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Association between Depression and All-cause and Cardiovascular Mortality in Chinese Adults

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Abstract

Importance—Depression is a leading cause of disease burden worldwide, and associated with higher risk of mortality in western populations.

Objective—To investigate whether depression is a risk factor for all-cause and cardiovascular mortality in Chinese adults.

Design, Setting, and Participants—We prospectively followed 512,712 adults (302,509 women and 21,0203 men) aged 30-79 years (mean 52.0, SD 10.7) in the China Kadoorie Biobank (CKB) study from 2004 to 2016, and 26,298 adults (14,508 women and 11,790 men) aged 32 to 104 years (mean 63.6, SD 7.8) in the Dongfeng-Tongji (DFTJ) study from 2008 to 2016.

Main Outcomes and Measures—Depression was evaluated by a Chinese version of the World Health Organization Composite International Diagnostic Interview Short-Form (CIDI-SF) in the CKB study and a 7-item symptoms questionnaire (modified from CIDI-SF) in the DFTJ study. Multivariable-adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between depression and mortality. Covariates in the final models included socio-demographic characteristics, lifestyle factors, personal and family medical history.

Results—We documented 44,065 and 2571 total deaths (including 18,273 and 1013 cardiovascular deaths) in the CKB and DFTJ studies, respectively. In the multivariable-adjusted model, depression was associated with an increased risk of all-cause and cardiovascular mortality in both cohorts, and the HR (95% CI) was 1.32 (1.20-1.46) for all-cause mortality and 1.22 (1.04-1.44) for cardiovascular mortality in the CKB cohort, and the corresponding HR (95% CI) was 1.17 (1.06-1.29) and 1.32 (1.14-1.53) in the DFTJ cohort. The associations were consistently found to be stronger in men while weaker or not significant in women for the two outcomes in the two cohorts, although the *P* values for interaction were not entirely significant.

Conclusions and Relevance—Depression was related to an elevated risk of all-cause and cardiovascular mortality in Chinese adults, particularly in men. Our findings highlight the importance and urgency of depression management as a measure of preventing premature deaths in China.

Keywords

Depression; All-cause mortality; Cardiovascular mortality; Prospective cohort study; Chinese

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Depression becomes increasingly common and is one of the leading disease burdens worldwide. The estimated current prevalence of major depressive disorder was 4.7% and the estimated annual incidence rate was 3.0% around the world.[1] The Global Burden of Disease Study 2016 reported that more than 34 million all-age disability-adjusted life-years (DALYs) were attributed to depression.[2] A recent meta-analysis showed that the overall estimation of current, 12-month and lifetime prevalence of major depressive disorder in China was 1.6%, 2.3%, and 3.3%, respectively.[3] It was estimated that over 10 million loss of DALYs were due to depressive disorders in China in 2013 and the number was projected to increase about 10% by 2025,[4] which highlights the importance and urgency of prevention and intervention on depression.

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

Nevertheless, very few prospective cohort studies have been conducted in Chinese adults on this topic. Four studies were found in Chinese adults with three of them in elderly Chinese aged 65 and above and one study in Chinese aged 55 and above.[7–10] Three studies found that the association between depressive symptoms and total mortality were stronger in men than that in women.[7,9,10] However, studies in younger Chinese adults are lacking and some meta-analyses found that depression also related to excess mortality in women, although not as much as in men.[11] Therefore, more cohort studies are urgently needed to examine the relations of depression with all-cause and cardiovascular mortality in Chinese populations.

In the current analysis, we used data from two large, well-established prospective cohort studies in mainland China to investigate whether depression was associated with all-cause and cardiovascular mortality in middle-aged and elderly Chinese. We also tested whether the associations could be modified by age and sex.

Methods

Study Populations

The study design and baseline characteristics of the two cohorts have been reported in detail elsewhere previously.[12,13] Briefly, the China Kadoorie Biobank (CKB) cohort is a prospective study with over 0.5 million individuals aged 30-79 years recruited from 10 areas between 2004 and 2008. The Dongfeng-Tongji (DFTJ) cohort was established in 2008-2010 with a total of 27,009 workers from Dongfeng Motor Cooperation with an age range of 32 to 104 years (majority of them were retired workers). At baseline, the estimated population response rate was about 30% (26-38% in the five rural areas and 16-50% in the five urban areas) in CKB cohort[12] and 87% in DFTJ cohort[13], respectively. In the CKB study, a detailed data collection protocol was developed in Chinese by experts from the Oxford University, local, regional and national Centers for Disease Control and Prevention of China, as part of a robust training program for the field workers and interviewers. Within a few weeks of the initial baseline survey, about 3% of participants were randomly selected to repeat selected items in the questionnaire (depression was not included) and measures as a quality control (QC) procedure. There was good agreement between baseline and QC surveys for several common variables.[12] Regular central monitoring, as well as on-site monitoring visits were also undertaken periodically by provincial CDC staff and Oxford/Beijing staff. In the DFTJ cohort, all interviewers received unified training and assessment before the field work, and they administered questionnaires during face-to-face interviews. The 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 BMI (n=2). In the DFTJ cohort, we excluded participants without sufficient information on depression (n=1), individuals with unreliable information on death date (n=1) and individuals lost to follow-up (n=709). The CKB study protocol was approved by the Oxford University Tropical Research Ethics Committee and the Chinese Center for Disease Control and Prevention (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 Cooperation. All participants provided written informed consents before enrolment in the study.

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Assessment of Depression

In the CKB baseline, participants were firstly asked whether they had the symptoms for two weeks or more in a row during the past 12 months: 1) feeling much more sad, or depressed than usual; 2) loss of interest in most things like hobbies or activities that usually give you pleasure; 3) felt so hopeless that you had no appetite to eat even your favorite food; and 4) feeling worthless and useless, everything went wrong was your fault and life was very difficult that there was no way out. If they answered “yes” to any of the four questions, they were then 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, seven additional yes-no questions were asked about symptoms during that two weeks, i.e., losing interest in things, feeling tired or low on energy, weight change, difficulty in sleeping, trouble concentrating, thoughts about death, feeling worthless. Participants who had three or more out of the seven depressive symptoms were classified as having major depression. A previous study reported that the sensitivity and specificity of CIDI questionnaire for major depression in Chinese population were 69.6% and 96.7%, respectively.[15]

In the DFTJ baseline, the participants were directly asked about the seven depressive symptoms in the past one month without inquiry of the screening questions. The participants with 3 or more symptoms during the past month were defined as having clinical significant depressive symptoms. “Depression” was used thereafter to simplify the terminology in the two cohorts.

Mortality Follow-up

In the CKB study, cause-specific mortality was monitored regularly through officially residential records and death certificates reported to China CDC Disease Surveillance Points system. The vital status of the participants was also checked annually against medical and health insurance records and supplemented by the street committee 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 of the company 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*) by the trained staff. The cardiovascular deaths were coded I00-99.

Assessment of Covariates

Information on the covariates in the two cohorts were collected through questionnaires and physical measurement at the baseline survey by trained health workers, including demographic or socioeconomic characteristics (age, sex, education, and marital status for both cohorts and region and household income for CKB study), lifestyle factors (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 in the two cohorts (random blood glucose in the CKB study and fasting blood glucose in the DFTJ cohort). Participants were asked about their

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history of chronic diseases, and a health index was created by counting the number of chronic diseases, including chronic obstructive pulmonary disease (COPD)/asthma, hypertension (measured blood pressure ≥140/90 mmHg, or self-reported diagnosis of hypertension or taking antihypertensive drugs at baseline), coronary heart disease (CHD), stroke, diabetes (self-reported diagnosis or medication use, or fasting glucose ≥7.0 mmol/L, or random glucose ≥11.1 mmol/L), and cancer. The health index variable was further categorized into four 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 (MET hours/day) spent on work and leisure activities for both farmers and non-farmer. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Statistical Analysis

Baseline characteristics of the respondents in our study were showed as means (±SD) for continuous variables, or percentages (%) for categorical variables based on their depression status, and Student *t* test or χ^2 test was used to test the differences, respectively. 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 for both cohorts, whichever came first. The association between depression and mortality was estimated using Cox proportional hazards regression model, which yielded hazard ratios (HRs) and corresponding 95% confidence intervals (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 socio-demographic characteristics, lifestyle factors, personal and family medical history as confounders in the multivariable-adjusted Cox models. The potential confounders including: age (continuous variable), sex, education level (less than primary school, middle school, high school and college or higher), BMI (continuous variable), marital status (with and without spouse), drinking status (never, former and current drinking), smoking status (never, former and current smoking), consumption frequency of meat (daily, 4-6 days per week, 1-3 days per week, <1 day per week), vegetables (daily, <1 per day), and fruits (daily, 4-6 days per week, 1-3 days per week, <1 day per week), health index (0, 1, 2, ≥3) and family history of cardiovascular disease (CVD). In the CKB cohort, study site (10 areas) and household income (<10,000, 10,000-19,999, 20,000-34,999, ≥35,000 yuan/year) were also included in the model. The confounders were selected based on *a priori* knowledge of underlying biological mechanisms and the literature reports.[5,6] We also examined the relations of depression with ischemic heart disease (IHD) mortality and cerebrovascular disease mortality. We also conducted stratified analyses by sex and age (≥65 years, or <65 years), and tested the significance of interaction by including a two-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 two years of follow-up were excluded to minimize the chance of reverse causality; 2) participants with baseline cancer, CHD, or stroke were excluded to examine the associations in relatively healthy individuals; 3) participants aged 80 or older in the DFTJ cohort were excluded to reduce the potential selection bias; 4) we adjusted for each chronic disease instead of the health index to fully account for the

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

We conducted all the analyses separately in each cohort, and the results were pooled together by an inverse variance–weighted meta-analysis approach using the random-effects model. The SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for all analyses and statistical significance level was set to 0.05.

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 study was 0.64%, and the 1-month prevalence of clinical significant depressive symptoms was 17.96% in the DFTJ study. Table 1 shows the distribution of baseline characteristics based on depression status in the two cohorts. Compared to participants without depression, those with depression were more likely to be female and never smokers, to have more comorbidities and higher family history of CVD, while less likely to be in married status, or to eat red meat and fresh fruits daily. In the CKB study, those with depression were more likely to be younger, inactive, never drinkers, to have lower education level, BMI and household income, while in the DFTJ cohort, those with depression were more likely to be current drinkers. In the CKB study, the top three out of the seven symptoms included “losing interest in things”, “feeling tired or low on energy” and “trouble concentrating”, while the top three symptoms in the DFTJ cohort included “trouble concentrating”, “feeling tired or low on energy” and “difficulty in sleeping” (eTable 1).

Depression and All-cause and Cardiovascular Mortality

In the CKB study, we documented 44,065 deaths (including 17,501 cardiovascular deaths) during 5,088,810 person-years of follow-up. In the DFTJ cohort, we documented 2571 deaths (including 1013 cardiovascular deaths) during 208,403 person-years of follow-up. The incidence rate of all-cause and cardiovascular 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 associated with an increased risk of all-cause and cardiovascular mortality in both cohorts, and the HR (95% CI) was 1.32 (1.20-1.46) for all-cause mortality and 1.22 (1.04-1.44) for cardiovascular mortality in the CKB cohort, and the corresponding HR (95% CI) was 1.17 (1.06-1.29) and 1.32 (1.14-1.53) in the DFTJ cohort. In the multivariable-adjusted model, the association between depression and IHD mortality and cerebrovascular disease mortality were significant in the model 1 for both outcomes in both cohorts and attenuated when adjusting for health index and family history of CVD, the HR (95% CI) was 1.27(0.97-1.67) for IHD mortality and 1.21 (0.98-1.51) for cerebrovascular disease mortality in the CKB cohort, and the corresponding HR (95% CI) was 1.21 (0.97-1.50) and 1.56 (1.24-1.96) in the DFTJ cohort. (eTable 2 in the Supplement).

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Stratified Analysis by Sex and Age

In the stratified analysis by sex, the associations were only significant in men compared to women in both cohorts for both outcomes except for all-cause mortality in CKB cohort. In the CKB cohort, the HR (95% CI) for all-cause mortality was 1.53 (1.32-1.76) in men and 1.19 (1.03-1.37) in women (*P* for interaction = .005), while the HR (95% CI) for cardiovascular mortality was 1.39 (1.10-1.76) in men and 1.11 (0.89-1.40) in women. In the DFTJ cohort, the HR (95% CI) for all-cause mortality was 1.24 (1.10-1.41) in men and 1.06 (0.91-1.24) in women, while the HR (95% CI) for cardiovascular mortality was 1.49 (1.23-1.80) in men and 1.09 (0.86-1.39) in women (Table 3).

In the stratified analysis by age, the associations were only significant in older people (aged ≥65 years) compared to younger participants (aged <65 years) in the DFTJ cohort for both outcomes (although the *P* values for interaction were not significant); however, the associations were only significant in younger compared to older participants in the CKB cohort for both outcomes (*P* values for interaction <.05) (Table 4).

Sensitivity Analysis

The association between depression and mortality remained unchanged in the sensitivity analysis of excluding individuals who died during the first two years of follow-up (CKB cohort: n=5261; DFTJ cohort: n=1204), or excluding participants with baseline history of cancer, CHD, or stroke (CKB cohort: n=25,514; DFTJ cohort: n=6633), or excluding individuals aged 80 or older in the DFTJ cohort (n=533), or using five or more symptoms as the cut-off point to define depression. The associations were slightly attenuated when adjusting for six specific diseases instead of the health index, but did not change materially (eTable 3 in the Supplement).

Discussion

In these two large prospective cohorts of Chinese adults, we found that depression was associated with a significantly elevated risk of all-cause mortality and cardiovascular mortality, and the associations were independent of socio-demographic factors, lifestyle factors, and health status. We further found that the associations were only significant in men. This is, to our knowledge, the first and largest study in mainland China to evaluate the relations of depression with all-cause and cardiovascular mortality.

A large body of evidence has demonstrated that depression is a risk factor for all-cause mortality. Many studies have been done on this topic in the general population as well as specific patient groups, and a meta-analysis of 293 studies with 1,813,733 participants from 35 countries showed that depression was associated with a 52% increased risk of total mortality.[5] Among the 293 studies, 78 were done in the community samples and the pooled HR was 1.59 (95% CI 1.47-1.71).[5] However, most of the investigations were performed in western countries, and high-quality studies in Chinese populations are lacking. In an early study among 280 adults aged 65 years and older living in a rural community in Taiwan, Fu et al.[8] reported that depressive symptoms, defined as the 20-item Center for Epidemiological Studies-Depression Scale (CES-D) score ≥15, were associated with higher mortality risk during 12 years of follow-up (HR, 1.55; 95% CI, 0.99-2.44). In another cohort study of 2416 men and women in Taiwan aged 65 or older, Teng et al.[9] reported that depressive symptoms, defined as the 10-item CES-D score ≥10, were associated with higher mortality risk during 8 years of follow-up only in men (HR, 1.27; 95% CI, 1.03-1.56), but not in women (HR, 1.10; 95% CI, 0.86-1.40). In a cohort study of 56,088 men and women in Hong Kong aged 65 or older, Sun et al.[7] reported that depressive symptoms, defined as the 15-item Geriatric Depression Scale (GDS) score ≥8, were associated with higher mortality risk during 8 years of follow-up only in men (HR, 1.21; 95% CI, 1.08-1.37), but not in women (HR, 1.00; 95% CI, 0.91-1.10). A recent study among 1999 participants in Beijing reported that time-dependent depressive symptoms, defined as 20-item CES-D score ≥16, were associated with higher mortality risk in men (HR, 1.66; 95% CI, 1.32-2.09) and women (HR, 1.42; 95% CI, 1.13-1.77).[10] Therefore, the present study is generally consistent with the literature, and is the largest cohort study on this topic in mainland China. The previous four studies in Chinese populations were all in people who aged 55 years and older, and our study also included people younger than 55 years old. In the stratified analysis by age, the associations were not consistently found in the CKB and DFTJ cohorts. The 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 depression-mortality association was more evident in men. This is consistent with three previous studies in the elderly Chinese in Taiwan, Hong Kong and Beijing.[7,9,10] In a recent meta-analysis, Miloyan & Fried evaluated the sex differences in the depression-mortality relation.[6] They found 33 estimates in men and 29 in women, and reported that the association was slightly stronger in men (HR, 1.41; 95% CI, 1.29-1.54) than that in women (HR, 1.23; 95% CI, 1.13-1.32).[6] Therefore, the current evidence suggests that there might be a potential sex difference in the depression-mortality association. Although the exact reasons for the sex difference are unclear, there are several potential biological and psychosocial explanations. First, depression associated oxidative stress[16–18] may explain the sex difference. Mounting evidence suggests that men express remarkably lower levels of antioxidants (superoxide dismutase[19] and glutathione[20]) in mitochondria than women, which would lead to greater oxidative damage in men. Second, although the prevalence of depression is generally higher in women compared to men, the strategies to overcome depression might be different. Compared to women, men are culturally less inclined to report mild depression or seek help until depression is in severe status.[21,22] In addition, the emotional processing in general in the brain is different in men and women, as indicated in some studies using functional magnetic resonance imaging.[23,24] Finally, some previous studies[25,26] have examined a number of risk factors related to CHD/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 cardiovascular mortality in the two cohorts of Chinese adults. Mounting evidence has showed that depression is a risk factor of cardiovascular mortality both in general population and in patients with known heart diseases, and a recent meta-analysis of 92 studies with 116,295,136 participants showed that depression was associated with a 63% higher risk of cardiovascular mortality.[27] Among the 92 studies, 7 were done in community samples and

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the pooled HR was 1.63 (95% CI, 1.25-2.13).[27] A meta-analysis of myocardial infarction (MI) and coronary events from 19 cohort studies with 323,709 participants and 8447 cases reported that depression was associated with a significantly increased risk of deaths of MI (HR, 1.31; 95% CI, 1.13-1.32) and coronary events (HR, 1.36; 95% CI; 1.14-1.63).[28] Another meta-analysis of stroke morbidity and mortality among 317,540 participants from 28 prospective cohort studies reported depression was associated with a 55% increase risk of stroke mortality.[29] Similar to all-cause mortality, most of the studies on cardiovascular mortality were conducted in western countries, and high-quality studies in Chinese populations are lacking. In a cohort study of 62,839 participants in Hong Kong aged 65 or older, Sun et al.[30] reported that depressive symptoms, defined as the 15-item GDS score ≥8, were associated with higher CHD mortality risk during 8.4 years of follow-up only in men (HR, 1.41; 95% CI, 1.08-1.84), but not in women (HR, 0.94; 95% CI, 0.75-1.16). In the cohort study among 1999 participants in Beijing, Li et al.[10] reported that time-dependent depressive symptoms were associated with higher cardiovascular mortality risk in men (HR, 1.59; 95% CI, 1.09-2.30), but not in women (HR, 1.23; 95% CI, 0.85-1.79). Therefore, the present study is generally consistent with the previous studies in this field. In addition, our previous analyses in the CKB study found that depression was associated with higher risks of incident IHD[31] and stroke.[32] The results of current analysis of depression and cardiovascular mortality were consistent with these results.

Previous studies had proposed several potential causal mechanisms for association between depression and mortality but there is no consensus yet.[5,33] Biologically, depression may cause dysregulation of central biological stress systems, including hypothalamic-pituitary-adrenal axis hyperactivity,[34] neuroimmune and sympathoadrenergic dysregulation,[35] which might all play a role in the association between depression and mortality. In addition, people with depression usually have unhealthy lifestyles,[36] including physical inactivity, smoking, heavy alcohol consumption, and poor diet patterns and low adherence to treatment, and those factors have been consistently shown to be causal risk factors for premature death. As for cardiovascular mortality, previous studies reported that depression was associated with vascular endothelial dysfunction,[37] a prolonged QT interval,[38] lower heart rate variability,[36] and increased platelet aggregation,[37] which would accelerate the deterioration of the condition.

Several strengths should be noted in the current study. To our knowledge, this is the largest study to investigate the association between depression and mortality in Chinese population. Participants from the CKB study were recruited from ten areas (five urban and five rural) across China, while participants from the DFTJ cohort were mostly from retired workers from a large company and most of them were living in the Shiyan City in central China. The characteristics of the participants in the two cohorts were different in many ways. The consistent results from the two cohort studies indicate that the findings might not be by chance. Furthermore, we collected detailed information on outcomes, followed-up a relative long time with the high follow-up rate, and adjusted for a number of potential confounding factors.

Several limitations should be noted in our study. First, the DFTJ cohort is an occupational cohort and healthy worker effect might be possible. However, the prevalence of clinical

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relevant depressive symptoms was similar to that in a meta-analysis of Chinese adults in the similar age range.[39] In the CKB study, the 12-month prevalence of depression detected by CIDI-SF was quite low (0.61%) compared to findings from previous studies in Western and Chinese populations,[40–42] which may be because of different depression measurement tools and procedures and study populations. The CKB study only recruited those who volunteered to participate, while more depressed patients would be less likely to be included because of their loss of interest in most things. In addition, the symptoms were asked differently which may also cause misclassifications, i.e. 2-week duration in the past 12 months in the CKB, and any time in the past 1 month in the DFTJ and we did not have the screening questions before asking the participants of the 7 symptoms in the DFTJ cohort. Despite the difference in the depression measurement and substantial differences in the prevalence of depression in the two cohorts, the consistent results in the two cohorts, again, reduced the possibility of chance findings. Second, we did not have clinical diagnosis of depression and its subtypes in our studies and did not measure depression status during the follow-up, thus, misclassifications of the depression status were possible. Further studies are also needed to investigate the long-term impact of different types of depression (e.g., melancholic and atypical depression) on health outcomes.[43] We used two different criteria to define depression in our analyses (having at least 3 symptoms in the main analysis and having at least 5 symptoms in the sensitivity analysis), the results remained similar, indicating that the cut-off points to detect depression did not change our findings. Furthermore, the misclassifications were more likely to be non-differential and were unrelated to the outcome, thus may underestimate the associations. Third, we did not collect the detailed information of anti-depressants use for people with depression. However, previous analysis in the CKB study[44] and some studies in the Chinese population[41] indicate that the proportion of people with depression who received treatment is low. Therefore, the influence of anti-depressant treatment on the results would be minimal. Finally, residual confounding is still possible although we have adjusted for various established and potential risk factors of mortality in the present study.

Conclusions

In conclusion, depression was an independent risk factor of all-cause mortality and cardiovascular mortality in the Chinese adults, especially in men. More studies with clinically diagnostic depression and repeated measures of depression are still needed to confirm our findings in Chinese populations and clarify the potential underling mechanisms. Given the high disease burdens by depression and CVD in the general population, and the substantial low treatment rate in Chinese population,[44] our findings have significant clinical and public health importance, and more efforts are needed in China to increase the awareness and improve the treatment strategies for patients with depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

Question: Is depression associated with higher all-cause and cardiovascular mortality in Chinese adults?

Finding: During the 5,088,810 and 208,403 person-years of follow-up of China Kadoorie Biobank (CKB) cohort and Dongfeng-Tongji (DFTJ) cohort, we respectively documented 44,065 and 2571 all-cause deaths (including 17,501 and 1013 cardiovascular deaths). The results of two cohorts consistently showed that depression was associated with higher risk of all-cause and cardiovascular mortality, and the associations were significant only in men.

Meaning: Depression is a risk factor for all-cause and cardiovascular mortality in Chinese adults, particularly in men.

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Table 1

The Distribution of Baseline Characteristics of Participants According to Depression Status[a]

	Baseline depression status					
	CKB cohort			DFTJ cohort		
	Yes	No	*P* value[b]	Yes	No	*P* value[b]
N	3280	509,432		4723	21,575	
Age (years)	51.5±10.0	52.0±10.7	<.001	63.5±7.8	63.6±7.8	.22
Activity, MET-hours/day [c]	19.9±14.1	21.1 ±13.9	<.001	4.25±6.62	4.38±7.18	.24
BMI (continuous, kg/m^2)	23.2±3.4	23.7±3.4	<.001	24.5±3.5	24.6±3.3	.21
BMI group (kg/m^2)						
<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)	
Female (%)	2331 (71.1)	300,178 (58.9)	<.001	2991 (63.3)	11,517(53.4)	<.001
Residential area				NA	NA	NA
Urban	1132(34.5)	225,049(44.2)				
Rural	2148(65.5)	284,383(55.8)				
Education (%)			<.001			.01
Less than primary school	1875 (57.1)	258,480 (50.7)		1455 (30.8)	6481 (30.0)	
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 (yuan/year, %)		<.001	NA	NA	NA	
<10000	1339 (40.8)	143,395 (28.1)				
10000-19999	939 (28.7)	148,017 (29.1)				
20000-34999	673 (20.5)	126,029 (24.7)				
⩾35000	329 (10.0)	91,991 (18.1)				
Marital status (%)			<.001			<.001
Married	2437 (74.3)	462,025 (90.7)		4002 (84.7)	18,971 (87.9)	

	Baseline depression status					
	CKB cohort			DFTJ cohort		
	Yes	No	*P* value[b]	Yes	No	*P* value[b]
Widowed	638 (19.5)	35,919 (7.1)		461 (9.8)	1669 (7.7)	
Separated / 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 (%)			<.001			<.001
Never/ Occasional/ Monthly	2762 (84.2)	412,858 (80.5)		3477 (73.6)	15,788 (73.2)	
Former/ 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 (%)			<.001			<.001
Never/ Occasional	2424 (73.9)	344,209 (67.6)		3410 (72.2)	15,089 (69.9)	
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 (%)			<.001			<.001
Daily	610 (18.6)	149,407 (29.3)		1152 (24.4)	5843 (27.1)	
4-6 days per week	462 (14.1)	91,340 (17.9)		348 (7.4)	1466 (6.8)	
1-3 days per week	1352 (41.2)	180,812 (35.5)		1976 (41.8)	9186 (42.6)	
<1 day per week	856 (26.1)	87,873 (17.3)		1247 (26.4)	5080 (23.5)	
Fresh vegetables (%)			.14			.08
Daily	3099 (94.5)	482,837 (94.8)		4400 (93.2)	20,246 (93.8)	
<1 per day	181 (5.5)	26,595 (5.2)		323 (6.8)	1329 (6.2)	
Fresh fruits (%)			<.001			.03
Daily	420 (12.8)	96,162 (18.9)		2232 (47.3)	10,715 (49.6)	
4-6 days per week	221 (6.8)	47,737 (9.3)		299 (6.3)	1271 (5.9)	
1-3 days per week	932 (28.4)	160,357 (31.5)		1297 (27.5)	5711 (26.5)	
<1 day per week	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 (%)			<.001			<.001
0	1921 (58.6)	306,564 (60.2)		1076 (22.8)	6746 (31.3)	
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)	

	Baseline depression status					
	CKB cohort			DFTJ cohort		
	Yes	No	*P* value[b]	Yes	No	*P* value[b]
≥3	59 (1.8)	4906 (0.9)		819 (17.3)	1906 (8.8)	
Chronic diseases						
COPD/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

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

[a]Data are shown as mean ± standard deviation for continuous variables, or percentage for categorical variables.

[b]P values were calculated by Student t-test for continuous variables or $\chi 2$ test for categorical variables.

[c]MET hours/day: metabolic equivalent of task value for a day's work and leisure activities for both farmers and non-farmer.

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Table 2

The Association between Depression and All-cause and Cardiovascular Mortality

	Cases/person-years	Incidence per 1,000 person-years	Unadjusted Model HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Depressive symptoms score[c]
All-cause mortality						
CKB						
No depression	43,681/50,55,739	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						
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						
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						
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)

Abbreviation: CI, confidence interval; CKB, China Kadoorie Biobank; CVD, cardiovascular diseases; DFTJ, Dongfeng-Tongji; HR: hazard ratio.

[a] Model 1: adjusted age, sex, education, BMI, spouse, drinking, smoking, consumption of meat, vegetables, and fruits; CKB cohort further adjusted region and household income.

[b] Model 2: adjusted model 1 plus health index and family history of CVD.

[c] The results were calculated by adjusting for confounders shown in Model 2.

Table 3

The Association between Depression and All-cause and Cardiovascular Mortality: Stratified Analysis by Sex

	Case/person-years	Incidence per 1,000 person-years	HR (95% CI)[a]	*P* for interaction[b]
All-cause mortality				
CKB				
Male	25,151/2,049,266	12.27	1.53 (1.32-1.76)	.005
Female	18,914/3,039,543	6.22	1.19 (1.03-1.37)	
DFTJ				
Male	1659/91,681	18.10	1.24 (1.10-1.41)	.21
Female	912/116,723	7.81	1.06 (0.91-1.24)	
CVD mortality				
CKB				
Male	9796/2,049,266	4.78	1.39 (1.10-1.76)	.10
Female	7852/3,039,543	2.58	1.11 (0.89-1.40)	
DFTJ				
Male	656/91,681	7.16	1.49 (1.23-1.80)	.06
Female	357/116,723	3.06	1.09 (0.86-1.39)	

Abbreviation: CI, confidence interval; CKB, China Kadoorie Biobank; CVD, cardiovascular diseases; DFTJ, Dongfeng-Tongji; HR, hazard ratio.

[a]The model adjusted age, sex, education, BMI, spouse, drinking, smoking, consumption of meat, vegetables, fruits, health index and family history of CVD; CKB cohort further adjusted region and household income.

[b]The results were calculated by adjusting for confounders shown above.

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Table 4

The Association between Depression and All-cause and Cardiovascular Mortality: Stratified Analysis by Age

	Case/person-years	Incidence per 1,000 person-years	HR (95% CI)[a]	*P* for interaction[b]
All-cause mortality				
CKB				
Age≥65	21,230/67,1594	31.81	1.08 (0.91-1.29)	<.001
Age <65	22,835/4,417,216	5.17	1.45 (1.28-1.64)	
DFTJ				
Age ≥65	1858/84,654	21.95	1.21 (1.08-1.35)	.39
Age <65	713/123,750	5.76	1.06 (0.88-1.28)	
CVD mortality				
CKB				
Age ≥65	9838/671,594	14.65	1.01 (0.78-1.32)	.02
Age <65	7810/4,417,216	1.76	1.34 (1.09-1.65)	
DFTJ				
Age ≥65	761/84,654	8.99	1.33 (1.12-1.58)	.98
Age <65	252/123,750	2.04	1.27 (0.94-1.71)	

Abbreviation: CI, confidence interval; CKB, China Kadoorie Biobank; CVD, cardiovascular diseases; DFTJ, Dongfeng-Tongji; HR, hazard ratio.

[a]The model adjusted age, sex, education, BMI, spouse, drinking, smoking, consumption of meat, vegetables, fruits, health index and family history of CVD; CKB cohort further adjusted region and household income.

[b]The results were calculated by adjusting for confounders shown above.