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Association between depressive symptoms and arterial stiffness: a cross-sectional study in the general Chinese population

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ABSTRACT

Objectives To determine the independent relationship between depressive symptoms and arterial stiffness in the general Chinese population, and to explore possible interactive factors in the relationship.

Design A cross-sectional study.

Setting and participants Consecutive participants who received routine health physical examination in an affiliated hospital of a comprehensive university in Hunan Province, China, between September 2013 and March 2014 were examined. After exclusion of subjects not meeting the criteria, a total of 1334 subjects aged 22–77 years were recruited for final analysis.

Measures The Patient Health Questionnaire-9 was employed to assess the degree of depressive symptoms: 0–4 no depressive symptoms, 5–9 mild depressive symptoms and 10–27 moderate to severe depressive symptoms. Brachial-ankle pulse wave velocity (baPWV) was measured to determine arterial stiffness.

Results There was a slight increase in baPWV across elevated degrees of depressive symptoms (p=0.025). Multivariate linear regression analysis revealed that mild depressive symptoms and moderate to severe depressive symptoms were independently associated with baPWV compared with no depressive symptoms after adjusting for baseline confounders (beta-coefficient: 40.3, 95% CI 6.6 to 74.1; beta-coefficient: 87.7, 95% CI 24.0 to 151.5, respectively). Further stratified analyses indicated that the relationship between degree of depressive symptoms and baPWV was predominant in subjects who had normal or normal-high blood pressure, or combined with hypertension (p for interaction=0.016), or in subjects with diabetes mellitus (p for interaction=0.004), examined in multivariate linear regressions. In addition, after adjustment, a significant association between moderate to severe depressive symptoms and baPWV was also found in female subjects younger than 60 years, although the interactive effect was not significant (p for interaction=0.056).

Conclusions Depressive symptoms are independently associated with arterial stiffness, especially in subjects whose blood pressures are beyond the optimal range and combined with diabetes mellitus.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychological disorders

Strengths and limitations of this study

► This study analysed the association between depressive symptoms and arterial stiffness in the general Chinese population covering a wide range of ages (22–77 years).

► The extent of depression was reflected by mild depressive symptoms and moderate to severe depressive symptoms, and the independent relationship of these indicators with brachial-ankle pulse wave velocity was examined in multivariate linear regression models.

► Various subgroup analyses were conducted to explore whether any interactive factors existed in the relationship between depressive symptoms and arterial stiffness.

► Diagnostic interviews according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, were not performed to obtain a diagnosis of major depressive disorder in subjects with moderate to severe depressive symptoms.

► Due to the cross-sectional design of the study, no clear cause–effect conclusion could be directly drawn.

that affect health-related quality of life.[1] The global prevalence of MDD is 4.7%, and its lifetime rate varies greatly across different races, cultures and regions, ranging from 3.3% in mainland China to 18.6% in the USA.[2–4] Furthermore, the prevalence of MDD in patients with cardiovascular disease (CVD) is much higher[5]: 26.8% in subjects with hypertension,[6] 21.5% in patients with heart failure[7] and 20.0% in patients with acute coronary syndrome (ACS).[8] In addition, MDD was demonstrated to be an independent risk factor for poor prognosis in patients with ACS.[8 9] It was estimated that almost two-thirds of middle-aged and older adults with depression also reported a diagnosis of comorbid CVD.[10] Therefore, there

exist manifold interrelations between MDD and CVD where both contribute to a poor prognosis.[5]

Arterial stiffness can reflect arterial elasticity and the burden of arteriosclerosis and atherosclerosis.[11] Pulse wave velocity (PWV) is regarded as the gold standard measurement of large artery stiffness and is one of the markers of hypertension-mediated organ damage, and should be assessed among patients with hypertension according to the guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC).[12] Previous meta-analyses have revealed that PWV was an independent predictor of the development of CVD, adverse cardiovascular events and all-cause mortality.[13–15] At present, PWV is extensively applied in both clinical practice and epidemiological studies based on its feasibility and clinical significance.

Large population-based studies on the relationship between depression and arterial stiffness are limited, and the results remain controversial. The Rotterdam Study (n=3704, ≥60 years) and the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study) (n=2058, mean age 79.6±4.6 years) reported that both depressive symptoms and major depression were associated with aortic stiffness reflected by carotid-femoral PWV (cfPWV).[16 17] The association between the severity of depressive symptoms and arterial stiffness reflected by cfPWV and the augmentation index was also verified in another two studies with small sample sizes which recruited adolescents (n=157, aged 16–21 years) and patients with depressive and/or anxiety disorder (n=449, aged 20–66 years), respectively.[18 19] The Maastricht Study (n=2757, aged 40–75 years) indicated that the independent associations of depressive symptoms and MDD with cfPWV were restricted among middle-aged men (aged 40–60 years).[20] Furthermore, the Health, Aging, and Body Composition Study (n=2488, aged 70–79 years) failed to establish a link between depressive symptoms and cfPWV.[21] Finally, the Netherlands Study of Depression and Anxiety (n=635, aged 20–66 years) also failed to identify an association between depression sensitivity and central arterial stiffness assessed by the augmentation index.[22]

The main reasons for the abovementioned diverse findings might be differences in the enrolled population, assessment methods of arterial stiffness and criteria for defining depression. We observed that most studies mainly focused on middle-aged and older participants, and none of the studies included subjects with a wide range of ages. In view of these findings, we selected a general population without a specific age restriction and aimed to test the relationship between depressive symptoms assessed by the Patient Health Questionnaire-9 (PHQ-9) and arterial stiffness reflected by brachial-ankle PWV (baPWV). Additionally, we explored whether the association (if present) differed among subgroups according to various baseline factors; this type of analysis was seldom performed in previous studies.

METHODS
Study subjects
The current study followed a cross-sectional design and recruited a general Chinese population. We collected the medical information of consecutive participants who received routine health physical examination voluntarily at the Health Management Center of Xiangya Hospital, Central South University between September 2013 and March 2014. Subjects meeting any of the following criteria were excluded: age <18 or ≥80 years; history of myocardial infarction, heart failure, stroke, cancer, and severe hepatic or renal dysfunction; serious mental disorders, such as schizophrenia, bipolar disorder and schizoaffective disorder; any missing data from PHQ-9 or baPWV; or unwillingness to participate in the survey. A total of 1632 patients were included during the entry period, and after further exclusion 1334 participants (860 men and 474 women, mean age 47.1±11.7 years) were finally analysed in this study.

Data collection
Participants' basic information was collected by experienced trained medical staff at the Health Management Center according to relevant standard procedures. All subjects were asked about their cigarette smoking status and medical history of hypertension and diabetes mellitus. Height was measured to the nearest 0.1 cm with the participants wearing no shoes, and weight was measured to the nearest 0.1 kg with the participants wearing light indoor clothing and no shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a mercury sphygmomanometer with the participants in a seated position after at least 5 min of rest. The mean of two separate readings of blood pressure with an interval of 3–5 min between measurements was used. Fasting blood samples were collected from the antecubital veins after an 8-hour overnight fast in the morning of the health check-up. Fasting blood glucose (FBG) and lipid profiles, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), were measured using an automatic biochemistry analyser (Beckman AU5800, Koutou-ku, Tokyo, Japan) in the central laboratory immediately after obtaining the blood samples.

All participants were classified into three categories based on their blood pressure and according to the ESC and ESH hypertension guidelines[12]: optimal blood pressure, normal and high-normal blood pressure, and hypertension. An optimal blood pressure was defined as SBP <120 mm Hg and DBP <80 mm Hg; a normal and high-normal blood pressure was defined as SBP between 120 and 139 mm Hg and/or DBP between 80 and 89 mm Hg; and hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg, a self-reported history of diagnosed hypertension, or currently under antihypertensive treatment. Diabetes mellitus was defined as FBG ≥7.0 mmol/L,

Table 1 Baseline characteristics of all subjects according to degree of depressive symptoms

Variables	Depressive symptoms			P value
	None (n=1053)	Mild (n=227)	Moderate to severe (n=54)	
Male, n (%)	714 (67.8)	120 (52.9)	26 (48.1)	<0.001
Age, years, n (%)				0.855
<40	324 (30.8)	67 (29.5)	14 (25.9)	
40–60	562 (53.4)	124 (54.6)	33 (61.1)	
≥60	167 (15.9)	36 (15.9)	7 (13.0)	
Smoking, n (%)	490 (46.5)	98 (43.2)	16 (29.6)	0.040
BP categories, n (%)				0.148
Optimal	368 (34.9)	75 (33.0)	17 (31.5)	
Normal and high-normal	437 (41.5)	113 (49.8)	24 (44.4)	
Hypertension	248 (23.6)	39 (17.2)	13 (24.1)	
Diabetes mellitus, n (%)	165 (15.7)	40 (17.6)	13 (24.1)	0.225
Dyslipidaemia, n (%)	686 (65.1)	165 (72.7)	37 (68.5)	0.088
SBP, mm Hg	126.1±16.6	125.0±16.5	127.9±14.7	0.445
DBP, mm Hg	75.0±10.5	74.4±9.7	73.8±8.5	0.513
FBG, mmol/L	5.30±1.58	5.32±1.42	5.64±1.92	0.275
TC, mmol/L	5.00±1.04	5.07±1.04	5.27±1.17	0.134
TG, mmol/L	2.12±1.57	2.07±1.21	2.07±1.04	0.881
HDL-C, mmol/L	1.49±0.37	1.50±0.38	1.49±0.38	0.996
LDL-C, mmol/L	2.63±0.74	2.69±0.74	2.86±0.82	0.057
BMI, kg/m^2, n (%)				0.061
<24	462 (43.9)	102 (45.1)	28 (51.9)	
24–28	405 (38.5)	69 (30.5)	18 (33.3)	
≥28	186 (17.7)	55 (24.3)	8 (14.8)	
PHQ-9 score	1.27±1.39	6.47±1.36	13.20±3.22	<0.001
baPWV, cm/s	1343.6±264.5	1372.9±312.3	1436.5±314.4	0.025

Data are presented as mean±SD or n (percentage) as appropriate.
baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PHQ-9, Patient Health Questionnaire-9; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

a self-reported history of diagnosed diabetes mellitus or currently undergoing hypoglycaemic therapy. The diagnosis of dyslipidaemia was made based on the Korean guidelines for dyslipidaemia in the general population.[23] BMIs of 24 kg/m^2 and 28 kg/m^2 were used to identify overweight and obesity, respectively, for the Chinese population.

The PHQ-9 is a self-administered questionnaire designed to screen depression in primary care and other settings, and consists of nine items that are each scored from 0 to 3 points depending on the frequency of the listed problems in the last 2 weeks. The total score on PHQ-9 ranges from 0 to 27, and scores are categorised according to the following: 0–4 no depression, 5–9 mild depression, 10–14 moderate depression, 15–19 moderately severe depression and 20–27 severe depression.[24] A cut-off value of 10 on PHQ-9 has been widely used in epidemiological

studies to diagnose MDD, with high sensitivity (85%) and specificity (89%).[25] Referring to previous relevant studies and considering the limited sample size of subjects with a PHQ-9 score ≥10 (n=54), in the current study we classified the entire population into three groups according to the following PHQ-9 scores: 0–4 no depressive symptoms, 5–9 mild depressive symptoms and 10–27 moderate to severe depressive symptoms.

baPWV was measured using an automatic baPWV instrument (Model BP-203RPE, Colin, Komaki City, Japan) by trained staff following standard procedures, and was measured with participants in supine position after 10 min of rest in a quiet room with comfortable temperature. Bilateral measurements of baPWV were recorded, and the higher reading was used for analysis. This automatic device and its reproducibility have been previously validated.

Table 2 Association between depressive symptoms and baPWV in univariate and multivariate linear analyses

Variables	Beta-coefficient (95% CI)		
	Model 1	Model 2	Model 3
Depressive symptoms			
None	Reference	Reference	Reference
Mild	29.3 (–10.2 to 68.8)	38.6 (1.5 to 75.6)***	40.3 (6.6 to 74.1)***
Moderate to severe	92.9 (17.6 to 168.2)***	104.6 (34.1 to 175.0)**	87.7 (24.0 to 151.5)**
Male		74.1 (45.0 to 103.1)*	47.7 (14.9 to 80.5)**
Age, years			
<40		Reference	Reference
40–60		142.9 (111.6 to 174.2)*	133.5 (104.6 to 162.3)*
≥60		281.2 (238.4 to 324.0)*	265.7 (226.0 to 305.3)*
Smoking			46.7 (15.4 to 78.1)**
BP categories			
Optimal			Reference
Normal and high-normal			131.9 (103.4 to 160.5)*
Hypertension			260.6 (226.7 to 294.6)*
Diabetes mellitus			110.1 (75.8 to 144.4)*
Dyslipidaemia			48.6 (20.4 to 76.7)*
BMI, kg/m^2			
<24			Reference
24–28			–20.9 (–49.9 to 8.1)
≥28			–91.8 (–128.3 to –55.3)*

*P<0.001, **P<0.01, ***P<0.05.
baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure.

Statistical analysis

Since the association between depression and arterial stiffness has been conflicting and the initial purpose of our data was not for the current study, we did not estimate the sample size needed to obtain significant results. In fact, in the final analysis after exclusion, all baseline characteristics were obtained from the entire population, so there were no missing data in our study. All subjects were divided into three groups according to degree of depressive symptoms as determined by the PHQ-9 score. Continuous variables are presented as mean and SD, while categorical variables are described as frequencies and percentages. Comparisons between groups were performed using analysis of variance for continuous variables and χ^2 test for categorical variables. The relationship between degree of depressive symptoms and baPWV was examined in linear regressions with three models. Model 1 was the crude model; model 2 adjusted for sex and age; and model 3 further adjusted for smoking status, blood pressure or BMI, and comorbidities of diabetes mellitus or dyslipidaemia. Stratified analyses of baseline factors, including sex, age, blood pressure or BMI, smoking status, and history of diabetes mellitus or dyslipidaemia, were also performed to test whether any potential interactive effects existed in the relationship between degree of depressive symptoms and baPWV, and each stratification

was adjusted for all other factors except the stratification factor itself. The group of no depressive symptoms was considered as reference in the regression models. Finally, we especially explored the joint roles of age and sex in the association between mild and moderate to severe depressive symptoms and baPWV in the adjusted models. All analyses were conducted using statistical software packages R V.3.4.3 (http://www.R-project.org; The R Foundation) and EmpowerStats (www.empowerstats.com; X&Y Solutions, Boston, Massachusetts). All tests were two-tailed, and a p value less than 0.05 was considered statistically significant.

Patient and public involvement

None of the participants or the public were involved in the study design, data analysis or interpretation of the results of the study.

RESULTS
Baseline characteristics

After exclusion of subjects not meeting the criteria, a total of 1334 subjects were included in the final analysis (mean age 41.7±11.7 years, 64.5% male). The detailed baseline characteristics of all subjects by degree of depressive symptoms are described in table 1. The results indicated there

Table 3 Association between depressive symptoms and baPWV according to subgroups of baseline characteristics

Subgroups	Beta-coefficient (95% CI)			P value for interaction
	None	Mild	Moderate to severe	
Sex				0.072
Male	Reference	65.6 (12.6 to 118.6)***	39.3 (−68.0 to 146.6)	
Female	Reference	11.5 (−47.1 to 70.1)	170.1 (66.2 to 274.0)**	
Age, years				0.242
<40	Reference	−19.2 (−79.4 to 40.9)	45.9 (−76.4 to 168.2)	
40–60	Reference	28.4 (−24.5 to 81.2)	109.0 (13.6 to 204.5)***	
≥60	Reference	112.3 (16.1 to 208.4)***	88.8 (−113.0 to 290.7)	
Smoking				0.162
Yes	Reference	69.9 (13.7 to 126.2)***	22.8 (−105.9 to 151.6)	
No	Reference	24.4 (−17.4 to 66.2)	109.8 (39.4 to 180.3)**	
BP categories				0.016
Optimal	Reference	−34.6 (−92.9 to 23.7)	2.2 (−112.1 to 116.4)	
Normal and high-normal	Reference	55.8 (3.4 to 108.2)***	77.6 (−26.6 to 181.7)	
Hypertension	Reference	109.0 (9.1 to 208.9)***	222.1 (57.1 to 387.1)**	
Diabetes mellitus				0.004
Yes	Reference	154.1 (45.0 to 263.2)**	216.4 (38.1 to 394.8)***	
No	Reference	0.6 (−40.6 to 41.8)	44.5 (−37.2 to 126.3)	
Dyslipidaemia				0.615
Yes	Reference	40.0 (−7.4 to 87.4)	95.3 (3.1 to 187.6)***	
No	Reference	−3.9 (−76.0 to 68.1)	85.9 (−44.4 to 216.1)	
BMI, kg/m^2				0.201
<24	Reference	3.1 (−56.5 to 62.6)	115.3 (9.3 to 221.2)***	
24–28	Reference	45.8 (−24.6 to 116.2)	−9.4 (−139.6 to 120.7)	
≥28	Reference	72.0 (−5.0 to 149.1)	208.0 (26.7 to 389.3)***	

Each stratification was adjusted for all other presented subgroups except the stratification factor itself.
*P<0.001, **P<0.01, ***P<0.05.
baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure.

were fewer male participants across increasing degrees of depressive symptoms (67.8%, 52.9% and 48.1%; p<0.001), as well as a decreasing proportion of participants with smoking history (46.5%, 43.2% and 29.6%; p=0.040). There was no significant difference in terms of age or age categories, comorbidities of diabetes mellitus or dyslipidaemia, blood pressure categories, BMI or BMI categories, levels of SBP or DBP, FBG, or lipid profiles. As expected, a higher baPWV was found in subjects with more severe depressive symptoms (1343.6±264.4 cm/s, 1372.9±312.3 cm/s and 1436.5±314.4 cm/s; p=0.025). The baseline characteristics of all subjects according to tertiles of baPWV (<1203 cm/s, 1203–1430 cm/s, ≥1430 cm/s) are presented in online supplementary table 1. The results showed that across increasing tertiles of baPWV, there were more subjects who were male, aged ≥60 years, had smoking history, hypertension, diabetes mellitus, dyslipidaemia and moderate to severe depressive symptoms. The levels of SBP, DBP, FBG, total cholesterol and LDL-C and PHQ-9 score also increased with increasing

tertiles of baPWV, while the proportion of subjects whose BMI ≥28 kg/m^2 decreased with increasing tertiles. There were no significant differences in terms of triglyceride and HDL-C among the three groups.

Depressive symptoms and baPWV

We assessed the association between degree of depressive symptoms and baPWV in linear regression models, and the beta-coefficients and 95% CI of both crude and adjusted models are shown in table 2, where subjects with no depressive symptoms were considered as reference. In crude model 1, a significant association between moderate to severe depressive symptoms and baPWV was detected, while the results were non-significant for mild depressive symptoms and baPWV. In model 2, which adjusted for sex and age, significant results were observed for both mild depressive symptoms and moderate to severe depressive symptoms and baPWV. The results remained significant in model 3, which further adjusted for smoking status, blood pressure, diabetes mellitus, dyslipidaemia and
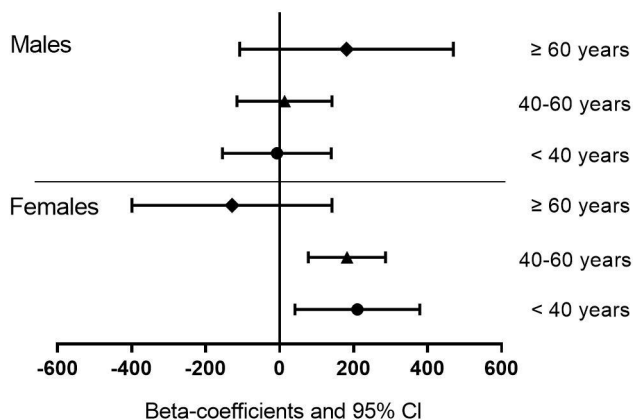
Figure 1 Beta-coefficients and 95% CI of the association between mild depressive symptoms and brachial-ankle pulse wave velocity stratified by age and sex. The results were adjusted for smoking history, blood pressure, diabetes mellitus, dyslipidaemia and body mass index.

BMI (beta-coefficient: 40.3, 95% CI 6.6 to 74.1; beta-coefficient: 87.7, 95% CI 24.0 to 151.5, for mild depressive symptoms and moderate to severe depressive symptoms, respectively).

Subgroup analysis of baseline factors

We also analysed the association between degree of depressive symptoms and baPWV in subgroups of sex, age, smoking status, blood pressure, diabetes mellitus, dyslipidaemia and BMI, and the results are shown in table 3, with the group with no depressive symptoms still considered as reference. In the stratified analysis of blood pressure, significant associations between mild depressive symptoms and baPWV were obtained in the subgroups of normal and high-normal blood pressure and hypertension (beta-coefficient: 55.8, 95% CI 3.4 to 108.2; beta-coefficient: 109.0, 95% CI 9.1 to 208.9, respectively), while a significant association between moderate to severe depressive symptoms and baPWV was observed
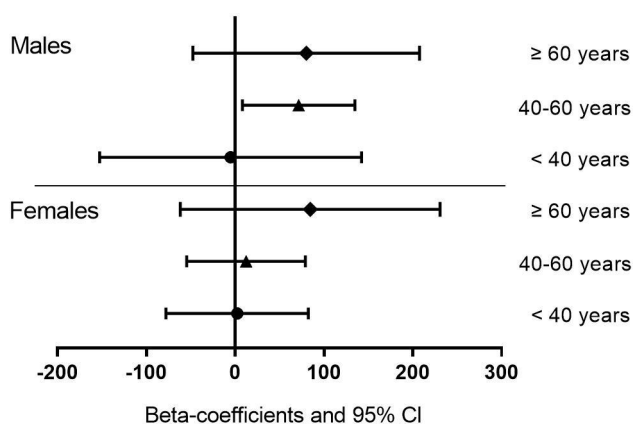

Figure 2 Beta-coefficients and 95% CI of the association between moderate to severe depressive symptoms and brachial-ankle pulse wave velocity stratified by age and sex. The results were adjusted for smoking history, blood pressure, diabetes mellitus, dyslipidaemia and body mass index.

only in the hypertension subgroup (beta-coefficient: 222.1, 95% CI 57.1 to 387.1), with the interaction also significant (p for interaction=0.016). In the subgroups of diabetes mellitus, significant associations between mild depressive symptoms and moderate to severe depressive symptoms and baPWV were found in those with diabetes mellitus (beta-coefficient: 154.1, 95% CI 45.0 to 263.2; beta-coefficient: 216.4, 95% CI 38.1 to 394.8) and the interaction was also significant (p for interaction=0.004). For other subgroups of sex, age, smoking status, dyslipidaemia and BMI, no significant interactions were found (p for interaction >0.05 for all).

Subgroups of age and sex

The beta-coefficients and the 95% CI of the association between mild depressive symptoms and baPWV according to age and sex are described in figure 1. Smoking history, blood pressure, diabetes mellitus, dyslipidaemia and BMI were adjusted in the regression models. The results showed that a significant association between mild depressive symptoms and baPWV was observed in male subjects aged 40–60 years (beta-coefficient: 71.6, 95% CI 8.2 to 135.0), but the result of interaction was not significant (p for interaction=0.260). The association between moderate to severe depressive symptoms and baPWV stratified by age and sex is presented in figure 2. There were significant associations between moderate to severe depressive symptoms and baPWV in female subjects younger than 40 years (beta-coefficient: 210.9, 95% CI 40.5 to 381.3) and aged 40–60 years (beta-coefficient: 185.2, 95% CI 79.5 to 290.9) after adjusting for the same variables in figure 1, although the result of interaction was not significant (p for interaction=0.056).

DISCUSSION

In the current cross-sectional study, we established an independent association between depressive symptoms and arterial stiffness in the general Chinese population. Subgroup analyses indicated that the associations between degree of depressive symptoms and arterial stiffness were most important in those whose blood pressures were not within the optimal range (including normal, high-normal and diagnosed hypertension) and in those combined with diabetes mellitus. In addition, significant associations between mild depressive symptoms and moderate to severe depressive symptoms and arterial stiffness were observed in male subjects aged 40–60 years and in female subjects younger than 60 years, respectively, in the stratified analysis of age and sex. However, the interactive effects were not significant for both.

The association between depressive symptoms and arterial stiffness in our study was in accordance with the findings of previous cross-sectional investigations.[16–19] However, the Health, Aging, and Body Composition Study failed to establish an association between depressive symptoms and arterial stiffness as reflected by cfPWV.[21] In addition, it was remarkable that the Maastricht Study

revealed that age and sex jointly influenced the associations between depressive symptoms, MDD and arterial stiffness as examined by cfPWV; significant associations existed only in the middle-aged male subgroup (aged 40–60 years).[20] In our study, no significant interactive effects were found for the subgroups of sex or age separately in the associations between depressive symptoms and baPWV. We further stratified all subjects by age and sex concurrently to examine whether the associations differed according to age and sex. Contrary to the findings of the Maastricht Study, our results indicated that significant associations between moderate to severe depressive symptoms and arterial stiffness were present only in women who were younger than 60 years, although the interactive effect was not statistically significant. The association between mild depressive symptoms and arterial stiffness was significant only in male subjects aged 40–60 years, which has not been reported before.

The prevalence of MDD in women largely exceeds that in men, a difference that has been reported worldwide.[26] This sex difference was also exhibited in specific depressive symptoms; for instance, women with depression tended to gain weight than men.[27] Moreover, an age–sex interaction was found in regard to an increase in carotid arterial stiffness.[28] It is reasonable that sex might have an interactive effect on the relationship between depression and arterial stiffness, but which sex is more vulnerable to the influence of depression on arterial stiffness seems conflicting according to our findings and the results of the Maastricht Study. It should be noted that the cohort of the Maastricht Study especially included individuals with diabetes according to their study design.[29] In the Maastricht Study, the prevalence of diabetes mellitus was 27% among subjects without depressive disorder and 49% among participants with MDD,[20] and these figures were higher than those in other cohorts, including ours (the prevalence of diabetes mellitus was 16.3%). Therefore, the large demographic difference might explain the opposite findings, and future studies are needed to elucidate clearly the role of age and sex in the relationship between depression and arterial stiffness.

We also classified the whole population into three subgroups based on blood pressure—optimal blood pressure, hypertension, and the rest which indicated normal or high-normal blood pressure—which was according to the current hypertension guidelines.[12] A significant interactive effect on the association between degree of depressive symptoms and arterial stiffness was found for blood pressure. One previous study showed that severe arterial stiffness was independently associated with progression of blood pressure (eg, normal blood pressure progressed to either high-normal blood pressure or hypertension; high-normal blood pressure progressed to hypertension).[30] Another longitudinal investigation revealed that in addition to an SBP >140 mm Hg, an SBP between 120 and 139 mm Hg was also associated with an increase in PWV compared with the PWV associated with SBP <120 mm Hg.[31] However, longitudinal studies have obtained inconsistent results with regard to the association between hypertension and depression.[32 33] In addition, one study inferred that, among the elderly, subjects with low blood pressure (SBP <120 mm Hg or DBP <75 mm Hg) were at increased risk of incident depression compared with those with normal blood pressure.[32] Another study revealed that anxiety or depression at baseline was associated with low blood pressure during follow-up.[34] The role of blood pressure in the interaction between depressive symptoms and arterial stiffness was first reported in our study, and limited by the cross-sectional study design we could not fully elucidate the causality or the underlying mechanism. However, one plausible explanation is that elevated blood pressure and advanced depressive symptoms might jointly promote the development of arterial stiffness. We also observed that older subjects with depressive symptoms tended to have lower night-time SBP fall,[35] and subjects with white coat hypertension or masked hypertension examined by ambulatory blood pressure monitoring had greater arterial stiffness.[36] Older subjects with depression were also associated with increased prevalence of left ventricular hypertrophy, which was independent of blood pressure levels.[37] All these studies indicated that there existed a more complicated relationship between depression, arterial stiffness and blood pressure, and the measures of blood pressure circadian and target organ damage might provide more information.

Another novel finding of the current study was that diabetes mellitus affected the relationship between depressive symptoms and arterial stiffness. Undoubtedly, diabetes mellitus is a well-known traditional risk factor for CVD and can accelerate progression of arterial stiffness. Meta-analyses have indicated that type 2 diabetes mellitus is a risk factor for new-onset depression, and that depression is also inversely associated with incident type 2 diabetes mellitus.[38 39] However, one recent study implied that the association between type 2 diabetes mellitus and MDD, which was examined at the epidemiological and genetic levels, does not exist, leading to controversial results.[40] Therefore, whether diabetes mellitus is a reliable interaction factor between depressive symptoms and arterial stiffness still needs further investigation.

The possible underlying mechanisms by which depression influences arterial stiffness include the following aspects: inflammation, endothelial dysfunction, dysregulation of the autonomic nerve system (ANS) and unhealthy behavioural patterns. As a result of psychosocial stressors, poor diet, physical inactivity, obesity and smoking,[41] a chronic and mild inflammatory response plays a role in the emergence of depression from childhood to adulthood, and a variety of proinflammatory cytokines are involved in this process.[42] In addition, endothelial dysfunction is independently associated with depressive disorders.[43] Endothelial damage is modulated by selective serotonin reuptake inhibitor treatment in patients with MDD and in vitro cell models.[44] Dysregulation of the ANS, especially sympathetic overactivity, and activated proinflammatory cytokines can cause imbalances in the kynurenine

pathway, leading to MDD.[45 46] Elevated heart rates and plasma catecholamine levels and low heart rate variability were found in the ANS dysfunction groups and were correlated with increased arterial stiffness.[47 48] Finally, patients with depression are vulnerable to unhealthy lifestyle behaviours such as smoking, overeating (leading to obesity, dyslipidaemia) and stressful emotional state, all of which are risk factors for coronary artery disease.[49]

The following several limitations should be considered in the current study. First, our study followed a cross-sectional design, so no clear cause–effect conclusion could be directly drawn. In addition, in some studies, standard diagnostic interviews according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria were performed to obtain the diagnosis of MDD,[16 19 20] while in others certain diagnostic scale was used.[16 17 20 21 50 51] However, in the current study, we did not have a clinical diagnosis of MDD, although we noted that a cut-off value of 10 on PHQ-9 to screen for MDD was both highly sensitive (85%) and specific (89%).[25] Further studies with optimal designs are needed. In addition, the covariate data we collected were limited, and we did not have information on socioeconomic level,[52 53] education level, physical activity level, dietary habits, assessment of cognitive impairment,[54] and medications taken by participants as different antidepressant medications might have opposite impact on arterial stiffness,[55] all of which might have influenced our results. Our study might still lack statistical power despite having a relatively large sample size (n=1334). For example, distinguished trends emerged among the subgroups of sex in the association between increased degree of depressive symptoms and baPWV; however, the result of the interaction was non-significant (p for interaction=0.072). Finally, our participants were from our health management centre, and although there were no specific restrictions for those who decided to receive health check-ups it should be noted that the costs of examinations were paid by the participants themselves. So a selection bias existed and our sample could not fully represent the general population in the real world. Therefore, extrapolation of our results to other populations should be done cautiously.

CONCLUSION

Our findings suggested that degree of depressive symptoms was independently associated with arterial stiffness, and further stratified analysis showed that subjects with depressive symptoms whose blood pressures were not optimal or complicated with diabetes mellitus were more susceptible to advanced arterial stiffness. Our results suggest that specific populations might need extra attention with regard to prevention of arterial stiffness due to the effect of depression.

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