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Association of depressive symptoms with the progression of carotid intima–media thickness in a community-based cohort in Beijing, China

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ABSTRACT

Objectives To determine the relationship between depressive symptoms and progression of carotid intima–media thickness (cIMT) in a Beijing community-based population.

Design Prospective cohort study between 2014 and 2018.

Setting Dwellers without cardiovascular disease, hypertension or diabetes from a Beijing community.

Participants 3849 Chinese community-dwelling individuals who underwent baseline screening for depressive symptoms were invited to participate in the study in 2014 and follow-up visit in 2018. Among them, 2124 participants completed carotid ultrasound examination both at baseline and a follow-up visit. After further excluding patients with a history of stroke, myocardial infarction or lower extremity arterial stenosis and those with a diagnosis of hypertension or diabetes and ankle–brachial index ≤0.9 at baseline, 1011 eligible participants were finally included.

Primary outcome measure The rate of mean cIMT change.

Results Over a median follow-up period of 4.40 years, the overall rate of mean cIMT change was 2.23% (−5.64% to 9.51%). After adjustment for 13 covariates, there was an increase of 2.36% (β=2.36, 95% CI: 0.37 to 4.36, p=0.020) for the rates of mean cIMT change in the depressive group compared with the control group. Furthermore, this association was modified by drinking status (β=3.22, 95% CI: 1.25 to 5.19, P-interaction=0.006).

Conclusion Depressive symptoms were independently associated with progression of mean cIMT in a community-based cohort in Beijing, China. Furthermore, this relationship was modified by drinking status.

Strengths and limitations of this study

- This is the largest Asian cohort study to date reporting the independent association of depressive symptoms for the progression of carotid intima–media thickness (cIMT).
- This study focused on Chinese community-dwelling individuals without cardiovascular disease, hypertension or diabetes.
- Participants in this study were recruited from a single community in Beijing, China.
- The assessment of depressive symptoms was made using the Zung Self-Rating Depression Scale, which is a common screening tool in the community.
- The progression of cIMT was evaluated as the rate of cIMT change during the follow-up.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide, with atherosclerosis being the main pathological mechanism.[1] As a non-invasive measurement using ultrasound imaging, carotid intima–media thickness (cIMT) has been widely used as a surrogate marker for the presence and progression of atherosclerosis.[2] In recent years, an increment in cIMT has been shown to be closely related to the increased risk of myocardial infarction (MI) and stroke[3]; hence, cIMT is considered as a predictor of future cardiovascular events according to most studies.[4–7] However, more than 60% of the cIMT variance cannot be explained by traditional cardiovascular risk factors, especially when cIMT is measured in plaque free locations.[8 9] Therefore, the measurement of cIMT and identification of its related novel risk factors are extremely important in the primary prevention of ASCVD.

Depression is an important contributor to the overall global burden of disease, affecting an estimated 300 million people.[10] In 2017, depression was ranked third among the leading causes of the global disease burden and it is expected to rise to first place by 2030.[11 12] Depression is a common mood disorder, typically characterised by either a persistent feeling of loss of interest, sadness

or both.[13] Apart from these fundamental symptoms, depression comprises a wide spectrum of manifestations including emotional, neurovegetative and neurocognitive symptoms, and it is highly correlated with premature mortality owing to suicide.[10 12]

Recent studies have shown that depression is present in 20% of patients with coronary artery disease, peripheral artery disease and heart failure, which is higher than the rate in the general population.[14] Depression is prevalent among two-thirds of patients with MI.[15] Although the association of depression and CVD may be bidirectional, further studies have shown that depression is considered as an independent risk factor for CVD, and it is correlated with increased mortality and poor quality of life in patients with CVD.[14] A meta-analysis of eight studies indicated a 60% higher adjusted risk of incident CVD in patients with depression.[16] The presence of depression in patients with a history of MI independently leads to a twofold to fourfold higher risk of subsequent cardiovascular events.[14] However, the association of depression with cIMT and its progression has been controversial,[17–21] and it requires further characterisation in Chinese population. Furthermore, a few previous studies focused on individuals at low risk of CVD. Besides, compared with recognised depression, the actual prevalence of depressive symptoms is much higher because many people experience depressive symptomology but do not meet the diagnostic criteria for depression.[22] Therefore, in the present study, we aimed to determine the relationship between depressive symptoms and progression of cIMT in a Beijing community-based population.

METHODS

Study population

Participants were recruited from a survey conducted as part of an ongoing atherosclerosis cohort study in the communities of Gucheng and Pingguoyuan, Shijingshan District in Beijing, China between May 2014 and July 2014. The detailed procedures of this cohort study have been described previously.[23 24] Initially, 3849 participants who underwent baseline screening for depressive symptoms were invited to participate in the study and follow-up visit in 2018. Complete data for carotid ultrasound examination at baseline and a follow-up visit were available for 2124 participants. After excluding patients with a history of stroke, MI or lower extremity arterial stenosis and those with a diagnosis of hypertension or diabetes and ankle–brachial index ≤0.9 at baseline, 1011 eligible participants were finally included in the analysis. Written informed consent was received from each participant.

Baseline data collection

All participants were interviewed by trained research coordinators using a standardised questionnaire to collect baseline data, which included sociodemographic and lifestyle information, history of disease and medication information. Anthropometric measurements were also taken according to a standard operating procedure. At baseline, current smoking was defined as smoking one cigarette per day for 6 months or more. Current drinking was defined as drinking once per week for 6 months or more. Body mass index (BMI) was calculated as body mass (kg) divided by height squared (m^2). After each participant had rested at least 5 min, seated brachial blood pressure (BP) was measured on the right arm using an Omron HEM-7117 electronic sphygmomanometer (Kyoto, Japan) with appropriately sized cuffs. Triplicate measurements were taken with ≥1 min between successive readings. The mean of three consecutive measurements of systolic BP (SBP) and diastolic BP (DBP) were used in the analysis. Dyslipidaemia was self-reported or defined as receiving any lipid-lowering medications or concentrations of triglyceride (TG) ≥1.7 mmol/L (150 mg/dL), total cholesterol (TC) ≥5.18 mmol/L (200 mg/dL), low-density lipoprotein-cholesterol (LDL-C) ≥3.37 mmol/L (130 mg/dL) or high-density lipoprotein-cholesterol (HDL-C) <1.04 mmol/L (40 mg/dL).[25]

After an overnight fast, a venous blood sample was obtained from each participant via venipuncture. Serum samples were separated within 30 min and used for the measurement of fasting blood glucose (FBG), TC, LDL-C, HDL-C and TG with a Hitachi 7180 Automatic Analyzer (Tokyo, Japan). Serum creatinine (Scr, μmol/L) was measured using the same instrument with Jaffe's kinetic method. The estimated glomerular filtration rate (eGFR) was determined according to the Modification of Diet in Renal Disease formula corrected for the Chinese population: eGFR (mL/min/1.73 m^2)=175 × Scr (mg/dL)$^{-1.234}$ × age$^{-0.179}$× (×0.79 if female sex).[26]

Carotid ultrasonography

Carotid ultrasonography was performed by certified sonographers both at the baseline in 2014 using a General Electric Company (GE) Medical Systems ultrasound scanner (Milwaukee, Wisconsin, USA) and at the follow-up visit in 2018 using a Terason Echo Ultrasound System (Burlington, Massachusetts, USA). The detailed procedure of carotid ultrasonography has been described previously.[24 27] Mean cIMT was measured from the far walls of the right and left common carotid artery (CCA) at end diastole (minimal lumen diameter) with an Medical Imaging Applications (MIA)-Carotid Analyzer V.6.0. The mean cIMT used in the analysis was the average of the bilateral mean cIMT. The measured segment of CCA was 10 mm in length in the CCA near the bulb and was free of plaques. The rate of cIMT change was calculated as (cIMT follow-up visit– cIMT baseline)/cIMT baseline ×100%.

Assessment of depressive symptoms

Depressive symptoms were assessed at baseline using a classical self-reported psychometric questionnaire, the Zung Self-Rating Depression Scale (SDS).[28 29] The SDS comprises 20 items with a four-point grading scale, as follows: a little of the time, some of the time, a good part of the time and most of the time. When scoring the

SDS, a value of 1, 2, 3 and 4 was assigned to each item according to whether the item was depicted positively or negatively; if depicted negatively, higher scores were assigned to more frequent symptoms; if depicted positively, more frequent symptoms were scored lower.[28] Raw scores were calculated as the sum of values obtained on the 20 items, with the total ranging from 20 to 80. Index scores were defined as (raw scores/80)×100. According to index scores, participants were divided into the following categories of depressive symptoms: controls (25–49), mild to moderate (50–59), moderate to severe (60–69) and severe (≥70).[29 30] However, owing to the relatively small size of the moderate to severe (60–69) and severe group (≥70) in our analysis, we combined the latter three groups into one group with scores ≥50 as the depressive group.

Statistical analysis

Normally distributed continuous variables are reported as mean±SD, and non-normally distributed variables are reported as median (IQR). Categorical variables are presented as number and percentage. The differences among participants classified according to SDS score (<50 or ≥50) were compared using Student's t-test for normally distributed continuous variables or the χ^2 test for categorical variables. For non-normally distributed data, the Kruskal-Wallis rank test was used. Univariate and multivariate linear regression models were used to determine the relationship of SDS score (both as a continuous and categorical variable) with the progression of cIMT. Two sets of multivariable linear regression models were used: Model 1, which was adjusted for baseline mean cIMT, sex, and age; and Model 2, which was further adjusted for BMI, eGFR, current smoking, current drinking, SBP, DBP, TG, TC, FBG and use of lipid-lowering agents. Interaction and stratified analyses were performed according to sex, age, BMI, eGFR, smoking and drinking status, SBP, DBP, TC, TG, FBG and use of lipid-lowering drugs. All statistical analyses were performed using Empower(R) (www.empowerstats.com, X&Y Solutions, Boston, Massachusetts, USA) and R (http://www.R-project.org). A two-tailed p<0.05 was considered to represent statistical significance.

RESULTS

Baseline patient characteristics

The characteristics of participants, both overall and stratified by SDS score, are shown in table 1. A total of 1011 participants with average age of 56.10±6.88 years were included in the analysis, and 29.57% (n=299) of them were men. Current tobacco use was present in 15.23% (n=154) of participants, current alcohol use in 12.56% (n=127), dyslipidaemia in 69.63% (n=704) and usage of lipid-lowering drugs in 4.75% (n=48). At the time of enrolment, the mean±SD score for the SDS index was 37.17±9.69. Those with SDS index score <50 and ≥50

Table 1 Characteristics of participants stratified by SDS index score

	All (n=1011)	SDS index score <50 (n=873)	SDS index score ≥50 (n=138)	P value
Age (years), mean±SD	56.10±6.88	56.11±6.95	56.08±6.43	0.966
Male sex, n (%)	299 (29.57)	263 (30.13)	36 (26.09)	0.334
BMI (kg/m^2), mean±SD	25.10±3.21	25.16±3.21	24.69±3.22	0.111
eGFR (mL/min/1.73 m^2), mean±SD	75.75±10.47	75.65±10.27	76.40±11.72	0.436
Current smoking, n (%)	154 (15.23)	132 (15.12)	22 (15.94)	0.803
Current drinking, n (%)	127 (12.56)	110 (12.60)	17 (12.32)	0.926
SBP (mmHg), mean±SD	117.81±10.84	118.04±10.81	116.34±10.97	0.086
DBP (mmHg), mean±SD	71.73±7.47	71.85±7.48	70.94±7.36	0.183
FBG (mmol/L), mean±SD	5.32±0.50	5.33±0.51	5.25±0.45	0.070
TC (mmol/L), mean±SD	5.09±0.92	5.10±0.93	5.03±0.84	0.386
TG (mmol/L), median (IQR)	1.31 (0.94–1.88)	1.30 (0.93–1.89)	1.34 (0.97–1.77)	0.966
SDS index score, mean±SD	37.17±9.69	34.61±7.62	53.40±3.96	<0.001
Baseline mean cIMT (mm), mean±SD	0.69±0.10	0.69±0.10	0.68±0.09	0.130
Follow-up mean cIMT (mm), mean±SD	0.70±0.11	0.70±0.11	0.71±0.11	0.676
Prevalence of disease				
Dyslipidaemia, n (%)	704 (69.63)	605 (69.30)	99 (71.74)	0.563
Medications				
Lipid-lowering drugs, n (%)	48 (4.75)	41 (4.70)	7 (5.07)	0.847

BMI, body mass index; cIMT, carotid intima–media thickness; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; SBP, systolic blood pressure; SDS, Self-Rating Depression Scale; TC, triglyceride; TG, total cholesterol.

Table 2 Regression model for effect of SDS index score on rate of cIMT change

	Crude		Model 1*		Model 2†	
Subgroup	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
SDS index score (per 10-point increase)	0.63 (–0.11 to 1.36)	0.096	0.62 (–0.09 to 1.33)	0.086	0.65 (–0.07 to 1.36)	0.076
SDS groups						
SDS index score <50	Ref.		Ref.		Ref.	
SDS index score ≥50	2.63 (0.56 to 4.70)	0.013	2.22 (0.23 to 4.22)	0.029	2.36 (0.37 to 4.36)	0.020

Rate of cIMT change: (cIMT follow-up visit – cIMT baseline)/cIMT baseline ×100%.
*Model 1: adjusted for baseline mean cIMT, sex and age.
†Model 2: adjusted for baseline mean cIMT, sex, age, body mass index, estimated glomerular filtration rate, current smoking and drinking, systolic blood pressure, diastolic blood pressure, triglyceride, total cholesterol, fasting blood glucose and use of lipid-lowering agents.
cIMT, carotid intima–media thickness; SDS, Self-Rating Depression Scale.

accounted for 86.35% (n=873) and 13.65% (n=138) of participants, respectively. The baseline mean cIMT was 0.69±0.10 mm overall, and there were no differences between groups with different SDS index scores (p=0.130). Additionally, no differences were observed in the average levels of baseline age, BMI, BP, FBG, lipid profiles and percentages of participants with male sex, current smoking and drinking between the two groups.

Predictive values of SDS index scores in the progression of cIMT

Table 2 displays the results of multivariate regression analysis for the effect of the SDS index score on mean cIMT progression. Over a median follow-up period of 4.40 years (25th–75th percentile: 4.30–4.40 years), the mean cIMT at follow-up was (0.70±0.11) mm in overall and was comparable between the two groups with different SDS index scores (p=0.676). The overall rate of mean cIMT change was 2.23% (–5.64% to 9.51%), and the rate in the groups with SDS index scores <50 and ≥50 was 1.80% (–5.88% to 9.22%) and 4.18% (–4.87% to 11.84%), respectively. Each 10-point increase in the SDS index score was associated with an increase of 0.62% and 0.65% in the rate of mean cIMT change in model 1 and model 2, respectively, but this relationship was not statistically significant (p=0.086 in model 1, p=0.076 in model 2). Compared with the control group (SDS index score <50), there was an increase of 2.36% (β=2.36, 95% CI: 0.37 to 4.36, p=0.020) in the rate of mean cIMT change in the depressive group (SDS index score ≥50) in the fully adjusted model. Figure 1 shows the interactions between covariates and SDS index score. When stratified by drinking status, the results showed that the SDS index score was significantly associated with the progression of cIMT in participants with current drinking (β=3.22, 95% CI: 1.25 to 5.19, p=0.001) but not in those without current drinking. There was an apparent interaction between drinking status and SDS index score with regard to progression of cIMT (P-interaction=0.006). No interaction was found between the other covariates and SDS index score in our cohort analysis.

DISCUSSION

The main findings of the present study are as follows. Depressive symptoms were independently associated with progression of mean cIMT in a community-based cohort in China. Furthermore, the relationship between depressive symptoms and progression of mean cIMT was modified by drinking status. To our knowledge, this is the largest Asian cohort study reporting the independent predictive value of depressive symptoms for the progression of cIMT and the first study to focus on relatively healthy people without CVD, hypertension or diabetes. Our results extend previous findings on the association between depression and atherosclerosis and suggest that assessment of depressive symptoms might be integrated into risk stratification of carotid atherosclerosis.

Various biological mechanisms have been proposed to explain the effect of depression on atherosclerosis, including inflammation, endothelium dysfunction, enhanced platelet reactivity, autonomic dysfunction and neuroendocrine imbalance.[14 31 32] Significantly higher concentrations of the proinflammatory cytokines tumour necrosis factor-α and interleukin-6 have been reported in patients with major depression compared with controls, indicating that depression is accompanied by activation of the inflammatory response system.[33] Impaired endothelial-derived nitric oxide production has been found in patients with depressive symptomatology.[14 31] Previous studies have also demonstrated an inverse association between depression and endothelium-dependent brachial artery flow-mediated dilatation (FMD), an indicator of endothelium function and impaired FMD can be revered using antidepressants.[32] Excessive activation of the hypothalamic–pituitary–adrenal (HPA) axis is common in depression, and the subsequent hypercortisolaemia might lead to hypertension and prothrombotic effects.[34] Lifestyle factors may also contribute. Depressive individuals are less likely to adhere to cardioprotective medications or to engage in healthy behaviours like physical activity and smoking cessation.[14]

Previous studies have demonstrated various traditional cardiovascular risk factors related to cIMT.[35–38] Among

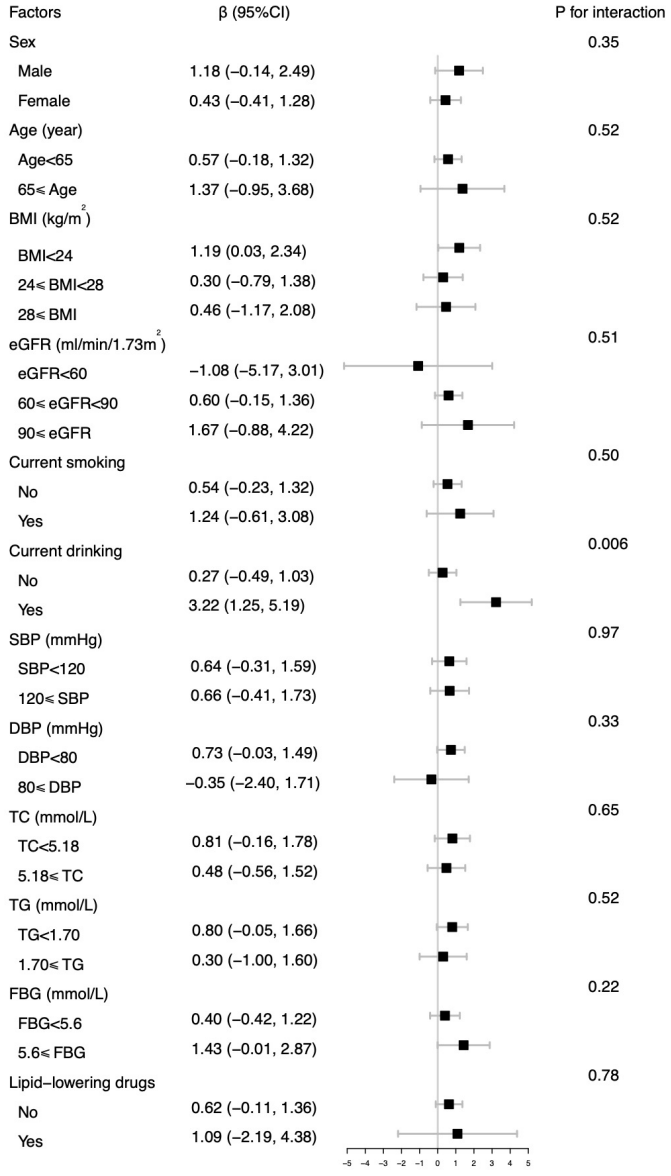

Figure 1 Subgroup analyses and interaction for the effect of SDS index score on rate of cIMT change according to different variables. Rate of cIMT change: (cIMT follow-up visit – cIMT baseline)/cIMT baseline ×100%. The SDS index score was considered as continuous variable and the effect of each 10-point increase in the SDS index score on rate of cIMT change was calculated. Adjusted for, if not stratified by sex, age, BMI, EGFR, current smoking and drinking, SBP, DBP, TC, TG, FBG, use of lipid-lowering drugs and baseline mean cIMT. BMI, body mass index; cIMT, carotid intima–media thickness; DBP, diastolic blood pressure; EGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; SDS, the Zung self-rating depression scale; SBP, systolic blood pressure; TC, triglyceride; TG, total cholesterol.

them, hypertension was found to be the greatest risk factor for increased cIMT,[35 36] while diabetes was also considered as a risk factor of cIMT progression.[37] Dyslipidaemia also seemed to be associated with cIMT but the influence of abnormity of its different components such as LDL-C, TG and HDL-C on cIMT have yet to be confirmed.[37 38] Therefore, we excluded patients with hypertension and diabetes, which may be important confounding factors for association of depressive symptoms with the progression of cIMT.

Using cIMT as a surrogate marker of carotid atherosclerosis, Poongothai *et al*[17] performed a cross-sectional study among 1505 Asian Indian participants aged 41±13 years and demonstrated that depressive symptoms were associated with mean cIMT, after adjusting for potential confounders (OR 2.17, 95% CI: 1.01 to 4.63). Ohira *et al*[18] analysed data from the first examination in the Multi-Ethnic Study of Atherosclerosis among 6561 participants (794 Chinese) aged 45–84 years included; however, they found no association of depressive symptoms with mean IMT. Recently, another cross-sectional study by Oikonomou *et al*[19] among 1510 Greek participants aged 40–99 years showed no difference in mean IMT between participants with and without depression. Faramawi *et al*[20] performed a longitudinal study with 3781 American participants older than 65 years. Those authors found that participants with depressive symptoms had a larger CCA-IMT than those without such symptoms (β=18.26 µm, SE=8.06, p=0.03). After excluding subjects with abnormal CCA IMT at baseline, those with depressive symptoms were 30% more likely to develop abnormal CCA IMT over 3 years. More recently, a prospective Finns population-based cohort study by Keltikangas-Järvinen *et al*[21] showed no association between depressive symptoms and mean cIMT progression in a total of 996 healthy participants aged 30–45 years old over a follow-up period of 6 years. The reason for the conflicting findings might be as follows. First, ethnic differences may lead to inconsistent results. A previous study found that South Asians have higher markers of subclinical atherosclerosis at earlier ages.[39] This might explain the positive results in the study by Poongothai *et al*[17] and ours conducted among Asian populations and the negative results in the studies by Oikonomou *et al*[19] and Keltikangas-Järvinen *et al*[21] that included Western populations. And when a relatively larger Western population was followed up like study of Faramawi *et al*[20], the positive relationship between depressive symptoms and increased cIMT could still be observed. Second, we uniformly used SDS for assessment of depressive symptoms in all age groups; the SDS has been reported to be a sensitive tool among older people in various studies.[40 41] Discrepancies in the assessment tools used in the above-mentioned studies may also contribute to the different results.

In the present study, we identified an interaction between drinking status and depressive symptoms with regard to progression of cIMT. As far as we know, this is a novel finding that has not been reported previously; possible mechanisms are proposed as follows. It is well documented that alcohol can activate the HPA axis in rodent models,[42] and chronic alcoholics could develop pseudo-Cushing's syndrome characterised by pathologically increased cortisol levels.[43] A population-based longitudinal study of adults in the Netherlands demonstrated that heavy alcohol use was related to higher mean

evening cortisol levels and enhanced cardiac sympathetic control.[44] The above-mentioned neuroendocrine imbalance and autonomic dysfunction are also involved in the pathophysiological mechanism of atherosclerosis promoted by depression. The functional overlap and interplay between alcohol and neuropsychiatric factors in regulating the neuroendocrine and autonomic systems may lead to their interaction in the progression of cIMT. However, more in-depth studies are needed to clarify the underlying mechanism. It could be argued that depressive symptoms are more likely to be associated with increased cIMT in older people[20] whereas null findings are usually observed in younger participants[21] and in groups comprising both younger and older people.[18 19] However, our stratified analyses according to age (<65 ≥65 years) showed no interaction between age and SDS index score. These findings can also be attributed to ethnic differences, as mentioned above, because positive findings have been found in groups comprising both young and older Asian people, in our study as well as in that of Poongothai *et al*.[17] Future studies are warranted to clarify whether there is a modifying effect of age on the relationship between depressive symptoms and cIMT across different ethnic groups.

The present study has several limitations. First, study participants were recruited from a single community in Beijing; therefore, the data might not be representative of populations in other locations of China. The non-random sampling might lead to uneven distribution of certain characteristics such as sex. Though stratified analysis was performed to compensate for this bias, further studies are warranted to validate the conclusions of our study. Second, there was lack of information regarding definite diagnosis of depression or usage of antidepressants in the present study, so the assessment of depressive symptoms was made using the SDS, rather than a clinical diagnosis of depression. This self-reporting scale might be affected by various patient factors and may be less accurate compared with assessment by a psychiatrist. However, because the SDS is a very convenient screening tool, identification of individuals in the community with depressed status contributes to intervention at an early stage, from the perspectives of both mental illness and atherosclerosis. In the future, repeated assessment by the SDS towards the participants during follow-up might be considered to improve the objectivity of depressive symptoms. Third, the sample size in the participant group with depressive symptoms was relatively small, which prevented us from further grouping. Fourth, we used cIMT as the marker of preatherosclerotic lesions. Though cIMT has been proved to be a predictor of future cardiovascular events, carotid plaque was considered to have higher diagnostic accuracy compared with that of cIMT regarding coronary artery events.[45] Therefore, larger studies should be conducted in the future to verify the effect of depressive symptoms on progression of cIMT and carotid plaque, which may improve risk prediction and assist with the identification of groups at higher risk of carotid atherosclerosis.

In conclusion, we found that depressive symptoms were independently associated with progression of cIMT in a Beijing community-based population, and this relationship was modified by drinking status. Early screening for depressive symptoms and appropriate intervention should be considered to prevent the progression of carotid atherosclerosis.

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Contributors ML and JJ contributed equally to this paper; these authors both participated in the study design, data collection, data analysis and wrote the manuscript. FF constructed the study dataset, participated in the data management and helped with statistical analysis. PS and ZW were involved in data management and interpreting the results. YJ, DH and BL participated in the epidemical survey and data collection. YY helped with the design and coordination of the study. YZ, the principal investigator of the present study, participated in the design of the study, provided guidance for the whole study, helped to analyse the data, and revised the manuscript. All authors reviewed and approved the manuscript and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Peking University First Hospital (No. 292).

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Data availability statement Data are available on reasonable request from the corresponding author YZ at drzhy1108@163.com.

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