9)	6 (1.9)	89 (1.9)
55–64	76 (18.5)	40 (21.9)	1117 (18.3)	67 (10.7)	29 (9.3)	435 (9.0)
65–74	107 (26.0)	43 (23.5)	1900 (31.1)	136 (21.7)	75 (24.0)	1084 (22.5)
75–84	162 (39.3)	66 (36.1)	2139 (35.0)	294 (46.9)	146 (46.7)	2149 (44.7)
85+	35 (8.5)	22 (12.0)	621 (10.2)	118 (18.8)	57 (18.2)	1053 (21.9)
Neighborhood SES						
High	178 (43.2)	103 (56.3)	2778 (45.5)	310 (49.4)	144 (46.0)	2376 (49.4)
Middle	164 (39.8)	53 (29.0)	2457 (40.2)	229 (36.5)	113 (36.1)	1655 (34.4)
Low	70 (17.0)	27 (14.8)	872 (14.3)	88 (14.0)	56 (17.9)	779 (16.2)
Marital status						
Married	224 (54.5)	93 (51.1)	3661 (60.2)	173 (27.7)	80 (25.6)	1438 (30.0)
Unmarried	31 (7.5)	17 (9.3)	587 (9.7)	36 (5.8)	25 (8.0)	343 (7.2)
Divorced	82 (20.0)	37 (20.3)	914 (5.0)	93 (14.9)	56 (18.0)	662 (13.8)
Widowed	74 (18.0)	35 (19.2)	922 (15.2)	323 (51.7)	151 (48.4)	2344 (49.0)
Educational level						
Compulsory school	139 (35.4)	79 (45.9)	2285 (39.6)	289 (51.6)	142 (51.5)	2216 (52.6)
Secondary school	164 (41.8)	63 (36.6)	2161 (37.4)	185 (33.0)	103 (37.3)	1378 (32.7)
College/university	89 (22.7)	30 (17.4)	1332 (23.0)	86 (15.4)	31 (11.2)	620 (14.7)
AF-related disease						
Hypertension	159 (38.6)	67 (36.6)	2596 (42.5)	318 (50.7)	166 (53.0)	2356 (49.0)
Coronary heart disease	101 (24.5)	51 (27.8)	1203 (19.7)	166 (26.5)	83 (26.5)	959 (19.9)
Heart failure	74 (18.0)	29 (15.9)	1060 (17.4)	137 (21.9)	67 (21.4)	973 (20.2)

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	Men			Women		
	With depression n = 412	**With anxiety n = 183**	**Without psychiatric disease n = 6107**	**With depression n = 627**	**With anxiety n = 313**	**Without psychiatric disease n = 4810**
Cerebrovascular disease	86 (20.9)	24 (13.1)	638 (10.5)	96 (15.3)	40 (12.8)	547 (11.4)
Diabetes mellitus	81 (19.7)	29 (15.9)	1212 (19.9)	120 (19.1)	62 (19.8)	936 (19.5)
Psychiatric disease						
Depression	412 (100.0)	56 (30.6)	0 (0.0)	627 (100.0)	113 (36.1)	0 (0.0)
Anxiety	56 (13.6)	183 (100.0)	0 (0.0)	113 (18.0)	313 (100.0)	0 (0.0)

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Table 2

Logistic regression models of risk of depression or anxiety for men aged 45 + years (n = 6646) with a diagnosis of atrial fibrillation in primary care.

	Depression		Anxiety	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Age group				
45–54 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)
55–64 years	0.67 (0.43–1.04)	0.66 (0.42–1.04)	1.02 (0.52–1.98)	1.15 (0.58–2.29)
65–74 years	**0.55 (0.36–0.84)**	**0.57 (0.37–0.88)**	0.64 (0.33–1.26)	0.80 (0.40–1.59)
75–84 years	0.68 (0.44–1.04)	0.69 (0.45–1.07)	0.81 (0.42–1.57)	0.94 (0.47–1.85)
85+ years	**0.32 (0.20–0.70)**	**0.38 (0.20–0.72)**	0.77 (0.33–1.81)	1.03 (0.43–2.47)
Neighbourhood SES				
High	0.96 (0.75–1.23)	1.03 (0.80–1.32)	**0.55 (0.38–0.81)**	**0.42 (0.25–0.70)**
Middle	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Low	1.31 (0.93–1.84)	1.32 (0.93–1.86)	1.01 (0.62–1.65)	1.19 (0.63–2.24)
Marital status				
Married	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unmarried	0.81 (0.54–1.22)	0.80 (0.53–1.21)	1.03 (0.59–1.77)	1.21 (0.62–2.35)
Divorced	**1.39 (1.06–1.82)**	**1.33 (1.01–1.76)**	1.47 (0.98–2.21)	1.19 (0.68–2.09)
Widowed	**1.41 (1.05–1.91)**	**1.36 (1.01–1.85)**	1.44 (0.93–2.24)	1.07 (0.59–1.92)
Educational level				
Compulsory school	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Secondary school	**1.30 (1.02–1.66)**	**1.32 (1.03–1.70)**	0.91 (0.64–1.29)	0.69 (0.47–1.02)
College/university	1.24 (0.92–1.66)	1.27 (0.94–1.71)	0.79 (0.50–1.24)	0.77 (0.49–1.23)
AF-related disease				
Hypertension	0.82 (0.66–1.02)	0.84 (0.68–1.05)	0.83 (0.60–1.14)	0.82 (0.59–1.14)
Coronary heart disease	1.25 (0.97–1.60)	1.20 (0.93–1.55)	**1.43 (1.00–2.04)**	1.38 (0.96–1.99)
Heart failure	1.07 (0.81–1.41)	1.09 (0.82–1.44)	0.82 (0.53–1.26)	0.81 (0.52–1.26)
Cerebrovascular disease	**2.21 (1.63–2.98)**	**2.19 (1.61–2.98)**	1.20 (0.70–2.04)	0.90 (0.41–2.00)
Diabetes mellitus	1.02 (0.78–1.33)	1.06 (0.81–1.38)	0.73 (0.48–1.12)	0.71 (0.46–1.10)
Psychiatric disease				
Depression	–	–	–	**9.21 (6.31–13.44)**
Anxiety	–	**7.41 (5.21–10.58)**	–	–

Model 1: age-group, educational level, marital status, neighborhood socio-economic groups (high, middle or low) including change of neighborhood socio-economic status during follow-up and diagnoses (anxiety or depression; hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease and diabetes, including relevant interaction terms); Model 2 as Model 1 and adjusted for anxiety in a depression model; or adjusted for depression in the anxiety model. Data are presented as odds ratios (95% confidence intervals). Statistically significant factors are shown in bold.

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Table 3

Logistic regression models of risk of depression or anxiety for women aged 45 + years (n = 5637) with a diagnosis of atrial fibrillation in primary care.

	Women			
	Depression		Anxiety	
	Model 1	Model 2	Model 1	Model 2
Age group				
45–54 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)
55–64 years	1.08 (0.56–2.09)	1.05 (0.54–2.06)	0.92 (0.37–2.31)	0.97 (0.37–2.50)
65–74 years	0.80 (0.42–1.52)	0.78 (0.41–1.49)	0.95 (0.40–2.29)	1.11 (0.45–2.77)
75–84 years	0.78 (0.42–1.48)	0.77 (0.41–1.47)	0.88 (0.37–2.11)	1.04 (0.42–2.59)
85+ years	0.61 (0.31–1.21)	0.62 (0.31–1.23)	0.71 (0.28–1.82)	0.89 (0.34–2.34)
Neighbourhood SES				
High	1.06 (0.86–1.27)	1.04 (0.84–1.29)	0.80 (0.43–1.50)	0.88 (0.46–1.66)
Middle	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Low	0.82 (0.61–1.11)	0.81 (0.59–10.9)	1.82 (0.82–3.99)	1.91 (0.85–4.29)
Marital status				
Married	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unmarried	1.17 (0.77–1.78)	0.85 (0.57–1.27)	**2.09 (1.03–4.22)**	1.15 (0.38–3.51)
Divorced	1.32 (0.97–1.80)	1.09 (0.82–1.46)	1.52 (0.82–2.81)	1.56 (0.75–3.25)
Widowed	**1.38 (1.08–1.78)**	**1.27 (1.01–1.59)**	**1.91 (1.17–3.13)**	1.77 (0.99–3.15)
Educational level				
Compulsory school	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Secondary school	1.04 (0.85–1.27)	1.01 (0.82–1.24)	1.19 (0.91–1.56)	1.16 (0.68–1.99)
College/university	1.10 (0.84–1.44)	1.13 (0.86–1.49)	0.77 (0.51–1.18)	0.90 (0.45–1.81)
AF-related disease				
Hypertension	1.09 (0.91–1.31)	1.07 (0.89–1.29)	**1.75 (1.15–2.65)**	**1.80 (1.17–2.77)**
Coronary heart disease	**1.41 (1.14–1.74)**	**1.34 (1.08–1.66)**	**1.38 (1.04–1.84)**	1.26 (0.94–1.69)
Heart failure	**1.72 (1.14–2.59)**	1.14 (0.91–1.43)	1.09 (0.80–1.48)	1.06 (0.77–1.45)
Cerebrovascular disease	**1.32 (1.03–1.71)**	**1.33 (1.03–1.72)**	0.97 (0.67–1.42)	0.89 (0.60–1.31)
Diabetes mellitus	**0.55 (0.34–0.88)**	0.90 (0.71–1.14)	1.00 (0.73–1.35)	1.05 (0.77–1.44)
Psychiatric disease				
Depression	–	–	–	**9.69 (6.02–15.60)**
Anxiety	–	**5.07 (3.88–6.62)**	–	–

Model 1: age-group, educational level, marital status, neighborhood socio-economic groups (high, middle or low) including change of neighborhood socio-economic status during follow-up and diagnoses (anxiety or depression; hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease and diabetes); Model 2 as Model 1 and adjusted for anxiety in a depression model; or adjusted for depression in the anxiety model. Data are presented as odds ratios (95% confidence intervals). Statistically significant factors are shown in bold.

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Table 4

All-cause mortality of patients (n = 12 283) with atrial fibrillation by diagnoses of depression and anxiety, respectively: the results of cox regression (a significant interaction between depression and sex was present).

Group	Events/ At Risk (n)	Incidence Rate per 100 Person-Years at Risk (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Men n = 6646	1983/6646	5.06 (4.85–5.29)			
No depression	1824/6234	4.97 (4.74–5.20)	1 (ref)	1 (ref)	1 (ref)
Depression	159/412	6.57 (5.63–7.68)	**1.31 (1.11–1.54)**	**1.32 (1.11–1.57)**	**1.28 (1.08–1.53)**
No anxiety	1921/6463	5.05 (4.83–5.28)	1 (ref)	1 (ref)	1 (ref)
Anxiety	62/183	5.73 (4.47–7.35)	1.15 (0.89–1.47)	1.04 (0.80–1.36)	0.99 (0.76–1.31)
Women n =5637	1971/5637	6.07 (5.81–6.35)			
No depression	1743/5010	6.06 (5.78–6.35)	1 (ref)	1 (ref)	1 (ref)
Depression	228/627	6.16 (5.41–7.02)	1.01 (0.88–1.16)	1.04 (0.89–1.22)	1.05 (0.90–1.23)
No anxiety	1869/5324	6.11 (5.84–6.39)	1 (ref)	1 (ref)	1 (ref)
Anxiety	102/313	5.50 (4.53–6.67)	0.89 (0.73–1.09)	0.93 (0.74–1.17)	0.93 (0.74–1.17)

Model 1 includes psychiatric diagnosis, and, Model 2 as Model 1 but also includes age group, educational level, marital status, neighborhood socio-economic score by three groups (high, medium and low) and change of neighborhood level, Model 3 as Model 2 but also includes diagnoses (anxiety or depression; hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease and diabetes, also including interaction terms between age group and diagnoses, i.e. for men and depression with diabetes and CHD; for women with CHD and CVS).