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The gender difference in quality of life and its explaining variables in patients with non-valvular atrial fibrillation

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Abstract

Background: Women with atrial fibrillation (AF) had worse quality of life (QoL) than men, while the contributing factors to worse QoL in women is unclear.

Methods: We analyzed the data of 3562 patients with non-valvular AF (NVAF) enrolled in the China Registry of Atrial Fibrillation. The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) was used to evaluate QoL and compared between women and men. Multivariate logistic regression analysis model was used to explore the factors might explain the sex disparity on QoL.

Results: Overall, 43.3% of the cohort were women (n=1541). Women were much older than men (72 ± 9.8 vs. 68 ± 11.9 years, $p < 0.001$). Compared to men, women were more likely to have more symptoms, hypertension, diabetes mellitus, and heart failure. Women were less like to receive catheter ablation (4.5% vs. 6.1%, $p = 0.044$). Women also had both lower physical component summary (PCS) scores (48±9 vs. 51±9, $p < 0.001$) and mental component summary (MCS) scores (49±10 vs. 51±10, $p < 0.001$) than men. In the multivariable analysis of the worse PCS scores in women, patients' age might explain 32.9%, low level of socioeconomic status 20.0%, lifestyle 14.3%, cardiovascular comorbidities 15.7%, more symptoms 5.7%, and less catheter ablation 1.4%. These factors could explain a similar proportion of the sex disparity in MCS scores. All together, these factors could explain 54.3% for worse physical function status and 46.8% for worse mental function status.

Conclusions: Women patients with AF had worse QoL than men. The following factors could partly explain the worse QoL in women: older age, low level of socioeconomic status, more cardiovascular comorbidities, less smoking and drinking, more symptoms and received less catheter ablation.

Keywords

Atrial fibrillation; Sex; Quality of life; Risk factor.

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1. Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that can contribute to adverse clinical outcomes and impaired quality of life (QoL) [1-3]. Although women have a lower incidence of AF, they usually experience a higher risk of death and stroke when compared to men [4-6]. Many studies have been reported on sex-related disparities in prevalence, risk factors, and clinical outcomes of patients with AF. Women also have poorer QoL than men in both Eastern and Western populations [5, 7, 8]. However, there are few studies that explored the factors that might explain the sex difference in QoL. Despite treatment for AF are also proved to be associated with QoL for patients with AF, such as a strict rate control, electrical cardioversion, and catheter ablation, there still remains a lower QoL in women than men after treatment [9, 10]. Given the rapid increase in the incidence of AF, particularly in China, it is critical to understand the factors potentially explaining the sex differences in QoL to minimize or even omit the sex disparities. [11]

The CRAF study was a national wide and cross-sectional research that collected information about clinical characteristics, treatment for AF and QoL scales in unselective patients with AF in China. We aimed to investigate whether symptoms, treatment strategies and QoL differed between women and men with AF and to explore the factors that might explain the difference in QoL between sexes.

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2. Methods

2.1. Study population

The China Registry of Atrial Fibrillation (CRAF) was a multicenter, cross-sectional, observational study which conducted in 111 hospitals included 89 tertiary hospitals and 22 Tier two hospitals between July 2012 and December 2012.The design of the study has been published before [12]. Briefly, the study used a simple random sampling method which could represent a nationally sample of AF patients. Patients were included if they were over the age of 18 years and had an electrocardiogram-verified diagnosis of AF. The study was performed according to the requirement of Declaration of Helsinki and obtained the approval of the ethics committees in Peking University People's hospital. Written informed consent were acquired from all participated patients in this study.

2.2. Data collection

Demographic parameters, socioeconomic information, clinical characteristics, medical history, the date of confirmed diagnosis of AF, AF-related symptoms, the types of AF, antiarrhythmic treatment, antithrombotic treatment, and QoL questionnaires were collected. The risk of stroke or bleeding was evaluated for each individual patient [13].

2.3. Assessment of Quality of Life

At enrollment into the registry, the QoL was assessed using the Chinese version of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) [14]. The questionnaire was

DOI: 10.55415/deep-2023-0023.v1

self-performed by patients with the help of trained research assistants at each local center. SF-36 questionnaire contains 36 items to evaluating eight dimensions of health condition including physical functioning (PF), role–physical (RP), or limitation in daily role functioning due to physical problems, bodily pain (BP), general health (GH), vitality (VT), role–emotional (RE), or limitation in daily role functioning due to emotional problems, social functioning (SF), and mental health(MH).The eight domains were subsequently grouped into a physical component summary (PCS) and a mental component summary (MCS). Each domain and component summary scores range from 0 to 100, with higher scores denoting better QoL. The definition of low QoL was PCS scores less than 50 or MCS scores less than 50 on the basis of previous study [15].

2.4. Statistical analysis

Continuous variables were presented as means ± standard deviation (SD) for normally distributed data and medians (25th and 75th percentiles) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The differences between continuous variables were evaluated using Student t-test or Mann-Whitney U test. The differences between categorical variables were estimated using the Chi-square test or Fisher exact test. Multivariate logistic regression analysis was performed to calculate odds ratio (OR) and corresponding 95% confidence intervals (CI) for QoL. To understand the sex difference in QoL, unadjusted OR was calculated as the base model which included only sex as the independent variable. To understand the role of each variable in explaining the sex difference in QoL, we added each variable into the base model and observed the change in the OR of sex and calculated the percent of the sex-associated risk difference accounted by each variable

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[(adjusted OR − unadjusted OR) / (unadjusted OR − 1.0) ∗ 100%]. We put variables into the model to understand how much of the sex difference in QoL could be explained by all variables in total. The variables included age (per 10 years), socioeconomic status (education level, marital status, living status, annual income, and type of medical insurance), lifestyle (current smoking and current drinking), cardiovascular comorbidities (hypertension, diabetes mellitus, heart failure, and systemic embolism), number of symptoms (0, 1, 2, and ≧3), and catheter ablation. We also analyzed the association of QoL with age (< 75 or ≥75 years) or antiarrhythmic treatment strategy stratified by sexes. All statistical analyses were performed using the SPSS software version 25.0 (IBM Corporation, Chicago, IL, USA) and a two-tailed value of $p < 0.05$ was defined as statistically significant.

3. Results

3.1. Baseline Characteristics

Overall, 3562 patients with non-valvular AF (NVAF) were included in this analysis after excluding 599 patients with rheumatic heart disease or mechanic valve replacement (Figure 1). 43.3% (1541) of the cohort were women. Clinical characteristics on the basis of sexes are shown in Table 1. Compared to men, women were much older (72±9.8 years vs. 68±11.9 years, $p < 0.001$) and had more cardiovascular comorbidities, including history of hypertension (64.8% vs. 59.5%, $p = 0.001$), diabetes mellitus (20.5% vs. 15.2%, $p < 0.001$), and heart failure (38.6% vs. 31.7%, $p < 0.001$). Women were less likely to have myocardial infarction (3.6% vs. 6.2%, $p < 0.001$) and chronic liver disease (2.7% vs. 4.8%, $p = 0.002$). The education level was lower in women than men (86.4 % vs. 73.3%, $p < 0.001$). Women were more likely to live alone (7.9% vs. 5.7%, $p = 0.010$), but less likely to be unmarried

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(0.8% vs. 1.6%, p = 0.031). The proportion of the patients with low annual income was higher in women (58.7% vs. 49.8%, p < 0.001) than men. Women had higher median CHA_2DS_2-VASc scores (4[2-5] vs. 2 [1-3], p < 0.001) than men. Although there was no significant difference in HAS-BLED scores between sexes, there were less woman with high bleeding risk (HAS-BLED scores ≥ 3) compared to men (15.2% vs. 18.7%, p < 0.001). There was no significant difference in the types of AF between sexes.

3.2. AF-related symptoms between men and women

The AF-related symptoms are presented in figure 2. Compared to men, less women were asymptomatic (3.6% vs 5.4%, p = 0.008). Women were more likely to experience palpitations (74.0% vs. 68.7%, p = 0.001). No significant differences were observed in other symptoms such as syncope, dizzy, dyspnea, fatigue, chest pain, and chest discomfort. Women were also more likely to experience at least 3 types of symptoms compared to men (32.3% vs. 28.8%, p =0.022).

3.3. Management of AF between men and women

Overall, there were 32.6% (n =1160) of the patients receiving rhythm control and 53.3% (n = 1899) receiving rate control (Table 2). Women were more likely to receive rate control treatment (54.8% vs. 52.2%, p = 0.025) compared with men. Of note, women were less likely to receive catheter ablation than men (4.5% vs. 6.1%, p = 0.044). There were no significant differences in the use of a class Ⅰc antiarrhythmic medications (3.8% vs. 3.3%, p = 0.366) and amiodarone (14.5% vs. 16.1%, p = 0.192) between women and men. Women were more often taking digoxin (22.8% vs. 19.0%, p = 0.006) and

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calcium-channel blockers (1.4% vs. 0.7%, $p = 0.030$) for the rate control than men. In terms of antithrombotic strategy, there were no significant differences in the treatment of antithrombotic medicines between women and men.

3.4. Comparison of the QoL between the men and women

Women had lower QoL scores when compared to men as shown in Figure 3. Both the PCS scores (48±9 vs. 51±9, $p < 0.001$) and the MCS scores (49±10 vs. 51±10, $p < 0.001$) were lower in women than in men. Women also had consistently lower scores in all the domains of SF-36 (Supplementary table 1). The sex differences for QoL persisted when restricting the analysis to those aged < 75 years or ≥ 75 years (Supplementary table 2). There was no significant interaction between age (< 75 or ≥75 years) and sex for the risk of poor QoL (Supplementary figure 1). The SF-36 scores were also lower in women compared with men in those treated with rhythm control strategy or rate control strategy (Supplementary table 3).

3.5. Factors explaining the gender differences of QoL

The results of the analysis of the association between sex and QoL are shown in Table 3. Women were associated with both low PCS scores (OR = 1.70; 95% CI, 1.49-1.95, $p < 0.001$) and low MCS scores (OR = 1.47; 95% CI,1.28-1.67, $p < 0.001$) compare to men. The variables that accounted the gender-associated risk differences were older age, lower socioeconomic status, lifestyle, cardiovascular comorbidities, more symptoms, and less catheter ablation. After adjustment of all above factors, the association was attenuated but still statistically significant for both low PCS scores

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(OR= 1.32; 95%CI 1.13-1.54, $p < 0.001$) and low MCS scores (OR = 1.25; 95%CI, 1.08-1.45, $p = 0.001$).

4. Discussion

In this nationwide large registry, we observed several major findings regarding the sex disparities in QoL in NVAF patients. We confirmed that women had worse QoL compared to men for both PCS and MCS scores. Moreover, for the first time, we clearly described that sex differences in QoL could partly be explained by older age, more cardiovascular comorbidities, lower socioeconomic status, healthier lifestyle, more symptoms, and less catheter ablation in women. Addressing the gap between sexes in patients with AF could yield clues to understanding mechanisms and management disparities between women and men.

The evaluation of QoL is particularly important for patients with chronic disorders such as AF. QoL may be impaired by both the disease itself as well as the management for the disease. Several questionnaires were used to measure generic QoL and other disease-specific symptoms, which included the SF-36, EuroQoL-5 Dimension (EQ-5D), the University of Toronto AF Severity Scale (AFSS), the Atrial fibrillation Quality of life (AF-QoL), the Atrial Fibrillation Effect on Quality of Life (AFEQT) and so on. We confirmed that women with NVAF had worse QoL using SF-36 compared to men, which was aligned with the previous study using different questionnaires [10]. An observation study including 1534 patients with AF found that women had worse QoL using the AFEQT questionnaire [7]. The European Heart Survey on Atrial Fibrillation study showed that women had a lower QoL measured by the EQ-5D questionnaire [16]. Our findings showed that both

DOI: 10.55415/deep-2023-0023.v1

PCS scores and MCS scores were lower in women than in men. However, some studies reported that women had significantly worse PCS scores when compared to men, but not on MCS scores [9, 17]. This could be partly explained by the different patient population enrolled in those studies. One study enrolled permanent patients with AF, who were tolerant to AF episodes and had a better QoL when compared to new onset patients with AF [18]. Another study enrolled highly selected AF patients who received catheter ablation [17]. Besides, the two studies enrolled a smaller sample of patients with AF, less than 650 patients in each study. In contrast, our study enrolled a large cohort with unselected AF patients with 21.1% having permanent AF. There was a small but significant difference in PCS scores and MCS scores between women and men, but it still remained statistically different. Previous studies also reported 3 points gap in PCS or MCS scores was significant between women and men, which indicated a minimal gap could lead to clinical importance difference [2, 10].

Factors accounting for the sex associated differences in QoL are unclear. It was proposed that genetic, socioeconomic, and clinical factors may play a role. First, women with AF were older than man, which could lead to worse QoL [5, 7]. A multicenter study enrolled 3128 NVAF patients found older AF patients had lower QoL than younger AF patients owing to women with more comorbidities, such as hypertension, and diabetes mellitus [19]. However, our study did not show the interaction between age and sex on the QoL. The Rate Control Efficacy in Permanent AF study found the number of AF risk factors was associated with a reduced QoL [9]. Second, the presence of socioeconomic status had been identified as possible reason for observed sex difference in QoL. Individuals with a lower socioeconomic status are less likely to engage in disease treatment, especially individuals with lower income and lower educational level [20-22]. Third, some studies found smokers and drinkers

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had better QoL in general population [23, 24], which might explain the sex difference between men and women in the AF population. We found smokers and drinker had less cardiovascular comorbidities and we guess they were healthy enough not to worry about their health condition. Fourth, the sex disparity in QoL may be related to greater symptom burden in women than men. Women were more sensitive to disease, and had a lower threshold for reporting illness burden than men [25]. Finally, one study found patients with permanent AF were more tolerant to AF episodes and had a better QoL when compared to patients with new-onset AF [18]. However, we did not find the differences in the types of AF between sexes in our cohort.

One of the goals of AF management is to reduce symptom burden and improve QoL [26]. Providers should make clinical decisions between rhythm control and rate control to reduce the burden of patients' symptoms. The CABANA trial showed catheter ablation did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest compared to medical therapy, but led to a significant improvement in QoL [27]. The CAPTAF trial also found that catheter ablation was better than antiarrhythmic drugs alone in improving AF patient's QoL [28]. Besides, one stratified pooled analysis of randomized data showed catheter ablation had significantly improved QoL in patients with AF and heart failure compared to those in antiarrhythmic medications [29]. However, Gleason et al. found women were associated with poorer AF symptom severity and QoL than men, regardless of whether the patients received rhythm control or rate control [30]. In our study, lower rate of catheter ablation in women could explain about 1.4% of the sex disparity on low PCS scores and 4.3% on low MCS scores. Whether the early use of rhythm control for the treatment of AF would result in better QoL in women needs further evidence.

DOI: 10.55415/deep-2023-0023.v1

This is by far the largest study to report the QoL in Chinese patients with NVAF. However, several study limitations should be mentioned. First, this was an observational study, which may lead to selection bias. However, patients were enrolled from 111 hospitals across China, which represented different geographic and economic regions. Second, some confounders were not collected, such as frailty, anxiety and depression, and cognitive function not measured in our study. Besides, the burden of AF is unavailable in our study. It was reported that the correlation between AF burden and QOL were manifested in patients with low burden of AF. Third, the proportion of patients receiving catheter ablation was relatively low in this study. Although the use of catheter ablation for AF has been increasing rapidly in the last decades [31], this would not change the difference of treatment strategy between sexes [10]. The sex disparity could be even worse if ablation did improve the QoL in patients with AF. Fourth, AF burden were not measured as we did not collect the data of disease-specific symptoms questionnaire, such as AF-QoL and AFEQT. However, SF-36 is one of the most widely used measurement for QoL and has been validated in AF patients. SF-36 may be appropriate for QoL measurement for patients with comorbidities and persistent AF. [32] The prior study showed the consistency between SF-36 and the disease-specific symptoms questionnaire. [33] Lastly, we did not collect the European Heart Rhythm Association score, which is a widely accepted measure of functional status, but is assessed from the physician's perspectives.

5. Conclusions

Women with NVAF were older, more symptomatic, having more cardiovascular comorbidities, having lower socioeconomic status, less smoking and drinking, and less likely to receive catheter ablation compared to men. Women also had worse QoL than men. However, the sex difference in QoL was only partly explained by the above factors. Future studies needed to explore psychological and physical factors underlying these differences, which may provide suggestions to further optimize the sex differences in patients with AF.

Data availability

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

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Conflict of interest

There are no conflicts of interest.

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Table

Table 1. Baseline Characteristics stratified by sex.

Variable	Overall (n=3562)	Men (n=2021)	Women (n=1541)	*P* value
Age, years	69 ± 11.2	68 ± 11.9	72 ± 9.8	<0.001
Duration of AF, years	2.5(0.4-5.9)	2.6(0.4-5.9)	2.5(0.4-5.9)	0.553
Education				
High school or less	2813(79.0%)	1482(73.3%)	1331(86.4%)	<0.001
Marital status				
Unmarried	44(1.2%)	32(1.6%)	12(0.8%)	0.031
Live Alone	238(6.7%)	116(5.7%)	122(7.9%)	0.010
Annual income				<0.001
Low	1911(53.6%)	1006(49.8%)	905(58.7%)	
Middle	1280(35.9%)	758(37.5%)	522(33.9%)	
High	371(10.4%)	257(12.7%)	114(7.4%)	
Type of medical insurance				<0.001
Basic medical insurance	3098(87.0%)	1732(85.7%)	1366(88.6%)	
Business health insurance	256(7.2%)	176(8.7%)	80(5.2%)	
None	208(5.8%)	113(5.6%)	95(6.2%)	
Current smoking	383(10.8%)	364(18.0%)	19(1.2%)	<0.001
Current drinking	276(7.7%)	272(13.5%)	4(0.3%)	<0.001
BMI, kg/m^2	24.3 ± 3.5	24.4 ± 3.3	24.1 ± 3.6	0.003
SBP, mmHg	130 ± 18.0	130 ± 17.3	131 ± 18.9	0.295
DBP, mmHg	79 ± 11.6	79 ± 11.2	78 ± 12.0	0.001
Comorbidities				
Hypertension	2201(61.8%)	1203(59.5%)	998(64.8%)	0.001
Diabetes mellitus	624(17.5%)	308(15.2%)	316(20.5%)	<0.001
Dyslipidemia	772(21.7%)	445(22.0%)	327(21.2%)	0.566
Prior MI	180(5.1%)	125(6.2%)	55(3.6%)	<0.001
Heart failure	1235(34.7%)	640(31.7%)	595(38.6%)	<0.001
Peripheral artery disease	161(4.5%)	84(4.2%)	77(5.0%)	0.232
Ischemic stroke	526(14.8%)	305(15.1%)	221(14.3%)	0.532
Non-CNS embolism	29(0.8%)	12(0.6%)	17(1.1%)	0.094
Bleeding	233(6.5%)	136(6.7%)	97(6.3%)	0.603
Chronic liver disease	139(3.9%)	97(4.8%)	42(2.7%)	0.002
Chronic kidney disease	167(4.7%)	102(5.0%)	65(4.2%)	0.246
AF type				0.052
New onset	471(13.2%)	256(12.7%)	215(14.0%)	
Paroxysmal	1263(35.5%)	690(34.1%)	573(37.2%)	
Persistent	1076(30.2%)	644(31.9%)	432(28.0%)	

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Permanent	752(21.1%)	431(21.3%)	321(20.8%)	
CHA_2DS_2-VASc score	3(2-4)	2(1-3)	4(2-5)	<0.001
HAS-BLED score	2(1-2)	2(1-2)	2(1-2)	0.332

AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI: myocardial ischemia; CNS, central nervous system.

CHA_2DS_2-VASc: cardiac failure or dysfunction, hypertension, aged 75 years or older (doubled), diabetes, stroke (doubled), vascular disease, aged 65 to 74 years, and sex category (female);

HAS-BLED: hypertension if systolic blood pressure > 160 mmHg, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, aged above 65 years, and received antiplatelet drugs or alcohol.

Continuous data are presented as means ± standard deviation (SD) or median (interquartile range) if appropriate and categorical data was shown as n (%).

P value in this table was analyzed between women and men.

DOI: 10.55415/deep-2023-0023.v1

Table 2. AF-related treatment between the sexes.

Variable	Overall (n=3562)	Men (n=2021)	Women (n=1541)	*P* value
Antiarrhythmic treatment				0.025
Non-treatment	503(14.1%)	313(15.5%)	190(12.3%)	
Rhythm control strategy	1160(32.6%)	653(32.3%)	507(32.9%)	
Rate control strategy	1899(53.3%)	1055(52.2%)	844(54.8%)	
Catheter ablation	193(5.4%)	123(6.1%)	70(4.5%)	0.044
Current rhythm-control drugs				
Class Ⅰc antiarrhythmic	125(3.5%)	66(3.3%)	59(3.8%)	0.366
Amiodarone	550(15.4%)	326(16.1%)	224(14.5%)	0.192
Current rate control drugs				
β-blocker	1826(51.3%)	1014(50.2%)	812(52.7%)	0.136
Calcium-channel blocker	36(1.0%)	14(0.7%)	22(1.4%)	0.030
Digoxin	737(20.7%)	385(19.0%)	352(22.8%)	0.006
Antithrombotic treatment				0.803
Non-treatment	436(12.2%)	241(11.9%)	195(12.7%)	
Anticoagulant	952(26.7%)	543(26.9%)	409(26.5%)	
Antiplatelet	2174(61.0%)	1237(61.2%)	937(60.8%)	
Current antithrombotic drugs				
Warfarin	912(25.6%)	521(25.8%)	391(25.4%)	0.783
Aspirin	2076(58.3%)	1193(59.0%)	883(57.3%)	0.300
Clopidogrel	533(15.0%)	315(15.6%)	218(14.1%)	0.233

Data was shown as n (%).

P value in this table was analyzed between women and men.

DOI: 10.55415/deep-2023-0023.v1

Table 3. Odds ratio (OR) for lower PCS score or lower MCS score in women over men with and without adjustment for variables, and percent of the sex-related risk difference accounted by each explaining variable.

Variables adjusted for	PCS			MCS		
	OR (95%CI)	*P* value	Percent of difference accounted	OR (95%CI)	*P* value	Percent of difference accounted
Base model: sex (reference = male)	1.70(1.49-1.95)	<0.001		1.47(1.28-1.67)	<0.001	
Age, per 10 years	1.47(1.28-1.69)	<0.001	−32.9%	1.36(1.19-1.56)	<0.001	−23.4%
Socioeconomic status	1.56(1.36-1.79)	<0.001	−20.0%	1.37(1.20-1.57)	<0.001	−21.2%
Lifestyle	1.60(1.39-1.84)	<0.001	−14.3%	1.41(1.23-1.63)	<0.001	−12.8%
Cardiovascular comorbidities	1.59(1.38-1.84)	<0.001	−15.7%	1.41(1.23-1.61)	<0.001	−12.8%
Number of symptoms	1.66(1.45-1.90)	<0.001	−5.7%	1.42(1.24-1.63)	<0.001	−10.6%
Catheter ablation	1.69(1.48-1.94)	<0.001	−1.4%	1.45(1.27-1.66)	<0.001	−4.3%
All above	1.32(1.13-1.54)	<0.001	−54.3%	1.25(1.08-1.45)	0.003	−46.8%

PCS, physical component summary; MCS, mental component summary.

Socioeconomic status: high school or less, unmarried, live alone, annual income, and type of medical insurance.

Lifestyle: current smoking and current drinking.

Cardiovascular co-morbidities: hypertension, diabetes mellitus, heart failure, and non-central nervous system embolism.

Number of symptoms: 0, 1, 2, and ≧3.

Percent of gender difference account: (adjusted OR − unadjusted OR) / (unadjusted OR − 1.0) ∗ 100%.

OR, odds ratio; CI, confidence interval.