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Association of Depression With All-Cause and Cardiovascular Disease Mortality Among Adults in China

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Abstract

IMPORTANCE Depression is associated with increased disease burden worldwide and with higher risk of mortality in Western populations.

OBJECTIVE To investigate whether depression is a risk factor for all-cause and cardiovascular disease (CVD) mortality in adults in China.

DESIGN, SETTING, AND PARTICIPANTS This cohort study prospectively followed adults aged 30 to 79 years in the China Kadoorie Biobank (CKB) study from June 1, 2004, to December 31, 2016, and adults aged 32 to 104 years in the Dongfeng-Tongji (DFTJ) study from September 1, 2008, to December 31, 2016. Data analysis was conducted from June 1, 2018, to March 31, 2019.

MAIN OUTCOMES AND MEASURES Depression was evaluated using the Chinese version of the World Health Organization Composite International Diagnostic Interview–Short Form in the CKB cohort and a 7-item symptoms questionnaire modified from the Composite International Diagnostic Interview–Short Form in the DFTJ cohort. Multivariable-adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs for the association of depression with mortality. Covariates in the final models included sociodemographic characteristics, lifestyle factors, and personal and family medical history.

RESULTS Among 512 712 individuals (mean [SD] age, 52.0 [10.7] years; 302 509 [59.0%] women) in the CKB cohort, there were 44 065 deaths, including 18 273 CVD deaths. The 12-month prevalence of major depressive episode in the CKB cohort was 0.64%, and the 1-month prevalence of clinically significant depressive symptoms was 17.96% in the DFTJ cohort. Among 26 298 individuals (mean [SD] age, 63.6 [7.8] years; 14 508 [55.2%] women) in the DFTJ cohort, there were 2571 deaths, including 1013 CVD deaths. In the multivariable-adjusted model, depression was associated with increased risk of all-cause mortality (CKB cohort: HR, 1.32 [95% CI, 1.20-1.46]; $P < .001$; DFTJ cohort: HR, 1.17 [95% CI, 1.06-1.29]; $P = .002$) and CVD mortality (CKB cohort: HR, 1.22 [95% CI, 1.04-1.44]; $P = .02$; DFTJ cohort: HR, 1.32 [95% CI, 1.14-1.54]; $P < .001$). In both cohorts, men had statistically significantly higher risk of all-cause mortality (CKB cohort: HR, 1.53 [95% CI, 1.32-1.76]; DFTJ cohort: HR, 1.24 [95% CI, 1.10-1.41]) and CVD mortality (CKB cohort: HR, 1.39 [95% CI, 1.10-1.76]; DFTJ cohort: HR, 1.49 [95% CI, 1.23-1.80]), while the association of depression with mortality among women was only significant for all-cause mortality in the CKB cohort (HR, 1.19 [95% CI, 1.03-1.37]).

CONCLUSIONS AND RELEVANCE These findings suggest that depression is associated with an increased risk of all-cause and CVD mortality in adults in China, particularly in men. These findings highlight the importance and urgency of depression management as a measure for preventing premature deaths in China.

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Key Points

Question Is depression associated with risk of all-cause and cardiovascular disease mortality in Chinese adults?

Finding In this cohort study including 512 712 adults from the China Kadoorie Biobank study and 26 298 adults from the Dongfeng-Tongji study, depression was consistently associated with higher risk of all-cause and cardiovascular disease mortality. However, when stratified by sex, the associations were significant only among men.

Meaning These findings suggest that depression is a risk factor for all-cause and cardiovascular disease mortality in adults in China, particularly in men.

+ Supplemental content

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Introduction

Depression has become increasingly common and is associated with increased disease burdens worldwide.[1,2] In 2013, the estimated worldwide prevalence of major depressive disorder was 4.7%, and the estimated annual incidence rate was 3.0%.[1] The Global Burden of Disease Study 2016[2] reported that more than 34 million all-age disability-adjusted life-years were associated with depression. A 2013 systematic review[3] reported that overall estimations of prevalence of major depressive disorders were 1.6% for current depression, 2.3% for depression in the previous 12 months, and 3.3% for any depression during an individual's lifetime. It was estimated that more than 10 million disability-adjusted life-years were associated with depressive disorders in China in 2013, and the number was projected to increase by approximately 10% by 2025,[4] which highlights the importance of depression prevention and intervention.

Numerous studies have been performed regarding the association of depression with increased risk of all-cause and cause-specific mortality in general populations and various patient groups, as summarized in a 2014 meta-analysis[5] that included 293 studies with 1 813 733 participants from 35 countries. That meta-analysis by Cuijpers et al[5] found that depression was associated with a 52% increased risk of all-cause mortality. However, the causal relationship between depression and mortality is still questionable, and a 2017 analysis[6] of 293 studies with 3 604 005 participants indicated that the positive association of depression with mortality was largely based on low-quality studies (eg, studies with small sample sizes and short follow-up durations or with inadequate adjustment of potential confounding factors, particularly comorbid mental disorders and health behaviors). Therefore, more high-quality research is still needed to examine the association of depression with mortality.

Very few prospective cohort studies have been conducted on this topic among adults in China, to our knowledge. We found 4 studies[7-10] in adults in China, including 3 studies in adults 65 years and older and 1 study in adults 55 years and older. Three studies[7,9,10] found that the association of depressive symptoms with all-cause mortality was stronger among men than women. However, studies in younger adults in China are lacking, and 1 meta-analysis[11] found that depression was also associated with excess mortality in women, although not as much as in men. Therefore, more studies are needed to examine the associations of depression with all-cause and cardiovascular disease (CVD) mortality in Chinese populations.

In this study, we used data from 2 large, well-established prospective cohort studies in mainland China to investigate whether depression was associated with all-cause and CVD mortality in middle-aged and elderly Chinese populations. We also tested whether the associations would be modified by age and sex.

Methods

Study Populations

The study design and baseline characteristics of the 2 cohorts have been reported in detail previously.[12,13] Briefly, the China Kadoorie Biobank (CKB) cohort is a prospective study with more than 500 000 individuals aged 30 to 79 years recruited from 10 areas in China between June 1, 2004, and July 31, 2008. The Dongfeng-Tongji (DFTJ) cohort was established from September 1, 2008, to June 1, 2010, with a total of 27 009 workers from Dongfeng Motor Corporation with an age range of 32 to 104 years (most participants were retired workers). At baseline in the CKB cohort,[12] the estimated population response rate was approximately 30% (26%-38% in 5 rural areas and 16%-50% in 5 urban areas), and the baseline response rate was 87% in the DFTJ cohort.[13] In the CKB study, a detailed data collection protocol was developed in Chinese by experts from the University of Oxford and local, regional, and national Centers for Disease Control and Prevention (CDC) in China as part of a robust training program for field workers and interviewers. Within a few weeks of the initial baseline survey, approximately 3% of participants were randomly selected to repeat selected

items (depression was not included) and measures in the questionnaire as a quality control (QC) procedure. There was good agreement between baseline and QC surveys for several common variables.[12] Regular central monitoring and periodical on-site monitoring visits were undertaken by provincial CDC staff and staff from the coordinating centers of Peking University and the University of Oxford. In the DFTJ cohort, all interviewers received unified training and assessment before field work, and they administered questionnaires during face-to-face interviews. On-site QC teams checked all questionnaires for missing and incorrect items every day, and the QC supervision team randomly checked 10% of the questionnaires every week, but a QC resurvey was not conducted in the DFTJ cohort. In the CKB cohort, we excluded participants with unreliable information on death date (n = 1) and individuals without information on body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) (n = 2). In the DFTJ cohort, we excluded individuals without sufficient information on depression (n = 1), individuals with unreliable information on death date (n = 1), and individuals who were lost to follow-up (n = 709). The CKB study protocol was approved by the Oxford University Tropical Research Ethics Committee and the China CDC Ethical Review Committee, and the DFTJ cohort was approved by the medical ethics committee of the Tongji Medical College, Huazhong University of Science and Technology, and Dongfeng General Hospital, Dongfeng Motor Corporation. All participants provided written informed consent before enrollment in the study. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Assessment of Depression

In the CKB cohort at baseline, participants were first asked whether they had the following symptoms for 2 weeks in a row or longer during the past 12 months: (1) feeling much more sad or depressed than usual; (2) loss of interest in most things, such as hobbies or activities, that usually give them pleasure; (3) felt so hopeless that they had no appetite to eat even their favorite food; and (4) feeling worthless and useless, that everything that went wrong was their fault, that life was very difficult, and that there was no way out. If they answered yes to any of these questions, they were further evaluated for major depression using a modified Chinese version of the World Health Organization Composite International Diagnostic Interview–Short Form (CIDI-SF)[14] in a face-to-face interview performed by trained health workers. In the CIDI-SF questionnaire, 7 additional yes-or-no questions were asked about symptoms during that 2 weeks (ie, losing interest in things, feeling tired or low on energy, weight change, difficulty in sleeping, trouble concentrating, thoughts about death, or feeling worthless). Participants who responded yes to 3 or more of the 7 depressive symptoms were classified as having major depression. A 2015 study[15] reported that the CIDI-SF questionnaire for major depression had a sensitivity of 69.6% and a specificity of 96.7% in a Chinese population.

In the DFTJ cohort at baseline, participants were directly asked about the 7 depressive symptoms in the past month without inquiry of the screening questions. Participants who reported 3 or more symptoms during the past month were defined as having clinically significant depressive symptoms. Thereafter, *depression* was used to simplify the terminology in the 2 cohorts.

Mortality Follow-up

In the CKB study, cause-specific mortality was monitored regularly through official residential records and death certificates reported to China CDC's Disease Surveillance Points system. The vital status of the participants was also checked annually against medical and health insurance records and supplemented by local street committees or village administrators, and if necessary, a verbal autopsy was conducted.[12] In the DFTJ cohort, each participant had a unique medical insurance card number and was tracked through the medical insurance system provided by Dongfeng Motor Corporation for the cause-specific mortality.[13] Causes of death were coded according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*)[16] by trained staff. The deaths related to CVD were classified as those coded *I00-99*.

Assessment of Covariates

Information on the covariates in the 2 cohorts was collected by trained health workers through questionnaires and physical measurements at the baseline survey, including demographic or socioeconomic characteristics (ie, age, sex, education, and marital status for both cohorts and region and household income for the CKB cohort), lifestyle factors (ie, drinking and smoking status, physical activity, and consumption of red meat, fresh fruits, and vegetables), and health status. The physical examinations included body weight and height, blood pressures, and blood glucose level (random blood glucose level in the CKB cohort and fasting blood glucose level in the DFTJ cohort). Participants were asked about their history of chronic diseases, and a health index score was created by counting the number of chronic diseases, including chronic obstructive pulmonary disease or asthma, hypertension (defined as measured blood pressure ≥140/90 mm Hg, self-reported diagnosis of hypertension, or use of antihypertensive drugs at baseline), coronary heart disease (CHD), stroke, diabetes (defined as self-reported diagnosis or medication use, fasting glucose level ≥126 mg/dL [to convert to millimoles per liter, multiply by 0.0555], or random glucose level ≥200 mg/dL), and cancer. The health index variable was categorized into 4 groups based on the number of chronic diseases: 0, 1, 2, and 3 or more. Physical activity was quantified as metabolic equivalent task hours per day spent on activities related to occupation, commuting, housework, and nonsedentary leisure-time activities in the CKB study[17] but only on nonsedentary leisure-time activities in the DFTJ cohort.[18]

Statistical Analysis

Baseline characteristics of the respondents in our study are presented as means with SDs for continuous variables, with differences calculated using *t* test, or percentages for categorical variables, with differences calculated using χ^2 test. Survival time was defined as the period from the date of baseline interview to the date of death, loss to follow-up, or December 31, 2016, whichever came first. The association of depression with mortality was estimated using Cox proportional hazards regression model, which yielded hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was tested by adding an interaction term of follow-up duration and depression variable in the models, and no violation was found. We adjusted the sociodemographic characteristics, lifestyle factors, and personal and family medical history as confounders in the multivariable-adjusted Cox models. The potential confounders included age (continuous variable); sex; education level (less than primary school, middle school, high school, or college or higher); BMI (continuous variable); marital status (married, widowed, separated or divorced, or never married); drinking status (never, occasionally, or monthly; former or reduced intake; or current); smoking status (never or occasional, former, or current); consumption frequency of meat (daily, 4-6 days per week, 1-3 days per week, or <1 day per week), vegetables (daily or <1 per day), and fruits (daily, 4-6 days per week, 1-3 days per week, or <1 day per week); health index score (0, 1, 2, or ≥3); and family history of CVD. In the CKB cohort, study site (10 sites) and household income (categorized as <¥10 000 [<US $1435.89], ¥10 000-¥19 999 [US $1435.89-$2871.65], ¥20 000-¥34 999 [US $2871.79-$5025.49], or ≥¥35 000 [≥US $5025.63] per year) were also included in the model. The confounders were selected based on a priori knowledge of underlying biological mechanisms and previous reports.[5,6] We also examined the associations of depression with ischemic heart disease mortality and cerebrovascular disease mortality. Additionally, we conducted stratified analyses by sex and age (≥65 years vs <65 years) and tested the significance of interaction by including a 2-way interaction term in the final model.

We performed a series of sensitivity analyses to test the robustness of the results: (1) the individuals who died within the first 2 years of follow-up were excluded to minimize the chance of reverse associations; (2) participants with baseline history of cancer, CHD, or stroke were excluded to examine the associations in relatively healthy individuals; (3) participants in the DFTJ cohort 80 years or older were excluded to reduce the potential selection bias; and (4) we adjusted for each chronic disease instead of the health index score to fully account for potential confounding by disease status.

In addition, we defined depression as having 5 or more symptoms in both cohorts to examine whether the associations could be changed by applying a more strict cutoff.

We conducted all analyses separately in each cohort. We used SAS statistical software version 9.3 (SAS Institute) for all analyses. *P* values were 2-tailed, and statistical significance was set at .05. Data analysis was conducted from June 1, 2018, to March 31, 2019.

Results

We included 512 712 participants (mean [SD] age, 52.0 [10.7] years; 302 509 [59.0%] women) in the CKB cohort and 26 298 individuals (mean [SD] age, 63.6 [7.8] years; 14 508 [55.2%] women) in the DFTJ cohort. The 12-month prevalence of major depressive episode in the CKB cohort was 0.64%, and the 1-month prevalence of clinically significant depressive symptoms was 17.96% in the DFTJ cohort. **Table 1** presents the distribution of baseline characteristics based on depression status. Compared with participants without depression, those with depression were more likely to be women (CKB cohort: 300 178 participants [58.9%] vs 2331 participants [71.7%]; *P* < .001; DFTJ cohort: 11 517 participants [53.4%] vs 2991 participants [63.3%]; *P* < .001), be never or occasional smokers (CKB cohort: 344 209 participants [67.6%] vs 2424 participants [73.9%]; *P* < .001; DFTJ cohort: 15 089 participants [69.9%] vs 3410 participants [72.2%]; *P* < .001), have 3 or more comorbidities (CKB cohort: 4906 participants [0.9%] vs 59 participants [1.8%]; *P* < .001; DFTJ cohort: 1906 participants [8.8%] vs 819 participants [17.3%]; *P* < .001), and have a family history of CVD (CKB cohort: 104 208 participants [20.5%] vs 847 [25.8%]; *P* < .001; DFTJ cohort: 1939 participants [9.0%] vs 7171 participants [15.2%]; *P* < .001); however, they were less likely to be married (CKB cohort: 462 025 participants [90.7%] vs 2437 participants [74.3%]; *P* < .001; DFTJ cohort: 18 971 participants [87.9%] vs 4002 participants [84.7%]; *P* < .001), be current drinkers (CKB cohort: 75 816 participants [14.9%] vs 1324 participants [9.9%]; *P* < .001; DFTJ cohort: 4606 participants [21.3%] vs 894 participants [18.9%]; *P* < .001), or report daily consumptions of red meat (CKB cohort: 149 407 participants [29.3%] vs 610 participants [18.6%]; *P* < .001; DFTJ cohort: 5843 participants [27.1%] vs 1152 participants [24.4%]; *P* < .001) or fresh fruits (CKB cohort: 96 162 participants [18.9%] vs 420 participants [12.8%]; *P* < .001; DFTJ cohort: 10 715 participants [49.6%] vs 2232 participants [47.3%]; *P* = .03). In the CKB study, compared with participants without depression, those with depression were more likely to be younger (mean [SD] age, 52.0 [10.7 years vs 51.5 [10.0] years; *P* < .001), less active (mean [SD], 21.1 [13.9] metabolic equivalent task–hours per day vs 19.9 [14.1] metabolic equivalent task–hours per day; *P* < .001), and never, occasional, or monthly drinkers (412 858 participants [80.5%] vs 2762 participants [84.2%]; *P* < .001) and to have less than primary school education level (258 480 participants [50.7%] vs 1875 participants [57.1%]; *P* < .001), lower BMI (mean [SD], 23.7 [3.4] vs 23.2 [3.4]), and household income less than ¥10 000 (US $1435.89) (143 395 participants [28.1%] vs 1339 participants [40.8%]; *P* < .001).

In the CKB study, the 3 most commonly reported symptoms reported by participants with depression were losing interest in things (2952 participants [90.0%]), feeling tired or low on energy (2676 participants [81.6%]), and having trouble concentrating (2653 participants [80.9%]). The 3 most commonly reported symptoms reported by participants with depression in the DFTJ cohort were having trouble concentrating (4322 participants [91.5%]), feeling tired or low on energy (4212 participants [89.2%]), and having difficulty sleeping (3626 participants [76.8%]) (eTable 1 in the Supplement).

Depression and All-Cause and Cardiovascular Mortality

In the CKB study, we documented 44 065 deaths, including 17 501 CVD deaths, during 5 088 810 person-years of follow-up. In the DFTJ cohort, we documented 2571 deaths, including 1013 CVD deaths, during 208 403 person-years of follow-up. The incidence rates of all-cause and CVD mortality among participants with depression were significantly higher than that among those without depression in both cohorts (**Table 2**). In the multivariable-adjusted model, depression was

Table 1. Distribution of Baseline Characteristics of Participants Stratified by Depression Status

Characteristic	Depression Status					
	CKB Cohort (n = 512 712)			DFTJ Cohort (n = 26 298)		
	No. (%)			No. (%)		
	Yes	No	*P* Value[a]	Yes	No	*P* Value[a]
No.	3280 (<0.01)	509 432 (99.4)		4723 (18.0%)	21 575 (82.0%)	
Age, mean (SD), y	51.5 (10.0)	52.0 (10.7)	<.001	63.5 (7.8)	63.6 (7.8)	.22
Physical activity, mean (SD), MET-hr/d[b]	19.9 (14.1)	21.1 (13.9)	<.001	4.25 (6.62)	4.38 (7.18)	.24
BMI						
Continuous, mean (SD)	23.2 (3.4)	23.7 (3.4)	<.001	24.5 (3.5)	24.6 (3.3)	.21
<18.0	140 (4.3)	13 927 (2.7)	<.001	104 (2.2)	359 (1.7)	.09
18.0-24.9	2232 (68.1)	327 501 (64.3)		2678 (56.7)	12 328 (57.1)	
25.0-29.9	790 (24.1)	147 156 (28.9)		1684 (35.7)	7699 (35.7)	
≥30.0	118 (3.6)	20 848 (4.1)		257 (5.4)	1189(5.5)	
Women	2331 (71.1)	300 178 (58.9)	<.001	2991 (63.3)	11 517(53.4)	<.001
Residential area						
Urban	1132 (34.5)	225 049 (44.2)	<.001	NA	NA	NA
Rural	2148 (65.5)	284 383 (55.8)		NA	NA	
Education						
Less than primary school	1875 (57.1)	258 480 (50.7)	<.001	1455 (30.8)	6481 (30.0)	.01
Middle school	889 (27.1)	143 983 (28.3)		1684 (35.7)	7721 (35.8)	
High school	386 (11.8)	77 122 (15.1)		1155 (24.4)	5081 (23.6)	
College or higher	130 (4.0)	29 847 (5.9)		429 (9.1)	2292 (10.6)	
Household income, ¥/y						
<10 000[c]	1339 (40.8)	143 395 (28.1)	<.001	NA	NA	NA
10 000-19 999[d]	939 (28.7)	148 017 (29.1)		NA	NA	
20 000-34 999[e]	673 (20.5)	126 029 (24.7)		NA	NA	
≥35 000[f]	329 (10.0)	91 991 (18.1)		NA	NA	
Marital status						
Married	2437 (74.3)	462 025 (90.7)	<.001	4002 (84.7)	18 971 (87.9)	<.001
Widowed	638 (19.5)	35 919 (7.1)		461 (9.8)	1669 (7.7)	
Separated or divorced	155 (4.7)	7787 (1.5)		247 (5.2)	872 (4.1)	
Never married	50 (1.5)	3701 (0.7)		13 (0.3)	63 (0.3)	
Drinking status						
Never, occasionally, or monthly	2762 (84.2)	412 858 (80.5)	<.001	3477 (73.6)	15 788 (73.2)	<.001
Former or reduced intake	194 (5.9)	20 758 (4.1)		352 (7.5)	1181 (5.5)	
Current	1324 (9.9)	75 816 (14.9)		894 (18.9)	4606 (21.3)	
Smoking status						
Never or occasional	2424 (73.9)	344 209 (67.6)	<.001	3410 (72.2)	15 089 (69.9)	<.001
Former	146 (4.4)	30 415 (6.0)		558 (11.8)	2545 (11.8)	
Current	710 (21.7)	134 808 (26.4)		755 (16.0)	3941 (18.3)	
Red meat consumption						
Daily	610 (18.6)	149 407 (29.3)	<.001	1152 (24.4)	5843 (27.1)	<.001
4-6 d/wk	462 (14.1)	91 340 (17.9)		348 (7.4)	1466 (6.8)	
1-3 d/wk	1352 (41.2)	180 812 (35.5)		1976 (41.8)	9186 (42.6)	
<1 d/wk	856 (26.1)	87 873 (17.3)		1247 (26.4)	5080 (23.5)	
Fresh vegetables consumption						
Daily	3099 (94.5)	482 837 (94.8)	.14	4400 (93.2)	20 246 (93.8)	.08
<1/d	181 (5.5)	26 595 (5.2)		323 (6.8)	1329 (6.2)	

(continued)

Table 1. Distribution of Baseline Characteristics of Participants Stratified by Depression Status (continued)

Characteristic	Depression Status					
	CKB Cohort (n = 512 712)			DFTJ Cohort (n = 26 298)		
	No. (%)			No. (%)		
	Yes	No	*P* Value[a]	Yes	No	*P* Value[a]
Fresh fruits consumption						
Daily	420 (12.8)	96 162 (18.9)	<.001	2232 (47.3)	10 715 (49.6)	.03
4-6 d/wk	221 (6.8)	47 737 (9.3)		299 (6.3)	1271 (5.9)	
1-3 d/wk	932 (28.4)	160 357 (31.5)		1297 (27.5)	5711 (26.5)	
<1 d/wk	1707 (52.0)	205 176 (40.3)		895 (18.9)	3878 (18.0)	
Family history of CVD	847 (25.8)	104 208 (20.5)	<.001	717 (15.2)	1939 (9.0)	<.001
Health index score						
0	1921 (58.6)	306 564 (60.2)	<.001	1076 (22.8)	6746 (31.3)	<.001
1	1017 (31.0)	165 952 (32.6)		161 (34.2)	8370 (38.8)	
2	283 (8.6)	32 010 (6.3)		1214 (25.7)	4553 (21.1)	
≥3	59 (1.8)	4906 (0.9)		819 (17.3)	1906 (8.8)	
Chronic disease						
COPD or asthma	172 (5.2)	15 125 (3.0)	<.001	927 (19.6)	2487 (11.5)	<.001
Hypertension	1047 (31.9)	173 405 (34.0)	.01	2718 (57.6)	11 825 (54.8)	<.001
CHD	161 (4.9)	15 311 (3.0)	<.001	1220 (25.8)	3228 (15.0)	<.001
Stroke	116 (3.5)	8768 (1.7)	<.001	378 (8.0)	1057 (4.9)	<.001
Diabetes	23 3(7.1)	30 066 (5.9)	.004	1078 (22.8)	3828 (17.7)	<.001
Cancer	43 (1.3)	2535 (0.5)	<.001	426 (9.0)	1163 (5.4)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CKB, China Kadoorie Biobank; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DFTJ, Dongfeng-Tongji; MET, metabolic equivalent of task value; NA, not available.

[a] Calculated using *t* test for continuous variables or χ^2 test for categorical variables.

[b] Calculated as a day's activities related to occupation, commuting, housework, and nonsedentary leisure-time activities in the CKB study, and only as a day's activities related to nonsedentary leisure-time activities in the DFTJ cohort.

[c] Less than US $1435.89.

[d] US $1435.89 to $2871.65.

[e] US $2871.79 to $5025.49.

[f] At least US $5025.63.

associated with an increased risk of all-cause mortality (CKB cohort: HR, 1.32 [95% CI, 1.20-1.46]; *P* < .001; DFTJ cohort: HR, 1.17 [95% CI, 1.06-1.29]; *P* = .002) and CVD mortality (CKB cohort: HR, 1.22 [95% CI, 1.04-1.44]; *P* = .02; DFTJ cohort: HR, 1.32 [95% CI, 1.14-1.53]; *P* < .001). In the partially adjusted model 1, depression was associated with ischemic heart disease mortality and cerebrovascular disease mortality, but when we adjusted for all covariates, the association only remained significant for depression and cerebrovascular mortality in the DFTJ cohort (HR, 1.56 [95% CI, 1.24-1.96]; *P* < .001) (eTable 2 in the Supplement).

Stratified Analysis by Sex and Age

In the stratified analysis by sex (**Table 3**), the HR for all-cause mortality was 1.53 (95% CI, 1.32-1.76) in men and 1.19 (95% CI, 1.03-1.37) in women (*P* for interaction = .005) in the CKB cohort, while the HR for CVD mortality was 1.39 (95% CI, 1.10-1.76) in men and 1.11 (95% CI, 0.89-1.40) in women (*P* for interaction = .19). In the DFTJ cohort, the HR for all-cause mortality was 1.24 (95% CI, 1.10-1.41) in men and 1.06 (95% CI, 0.91-1.24) in women (*P* for interaction = .21), while the HR for CVD mortality was 1.49 (95% CI, 1.23-1.80) in men and 1.09 (95% CI, 0.86-1.39) in women (*P* for interaction = .06) (Table 3).

In the stratified analysis by age (**Table 4**), the associations were only significant in people 65 years or older compared with participants younger than 65 years in the DFTJ cohort for all-cause mortality (HR, 1.21 [95% CI, 1.08-1.35] vs 1.06 [95% CI, 0.88-1.28]) and CVD mortality (HR, 1.33 [95%

CI, 1.12-1.58] vs 1.27 [95% CI, 0.94-1.71]), although the *P* values for interactions were not significant. However, the associations were only significant in the CKB cohort for participants younger than 65 years compared with those 65 years or older for all-cause mortality (HR, 1.45 [95% CI, 1.28-1.64] vs 1.08 [95% CI, 0.91-1.29]; *P* for interaction < .001) and CVD mortality (HR, 1.34 [95% CI, 1.09-1.65] vs 1.01 [95% CI, 0.78-1.32]; *P* for interaction = .02).

Sensitivity Analysis

The association of depression with mortality remained unchanged in the sensitivity analyses excluding participants who died during the first 2 years of follow-up (CKB cohort: 5261 participants [1.0%]; DFTJ cohort: 1204 participants [4.6%]); participants with baseline history of cancer, CHD, or stroke (CKB cohort: 25 514 participants [5.0%]; DFTJ cohort: 6633 participants [25.2%]); or

Table 2. Association of Depression With All-Cause and CVD Mortality

Group	No. of Cases/Person-Years	Incidence per 1000 Person-Years	HR (95% CI)			
			Unadjusted Model	Model 1[a]	Model 2[b]	Depressive Symptoms Score[c]
All-Cause Mortality						
CKB cohort						
No depression	43 681/5 055 739	8.64	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Depression	384/33 071	11.61	1.56 (1.41-1.73)	1.39 (1.26-1.54)	1.32 (1.20-1.46)	1.06 (1.04-1.08)
DFTJ cohort						
No depression	2027/171 375	11.83	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Depression	544/37 028	14.69	1.36 (1.24-1.50)	1.31 (1.19-1.44)	1.17 (1.06-1.29)	1.04 (1.02-1.07)
CVD Mortality						
CKB cohort						
No depression	17 501/5 055 739	3.46	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Depression	147/33 071	4.44	1.48 (1.26-1.74)	1.31 (1.11-1.54)	1.22 (1.04-1.44)	1.04 (1.01-1.07)
DFTJ cohort						
No depression	772/171 375	4.50	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Depression	241/37 028	6.51	1.59 (1.37-1.84)	1.55 (1.34-1.80)	1.32 (1.14-1.53)	1.08 (1.04-1.12)

Abbreviations: CKB, China Kadoorie Biobank; CVD, cardiovascular disease; DFTJ, Dongfeng-Tongji; HR, hazard ratio.

[a] Model 1 is adjusted for age, sex, education level, body mass index, marital status, drinking status, smoking status, and frequency of consumption of meat, vegetables, and fruits. Data for the CKB cohort are further adjusted for region and household income.

[b] Model 2 is adjusted for all variables in model 1 plus health index score and family history of CVD.

[c] Calculated by adjusting for confounders in model 2.

Table 3. Association of Depression With All-Cause and CVD Mortality Stratified by Sex

Group	No. of Cases/Person-Years	Incidence per 1000 Person-Years	HR (95% CI)[a]	*P* for Interaction[b]
All-Cause Mortality				
CKB cohort				
Men	25 151/2 049 266	12.27	1.53 (1.32-1.76)	.005
Women	18 914/3 039 543	6.22	1.19 (1.03-1.37)	
DFTJ cohort				
Men	1659/91 681	18.10	1.24 (1.10-1.41)	.21
Women	912/116 723	7.81	1.06 (0.91-1.24)	
CVD Mortality				
CKB cohort				
Men	9796/2 049 266	4.78	1.39 (1.10-1.76)	.10
Women	7852/3 039 543	2.58	1.11 (0.89-1.40)	
DFTJ cohort				
Men	656/91 681	7.16	1.49 (1.23-1.80)	.06
Women	357/116 723	3.06	1.09 (0.86-1.39)	

Abbreviation: CKB, China Kadoorie Biobank; CVD, cardiovascular disease; DFTJ, Dongfeng-Tongji; HR, hazard ratio.

[a] Adjusted for age; sex; education level; body mass index; marital status; drinking status; smoking status; frequency of consumption of meat, vegetables, and fruits; health index score; and family history of CVD. Data for the CKB cohort are further adjusted for region and household income.

[b] Calculated by adding an interaction term of sex and depression in the model.

participants 80 years or older in the DFTJ cohort (533 participants [2.0%]); or by using 5 or more symptoms as the cutoff to define depression. The associations were slightly attenuated when adjusting for 6 specific diseases instead of the health index score but did not change materially (eTable 3 in the Supplement).

Discussion

In this large prospective cohort study of adults in China, we found that depression was associated with a significantly elevated risk of all-cause and CVD mortality, and the associations were independent of sociodemographic factors, lifestyle factors, and health status. Furthermore, we found that the associations were only significant in men. To our knowledge, this is the first and largest study in mainland China to evaluate the associations of depression with all-cause and CVD mortality.

A large body of evidence has suggested that depression is a risk factor for all-cause mortality. Many studies have been performed on this topic in the general population as well as specific patient groups, and a 2014 meta-analysis of 293 studies with 1 813 733 participants from 35 countries[5] reported that depression was associated with a 52% increased risk of all-cause mortality. However, most of the investigations were performed in Western countries, and high-quality studies in Chinese populations are lacking, to our knowledge. In an early study among 280 adults 65 years or older living in a rural community in Taiwan, Fu et al[8] reported that depressive symptoms, defined as a score of 15 or higher on the 20-item Center for Epidemiological Studies–Depression Scale (CES-D), were associated with higher mortality risk during 12 years of follow-up. In another cohort study of 2416 men and women in Taiwan 65 years or older, Teng et al[9] reported that depressive symptoms, defined as a score of 10 or higher on the 10-item CES-D, were associated with higher mortality risk during 8 years of follow-up only in men and not in women. Similarly, in a cohort study of 56 088 men and women in Hong Kong 65 years or older, Sun et al[7] reported that depressive symptoms, defined as a score of 8 or higher on the 15-item Geriatric Depression Scale, were associated with higher mortality risk during 8 years of follow-up only in men and not in women. A 2018 study[10] among 1999 participants in Beijing reported that time-dependent depressive symptoms, defined as a score of 16 or higher on the 20-item CES-D, were associated with higher mortality risk in men and women. Therefore, this study, the largest cohort study on this topic in mainland China to our knowledge, is generally consistent with the literature. The previous 4 studies in Chinese populations were all in people 55 years or older, and our study also included people younger than 55 years. In the stratified analysis by age, we did not find consistent associations of age with all-cause or CVD mortality. The

Table 4. Association of Depression With All-Cause and CVD Mortality Stratified by Age

Group	No. of Cases/Person-Years	Incidence per 1000 Person-Years	HR (95% CI)[a]	*P* for Interaction[b]
All-Cause Mortality				
CKB cohort, age, y				
≥65	21 230/671 594	31.81	1.08 (0.91-1.29)	<.001
<65	22 835/4 417 216	5.17	1.45 (1.28-1.64)	
DFTJ cohort, age, y				
≥65	1858/84 654	21.95	1.21 (1.08-1.35)	.39
<65	713/123 750	5.76	1.05 (0.87-1.27)	
CVD Mortality				
CKB cohort, age, y				
≥65	9838/671 594	14.65	1.01 (0.78-1.32)	.02
<65	7810/4 417 216	1.76	1.34 (1.09-1.65)	
DFTJ cohort, age, y				
≥65	761/84 654	8.99	1.33 (1.12-1.58)	.98
<65	252/123 750	2.04	1.27 (0.94-1.71)	

Abbreviation: CKB, China Kadoorie Biobank; CVD, cardiovascular disease; DFTJ, Dongfeng-Tongji; HR, hazard ratio.

[a] Adjusted for age; sex; education level; body mass index; marital status, drinking status; smoking status; frequency of consumption of meat, vegetables, and fruits; health index score; and family history of CVD. Data for the CKB cohort are further adjusted for region and household income.

[b] Calculated by adding an interaction term of age group and depression in the model.

exact reasons for this disparity are unknown, and more prospective studies are needed to explore whether age-specific associations exist for depression and mortality.

We also observed that the association of depression with mortality was more evident in men. This is consistent with 3 previous studies in elderly Chinese populations in Taiwan,[9] Hong Kong,[7] and Beijing, China.[10] In a 2017 meta-analysis, Miloyan and Fried[6] evaluated sex differences in the association of depression with mortality. They found 33 estimates in men and 29 in women and reported that the association was slightly stronger in men than women.[6] Therefore, the evidence suggests that there may be a sex difference in the association of depression with mortality. Although the exact reasons for the sex difference are unclear, there are several potential biological and psychosocial explanations. First, depression-associated oxidative stress[19-21] may play a role: mounting evidence suggests that men express lower levels of antioxidants (eg, superoxide dismutase[22] and glutathione[23]) in mitochondria than women do, which would lead to greater oxidative damage in men. Second, although the prevalence of depression is generally higher in women than men, the strategies to overcome depression might be different. Compared with women, men may be culturally less inclined to report mild depression or seek help until depression is severe.[24,25] In addition, emotional processing in the brain may be generally different in men compared with women, as indicated in 2 studies using functional magnetic resonance imaging.[26,27] Finally, 2 previous studies[28,29] have examined a number of risk factors associated with CHD and stroke that might be different in men and women, and the underlying biological, behavioral, or social mechanisms are still unclear.

We also found that depression was associated with significantly higher risk of CVD mortality. Mounting evidence has suggested that depression is a risk factor of CVD mortality in the general population and in patients with known CVDs, and a 2017 meta-analysis of 92 studies with 116 295 136 participants[30] reported that depression was associated with a 63% higher risk of CVD mortality. A 2016 meta-analysis of myocardial infarction and coronary events from 19 cohort studies with 323 709 participants and 8447 events[31] reported that depression was associated with a significantly increased risk of deaths of myocardial infarction and coronary events. Another meta-analysis of stroke morbidity and mortality among 317 540 participants from 28 prospective cohort studies[32] reported depression was associated with a 55% increase risk of stroke mortality. Similar to all-cause mortality, most of the studies on CVD mortality were conducted in Western countries, and high-quality studies in Chinese populations are lacking. In a 2013 cohort study of 62 839 participants in Hong Kong 65 years or older, Sun et al[33] reported that depressive symptoms, defined as a score of 8 or higher on the 15-item Geriatric Depression Scale, were associated with higher CHD mortality risk in men but not in women. In a cohort study among 1999 participants in Beijing, China, Li et al[10] reported that time-dependent depressive symptoms were associated with higher CVD mortality risk in men but not in women. Therefore, our study is generally consistent with previous studies in this field. In addition, our previous analyses of the CKB study found that depression was associated with higher risks of incident ischemic heart disease[34] and stroke.[35] The results of this analysis of the association of depression with CVD mortality were consistent with these results.

Previous studies had proposed several potential mechanisms for the association of depression with mortality, but there is no consensus yet.[5,36] Biologically, depression may cause dysregulation of central biological stress systems, including hypothalamic-pituitary-adrenal axis hyperactivity[37] and neuroimmune and sympathoadrenergic dysregulation,[38] which may all play a role in the association of depression with mortality. In addition, people with depression often have unhealthy lifestyles,[36] including physical inactivity, smoking, heavy alcohol consumption, and poor diet, and low adherence to treatment, and those factors have been consistently shown to be risk factors for premature death. As for CVD mortality, previous studies have reported that depression is associated with vascular endothelial dysfunction,[39] a prolonged QT interval,[40] lower heart rate variability,[36] and increased platelet aggregation,[39] which would accelerate the deterioration of the condition.

Strengths and Limitations

Several strengths should be noted in this study. To our knowledge, this is the largest study to investigate the association of depression with mortality in Chinese populations. Participants from the CKB study were recruited from 10 areas (5 urban and 5 rural) across China, while participants from the DFTJ cohort were mostly recruited among retired workers from a large company, and most of whom were living in Shiyan City in central China. The characteristics of the participants in the 2 cohorts were different in many ways. The consistent results from the 2 cohort studies indicate that the findings might not be due to random error. Furthermore, we collected detailed information on outcomes, had a relatively long follow-up period and high follow-up rate, and adjusted for a number of potential confounding factors.

Several limitations should also be noted in our study. First, the DFTJ cohort is an occupational cohort, and the healthy worker effect might be possible. However, the prevalence of clinically relevant depressive symptoms was similar to that in a 2014 meta-analysis of Chinese adults with a similar age range.[41] In the CKB study, the 12-month prevalence of depression detected by CIDI-SF was low (0.61%) compared with findings from previous studies in Western and Chinese populations,[42-44] which may be owing to different depression measurement tools, procedures, and study populations. The CKB study only recruited individuals who volunteered to participate; therefore, depressed patients may have been less likely to be included because of their loss of interest in most things. In addition, the questions regarding symptoms were asked differently, which may also cause misclassifications (ie, 2-week duration in the past 12 months in the CKB vs any time in the past 1 month in the DFTJ), and participants in the DFTJ cohort were not asked the depression screening questions before giving answers regarding symptoms of depression. Despite the difference in the depression measurement and substantial differences in the prevalence of depression in the 2 cohorts, the consistent results in the 2 cohorts reduced the possibility of chance findings. Second, we did not have information on clinical diagnoses of depression and its subtypes in our studies and did not measure depression status during the follow-up; thus, misclassifications of depression status were possible. Further studies are also needed to investigate the long-term associations of different types of depression (eg, melancholic and atypical depression) with health outcomes.[45] We used 2 different criteria to define depression in our analyses (having $\geq$3 symptoms in the main analysis and having $\geq$5 symptoms in the sensitivity analysis), but the results remained similar, indicating that the cutoffs to detect depression did not change our findings. Furthermore, misclassifications were more likely to be nondifferential and were unrelated to the outcome; thus, they may underestimate the associations. Third, we did not collect detailed information of use of antidepressant medications among people with depression. However, previous analysis of the CKB study[46] and an epidemiological survey in Chinese populations[43] have suggested that the proportion of people with depression who received treatment is low. Therefore, the influence of antidepressant treatment on our results would be minimal. Fourth, residual confounding is still possible, although we have adjusted for various established and potential risk factors for mortality.

Conclusions

The findings of this cohort study suggest that depression is an independent risk factor of all-cause and CVD mortality in adults in China, especially in men. More studies with clinically diagnosed depression and repeated measures of depression in Chinese populations are still needed to confirm our findings and clarify the potential underlying mechanisms. Given the high disease burdens associated with depression and CVD in the general population and the low treatment rate in Chinese population,[46] our findings have significant clinical and public health importance, and more efforts are needed in China to increase awareness and improve treatment strategies for individuals with depression.

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SUPPLEMENT.

eTable 1. Prevalence of Symptoms of Depression in the CKB and DFTJ Cohorts

eTable 2. Association of Depression With IHD Mortality and Cerebrovascular Disease Mortality

eTable 3. Sensitivity Analysis of the Association of Depression With All-Cause and Cardiovascular Disease Mortality