Association of Major Depression With Risk of Ischemic Heart Disease in a Mega-Cohort of Chinese Adults: The China Kadoorie Biobank Study

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Background—Increasing evidence has suggested that major depression (MD) is associated with an increased risk of ischemic heart disease (IHD). We examined this association in Chinese adults using data from the China Kadoorie Biobank study.

Methods and Results—Over 0.5 million adults aged 30 to 79 years were followed from baseline interview (2004–2008) until December 31, 2013. Past year MD was measured with the modified Chinese version of Composite International Diagnostic Interview-Short Form at baseline. Incident IHD cases were identified through linkage to related medical databases, and defined as having International Statistical Classification of Diseases and Related Health Problems 10th Revision codes of I20 to I25. Cox proportional hazards regression models were used to estimate hazard ratios and 95% CIs for the MD-IHD association with adjustment for sociodemographic variables and established cardiovascular risk factors. During 3 423 542 person-years of follow-up, 24 705 incident IHD cases were documented. Higher IHD incidence was observed in participants with MD compared with those without (8.76 versus 7.21 per 1000 person-years), and the multivariable-adjusted hazard ratio was 1.32 (95% CI 1.15–1.53).

Geographic location modified the association (P for interaction = 0.005), and a positive association was observed in urban residents (hazard ratio 1.72; 95% CI 1.39–2.14) but not rural residents (1.13; 0.93–1.37). Compared with participants without depressive symptoms, the hazard ratio (95% CI) of IHD was 1.13 (1.04–1.23) for those with depressive symptoms only and 1.33 (1.15–1.53) for those with MD.

Conclusions—Past year major depression was associated with an increased risk of IHD in Chinese adults, independent of other major cardiovascular risk factors. (J Am Heart Assoc. 2016;5:e004687 doi: 10.1161/JAHA.116.004687)

Key Words: Chinese • depression • ischemic heart disease • prospective cohort study

B ased on the Global Burden of Disease Study 2010, ischemic heart disease (IHD) caused an estimated over 129 million disability-adjusted life years in 2010, about a 29% increase from 1990. IHD remained as one of the leading causes of death and disability-adjusted life years in the Global Burden of Disease Study 2013. In China, a total of 230 million adults suffered from IHD in 2010, and the number will continue to increase dramatically because of aging, urbanization, and lifestyle changes. As predicted, the number of IHD patients in Chinese adults aged 35 to 84 years old would increase by 64% during 2020 and 2029. Therefore, identification of risk factors for IHD and implementation of public health measures to reduce the risk factors in Chinese adults will have a tremendous impact on national and global population health.
Major depression (MD), featuring sadness or irritability accompanied by a cluster of psychophysiological disturbances (such as weight change, sleeping problems, inability to experience pleasure in daily life, difficulty in concentrating, and thoughts of death) can lead to severe impairment in quality of life and physical functioning. The Global Burden of Disease Study 2013 showed that MD was among the top causes of disability-adjusted life years and years lived with disability worldwide. Mounting evidence indicates that MD is related to an increased risk of morbidity and mortality of IHD as reviewed in previous meta-analyses. However, most studies were conducted in Western populations, and few were in Asian or Chinese populations. One study in Chinese adults aged 20 years and older using data from the Taiwan Health Insurance database found a significant increased risk of composite coronary events associated with clinically diagnosed MD, while another study in Chinese adults aged 65 years or older in Hong Kong found a significant association between self-reported depressive symptoms and mortality from coronary heart disease (CHD) only in men but not in women.

To the best of our knowledge, no prospective cohort study has been conducted in mainland China to examine the relation of depression with incident IHD. To address the gap, we aim to examine the association between MD and risk of IHD using data from the China Kadoorie Biobank (CKB) study.

Methods

Study Population

The CKB study is a prospective population-based cohort study among adults aged 30 to 79 years from 10 geographically defined regions of China (5 urban and 5 rural). These regions were selected according to disease patterns and risk exposures, economic development, population stability, and other major population characteristics. A detailed description about the CKB study has been published previously. All participants were interviewed face-to-face at baseline by trained staff using a standardized electronic questionnaire that covered demographic characteristics, socioeconomic status, personal behaviors, general health, family history, mental health, and for women only, reproductive history.

A total of 512,891 individuals (210,259 men, 41.0%) were enrolled at the baseline interview (2004–2008). In the current study, 26,350 participants were excluded because of previous diagnosis of cancer (n=2577), CHD (n=15,472), rheumatic heart disease (n=938), stroke or transient ischemic attack (n=8884), and missing value on body mass index (BMI) (n=2), leaving 486,541 participants in the final analysis. Ethical approval has been obtained from the Ethics Review Committee of the Chinese Center for Disease Control and Prevention, Beijing, China, and Oxford Tropical Research Ethics Committee, University of Oxford, Oxford, United Kingdom. Written informed consent was obtained from each study participant.

Assessment of Major Depression

At baseline, participants were asked whether they had had situations for 2 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 that went wrong was your fault and life was very difficult so that there was no way out. If the answer was “yes” to any of the 4 questions, the participants were further assessed for MD using the modified Chinese version of Composite International Diagnostic Interview-Short Form in a face-to-face interview by trained health workers at study clinics. The Composite International Diagnostic Interview, a fully structured diagnostic instrument, is based on the case definition from the Diagnostic and Statistical Manual of Mental Disorders IV and has shown moderate concordance with clinical psychiatric interviews. The validity of the Chinese version has been published elsewhere. Participants were defined as having past year MD if they had felt sad, blue, or depressed for ≥2 weeks during the past 12 months, and if they had at least 3 of 7 additional symptoms, including loss of interest and pleasure, loss of energy or fatigue, weight change, sleep problems, concentration problems, feelings of worthlessness, and thoughts of suicide. In our current analysis, participants who responded positively to the screening questions but did not fulfill the criteria for MD were categorized as having depressive symptoms only.

Assessment of IHD

The main outcome of interest was incident IHD, which was defined as categories I20 to I25 according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision. In the CKB study, incident IHD was collected by linkage to established disease registries and national health insurance claim databases. The disease registries were currently available in 8 of the 10 study areas, while the national health insurance claim databases covered all study areas and recorded details of all hospitalized episodes including disease characteristics, diagnostic procedures, and International Statistical Classification of Diseases and Related Health Problems 10th Revision codes. The linkage to the health insurance database was renewed annually, and those who failed to be linked were actively followed annually by local research staff to ascertain their
status, including hospital admission, death, and migration. Only new IHD cases confirmed by medical records were considered as incident cases.

**Assessment of Covariates**

Sociodemographic characteristics, lifestyle factors, and medical history were collected at the baseline interview through a laptop-based questionnaire. Sociodemographic characteristics included age, sex, education level (categorized as no formal school, primary school, middle school, high school, and college/university or more), annual household income (categorized as less than 5000, 5000–9999, 10 000–19 999, and 20 000 or more, in RMB Yuan), and marital status (categorized as married, widowed, separated/divorced, and never married). Lifestyle factors included smoking (categorized as never, former, occasional and current), alcohol drinking (categorized as less than weekly and weekly or more), and total physical activity (calculated as metabolic equivalent task hours per day [MET-hours/day] spent on work and leisure activities). Participants were also asked about their personal medical history and family history of major chronic diseases.

Body weight, height, and blood pressure were measured at baseline by trained staff using calibrated instruments according to standardized protocols. BMI was calculated as weight in kilograms divided by height in meters squared. Prevalent hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported diagnosis of hypertension, or self-reported use of antihypertensive medication at baseline. Prevalent diabetes mellitus was defined as fasting blood glucose ≥7.0 mmol/L, random blood glucose ≥11.1 mmol/L, self-reported diagnosis of diabetes mellitus, or use of antidiabetic medications.

**Statistical Analysis**

Baseline characteristics were compared according to MD status using Student t test for continuous variables and χ² test for categorical variables. Follow-up time was defined as the time interval between the date of baseline interview and the date of IHD diagnosis, death of any cause, loss to follow-up, or December 31, 2013, whichever occurred first. The association between baseline MD status and incident IHD was estimated by Cox proportional hazards regression models. We examined the proportional hazards assumptions and no violations were found. We adjusted for sociodemographic factors (including age, sex, geographic location, marital status, education level, and annual household income) in the first model, and additionally adjusted for lifestyle factors (smoking status, drinking status, and physical activity) in the second model. Finally, family history of heart attack, BMI, history of diabetes mellitus, and hypertension were included in the third model.

Stratified analyses were conducted to investigate whether the association between MD and incident IHD varied by prespecified factors, including sex, age, BMI, and geographic location. Effect modification by these factors was assessed by including an interaction term in the final model. To explore whether there was dose–response relationship, we repeated the multivariable analysis using reclassified MD status (no depressive symptoms, depressive symptoms only, and MD). To minimize the possibility of reverse causality, a sensitivity analysis was conducted by removing all incident cases that occurred within the first 2 years of follow-up (n=5268).

All analyses were performed using SAS software, version 9.2 (SAS Institute). All P values were 2 sided, and the level of statistical significance was defined at P<0.05.

**Results**

The overall prevalence of MD was 0.61% (n=2972) among 486 541 Chinese adults. All differences in baseline characteristics between participants with and without MD were statistically significant (Table 1). Participants who reported MD in the past 12 months were younger and less educated, were more likely to be females, rural residents, never smokers, and light drinkers, and they had lower BMI and were less likely to be physically active. They were also less likely to be married and wealthy. For women, those with MD were more likely to be at their perimenopause period. In addition, those with MD tended to have a family history of heart attack, and suffer from diabetes mellitus but not hypertension.

A total of 24 705 incident cases of IHD were identified over a median follow-up of 7.2 years. The incidence rate of IHD was 8.76 per 1000 person-years among participants with MD versus 7.21 per 1000 person-years among those without MD (Table 2). The hazard ratio (HR) and 95% CI between baseline MD status and incident IHD was 1.32 (1.14–1.52) after adjustment for sociodemographic factors (Table 2). The positive association remained after further adjustment for lifestyle factors, baseline comorbidities, and family history of heart diseases (HR 1.32, 95% CI 1.15–1.53).

Geographic location modified the association between MD and risk of IHD (P for interaction=0.005; Table 2): MD was associated with risk of IHD in urban (HR 1.72, 95% CI 1.39–2.14) but not rural residents (HR 1.13, 95% CI 0.93–1.37) (Table 2). The association between MD and risk of IHD was not modified by sex (P for interaction=0.23), age (P for interaction=0.10), or BMI (P for interaction=0.98).

The sensitivity analysis, after excluding incident IHD cases diagnosed within the first 2 years of follow-up, showed that the positive association did not change (HR 1.29, 95% CI 1.10–1.52) (Table 2). When the effect of severity of
**Table 1.** Baseline Characteristics of Participants by MD Status†

| Variables                        | Overall             | Participants With MD | Participants Without MD | P Values |
|----------------------------------|---------------------|----------------------|-------------------------|----------|
| N                                | 486 541             | 2972                 | 483 569                 |          |
| Age, y                           | 51.0±10.5           | 50.4±9.9             | 51.0±10.5               | <0.001   |
| Sex                              |                     |                      |                         | <0.001   |
| Male                             | 199 113             | 837 (28.2)           | 198 276 (41.0)          |          |
| Female                           | 287 428             | 2135 (71.8)          | 285 293 (59.0)          |          |
| Menopausal status (women only)   |                     |                      |                         | <0.001   |
| Premenopause                     | 127 325             | 869 (40.7)           | 126 456 (44.3)          |          |
| Perimenopause                    | 14 354              | 128 (6.0)            | 14 226 (5.0)            |          |
| Postmenopause                    | 145 749             | 1138 (53.3)          | 144 611 (50.7)          |          |
| Marital status                   |                     |                      |                         | <0.001   |
| Married                          | 442 228             | 2220 (74.7)          | 440 008 (91.0)          |          |
| Widowed                          | 33 081              | 570 (19.2)           | 32 511 (6.7)            |          |
| Separated/divorced               | 7579                | 139 (4.7)            | 7440 (1.5)              |          |
| Never married                    | 3653                | 43 (1.5)             | 3610 (0.8)              |          |
| Education level                  |                     |                      |                         | <0.001   |
| No formal school                 | 90 829              | 654 (22.0)           | 90 175 (18.7)           |          |
| Primary school                   | 156 407             | 1048 (35.3)          | 155 359 (32.1)          |          |
| Middle school                    | 138 361             | 800 (26.9)           | 137 561 (28.5)          |          |
| High school                      | 73 322              | 353 (11.9)           | 72 969 (15.1)           |          |
| College/university or more       | 27 622              | 117 (3.9)            | 27 505 (5.7)            |          |
| Annual household income, RMB     |                     |                      |                         | <0.001   |
| <5000                            | 47 472              | 565 (19.0)           | 46 907 (9.7)            |          |
| 5000 to 9999                     | 90 421              | 635 (21.4)           | 89 786 (18.6)           |          |
| 10 000 to 19 999                 | 140 432             | 855 (28.8)           | 139 577 (28.9)          |          |
| ≥20 000                          | 208 216             | 917 (30.9)           | 207 299 (42.9)          |          |
| Geographic location              |                     |                      |                         | <0.001   |
| Urban                            | 209 786             | 1001 (33.7)          | 208 785 (43.2)          |          |
| Rural                            | 276 755             | 1971 (66.3)          | 274 784 (56.8)          |          |
| Smoking status                   |                     |                      |                         | <0.001   |
| Never                            | 301 601             | 2054 (69.1)          | 299 547 (62.0)          |          |
| Former                           | 26 807              | 108 (3.6)            | 26 699 (5.5)            |          |
| Occasional                       | 27 872              | 171 (5.8)            | 27 701 (5.7)            |          |
| Current                          | 130 261             | 639 (21.5)           | 129 622 (26.8)          |          |
| Drinking status                  |                     |                      |                         | <0.001   |
| Less than weekly                 | 412 950             | 2672 (89.9)          | 410 278 (84.8)          |          |
| Weekly or more                   | 73 591              | 300 (10.1)           | 73 291 (15.2)           |          |
| Family history of heart attack   |                     |                      |                         | <0.005   |
| Yes                              | 13 269              | 109 (3.7)            | 13 160 (2.7)            |          |
| No                               | 473 272             | 2863 (96.3)          | 470 409 (97.3)          |          |
| BMI, kg/m²                       | 23.6±3.4            | 23.1±3.4             | 23.6±3.4                | <0.001   |
| Physical activity, MET-hours/day | 21.6±13.9           | 20.7±14.2            | 21.6±13.9               | 0.001    |

Continued
Depression and Ischemic Heart Disease  

Table 1. Continued

| Variables                        | Overall     | Participants With MD | Participants Without MD | P Values |
|----------------------------------|-------------|-----------------------|--------------------------|----------|
| Baseline history of diabetes mellitus |            |                       |                          | 0.025    |
| Yes                              | 26 118      | 187 (6.3)             | 25 931 (5.4)             |          |
| No                               | 460 423     | 2785 (93.7)           | 457 638 (94.6)           | <0.001   |
| Baseline history of hypertension |            |                       |                          |          |
| Yes                              | 158 473     | 874 (29.4)            | 157 599 (32.6)           |          |
| No                               | 328 068     | 2098 (70.6)           | 325 970 (67.4)           |          |

BMI indicates body mass index; MD, major depression; MET, metabolic equivalent task.
*Data are shown as n (%) or mean±SD, unless otherwise specified. P values were derived from Student t test for continuous variables and χ² test for categorical variables.

depression on the risk of IHD was assessed, we found that the HR (95% CI) of IHD was 1.13 (1.04–1.23) for those with depressive symptoms only and 1.33 (1.15–1.53) for those with MD versus those without depressive symptoms (Table 3).

Discussion
In this large-scale prospective cohort study, we found that past year MD was associated with a 32% higher risk of developing IHD among Chinese adults aged 30 to 79 years. The association was independent of sociodemographic characteristics, family history, lifestyle factors, and baseline comorbidities (obesity, diabetes mellitus, and hypertension). In addition, the association was more evident in urban than rural residents.

In our study, we have found a statistically significant association between MD and risk of IHD with a multivariable-adjusted HR of 1.32. The result is consistent with the finding from a systematic review of 30 cohort studies that reported a pooled relative risk of 1.30 (95% CI 1.22–1.40). In this review, most studies were conducted in the United States (n=15) or European countries (n=12), while only 2 studies were in Asians: 1 in Chinese Taiwan and the other in Hong Kong. The study population in Chinese Taiwan comprised clinically diagnosed depression patients (n=7937) and non-depressed individuals (n=31 748) selected from an insurance database in a follow-up to 9 years. Coronary events (myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting) were used as study outcomes. After controlling for established cardiovascular risk factors, depression was associated with a 38% increased risk of coronary events (HR 1.38; 95% CI 1.19–1.60). In the study among elderly Chinese in Hong Kong, depressive symptoms were screened using the 15-item Geriatric Depression Scale among 21 473 men and 41 366 women at Elderly Health Centers. Incident nonfatal CHD cases were not available, and CHD mortality was assessed as the outcome. A positive association was reported between depressive symptoms and CHD mortality in men (HR 1.41; 95% CI 1.08–1.84) but not women (HR 0.94; 95% CI 0.75–1.16). Therefore, our study is the first on this topic in mainland China using a community-based population from 10 regions across China. We also found that the association was stronger in men compared to that in women (HR 1.50 versus 1.26), although there was no significant effect modification (P for interaction=0.23), which may be attributable to the small number of depressed individuals. The difference between men and women was also consistent with the overall finding from the systematic review, in which the pooled HR was 1.38 among men versus 1.17 among women.

With a sample size of about 0.5 million, our study has been the largest one on this research topic so far. We analyzed data from 486 541 participants with 24 705 incident IHD cases during a median follow-up of 7.2 years. The systematic review of 30 prospective cohort studies included a total of 893 850 participants with 24 705 incident IHD cases. The largest original study prior to our investigation used data from the US Veterans Administration electronic medical records and included 345 949 men and women aged 25 to 80 years, in which the authors reported that depression was associated with a 29% increased risk of myocardial infarction. Therefore, our main finding was consistent with that from the other large cohort studies, and provides strong evidence from Chinese populations that depression is an independent risk factor for heart disease.

Most previous studies used self-reported questionnaires to screen for depressive symptoms and only a few used clinical diagnosis of depression as the exposure. There is controversy over whether the association between depression and risk of IHD would differ when depression was identified using self-reported scales and structured clinical diagnostic interviews. Such controversy was reflected in the contrasting results from 2 previous meta-analyses. In our study, depression was screened by a few screening questions, followed by the diagnostic Composite International Diagnostic Interview-Short Form. We compared individuals who responded positively to screening questions but did not meet the diagnostic criteria (depressive symptoms only) with those who had no
depressive symptoms. Although statistically significant, the effect size (HR 1.13) for the association between depressive symptoms and IHD risk was much lower than that for MD. It suggests that more severe depression bears a higher risk of IHD and the dose–response relationship may exist. Although the current analysis revealed that MD was significantly more prevalent in rural areas than in urban areas (0.71% versus 0.48%), the multivariable-adjusted MD–IHD association was

Table 2. MD and Risk of Incident Ischemic Heart Disease: Stratified Analysis and Sensitivity Analysis

|                          | Incidence Rate (1000 Person-Years) | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) | P for Interaction* |
|--------------------------|------------------------------------|---------------------|---------------------|---------------------|-------------------|
| Overall                  |                                    |                     |                     |                     |                   |
| No MD                    | 7.21                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 8.76                               | 1.32 (1.14–1.52)    | 1.30 (1.13–1.50)    | 1.32 (1.15–1.53)    |                   |
| Sex                      |                                    |                     |                     |                     | 0.23              |
| Men                      |                                    |                     |                     |                     |                   |
| No MD                    | 7.34                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 9.55                               | 1.53 (1.18–1.98)    | 1.47 (1.13–1.91)    | 1.50 (1.15–1.94)    |                   |
| Women                    |                                    |                     |                     |                     |                   |
| No MD                    | 7.12                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 8.47                               | 1.25 (1.05–1.48)    | 1.24 (1.05–1.48)    | 1.26 (1.07–1.50)    |                   |
| Age                      |                                    |                     |                     |                     | 0.10              |
| <60 years old            |                                    |                     |                     |                     |                   |
| No MD                    | 4.76                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 6.93                               | 1.42 (1.19–1.69)    | 1.39 (1.17–1.66)    | 1.42 (1.19–1.69)    |                   |
| ≥60 years old            |                                    |                     |                     |                     |                   |
| No MD                    | 16.35                              | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 17.42                              | 1.14 (0.89–1.45)    | 1.12 (0.88–1.43)    | 1.15 (0.90–1.46)    |                   |
| BMI                      |                                    |                     |                     |                     | 0.98              |
| <24 kg/m²                |                                    |                     |                     |                     |                   |
| No MD                    | 6.26                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 7.88                               | 1.33 (1.10–1.61)    | 1.31 (1.09–1.59)    | 1.31 (1.08–1.58)    |                   |
| ≥24 kg/m²                |                                    |                     |                     |                     |                   |
| No MD                    | 8.46                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 10.28                              | 1.34 (1.08–1.66)    | 1.33 (1.07–1.65)    | 1.33 (1.07–1.66)    |                   |
| Geographic location      |                                    |                     |                     |                     | 0.005             |
| Rural                    |                                    |                     |                     |                     |                   |
| No MD                    | 6.60                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 7.35                               | 1.14 (0.94–1.38)    | 1.12 (0.92–1.35)    | 1.13 (0.93–1.37)    |                   |
| Urban                    |                                    |                     |                     |                     |                   |
| No MD                    | 8.03                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 11.65                              | 1.72 (1.38–2.13)    | 1.68 (1.35–2.08)    | 1.72 (1.39–2.14)    |                   |
| Excluding cases occurring within the first 2 years | | | | | |
| No MD                    | 5.68                               | 1.00                | 1.00                | 1.00                |                   |
| Past year MD             | 6.98                               | 1.29 (1.10–1.51)    | 1.27 (1.08–1.49)    | 1.29 (1.10–1.52)    |                   |

Model 1: adjusted for age, sex, geographic location, marital status, education, and annual household income; Model 2: model 1 plus smoking status, drinking status, and physical activity; Model 3: model 2 plus body mass index, history of diabetes mellitus and hypertension, and family history of heart attack. BMI indicates body mass index; HR, hazard ratio; MD, major depression. *P values for interaction were assessed by including an interaction term of MD and corresponding stratified factor in model 3.
Table 3. Depressive Symptoms With/Without Major Depression (MD) and Risk of Incident Ischemic Heart Disease*

| Cases/ person-years | No Depressive Symptoms | Depressive Symptoms Only | MD |
|---------------------|------------------------|-------------------------|-----|
| Model 1             | 23 947/323 751         | 568/78 110              | 190/21 681 |
| Model 2             | 1.00                   | 1.11 (1.02–1.21)        | 1.32 (1.15–1.53) |
| Model 3             | 1.00                   | 1.12 (1.03–1.22)        | 1.31 (1.13–1.51) |
|                     |                        | 1.13 (1.04–1.23)        | 1.33 (1.15–1.53) |

Model 1: adjusted for age, sex, geographic location, marital status, education, and annual household income; Model 2: model 1 plus smoking status, drinking status, and physical activity; Model 3: model 2 plus body mass index, history of diabetes mellitus and hypertension, and family history of heart attack.

*Data are shown as hazard ratio (95% CI).

diabetes mellitus in our study. We have adjusted for baseline comorbidities and various behavior factors in the model and the results remained unchanged, although residual confounding because of lack of information for other potential factors (such as other comorbidities related to both depression and IHD, poor diet, and lack of medication adherence) was still possible.

Our study has the strengths of large sample size, a relatively long follow-up, standardized measure of depression by the structured diagnostic interviews, well-documented IHD incidence, and adjustment for multiple potential confounders. However, some limitations still need to be acknowledged. First, the 12-month prevalence of MD detected by Composite International Diagnostic Interview-Short Form in our study (0.61%) was quite low compared to findings from previous studies in Western and Chinese populations. For example, the US National Comorbidity Survey Replication in a targeted population aged 18 years or older reported a 12-month prevalence of 6.6%26; a previous study in 4 provinces of China found that the adjusted 1-month prevalence of major depressive disorder was 2.1%17; and in the World Health Organization World Mental Health Surveys, the 1-year prevalence of major depressive episode was 1.8% for adults aged 18 years and older in Beijing and Shanghai.27 The differences in prevalence across countries and studies could partly be attributable to different tools used to assess MD, different study populations, or cultural backgrounds. For example, the previous study in 4 provinces of China detected MD through a semistructured interview administered by psychiatric nurses,17 which allowed them to rephrase the screening questions according to local dialect, while ours was a fully structured assessment performed by health workers. In addition, health workers’ ability to detect depression may not be as optimal as psychiatric nurses’ ability. In specific cultural context, Chinese adults may deem MD a stigma and deny their mental condition or experience MD in a nontraditional way.28 Furthermore, the current 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. All of the factors mentioned above may eventually lead to the low detection rate of MD.

The impact of the relatively low prevalence of depression in our study on the association between MD and risk of IHD remains unclear. On the one hand, more severe cases could be easier to be screened and detected in population-based studies and a stronger MD–IHD association could be observed; on the other hand, severely depressed individuals may not be willing to participate in a long-term follow-up study, and a weaker MD–IHD association may be expected. Therefore, a validation study of sensitivity and specificity of the instrument used in our study against clinical diagnosis is preferred, but unfortunately this is not currently available.

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Second, information about the change and duration of depression status during the follow-up was not available in our study. Third, although we have adjusted for many cardiovascular risk factors in the model, residual confounding may still remain. Finally, we were unable to distinguish fatal and nonfatal IHD in our analysis because of data limits, although differences in risk estimates for fatal and nonfatal events have been shown to be nonsignificant.9

Conclusions
In conclusion, we found a 32% higher risk of developing IHD for participants with baseline MD in a mega-cohort of about 0.5 million Chinese adults, independent of other major cardiovascular risk factors. Future studies might direct attention to potential strategies to prevent IHD among people with depression, such as cognitive behavioral therapy for stress management and stigma reduction, or preventive measures for modifiable risk factors for IHD.

Appendix
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Jiangsu
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Suzhou CDC: Yeyuan Wang, Yihe Hu, Liangcai Ma, Renxian Zhou, Guanqun Xu.
Guangxi
Provincial CDC: Baiqing Dong, Naying Chen, Ying Huang.
Liuzhou CDC: Mingqiang Li, Jinhuai Meng, Zhigao Gan, Jiujiu Xu, Yun Liu.
Sichuan
Provincial CDC: Xianping Wu, Yali Gao, Ningmei Zhang.
Pengzhou CDC: Guojin Luo, Xiangsan Que, Xiaofang Chen.
Gansu
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Maiji CDC: Hui Zhang, Enke Mao, Guanzhong Li, Zhongxiao Li, Jun He.
Henan
Provincial CDC: Guohua Liu, Baoyu Zhu, Gang Zhou, Shixian Feng.
Huitian CDC: Yulian Gao, Tianyou He, Li Jiang, Jianhua Qin, Huarong Sun.
Zhejiang
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Tongxiang CDC: Zhixiang Hu, Jianjin Hu, Yijian Qian, Zhiying Wu, Lingli Chen.
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