



REVIEW

Depression, Anxiety, and Cardiovascular Disease in Chinese: A Review for a Bigger Picture

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Abstract

Cardiovascular disease (CVD) and depression and anxiety contribute substantially to the current disease burden worldwide as well as in China. Both depression and anxiety are highly prevalent among patients with CVD. We systematically reviewed the literature to disentangle the role of depression and anxiety disorders in the onset and prognosis of CVD with an emphasis on cohort studies conducted in the Chinese population. Despite the lack of large-scale prospective studies in China, the available evidence implies that both depression and anxiety are closely associated with the onset and prognosis of CVD, including ischemic heart disease and stroke, in Chinese adults. Putative behavioral and biological mechanisms are implicated in the link between depression/anxiety and CVD. Timely screening and diagnosis followed by proper treatment should be implemented for depression and anxiety in both the general population and patients with CVD. Current standard treatments such as selective serotonin reuptake inhibitors and psychotherapies are recommended for CVD patients with depression, although their efficacy for reducing CVD morbidity and mortality remains uncertain. In conclusion, prospective studies on the link between depression/anxiety and the onset and prognosis of CVD are urgently needed in the Chinese population, and more efforts are warranted to examine the efficacy of depression and anxiety treatments for CVD patients, particularly the integrated care model of including psychiatrists in a multidisciplinary clinical group.

Keywords: cardiovascular disease; depression; anxiety; coronary heart disease; stroke; risk; mortality; prognosis

Introduction

China has experienced rapid economic development in the past several decades. With economic prosperity, urbanization, rapid lifestyle change, rising income, and aging, noncommunicable diseases have surpassed infectious diseases as the major burden among diseases. Cardiovascular disease

(CVD), particularly stroke (1.7 million deaths) and ischemic heart disease (0.9 million deaths), was the leading cause of death in China in 2013 [1]. In the same year, CVD accounted for 40.7% of all deaths, and the age-standardized CVD mortality reached 307 per 100,000 persons. From 1990 to 2013, total deaths caused by CVD increased from 2.6 million to 3.7 million in China [1]. Despite increasing average life expectancy in the past few decades in China, it is projected that the increasing trend of noncommunicable diseases, particularly CVD, might be a hurdle to such progress in the next two decades [2].

Multiple risk factors have been implied in the pathophysiology of CVD. Among them, mental

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health has received considerable attention recently. Depression and anxiety are two major forms of mental health issues in China. According to estimates from the 2010 Global Burden of Disease Study [3], depression was the fourth leading cause of disability-adjusted life years in China in 2010. Depression can range from mild depressive symptoms to major depressive disorder (MDD). Many questionnaires have been developed to screen patients for depressive symptoms, but MDD is mainly diagnosed by a psychiatrist on the basis of a clinical diagnostic interview and requires persistence of certain symptoms for a period. Similarly, although anxiety can occur as a symptom at some point of any individual's life, the diagnosis of anxiety disorder requires the individual to meet certain criteria, and it includes several subtypes, such as generalized anxiety disorder, panic disorder, and phobia. A few studies have reported high prevalence of depression and anxiety in the Chinese population. In a large study in four provinces of China in 2001–2005, the 1-month prevalence of MDD and anxiety disorders was estimated to be 2.1 and 5.6%, respectively [4]. Both were more prevalent in women and in older individuals compared with their counterparts. A review of 17 studies showed that the overall estimates of current, 12-month, and lifetime prevalence of MDD were 1.6, 2.3, and 3.3%, respectively [5]. Meanwhile, the prevalence of depressive symptoms in Chinese older adults was 23.6% from a meta-analysis of 81 cross-sectional studies [6]. Another review, of 21 cross-sectional studies in Chinese adults, showed that the pooled estimates of current and lifetime prevalence of anxiety disorders were 2.4 and 4.1%, respectively [7]. Therefore depression and anxiety have become major public health challenges and warrant more studies on their primary prevention, early detection, and effective treatment programs [8].

It is widely acknowledged that depression and anxiety are intercorrelated with CVD: patients with CVD usually have higher prevalence of depression and anxiety than the general population, and individuals who have depressive and anxiety disorders tend to have a higher likelihood of cardiac events and even death [9]. However, there is generally lack of original studies on this topic in the Chinese population. In such a context, we aimed to summarize the latest evidence for the role of depression and anxiety in the onset and prognosis of CVD, with emphasis on cohort

studies conducted in Chinese settings. Our review is limited to studies that used a standard screening scale for depressive or anxiety symptoms, or a structured clinical interview for diagnosis. In this review, we use the term “disorder” mostly when structured clinical interviews were applied or when more severe cases were indicated, and otherwise use “depressive symptoms” and “anxiety symptoms,” while more general terms such as “anxiety” and “depression” are meant to include both symptoms and disorders.

Literature Search and Evidence Synthesis

A literature search was conducted in four English-language and three Chinese-language databases for original articles published in China (including mainland China, Hong Kong, and Taiwan). The English-language databases were PubMed/MEDLINE, Embase, SCOPUS, and ISI Web of Knowledge. The Chinese-language databases were China National Knowledge Infrastructure, Wanfang, and Chongqing VIP. Chinese-language and English-language search algorithms were established for searches in the seven databases. Six groups of MeSH terms, keywords, and free text were used in different combinations, including “depression,” “anxiety,” “cardiovascular disease,” “risk,” “prognosis,” and geographical area limitations to China. References cited in the articles were also manually reviewed to identify any additional articles. The search ended on November 31, 2016, with no lower time limit.

Studies were eligible for assessment if (1) they had a cohort study design (particularly a prospective study design), (2) the exposure of interest was depression or anxiety (either screened or diagnosed), and (3) the outcome was CVD incidence or death when the study participants had no CVD at the baseline, or recurrent cardiovascular events (including death) when study participants had CVD at the baseline. Abstracts from preliminary searches were screened to exclude irrelevant articles, followed by a review of the full text for the remaining articles. All original studies identified were qualitatively appraised, and major information such as participant characteristics, study setting, exposures, outcomes, and findings were extracted (Table 1).

Table 1 Summary of Cohort Studies on the Association Between Depression/Anxiety and Cardiovascular Disease in Chinese Populations.

Authors, year, and area	Study setting	Sample size	Exposure group		Comparison group		Follow-up (years)	Outcomes		Adjusted HR	Adjustments
			Assessment	No. of participants	Assessment	No. of participants		Measures	Exposure group (n)*		
Liu et al. [10], 2016, mainland China	Population based	486,541	Persons with a major depressive episode, as assessed by a triage series of four questions followed by the modified Chinese version of the Composite International Diagnostic Interview-Short Form	2972 (6.1%)	Persons without a major depressive episode in the cohort	483,569 (93.9%)	7.2	Ischemic heart disease, collected by disease registries and national health insurance claim databases	190 (6.4%)	24,515 (5.1%)	1.32 (95% CI 1.15–1.53) Age, sex, geographical location, marital status, education, annual household income, smoking status, drinking status, physical activity, body mass index, history of diabetes and hypertension, and family history of MI
Huang et al. [11], 2013, Taiwan	Health insurance system based	39,685	Persons with a clinically diagnosis of a depressive disorder on at least two occasions, registered in the health insurance system	7937 (20.0%)	Persons without depression registered in the health insurance system, frequency matched by age and sex at 1:4	31,748 (80.0%)	8.8	CHD, collected by the health insurance system	Unknown	Unknown	1.49 (95% CI 1.29–1.74) Diabetes mellitus, hypertension, alcohol-related illness, chronic obstructive pulmonary disease, influenza vaccination, and cardiology clinic visits
Lin et al. [12], 2014, Taiwan	Health insurance system based	54,355	Persons with a clinical diagnosis of a depressive disorder from both ambulatory care and inpatient care	10,871 (20.0%)	Persons without depression registered in the health insurance system, frequency matched by age, sex, and the year of index date at 1:4	43,484 (80.0%)	10	Acute coronary syndrome, collected by the health insurance system	379 (4.5%)	562 (1.6%)	1.88 (95% CI 1.63–2.17) Age, sex, and comorbidities
Sun et al. [13], 2013, Hong Kong	Elderly health centers based	62,839	Persons with depressive symptoms, as assessed by the Chinese version of the 15-item Geriatric Depression Scale	6059 (9.6%)	Persons without depressive symptoms in the cohort	56780 (90.4%)	8.4	Death from CVD, including CHD and stroke	Unknown	Unknown	1.07 (95% CI 0.97–1.19), 1.10 (95% CI 0.93–1.30), and 1.16 (95% CI 0.97–1.37) for death from CVD, CHD, and stroke, respectively Age, education, monthly expenditure, smoking, alcohol drinking, physical activity, body mass index, sex, health status, and self-rated health

Table 1 (continued)

Authors, year, and area	Study setting	Sample size	Exposure group		Comparison group		Follow-up (years)	Outcomes		Adjusted HR	Adjustments	
			Assessment	No. of participants	Assessment	No. of participants		Measures	Exposure group (n)*			Comparison group (n)*
Lee et al. [14], 2008, Taiwan	Health insurance system based	4962	Patients with a diagnosis of a severe depressive disorder and discharged in 1998	827 (16.7%)	Persons without depression registered in the health insurance system, matched by age, sex, and the date of discharge at 1:5	4135 (83.3%)	5	Stroke, collected by the health insurance system	50 (6.1%)	48 (1.2%)	5.43 (95% CI 3.47–8.51)	Sociodemographic variables, comorbid medical disorders, and substance abuse
Li et al. [15], 2012, Taiwan	Health insurance system based	5105	Persons with a clinical diagnosis of MDD at least twice in 2001	1003 (19.6%)	Persons without a history of MDD or bipolar disorder registered in the health insurance system, matched by age, sex, and index date at 1:4	4012 (80.4%)	9	Stroke, collected by the health insurance system	43 (4.3%)	113 (2.8%)	1.38 (95% CI 0.96–1.99)	Age, sex, major metabolic diseases, and substance comorbidities
Sun et al. [16], 2016, mainland China	Population based	487,377	Persons with a major depressive episode, as assessed by a triage series of four questions followed by the modified Chinese version of the Composite International Diagnostic Interview-Short Form	2988 (0.6%)	Persons without a major depressive episode in the cohort	484,389 (99.4%)	7.2	Stroke, collected by disease registries and national health insurance claim databases	183 (6.1%)	27,440 (5.7%)	1.15 (95% CI 0.99–1.33)	Age, sex, marital status, household income, education, region, smoking status, alcohol consumption, physical activity, body mass index, history of hypertension, and history of diabetes mellitus

Table 1 (continued)

Authors, year, and area	Study setting	Sample size	Exposure group		Comparison group		Follow-up (years)	Outcomes		Adjusted HR	Adjustments
			Assessment	No. of participants	Assessment	No. of participants		Measures	Exposure group (n)*		
Wang et al. [17], 2013, mainland China	Hospital based	400	Patients undergoing percutaneous coronary intervention with depression, as assessed by the Hospital Anxiety and Depression Scale followed by the Mini-International Neuropsychiatric Interview	154 (38.5%)	Patients undergoing percutaneous coronary intervention without depression	246 (61.5%)	3	Major adverse cardiovascular event (a composite of all-cause mortality, nonfatal MI, and repeated revascularization), all-cause mortality, repeated revascularization	42 (27.3%), 9 (5.8%), and 20 (10.4%) for three measures	2.51 (95% CI 1.57–4.02) for major adverse cardiovascular event, 3.60 (95% CI 1.16–11.22) for all-cause mortality, and 2.22 (95% CI 1.09–4.51) for repeated revascularization	Sex, age, prior MI, diabetes, hypertension, acute coronary syndrome, and complex coronary lesions
Chen et al. [18], 2009, Taiwan	Health insurance system based	38,564	Persons with ambulatory psychiatric treatment and clinical diagnosis of panic disorder in 2004	9641 (25%)	Persons without panic disorder, registered in the health insurance system, matched by age and sex at 1:3	28,923 (75%)	1	Acute MI diagnosed on the basis of WHO guidelines, collected by the health insurance system	460 (4.8%)	1.75 (95% CI 1.55–1.97)	Sex, age, diabetes, hyperlipidemia, renal disease, coronary heart disease, monthly income, and urbanization level
Cheng et al. [19], 2013, Taiwan	Health insurance system based	42,768	Persons with clinical diagnosis of panic disorder between 2000 and 2001	3888 (9.1%)	Persons without a diagnosis of panic disorder registered in the health insurance system, matched by propensity scoring at 1:10	38,880 (90.9%)	7	Atrial fibrillation, collected by the health insurance system	48 (1.2%)	1.73 (95% CI 1.26–2.37)	Age, sex, hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure, valvular heart disease, chronic obstructive pulmonary disease, chronic renal disease, depression, monthly income, urbanization, and frequency of cardiology clinic visits

Table 1 (continued)

Authors, year, and area	Study setting	Sample size	Exposure group		Comparison group		Follow-up (years)	Outcomes		Adjusted HR	Adjustments
			Assessment	No. of participants	Assessment	No. of participants		Measures	Exposure group (n)*		
Chen et al. [20], 2010, Taiwan	Health insurance system based	23,346	Persons with ambulatory psychiatric care and clinical diagnosis of panic disorder on at least two occasions between 2002 and 2003	3891 (16.7%)	Persons without panic disorder registered in the health insurance system, matched by age and sex at 1:5	19,455 (83.3%)	3	Stroke, collected by the health insurance system	647 (16.6%)	1382 (7.1%)	Sex, age, hypertension, diabetes, hyperlipidemia, renal disease, monthly income, and urbanization
Chou et al. [21], 2012, Taiwan	Health insurance system based	390,309	Persons with ambulatory psychiatric care and clinical diagnosis of panic disorder on at least two occasions between 2001 and 2007	1725 (0.4%)	Patients without a diagnosis of any mental illness during 2001–2009	388,584 (99.6%)	9	Stroke, collected by the health insurance system	88 (5.1%)	19060 (4.9%)	Age, sex, aspirin use, use of nonsteroidal anti-inflammatory drugs, angina pectoris, diabetes mellitus, hypertension, hyperlipidemia, and renal disease
Wang et al. [22], 2013, mainland China	Hospital based	1007	Patients with CHD who had anxiety, assessed by the Zung Self-rating Anxiety Scale	187 (18.6%)	Patients with CHD who did not have anxiety as assessed by the Zung Self-rating Anxiety Scale	820 (81.4%)	1.5	Composite of all-cause mortality and nonfatal MI; unscheduled coronary revascularization; assessed on the basis of medical records, phone interviews, and death certificates	14 (7.5%) and 7 (3.7%) for two measures	26 (3.2%) and 26 (3.2%) for two measures	Age, sex, cigarette smoking, previous MI, hypertension, diabetes mellitus, and Gensini score (indicator of the severity of coronary atherosclerosis) revascularization

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MDD, major depressive disorder; MI, myocardial infarction.

*The cumulative incidence is given in parentheses.

Besides searching for original studies, we performed a complementary search for reviews on the basis of similar search terms in the abovementioned databases and the Cochrane Library, but without geographical area limitation to China. The purpose of the search for reviews was to provide international evidence in the case of a lack of Chinese original studies.

Depression and CVD

Depression and Risk of CVD

Several meta-analyses of cohort studies at different times have demonstrated that depression is a risk factor for incident CVD [23–28]. Three early meta-analyses consistently found that depression conferred about 60% increased risk of coronary heart disease (CHD) [23–25]. In addition, MDD was a stronger predictor for the development of CHD than depressive mood, suggesting a dose-response relationship between depression and CHD [24, 28]. A later meta-analysis showed that depression was associated with about 30% increased risk of CHD and myocardial infarction (MI) combined [26]. A recent meta-analysis also reported similar results for MI and cardiac death [27].

However, studies in the Chinese population are still lacking, and only a few large-scale cohort studies in mainland China [10], Taiwan [11, 12], and Hong Kong [13] add to the evidence that depression is a risk factor for CVD. A recent study published by our group found that participants with a major depressive episode had a higher incidence rate of ischemic heart disease compared with those without a major depressive episode (8.76 versus 7.21 per 1000 person-years) during a median follow-up of 7.2 years [10]. We used data from the China Kadoorie Biobank (CKB) study, which is a community-based cohort established since 2004 with more than 0.5 million Chinese aged 30–79 years. After adjustment for other CVD risk factors, participants with a major depressive episode in the past year were 1.32 times as likely to have ischemic heart disease as those without a major depressive episode in the past year [hazard ratio (HR) 1.32, 95% confidence interval (CI) 1.15–1.53]. In addition, we found that the adjusted HR of ischemic heart disease was 1.13 (95% CI 1.04–1.23) for participants with depressive

symptoms only and 1.33 (95% CI 1.15–1.53) for those with a major depressive episode versus those without depression, indicating a dose-response relation. Two large cohort studies analyzed the relations between depression and new-onset coronary events and acute coronary syndrome on the basis of data from the Taiwan National Health Insurance Program [11, 12]. One study randomly selected 39,685 individuals (7937 with depression and 31,748 without depression) aged 20–99 years to examine risk factors for incident coronary events during a median follow-up period of 8.8 years [11]. The multivariable-adjusted HR was 1.49 (95% CI 1.29–1.74) for individuals with depression compared with age- and sex-matched controls. In a separate study, 10,871 patients with newly diagnosed MDD were included, and each patient was randomly frequency-matched for age and sex with four participants [12]. The risk of developing acute coronary syndrome was 88% higher (HR 1.88, 95% CI 1.63–2.17) in those with MDD versus those without MDD. In a study among elderly Chinese in Hong Kong [13], depressive symptoms were screened with use of the 15-item Geriatric Depression Scale among 21,473 men and 41,366 women at elderly health centers. A positive association was reported between depressive symptoms and CHD death in men (HR 1.41, 95% CI 1.08–1.84) but not in women (HR 0.94, 95% CI 0.75–1.16). However, such sex-specific estimates were not reported in other cohort studies [10–12].

With regard to stroke, a previous meta-analysis of 28 cohort studies demonstrated that depression is associated with 45% increased risks of stroke morbidity and death, and strong associations were evident particularly for fatal and ischemic stroke [29]. An updated meta-analysis published in 2015 reached similar conclusions [30]. So far, only four cohort studies have been conducted in the Chinese population [13, 14–16], of which two were based on the Taiwan National Health Insurance database [14, 15]. In a study of 827 patients (aged 18–44 years) hospitalized for depressive disorder and 4135 individuals matched at 1:5 for sex, age, and date of discharge, depressed patients were 5.43 times (95% CI 3.47–8.51) as likely to develop stroke as nondepressed individuals during a 5-year follow-up [14]. The large effect size of depression in that study might be due to the inclusion of hospitalized severely depressed patients as cases. In a separate

cohort study among 5015 participants (1003 MDD patients and 4012 control individuals without MDD) for a follow-up of up to 9 years, patients with MDD had a higher risk of stroke (HR 1.44, 95% CI 1.01–2.06) after adjustment for age, sex, and substance dependence [15]. However, since the association became not statistically significant after additional adjustment for major metabolic diseases (including diabetes, hypertension, and hyperlipidemia), it was suspected that the risk of stroke among MDD patients was mediated by the development of major metabolic diseases. A more recent study using the CKB data found that major depressive episode was associated with a 1.15-fold increased risk of stroke (95% CI 0.99–1.33) [16]. In addition, there was a positive dose-response relationship between the number of depressive symptoms and stroke risk (P for trend of 0.011). Of note, in the cohort study among elderly adults in Hong Kong, the positive association between depressive symptoms and death from stroke did not show statistical significance (HR 1.16, 95% CI 0.97–1.37), even in subgroup analysis by sex (HR 1.21, 95% CI 0.90–1.63 in men; HR 1.16, 95% CI 0.94–1.43 in women) [13].

In summary, a few cohort studies suggested that depression was associated with increased risks of CHD and stroke in the Chinese population in a dose-response manner. However, several studies were based on the Taiwan National Health Insurance database, and more studies in the general populations, like the CKB study, are needed to better control for other covariates and understand the role of different magnitudes of depression (from mild symptoms to MDD) in the development of CVD.

Depression and Cardiovascular Prognosis

Depression is highly prevalent among patients with CVD. A systematic review of eight studies including 10,785 patients with acute MI showed that the prevalence of MDD was 19.8% (95% CI 19.1–20.6%) by means of structured clinical interviews [31]. The prevalence of significant depressive symptoms ranged from 7.3% (Hospital Anxiety and Depression Scale score ≥ 11) to 31.1% (Beck Depression Inventory score ≥ 10) depending on the screening scales. In addition, in a meta-analysis of 61 studies with 25,488 patients with stroke, 31% (95% CI 28–35%) experienced depression

after stroke [32], which was consistent with the finding from a review (33%; 95% CI 29–36%) a decade ago [33]. More importantly, 23% (95% CI 14–31%) of patients had depression even 5 years after stroke (Beck Depression Inventory score ≥ 10) [32]. The prevalence of depression is similarly high among Chinese patients with CVD. A 2013 review included 23 studies with 5236 CHD patients in hospital settings and four studies with 1353 patients in community settings in China [34]. The overall prevalence of depression was 51% (95% CI 43–58%) in patients with CHD in hospital settings, and was between 34.6 and 45.8% in community settings depending on the screening technique.

Several systematic reviews have consistently demonstrated the substantial impact of depression in patients with CVD on the recurrence of nonfatal cardiac events, and even death [28, 35–43]. Two systematic reviews showed that depression was associated with an 80% increased risk of all-cause death among CHD patients [28, 35]. In particular, a review qualitatively assessed the available literature for depression's negative impact on the prognosis for acute coronary syndrome, and found that depression was associated with all-cause and cardiac death, as well as composite outcomes that combined death and nonfatal cardiac events [36]. A pooled analysis of 10,175 patients with MI from 30 studies found that a standard deviation increase in post-MI depression z scores was associated with an increased risk of all-cause mortality (HR 1.32, 95% CI 1.26–1.38) and cardiovascular events (HR 1.19, 95% CI 1.14–1.24) [37]. The association between post-MI depression and all-cause mortality was stronger in men than in women [38]. Consistently, two reviews focusing on short-term prognosis showed that post-MI depression was associated with a 1.6- to 2.7-fold increased risk of impaired cardiovascular outcomes within 2 years after the index MI [39, 40]. Another two reviews examined the impact of depression after heart failure on all-cause and cardiovascular death [41, 42]. Depression was associated with an about 1.5-fold increased risk of all-cause mortality [41, 42], and the association was evident for major depression (HR 1.98, 95% CI 1.23–3.19) but not mild depression (HR 1.04, 95% CI 0.75–1.45) [41]. In addition, depression after heart failure was associated with a more than twofold (HR 2.19, 95% CI 1.46–3.29) increased risk of cardiovascular death

[41]. With regard to stroke, a review including 14 studies with 4498 stroke patients found that depression was associated with adverse prognosis, such as higher mortality and poor life satisfaction, and less efficient use of rehabilitation services [43].

Few prospective studies have examined the association between depression and prognosis among CVD patients in China. Some studies found that depression was associated with increased mortality [17], poor health-related quality of life [44, 45], and even longer hospital stay [46] among Chinese patients with CVD. In particular, a study of 400 CHD patients during a 3-year follow-up found that depression (as assessed by the Hospital Anxiety and Depression Scale and Mini-International Neuropsychiatric Interview) after percutaneous coronary intervention was positively associated with all-cause mortality (HR 3.60, 95% CI 1.16–11.22) and repeated revascularization (HR 2.22, 95% CI 1.09–4.51) [17]. Since most of these Chinese studies were cross-sectional with small sample sizes, efforts are urgently needed to generate Chinese evidence in this area.

In summary, although studies have provided ample evidence for the association between depression and poor cardiovascular prognosis in other countries, there is a lack of robust prospective Chinese studies on this topic, which reflects inadequate attention to the mental status of CVD patients in clinical practice in China. Evidence from long-term cohort studies is needed to understand the role of depression in the prognosis of patients with CVD in Chinese settings.

Anxiety and CVD

Anxiety and Risk of CVD

The association between anxiety and the risk of CVD has been studied in multiple populations, and a positive association has been consistently reported [47–50]. Two systematic reviews published in 2016 examined the association between anxiety and the risk of multiple CVD outcomes [49, 50]. The overall risk of CVD increased by 52% (HR 1.52, 95% CI 1.36–1.71) among anxious individuals compared with those without anxiety among 1,565,699 individuals from 37 cohort studies [49]. Specifically, anxiety was associated with increased risks of CHD

[relative risk (RR) 1.49, 95% CI 1.31–1.69; 26 studies], stroke (RR 1.74, 95% CI 1.25–2.43; 7 studies), MI (RR 1.38, 95% CI 1.16–1.64; 11 studies), and CVD death (RR 1.61, 95% CI 1.22–2.12; 14 studies). A separate review included 2,017,126 participants from 46 cohort studies or nested case-control studies [50]. Besides CHD, stroke, and CVD death, anxiety was also associated with an elevated risk of heart failure (RR 1.35, 95% CI 1.11–1.64). However, the association between anxiety and atrial fibrillation was not statistically significant (RR 1.27, 95% CI 0.90–1.80), maybe because there were only three studies on this topic. Among all subtypes of anxiety, phobic anxiety was more strongly associated with CVD risk than other anxiety disorders, and posttraumatic stress disorder was more associated with stroke risk [50].

Two studies in Taiwan investigated the relation between anxiety or its subtypes and incident MI [18] and atrial fibrillation [19]. In a large cohort study of 9641 patients with panic disorder and 28,923 without panic disorder [18], 4.8% of patients with panic disorder and 2.7% of patients without panic disorder experienced an acute MI within 1 year of follow-up. The corresponding RR was 1.75 (95% CI 1.55–1.97), and the association persisted in stratified analyses by hypertension, CHD, and age. Besides acute MI, another study, of 42,768 individuals (300 patients with panic disorder and 38,880 individuals without panic disorder, mean age of 42 years), showed that panic disorder was associated with an increased risk of atrial fibrillation (RR 1.73, 95% CI 1.26–2.37) [19].

Two large studies also specifically assessed the association between panic disorder and the risk of stroke on the basis of the Taiwan National Health Insurance database [20, 21]. One study included 3891 patients with panic disorder and 19,455 individuals without panic disorder matched for sex and age in 2010 [20]. In a follow-up of three years, 16.6% of patients with panic disorder and 8.7% of individuals without panic disorder developed stroke, and the corresponding HR was 2.37 (95% CI 2.12–2.67) after adjustment for sex, age, income, level of urbanization, and comorbidities. The strong association persisted in stratified analyses by medical conditions and age. However, the validity of this study was weakened by no explicit exclusion of individuals with a history of stroke at the baseline.

In a similar study of 390,309 individuals (1725 patients with panic disorder and 388,584 without panic disorder) enrolled in 2001–2007, the cumulative incidence rate of stroke was 5.1% in the panic disorder group and 4.9% in the companion group by the end of 2009 [21]. The RR was 1.38 (95% CI 1.12–1.71) after for sex, age, medications, and comorbidities had been controlled for.

In conclusion, consistent with systematic reviews, current studies in the Chinese population support the proposition that anxiety might be a risk factor for CVD. Since most of the original studies [18–21] were based on the Taiwan Health Insurance database, which may be subject to unmeasured/residual confounding and limited generalizability, more population-based cohort studies are urgently needed to explore the relation between anxiety and the risk of CVD in Chinese adults.

Anxiety and Cardiovascular Prognosis

In the general population, the 1-year and lifetime prevalence of anxiety disorders was estimated to be 11.0% (95% CI 7.5–14.3%) and 16.6% (95% CI 12.7–21.1%), respectively [51]. A systematic review reported that the prevalence of anxiety disorders in stroke patients was 18% (95% CI 8–29%) if clinical interview was used and 25% (95% CI 21–28%) if screening scales were used [52]. In particular, the prevalence of generalized anxiety disorder was 10.9% (95% CI 7.8–14%) among patients with CHD, and the lifetime prevalence could be as high as 25.8% (95% CI 20.8–30.8%) [53]. Available Chinese studies also reported a high prevalence of anxiety among CVD patients. In a study of 700 Chinese inpatients with CVD, the prevalence of anxiety symptoms (Zung Self-rating Anxiety Scale score ≥ 50) was 26.7%, and the prevalence was higher in women (31.5%) than in men (21.4%) [54]. Another study, of 509 hospitalized patients with CHD, reported a similar prevalence of 23.4% [55]. In a multicenter study of 1144 patients with premature ventricular contraction but no structural heart disease in 12 hospitals from five provinces across China, 33.3% had anxiety symptoms (Zung Self-rating Anxiety score ≥ 40) [56]. The prevalence was higher in patients aged more than 45 years than in those aged 45 years or younger (52.1 versus 17.4%),

and was higher in women than in men (36.1 versus 29.6%).

Anxiety may arise before or after diagnosis of CVD, and may further trigger recurrent cardiac events or other adverse events. Two major reviews systematically evaluated the association between anxiety and the risk of cardiac events among CVD patients [57, 58]. One systematic review included 5750 patients with MI from 12 cohort studies with at least 6 months of follow-up [57]. Post-MI anxiety was associated with all-cause mortality [odds ratio (OR) 1.47, 95% CI 1.02–2.13; four studies], cardiac death (OR 1.23, 95% CI 1.03–1.47; four studies), and new cardiac events (OR 1.71, 95% CI 1.31–2.23; seven studies). Another review evaluated the relationship between anxiety and death in 30,527 patients with CHD from 44 studies [58]. Anxiety was associated with an increased risk of poor outcomes (death and other negative outcomes, such as rehospitalizations or recurrent cardiac events) only in patients with stable CHD, but not in those who just had acute coronary syndrome. The authors hypothesized that the discrepancy was because anxiety symptoms in the immediate post-acute coronary syndrome period may be transient and related to the cardiac event itself instead of its prognosis.

Despite evidence from systematic reviews, very few prospective studies have explored the relationship between anxiety and adverse prognosis in Chinese CVD patients. A Chinese study examined the association between anxiety after coronary angiography or percutaneous coronary intervention and the risk of all-cause mortality and nonfatal MI in 1007 CHD patients with a mean follow-up of 17 months after hospital discharge [22]. The Zung Self-rating Anxiety Scale score was associated with coronary atherosclerosis as determined by the Gensini score ($\beta=1.35$, $P<0.001$). In addition, anxiety symptoms (Zung Self-rating Anxiety Scale score ≥ 50) were associated with increased risk of all-cause mortality and nonfatal MI (adjusted HR 2.43, 95% CI 1.24–4.75).

In summary, existing evidence shows that anxiety is associated with increased risks of adverse outcomes in patients with CVD. However, more studies are needed in the Chinese population to examine the relationship. Since depression and anxiety coexist in many CVD patients [53], future studies may need to consider their independent and synergetic effects for the risk of adverse cardiovascular outcomes.

Mechanisms for the Link Between Depression and Anxiety and CVD

The mechanisms underlying the link between depression, anxiety, and CVD are still uncertain, and results from etiological studies are inconsistent. However, two plausible levels of mechanisms have been proposed: behavioral and biological pathways [9, 59]. At the behavioral level, depression and/or anxiety may be associated with unhealthy lifestyles and behaviors that lead to the occurrence of CVD, and nonadherence with interventions for CVD that contribute to adverse prognosis. Both depression and anxiety are associated with several major risk factors for CVD, such as physical inactivity, cigarette smoking, and excessive alcohol consumption [9]. On the one hand, these risk factors may partially account for the effects of depression and anxiety on CVD [60]. On the other hand, depression and anxiety may potentiate the effects of these risk factors for CVD. Patients with depression and anxiety may be less likely to adhere to medications, lifestyle interventions, and rehabilitation programs, which may result in compromised effectiveness [9, 60]. In addition, the existence of depression and anxiety among patients with CVD may reflect a higher severity of CVD [61], and thus result in an increased risk of death or morbidity in patients with CVD.

At the biological level, depression and anxiety might induce autonomic nervous system dysfunction, cardiac rhythm disturbances, inflammation, platelet dysfunction, and hypercoagulability [9, 59, 62, 63]. Depression and anxiety are associated with neurohormonal abnormalities that cause an imbalance in sympathetic and parasympathetic activity, leading to increased heart rate and blood pressure as well as increased risk of atherosclerotic plaque rupture and acute coronary thrombosis [9, 64]. The neurohormonal abnormalities also increase irritability of the heart muscle, which causes a disturbance in heart rhythm, leading to ventricular fibrillation and cardiac arrest. In addition, depression and anxiety may increase inflammatory reactions associated with unstable coronary artery plaques that contribute to coronary syndromes [63, 64]. Moreover, depression may induce platelet dysfunction, which may cause vascular damage, thrombus formation, and even coronary events. Since depression and

anxiety are often coexistent and their associations with CVD can be bidirectional, the etiological model might be multifaceted and even form feedback loops [9].

Implications for Interventions

Psychological disorders are generally stigmatized, and there is a lack of optimal investment in health services in China [65]. They are often unrecognized and untreated in clinical practice. The current body of evidence demonstrates that both depression and anxiety are involved in the onset and prognosis of CVD. Given the disease burden of anxiety and depression and their role in CVD, it is imperative to target primary interventions to prevent CVD onset and secondary/tertiary interventions to improve prognosis. Generally, depression and anxiety should be screened and diagnosed in a timely manner, and should be treated appropriately once they have been diagnosed in any setting [66, 67]. Depressive and anxiety symptoms can occur at any point in the lifetime and can be transient, and their impact on the cardiovascular system is invisible. Several scales can be used for screening purposes in different settings, such as the Beck Depression Inventory [68] for depression and the Zung Self-rating Anxiety Scale [69] for anxiety, most of which have been adapted for Chinese settings and tested for validity and reliability. Once individuals have been assessed as probably having depression or anxiety disorders, they should be referred to qualified psychiatrists for clinical diagnosis based on the Chinese Classification of Mental Disorders III, which is similar in structure and classification to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* or the tenth revision of the International Statistical Classification of Diseases and Related Health Problems. Current standard treatments for depressive and anxiety disorders in the general population include psychotherapies such as cognitive behavioral therapy and medications such as selective serotonin reuptake inhibitors, and they are recommended for the two conditions among CVD patients by professional organizations [67]. Although selective serotonin reuptake inhibitors and certain psychotherapies are generally proven to be safe for patients with CVD in clinical trials, their efficacy in reducing cardiac morbidity

and mortality remains unclear because of the lack of large controlled trials [9, 70]. Thus current treatment recommendations among patients with CVD target only the two psychological conditions themselves, and aim to reduce the symptoms and improve the health-related quality of life. In addition, patients with CVD being treated for these conditions should still be closely monitored for adherence to medical care, drug efficacy, and safety with respect to their cardiovascular and mental health [67]. In Chinese settings, because few CVD patients ever receive a diagnosis or treatment for mental disorders in clinical practice [71], future efforts might be directed toward inclusion of psychiatrists in the multidisciplinary clinical group for CVD treatment, a collaborative care model that shows a potential advantage for management of psychological conditions and physical diseases [72].

Conclusions

Both depression and anxiety are highly prevalent among patients with CVD compared with the

general population in China. Current evidence from other populations and only a few Chinese studies suggests that depression and anxiety are associated with an increased risk of CVD onset in the general population and adverse outcomes in CVD patients. More high-quality and large-scale prospective studies are urgently needed to investigate the impact of depression/anxiety on the cardiovascular system in the Chinese population, particularly for the prognosis among CVD patients. The available evidence does not sufficiently support the efficacy of depression or anxiety treatments for reducing CVD mortality or morbidity, but they are recommended for mitigating symptoms and improving the mental health-related quality of life for CVD patients with depression and/or anxiety. Finally, the collaborative care model needs to be tested in clinical settings in China.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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