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Association between depression and arterial stiffness: a cross-sectional study in a general population

Keywords: arterial stiffness; depressive symptoms; major depressive disorder.

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ABSTRACT

Objective: To determine the independent relationships of depressive symptoms and major depressive disorder (MDD) with arterial stiffness in a general population and explore possible interaction factors in the above relationships.

Design: A cross-sectional study.

Settings and participants: Consecutive participants who received routine health physical examinations in an affiliated hospital of a comprehensive university in Hunan Province, China, between September 2013 and March 2014 were examined. After exclusion, a total of 1334 subjects aged 22-77 years were recruited for the final analysis.

Measures: The Patient Health Questionnaire-9 (PHQ-9) was applied to assess the degrees of depression as follows: non-depression: PHQ-9 <5, presence of depressive symptoms: PHQ-9 ≥5, and moderate-to-severe depressive symptoms or MDD: PHQ-9 ≥10. Brachial-ankle pulse wave velocity (baPWV) was performed to assess arterial stiffness.

Results: Overall, the prevalence rates of depressive symptoms and MDD among all subjects were 21.1% and 4.0%, respectively. There was a slight increase in baPWV across depression degrees (p=0.025). Multivariate linear and logistic regression analyses revealed that depressive symptoms were independently associated with baPWV and a high baPWV (more than the upper 80% range of all subjects, 1576 cm/s). Subgroup analyses indicated that the associations were predominant in subjects aged ≥47 years (the median of all subjects) whose systolic blood pressure (SBP) was ≥120 mmHg or

whose fasting blood glucose (FBG) was ≥6.1 mmol/L (interaction p<0.05 for all) based on both linear and logistic regressions. While the association between MDD and baPWV or a high baPWV lost statistical significance after adjusting for baseline confounders, the association remained in female subjects (interaction p<0.05).

Conclusions: Depressive symptoms are independently associated with arterial stiffness, especially in relatively older subjects and those with high-normal SBP or FBG. However, the relationship between MDD and arterial stiffness is prominent in only female subjects.

Keywords: arterial stiffness; depressive symptoms; major depressive disorder.

Strengths and limitations of this study

1. The current study first analysed the association between depression and arterial stiffness in a Chinese general population that covered a wide range of ages (22-77 years).
2. The extent of depression was reflected by depressive symptoms and MDD, and the independent relationships of these indicators with baPWV were examined by multivariate linear and logistic regression models.
3. Various subgroup analyses were conducted to explore whether any interacting factors existed in the connection between depression and arterial stiffness.
4. The diagnosis of MDD was obtained based on self-reported questionnaires (PHQ-9) and was not further verified by diagnostic interviews according to DSM-IV criteria, which could slightly influence our results.
5. Due to the cross-sectional design of the study, no clear cause-effect conclusion could

be directly drawn.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychological disorders that affects health-related quality of life.[1] The global prevalence of MDD is 4.7%, and the lifetime rates of MDD vary greatly across different races, cultures and regions, ranging from 3.3% in mainland China to 18.6% in the United States.[2-4] Furthermore, the prevalence of MDD in patients with cardiovascular disease (CVD) is much higher:[5] 26.8% in hypertensive subjects,[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] In addition, it was estimated that almost two-thirds of depressed middle-aged and older adults also reported a diagnosis of comorbid CVD.[10] Therefore, there is an interaction between MDD and CVD in which 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 one of the markers of hypertension-mediated organ damage and should be assessed among hypertensive patients according to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) hypertension guidelines.[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 concerning the relationship between depression and arterial stiffness are limited, and the results remain controversial. The Rotterdam Study (n=3704, ≥60 years) and the 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 was also verified in 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] In addition, the Netherlands Study of Depression and Anxiety Study (n=635, aged 20-66 years) also failed to identify the association between depression sensitivity and central arterial stiffness assessed by augmentation index.[22]

The main reasons for the abovementioned diverse findings might be the differences in the enrolled population, the assessment methods of arterial stiffness, and the criteria for defining depression. We noticed 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, MDD and arterial stiffness reflected by brachial-ankle PWV (baPWV). Additionally, we explored whether the associations (if present) differed among subgroups according to various factors; this type of analysis was seldom performed in previous studies.

METHODS

Study subjects

The current study followed a cross-sectional design, and a general Chinese population was recruited. We collected the medical information of consecutive participants who received routine health physical examinations 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: an age of <18 or ≥80 years; a history of myocardial infarction, heart failure, stroke, cancer, severe hepatic or renal dysfunction; serious mental disorders; any missing data from the Patient Health Questionnaire-9 (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 of 47.1 ± 11.7 years) were ultimately analysed in this study. Our study protocol was approved by the Ethics Committee of Xiangya Hospital, Central South University, and all participants provided written informed consent.

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 past medical histories of hypertension and diabetes mellitus. Height was measured while the participants were without shoes to the nearest 0.1 cm, and weight was measured with the participants in light indoor clothing and without shoes to the nearest 0.1 kg. Then, 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 minutes of rest. The means of two separate readings of blood pressure with an interval of 3-5 minutes between measurements were used. Fasting blood samples were collected from antecubital veins after an 8-hour overnight fast in the morning of the health check-up days. Fasting blood glucose (FBG), 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.

Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, a self-reported history of diagnosed hypertension, or current anti-hypertensive treatment. Diabetes mellitus was defined as FBG ≥7.0 mmol/L, a self-reported history of diagnosed

diabetes mellitus, or current hypoglycaemic therapy. The diagnosis of hypertension and diabetes mellitus was based on current relevant guidelines.

The PHQ-9, which consists of 9 questions that are each scored from 0-3 points, was used in our study to assess the degrees of depressive symptoms and achieve a diagnosis of MDD. Normally, subjects were defined as having no depressive symptoms if their PHQ-9 score was less than 4, mild depressive symptoms if they had a PHQ-9 score between 5 and 9 and moderate to severe depressive symptoms if their PHQ-9 score was equal to or greater than 10; participants with moderate to severe depressive symptoms were also considered to have MDD as this cut-off value (10 on the PHQ-9) has been widely used in epidemiological studies for diagnosing MDD with high sensitivity and specificity.[23] Accordingly, a lack of depressive symptoms was defined as a PHQ-9 score of less than 5.

BaPWV was automatically measured using baPWV instruments (model BP-203RPE, Colin, Komaki City, Japan) by trained staff following the standard procedure. Participants were measured in the supine position after 10 minutes of rest in a quiet room with a comfortable temperature. Bilateral measurements of baPWV were recorded, and the higher reading was used for analysis. The validation of this automatic device and its reproducibility have been previously demonstrated.

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. Actually, all baseline characteristics were acquired from the entire population, so no missing data existed in our study. All subjects were divided into three groups according to their degrees of depressive symptoms determined by the PHQ-9 score. Continuous variables are presented as the means and standard deviations, while categorical variables are presented as frequencies and percentages. Comparisons between groups were performed using analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. We defined a high baPWV as more than 1576 cm/s (80th percentile of all subjects). Multivariate linear regression and multivariate logistic regression models were used to assess the associations of depressive symptoms and MDD with baPWV and a high baPWV, respectively. All baseline factors were included in the adjusted models. Analyses were also stratified to examine any possible interactions of depressive symptoms and MDD with baPWV and a high baPWV using multiple clinically meaningful cut-off values of baseline parameters: a 10 mmHg increase in SBP; a 5 mmHg increase in DBP; a FBG level of 5.6 and 6.1 mmol/L for diagnosing elevated blood glucose and impaired fasting glucose (IFG), respectively, as recommended by the 2005 National Cholesterol Education Program (NCEP) ATP3 and the World Health Organization (WHO) 1999 criteria; abnormal lipid profiles based on the Korean guideline of dyslipidaemia for the general population;[24] and BMIs of 24 or 28 kg/m^2 were used to identify overweight and obesity, respectively, for the Chinese population. All analyses were conducted using the statistical software

packages R (R 3.4.3, http://www.R-project.org, The R Foundation) and EmpowerStats (www.empowerstats.com, X&Y solutions, Inc., Boston, MA). 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 the interpretation of the results of the current study.

RESULTS

Baseline characteristics

After exclusion, a total of 1334 subjects were finally included in our final analysis (mean age 41.7 ± 11.7 years, 64.5% male). The detailed baseline characteristics of all subjects by degree of depression are described in table 1. Accordingly, the prevalence of mild depressive symptoms was 17.0%, the prevalence of moderate to severe depressive symptoms of MDD was 4.0%, and the prevalence of the absence of depressive symptoms (including MDD) was 21.1%. In addition, the results indicated that fewer male participants were present across increasing degrees of depressive symptoms (67.8%, 52.9% and 48.1%, p<0.001), as well as a decreasing proportion of participants who smoked (46.5%, 43.2% and 29.6%, p=0.040). There was no significant difference in terms of age, comorbidities of hypertension or diabetes mellitus, levels of SBP or DBP, BMI, FBG, or lipid profiles. As expected, a higher baPWV was found in subjects with advanced

depressive symptoms (1343.6 ± 264.4, 1372.9 ± 312.3 and 1436.5 ± 314.4 cm/s, p=0.025).

Depressive symptoms and baPWV

Then, we performed multivariate linear regressions for the association between depressive symptoms and baPWV among all subjects and in subgroups, and all baseline potential confounding factors were included in the adjusted models unless the variable was used to classify the subgroups. Moreover, interaction analyses were also conducted for any possible interaction effect. Table 2 shows a significant association between depressive symptoms and baPWV in both the crude and adjusted models (adjusted model: beta-coefficient: 46.3; 95% confidence interval [CI]: 17.0-75.7; p=0.002). In addition, the associations between depressive symptoms and baPWV were stronger in subgroups of individuals whose age was ≥47 years (the median of all subjects, beta-coefficient: 77.0 versus 22.9, interaction p=0.030), subjects with diabetes mellitus (beta-coefficient: 124.9 versus 24.8, interaction p=0.005), subjects with a SBP ≥120 mmHg (beta-coefficient: 64.0 versus 2.75, interaction p=0.049) and subjects with FBG ≥6.1 mmol/L (beta-coefficient: 105.2 versus 31.5, interaction p=0.038). However, no significant interactions were identified for subgroups of sex, smoking status, hypertension or DBP with a cutoff of 80 mmHg. Similarly, no significant results were shown for subgroups of age (grouped by 40 and 60 years), FBG (5.6 mmol/L), lipid parameters or BMI (presented in supplemental table 1).

MDD and baPWV

We also conducted multivariate linear regressions for the association between MDD and baPWV among all subjects and in subgroups, and for a consistent format, we presented the results of subgroups in table 3 in the same way as in table 2. The results revealed a significant correlation between MDD and baPWV in the crude model (beta-coefficient: 87.7; 95% CI: 12.7-162.7; p=0.022); however, the association was attenuated and statistically nonsignificant after adjusting for confounders (beta-coefficient: 57.6; 95% CI: -3.0 to 118.2; p=0.063). Subgroup analyses showed that a significant association existed among female subjects (beta-coefficient: 133.6, 95% CI: 53.5-213.8, p=0.001) and non-smokers (beta-coefficient: 91.0, 95% CI: 25.8-156.2, p=0.006), but only the interaction analysis for subgroup by sex reached statistical significance (interaction p=0.022). No meaningful results were obtained in subgroups of age, smoking status, hypertension, diabetes mellitus, SBP, DBP and FBG. Subgroup analyses based on other classification methods of age, FBG, lipid profiles and BMI are described in supplemental table 2, and none of the interaction results were significant.

Depressive symptoms, MDD and a high baPWV

We defined a high baPWV as 1576 cm/s: the 80% cut-off value among all subjects. Then, we conducted multivariate logistic regression analysis with depressive symptoms, MDD and a high baPWV among all subjects and in the subgroups, and the results including the forest plots of odds ratios (ORs) are presented in figure 1 and figure 2, respectively. As

shown in figure 1, the crude OR of depressive symptoms and a high baPWV was 1.53 (95% CI: 1.12-2.08, p=0.008), and the result was similar after adjusting for all baseline factors (OR: 1.61, 95% CI: 1.12-2.31, p=0.011). For subgroup analyses, a significant interaction between depressive symptoms and a high baPWV existed in subgroups of age divided by a cutoff of 47 years (OR: 2.16 [1.40-3.34] versus 0.91 [0.45-1.84], interaction p=0.019), SBP grouped by a cutoff of 120 mmHg (OR: 1.95 [1.29-2.97] versus 0.79 [0.32-1.94], interaction p=0.041) and FBG classified by a cutoff of 6.1 mmol/L (OR: 3.58 [1.68-7.63] versus 1.31 [0.88-1.94], interaction p=0.029). Significant ORs were also obtained among female subjects (OR: 2.53, 95% CI: 1.36-4.37, p=0.004), but further interaction analysis was not significant (interaction p=0.160). For the relationship between MDD and a high baPWV, a significant correlation was obtained only in the crude model (OR: 1.90; 95% CI: 1.05-3.43, p=0.033), and the result lost statistical significance after adjusting for confounders as described in figure 2 (OR: 1.59, 95% CI: 0.79-3.21, p=0.198). With respect to subgroup analyses, significant ORs were obtained only among females (OR: 5.54; 95% CI: 2.05-14.97, p<0.001), and the interaction effect was significant (interaction p=0.003). In the same manner as in table 2 and table 3, we also divided all participants into subgroups by other baseline parameters to analyse the relationship of depressive symptoms and MDD with a high baPWV, but none of the results were significant (shown in supplemental table 3 and supplemental table 4).

DISCUSSION

In the current cross-sectional study, the prevalence of depressive symptoms and MDD according to PHQ-9 scores was 21.1% and 4.0%, respectively. A previous study indicated that the current prevalence of MDD is 1.7% in the urban general population of mainland China,[3] and another study conducted in a nearby rural region reported that the prevalence of MDD in the older population was 6.8%.[25] The prevalence of depressive symptoms could be as high as 23.6% in older Chinese adults.[26] Hence, according to our study, the prevalence rates of both depressive symptoms and MDD were similar as those in the above data. Importantly, we established an independent association between depressive symptoms and arterial stiffness in a general population. Subgroup analyses indicated that the abovementioned association was most common in those older than 47 years, whose SBP was ≥120 mmHg or whose FBG was ≥6.1 mmol/L; the association was examined both in linear and logistic regressions. While the correlation between MDD and arterial stiffness lost significance after adjusting for confounding factors, this association remained notable among females, and the interaction was statistically significant.

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 the association between depressive symptoms and arterial stiffness.[21] The association between MDD and arterial stiffness lost statistical significance after adjusting for baseline factors in the present study, which was not consistent with the results of previous studies.[16,17] Interestingly, the Maastricht Study revealed that the independent association between

depressive symptoms, MDD and arterial stiffness existed in only the middle-aged male subgroup (aged 40-60 years).[20] In contrast, our results indicated that the link between MDD and arterial stiffness was present only in females (interaction $p<0.05$), which had not been described before. The prevalence of MDD among females largely exceeds that among males, which is a difference that has been reported worldwide.[27] This sex difference was also exhibited in specific depressive symptoms; for instance, more depressed females tended to gain weight than males.[28] Moreover, an age-sex interaction was found in regard to the increase in carotid arterial stiffness.[29] It is possible that sex might have an interaction effect on the relationship between depression and arterial stiffness, but the sex that is more vulnerable to the influence of depression on arterial stiffness seems conflicting according to our findings.

With respect to age, which was divided according to the median age of the entire sample in our study, we provided new information that subjects older than 47 years were more vulnerable to the impact of depressive symptoms on arterial stiffness, but the same results were not found for MDD. Indeed, only the Maastricht Study performed a subgroup analysis by age, and they found that the association of depressive symptoms and MDD with arterial stiffness was notable in subjects younger than 60 years, especially among males.[20] We covered a wider range of ages (22-77 years) than the Maastricht Study (45-75 years). We also divided the sample according to the age of 60 years as in the Maastricht Study and evaluated the interaction between age and sex, but the results remained nonsignificant. It should be noted that the cohort of the Maastricht Study

included diabetic individuals according to their study design.[30] The prevalence of diabetes mellitus was 27% among subjects without depressive disorder and 49% among participants with MDD in the Maastricht Study;[20] these figures were higher than those in other cohorts including ours (16.3%). Importantly, the age range in the Maastricht Study was relatively limited compared to that in ours. Therefore, the large demographic difference might explain the different results, and future studies with subjects with a wide range of ages are needed to verify the role of age and sex in the connection between depression and arterial stiffness.

Another novel finding of the current study was that FBG ≥6.1 mmol/L affected the relationship between depressive symptoms and arterial stiffness. Undoubtedly, diabetes mellitus or elevated plasma glucose is a well-known traditional risk factor for CVD and can accelerate the progression of arterial stiffness. Meta-analyses have indicated that type 2 diabetes mellitus (T2DM) is a risk factor for new-onset depression and that depression is also inversely associated with incident T2DM.[31,32] However, one recent study implied that the association between T2DM and MDD, which was examined at the epidemiologic and genetic levels, does not exist, leading to controversial results.[33] Therefore, whether diabetes mellitus or FBG ≥6.1 mmol/L is a reliable interaction factor between depression and arterial stiffness still needs further investigation to be verified.

We also classified the subjects based on different cut-off values of SBP and DBP using 10 mmHg as an interval for SBP and 5 mmHg for DBP, but the results were not significant except for a SBP of 120 mmHg in the association between depressive

symptoms and arterial stiffness. It should be noted that a SBP <120 mmHg and a DBP <80 mmHg is considered the optimal blood pressure for all individuals older than 16 years of age according to the current hypertension guidelines.[12] Elevated SBP is a traditional risk factor for CVD and affects the increase in arterial stiffness that occurs with ageing;[34] one longitudinal investigation revealed that in addition to SBP >140 mmHg, SBP between 120 and 139 mmHg was also associated with an increase in PWV compared with the PWV associated with SBP <120 mmHg.[34] However, longitudinal studies have obtained inconsistent results regarding the association between hypertension and depression.[35,36] In addition, one study inferred that subjects with low blood pressure (SBP <120 mmHg or DBP <75 mmHg) were at increased risk of incident depression compared with those with normal blood pressure among the elderly.[35] Another study revealed that anxiety or depression at baseline was associated with low blood pressure during follow-up.[37] The interaction role of SBP with depressive symptoms and arterial stiffness was first reported in our study. Limited by the cross-sectional study design, we could not fully elucidate the causality or the underlying mechanism, but one plausible explanation is that increased SBP and depressive symptoms might jointly promote the development of arterial stiffness.

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,[38] a chronic and mild inflammatory response participates in the emergence of depression from childhood

to adulthood, and a variety of proinflammatory cytokines are involved in this process.[39] In addition, endothelial dysfunction is independently associated with depressive disorders.[40] Endothelial damage is modulated by selective serotonin reuptake inhibitor (SSRI) treatment in patients with MDD and in vitro cell models.[41] Dysregulation of the ANS, especially sympathetic over-activity, and activated proinflammatory cytokines can cause imbalances in the kynurenine pathway, leading to MDD.[42,43] 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.[44,45] Finally, depressed patients are vulnerable to the adoption of unhealthy lifestyle behaviours such as smoking, overeating (leading to obesity, dyslipidaemia) and a stressful emotional state, all of which are risk factors for coronary artery disease (CAD).[46]

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 from our study. In addition, in some studies, standard diagnostic interviews according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were performed to diagnose MDD,[16,19,20] while in others, another diagnostic scale was used instead.[16,17,20,21,47,48] Our diagnosis of MDD was also derived from a self-administered questionnaire, and no further face-to-face interviews were carried out by psychiatrists. Although we noted that a cut-off value of 10 on the PHQ-9 to screen depression was both highly sensitive (85%) and specific (89%),[23] further studies with optimal designs are still needed. Finally, the covariate data we collected were limited, and

we did not have information regarding education level, physical activity level, dietary habits, or medications taken by participants, all of which might have influenced our results.

CONCLUSION

Our findings suggested that depressive symptoms were independently associated with arterial stiffness, and further interaction analysis showed that subjects with depressive symptoms who were older than 47 years and who had a SBP ≥120 mmHg or FBG ≥6.1 mmol/L were more susceptible to advanced arterial stiffness. However, the independent relationship between MDD and arterial stiffness or severe arterial stiffness was restricted to only female subjects. Our results suggest that specific populations might need extra attention in regard to the prevention of arterial stiffness due to the effect of depression.

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval Our study protocol was approved by the Ethics Committee of Xiangya

Hospital, Central South University, and all the procedures were conducted in accordance with the ethical standards.

Provenance and peer review Not commissioned; externally peer reviewed.

Data-sharing statement The data from the current study are available from the corresponding author at chenglongzhang@csu.edu.cn upon reasonable request.

REFERENCES

1. Cao Y, Li W, Shen J, Malison RT, Zhang Y, Luo X. Health-related quality of life and symptom severity in Chinese patients with major depressive disorder. *Asia-Pacific psychiatry.* 2013;5(4):276-283.
2. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological medicine.* 2013;43(3):471-481.
3. Gu L, Xie J, Long J, et al. Epidemiology of major depressive disorder in mainland china: a systematic review. *PloS one.* 2013;8(6):e65356.
4. Gonzalez HM, Tarraf W, Whitfield KE, Vega WA. The epidemiology of major depression and ethnicity in the United States. *Journal of psychiatric research.* 2010;44(15):1043-1051.
5. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *European heart journal.* 2014;35(21):1365-1372.
6. Li Z, Li Y, Chen L, Chen P, Hu Y. Prevalence of Depression in Patients With Hypertension: A Systematic Review and Meta-Analysis. *Medicine.* 2015;94(31):e1317.
7. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-

analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology.* 2006;48(8):1527-1537.

8. Osler M, Martensson S, Wium-Andersen IK, et al. Depression After First Hospital Admission for Acute Coronary Syndrome: A Study of Time of Onset and Impact on Survival. *American journal of epidemiology.* 2016;183(3):218-226.
9. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation.* 2014;129(12):1350-1369.
10. Gonzalez HM, Tarraf W. Comorbid cardiovascular disease and major depression among ethnic and racial groups in the United States. *International psychogeriatrics.* 2013;25(5):833-841.
11. Tomiyama H. Arterial Stiffness: Is This a Marker for the Current Status or Future? *Journal of atherosclerosis and thrombosis.* 2016;23(9):1026-1027.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal.* 2018;39(33):3021-3104.
13. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *Journal of the American College of Cardiology.* 2014;63(7):636-646.
14. Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. *Hypertension.* 2017;69(6):1045-1052.
15. Vlachopoulos C, Aznaouridis K, Terentes-Printzios D, Ioakeimidis N, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with brachial-ankle elasticity index: a systematic review and meta-analysis. *Hypertension.* 2012;60(2):556-562.
16. Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. *Journal of the American Geriatrics Society.* 2003;51(8):1105-1110.
17. van Sloten TT, Mitchell GF, Sigurdsson S, et al. Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. *Journal of psychiatry & neuroscience.* 2016;41(3):162-168.
18. Dietz LJ, Matthews KA. Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. *The Journal of adolescent health.* 2011;48(6):579-584.
19. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Depression, anxiety, and arterial stiffness. *Biological psychiatry.* 2011;69(8):795-803.
20. Onete V, Henry RM, Sep SJS, et al. Arterial stiffness is associated with depression in middle-aged men - the Maastricht Study. *Journal of psychiatry & neuroscience.* 2018;43(2):111-119.
21. Lewis TT, Sutton-Tyrrell K, Penninx BW, et al. Race, psychosocial factors, and aortic pulse wave velocity: the Health, Aging, and Body Composition Study. *The journals of gerontology.* 2010;65(10):1079-1085.
22. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Sensitivity to depression or anxiety and subclinical cardiovascular disease. *Journal of affective disorders.* 2013;146(1):126-131.

23. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *Canadian Medical Association journal.* 2012;184(3):E191-196.
24. Committee for the Korean Guidelines for the Management of Dyslipidemia. 2015 Korean Guidelines for the Management of Dyslipidemia: Executive Summary (English Translation). *Korean circulation journal.* 2016;46(3):275-306.
25. Liu ZW, Yu Y, Hu M, Liu HM, Zhou L, Xiao SY. PHQ-9 and PHQ-2 for Screening Depression in Chinese Rural Elderly. *PloS one.* 2016;11(3):e0151042.
26. Li D, Zhang DJ, Shao JJ, Qi XD, Tian L. A meta-analysis of the prevalence of depressive symptoms in Chinese older adults. *Archives of gerontology and geriatrics.* 2014;58(1):1-9.
27. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological bulletin.* 2017;143(8):783-822.
28. Schuch JJ, Roest AM, Nolen WA, Penninx BW, de Jonge P. Gender differences in major depressive disorder: results from the Netherlands study of depression and anxiety. *Journal of affective disorders.* 2014;156:156-163.
29. Vermeersch SJ, Rietzschel ER, De Buyzere ML, et al. Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population. *Journal of hypertension.* 2008;26(7):1411-1419.
30. Schram MT, Sep SJ, van der Kallen CJ, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *European journal of epidemiology.* 2014;29(6):439-451.
31. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia.* 2006;49(5):837-845.
32. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia.* 2010;53(12):2480-2486.
33. Samaan Z, Garasia S, Gerstein HC, et al. Lack of association between type 2 diabetes and major depression: epidemiologic and genetic evidence in a multiethnic population. *Translational psychiatry.* 2015;5:e618.
34. AlGhatrif M, Strait JB, Morrell CH, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension.* 2013;62(5):934-941.
35. Godin O, Elbejjani M, Kaufman JS. Body mass index, blood pressure, and risk of depression in the elderly: a marginal structural model. *American journal of epidemiology.* 2012;176(3):204-213.
36. Zimmerman JA, Mast BT, Miles T, Markides KS. Vascular risk and depression in the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE). *International journal of geriatric psychiatry.* 2009;24(4):409-416.
37. Hildrum B, Mykletun A, Holmen J, Dahl AA. Effect of anxiety and depression on blood pressure: 11-year longitudinal population study. *The British journal of psychiatry.* 2008;193(2):108-113.
38. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does

the inflammation come from? *BMC medicine.* 2013;11:200.

39. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin.* 2014;140(3):774-815.
40. van Dooren FE, Schram MT, Schalkwijk CG, et al. Associations of low grade inflammation and endothelial dysfunction with depression - The Maastricht Study. *Brain, behavior, and immunity.* 2016;56:390-396.
41. Lopez-Vilchez I, Diaz-Ricart M, Navarro V, et al. Endothelial damage in major depression patients is modulated by SSRI treatment, as demonstrated by circulating biomarkers and an in vitro cell model. *Translational psychiatry.* 2016;6(9):e886.
42. Won E, Kim YK. Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression. *Current neuropharmacology.* 2016;14(7):665-673.
43. Wang SY, Duan KM, Tan XF, et al. Genetic variants of the kynurenine-3-monooxygenase and postpartum depressive symptoms after cesarean section in Chinese women. *Journal of affective disorders.* 2017;215:94-101.
44. Whelton SP, Blankstein R, Al-Mallah MH, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension.* 2013;62(3):477-484.
45. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. *Diabetes care.* 2013;36(8):2351-2358.
46. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological psychiatry.* 2003;54(3):216-226.
47. van Sloten TT, Boutouyrie P, Tafflet M, et al. Carotid Artery Stiffness and Incident Depressive Symptoms: The Paris Prospective Study III. *Biological psychiatry.* 2018.
48. Lin IM, Lu HC, Chu CS, Lee CS, Lu YH, Lin TH. The Relationship between Brachial-Ankle Pulse Wave Velocity and Depressive Symptoms among Patients with Coronary Artery Disease. *Acta Cardiologica Sinica.* 2017;33(3):303-309.

Figure legends

Figure 1 Multivariate logistic regression analysis between depressive symptoms and a high brachial-ankle pulse wave velocity among all subjects and subgroups.

CI, confidence interval; FBG, fasting blood glucose; SBP, systolic blood pressure.

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

Figure 2 Multivariate logistic regression analysis between major depressive disorder and a high brachial-ankle pulse wave velocity among all subjects and subgroups.

CI, confidence interval; FBG, fasting blood glucose; SBP, systolic blood pressure.

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

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

Variables	No depressive symptoms	Mild depressive symptoms	Moderate-to-severe depressive symptoms	P value
No. (%)	1053 (78.9)	227 (17.0)	54 (4.0)	
Males (%)	714 (67.8)	120 (52.9)	26 (48.1)	**<0.001**
Age, years	46.9 ± 11.8	47.5 ± 11.2	48.5 ± 11.7	0.523
Smoking (%)	490 (46.5)	98 (43.2)	16 (29.6)	**0.040**
Hypertension (%)	248 (23.6)	39 (17.2)	13 (24.1)	0.109
Diabetes mellitus (%)	165 (15.7)	40 (17.6)	13 (24.1)	0.225
SBP, mmHg	126.1 ± 16.6	125.0 ± 16.5	127.9 ± 14.7	0.445
DBP, mmHg	75.0 ± 10.5	74.4 ± 9.7	73.8 ± 8.5	0.513
BMI, kg/m^2	24.7 ± 3.8	24.9 ± 4.3	23.8 ± 3.5	0.147
FBG, mmol/L	5.30 ± 1.58	5.32 ± 1.42	5.64 ± 1.92	0.300
Total cholesterol, mmol/L	5.00 ± 1.04	5.07 ± 1.04	5.27 ± 1.17	0.134
Triglycerides, mmol/L	2.12 ± 1.58	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
PHQ-9 score	1.28 ± 1.39	6.47 ± 1.36	13.20 ± 3.22	**<0.001**
baPWV, cm/s	1343.6 ± 264.4	1372.9 ± 312.3	1436.5 ± 314.4	**0.025**

Data are presented as the mean ± standard deviation or n (percentage) as appropriate.

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PHQ-9, the Patient Health Questionnaire-9; SBP, systolic blood pressure.

Table 2 Multivariate linear regression analysis between depressive symptoms and brachial-ankle pulse wave velocity among all subjects and subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
All subjects	Crude	1334	41.5 (5.3, 77.8)	**0.025**	
	Adjusted	1334	46.3 (17.0, 75.7)	**0.002**	
Sex	Male	860	49.5 (9.5, 89.6)	**0.016**	0.956
	Female	474	46.4 (4.1, 88.7)	**0.032**	
Age, years	< 47	672	22.9 (-14.4, 60.2)	0.229	**0.030**
	≥ 47	662	77.0 (27.9, 126.1)	**0.002**	
Smoking	No	730	34.6 (-0.7, 69.8)	0.055	0.212
	Yes	604	63.9 (14.2, 113.6)	**0.012**	
Hypertension	No	1034	32.1 (1.0, 63.3)	**0.044**	0.055
	Yes	300	91.2 (14.6, 167.8)	**0.020**	
Diabetes mellitus	No	1116	24.8 (-6.9, 56.4)	0.124	**0.005**
	Yes	218	124.9 (46.4, 203.4)	**0.002**	
SBP, mmHg	< 120	512	2.75 (-41.3, 46.8)	0.903	**0.049**
	≥ 120	822	64.0 (24.6, 103.5)	**0.002**	
DBP, mmHg	< 80	935	44.6 (11.0, 78.2)	**0.010**	0.591
	≥ 80	399	63.4 (2.1, 124.6)	**0.043**	
FBG, mmol/L	< 6.1	1134	31.5 (-0.1, 63.1)	0.051	**0.038**
	≥ 6.1	200	105.2 (22.7, 187.7)	**0.013**	

The results were adjusted for age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, body mass index, fasting blood glucose and lipid profiles if the variable was not stratified. CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; SBP, systolic blood pressure.

Table 3 Multivariate linear regression analysis between major depressive disorder and brachial-ankle pulse wave velocity among all subjects and subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
All subjects	Crude	1334	87.7 (12.7, 162.7)	**0.022**	
	Adjusted	1334	57.6 (-3.0, 118.1)	0.063	
Sex	Male	860	-13.7 (-101.8, 74.5)	0.762	**0.022**
	Female	474	133.6 (53.5, 213.8)	**0.001**	
Age, years	< 47	672	41.4 (-42.0, 124.9)	0.331	0.542
	≥ 47	662	54.3 (-39.5, 148.1)	0.257	
Smoking	No	730	91.0 (25.8, 156.2)	**0.006**	0.138
	Yes	604	-21.3 (-142.1, 99.4)	0.729	
Hypertension	No	1034	29.6 (-36.8, 96.0)	0.383	0.150
	Yes	300	129.7 (-11.6, 271.0)	0.073	
Diabetes mellitus	No	1116	36.2 (-30.8, 103.2)	0.290	0.178
	Yes	218	130.3 (-16.0, 276.5)	0.082	
SBP, mmHg	< 120	512	27.3 (-72.5, 127.1)	0.592	0.376
	≥ 120	822	74.9 (-2.9, 152.7)	0.060	
DBP, mmHg	< 80	935	52.4 (-14.5, 119.3)	0.125	0.690
	≥ 80	399	68.3 (-76.3, 212.8)	0.355	
FBG, mmol/L	< 6.1	1134	56.7 (-10.1, 123.4)	0.097	0.788
	≥ 6.1	200	78.8 (-73.2, 230.7)	0.331	

The results were adjusted for age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, body mass index, fasting blood glucose and lipid profiles if the variable was not stratified. CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; SBP, systolic blood pressure.

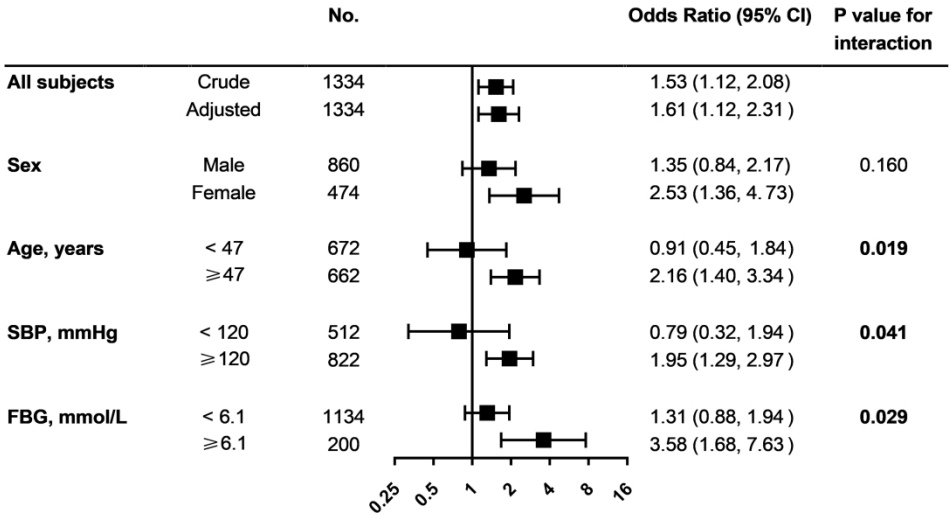

Figure 1

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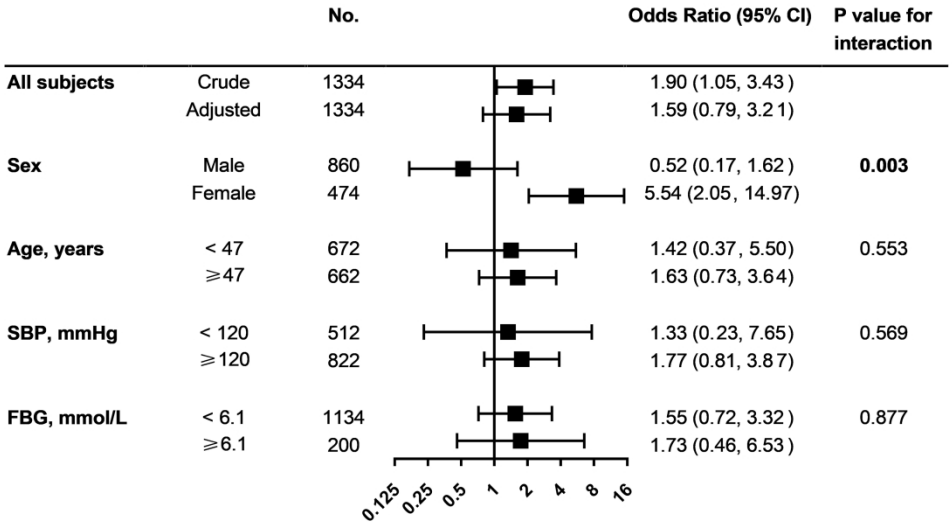

Figure 2

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Supplemental table 1 Multivariate linear regression analysis between depressive symptoms and brachial-ankle pulse wave velocity among subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
Age, years	< 40	404	27.5 (-22.1, 77.1)	0.278	0.532
	40-60	719	63.3 (21.9, 104.7)	**0.003**	
	≥ 60	211	73.6 (-17.6, 164.7)	0.115	
FBG, mmol/L	< 5.6	1039	31.1 (-1.5, 63.7)	0.062	0.083
	≥ 5.6	295	85.3 (17.4, 153.2)	**0.014**	
Total cholesterol, mmol/L	< 5.2	812	19.5 (-18.0, 56.9)	0.309	0.067
	≥ 5.2	522	83.4 (35.8, 131.0)	**<0.001**	
Triglycerides, mmol/L	< 1.7	659	37.1 (-10.8, 85.0)	0.130	0.838
	≥ 1.7	675	50.5 (4.9, 96.1)	**0.030**	
HDL-C, mmol/L	< 1.0	85	20.6 (-90.6, 131.8)	0.718	0.382
	≥ 1.0	1249	43.7 (13.2, 74.2)	**0.005**	
LDL-C, mmol/L	< 3.4	1136	37.6 (6.0, 69.2)	**0.020**	0.209
	≥ 3.4	208	97.0 (15.9, 178.1)	**0.020**	
BMI, kg/m^2	< 24	592	32.1 (-13.6, 77.7)	0.169	0.659
	24-28	492	58.1 (5.5, 110.7)	**0.031**	
	≥ 28	250	62.5 (5.7, 119.4)	**0.032**	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplemental table 2 Multivariate linear regression analysis between major depressive disorder and brachial-ankle pulse wave velocity among subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
Age, years	< 40	404	82.7 (-24.4, 189.8)	0.131	0.647
	40-60	719	79.9 (-2.4, 162.3)	0.057	
	≥ 60	211	-0.06 (-202.4, 202.3)	0.999	
FBG, mmol/L	< 5.6	1039	38.0 (-29.1, 105.1)	0.267	0.086
	≥ 5.6	295	147.8 (8.66, 286.9)	**0.038**	
Total cholesterol, mmol/L	< 5.2	812	28.2 (-48.7, 105.2)	0.472	0.288
	≥ 5.2	522	107.8 (8.5, 207.0)	0.034	
Triglycerides, mmol/L	< 1.7	659	72.3 (-30.0, 174.6)	0.167	0.815
	≥ 1.7	675	94.8 (3.8, 185.8)	**0.042**	
HDL-C, mmol/L	< 1.0	85	21.5 (-171.2, 214.1)	0.828	0.545
	≥ 1.0	1249	53.8 (-10.1, 117.7)	0.099	
LDL-C, mmol/L	< 3.4	1136	45.6 (-24.4, 115.6)	0.202	0.547
	≥ 3.4	208	107.8 (-25.9, 241.6)	0.116	
BMI, kg/m^2	< 24	592	34.7 (-54.8, 124.3)	0.447	0.226
	24-28	492	52.0 (-54.9, 158.9)	0.341	
	≥ 28	250	198.7 (60.0, 337.4)	**0.005**	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressure, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplemental table 3 Multivariate logistic regression analysis between depressive symptoms and a high brachial-ankle pulse wave velocity among subgroups

		No.	Odd ratios (95% CI)	P value	P value for interaction
Age, years	< 40	404	1.76 (0.68, 4.56)	0.248	0.477
	40-60	719	1.46 (0.91, 2.36)	0.119	
	≥ 60	211	3.09 (1.40, 6.80)	**0.005**	
Hypertension	No	1034	1.56 (1.01, 2.42)	**0.044**	0.726
	Yes	300	1.76 (0.85, 3.65)	0.127	
Diabetes mellitus	No	1116	1.31 (0.86, 2.01)	0.207	0.085
	Yes	218	3.37 (1.48, 7.64)	**0.004**	
FBG, mmol/L	< 5.6	1039	1.50 (0.97, 2.21)	0.066	0.540
	≥ 5.6	295	1.98 (0.97, 4.06)	0.063	
Total cholesterol, mmol/L	< 5.2	812	1.23 (0.75, 2.04)	0.412	0.157
	≥ 5.2	522	2.50 (1.41, 4.43)	**0.002**	
Triglycerides, mmol/L	< 1.7	659	1.21 (0.72, 2.04)	0.466	0.192
	≥ 1.7	675	1.94 (1.25, 3.01)	**0.003**	
HDL-C, mmol/L	< 1.0	85	1.05 (0.14, 7.99)	0.964	0.926
	≥ 1.0	1249	1.63 (1.12, 2.37)	**0.011**	
LDL-C, mmol/L	< 3.4	1136	1.36 (0.90, 2.06)	0.140	0.082
	≥ 3.4	208	4.09 (1.60, 10.5)	**0.003**	
BMI, kg/m^2	< 24	592	1.25 (0.75, 2.08)	0.396	0.265
	24-28	492	2.70 (1.38, 5.29)	**0.004**	
	≥ 28	250	1.98 (0.76, 5.14)	0.163	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplemental table 4 Multivariate logistic regression analysis between major depressive disorder and a high brachial-ankle pulse wave velocity among subgroups

		No.	Odd ratios (95% CI)	P value	P value for interaction
Age, years	< 40	404	6.25 (1.34, 29.2)	**0.020**	0.415
	40-60	719	1.32 (0.54, 3.26)	0.544	
	≥ 60	211	2.62 (0.38, 18.0)	0.328	
Hypertension	No	1034	1.46 (0.63, 3.40)	0.380	0.774
	Yes	300	2.24 (0.56, 8.93)	0.251	
Diabetes mellitus	No	1116	1.48 (0.64, 3.42)	0.353	0.678
	Yes	218	2.09 (0.46, 9.49)	0.337	
FBG, mmol/L	< 5.6	1039	1.52 (0.67, 3.45)	0.322	0.478
	≥ 5.6	295	2.48 (0.55, 11.1)	0.237	
Total cholesterol, mmol/L	< 5.2	812	0.96 (0.37, 2.50)	0.932	0.111
	≥ 5.2	522	4.35 (1.49, 12.7)	**0.007**	
Triglycerides, mmol/L	< 1.7	659	0.94 (0.32, 2.83)	0.918	0.096
	≥ 1.7	675	2.77 (1.33, 5.81)	**0.007**	
HDL-C, mmol/L	< 1.0	85	4.22 (0.16, 109.5)	0.386	0.296
	≥ 1.0	1249	1.47 (0.70, 3.06)	0.308	
LDL-C, mmol/L	< 3.4	1136	1.14 (0.47, 2.72)	0.774	0.166
	≥ 3.4	208	6.09 (1.38, 26.8)	**0.017**	
BMI, kg/m^2	< 24	592	1.03 (0.42, 2.57)	0.943	0.190
	24-28	492	2.62 (0.65, 10.6)	0.177	
	≥ 28	250	9.16 (1.49, 56.4)	**0.017**	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	8-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	8-10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8-10
		(*e*) Describe any sensitivity analyses	8-10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	10-13
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	10-13
Outcome data	15*	Report numbers of outcome events or summary measures	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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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

Objective: To determine the independent relationship between depressive symptoms and arterial stiffness in a general population and explore possible interactive factors in the above relationship.

Design: A cross-sectional study.

Settings and participants: Consecutive participants who received routine health physical examinations in an affiliated hospital of a comprehensive university in Hunan Province, China, between September 2013 and March 2014 were examined. After exclusion, a total of 1334 subjects aged 22-77 years were recruited for the final analysis.

Measures: The Patient Health Questionnaire-9 (PHQ-9) was applied to assess the degrees of depressive symptoms as follows: non-depression: PHQ-9 <5, mild depressive symptoms: PHQ-9 ≥5 and <10, and moderate to severe depressive symptoms: PHQ-9 ≥10. Brachial-ankle pulse wave velocity (baPWV) was performed to reflect arterial stiffness and a high baPWV was defined as above the upper 20th percentile of baPWV (1576 cm/s) in all subjects.

Results: Overall, there was a slight increase in baPWV across elevated degrees of depressive symptoms (p=0.025). Multivariate linear and logistic regression analyses revealed that depressive symptoms were independently associated with baPWV and a high baPWV. Subgroup analyses indicated that the associations were predominant in subjects aged ≥47 years (the median of all subjects), whose systolic blood pressure (SBP) was ≥120 mmHg or whose fasting blood glucose (FBG) was ≥6.1 mmol/L (interaction

p<0.05 for all) based on both linear and logistic regressions. While the association between moderate to severe depressive symptoms and baPWV or a high baPWV lost statistical significance after adjusting for baseline confounders, the association remained in female subjects (interaction p<0.05).

Conclusions: Depressive symptoms are independently associated with arterial stiffness, especially in relatively older subjects and those with high-normal SBP or FBG. However, the relationship between moderate to severe depressive symptoms and arterial stiffness is prominent in only female subjects.

Strengths and limitations of this study

1. The current study first analysed the association between depressive symptoms and arterial stiffness in a Chinese general population which covered a wide range of ages (22-77 years).
2. The extent of depression was reflected by the presence of depressive symptoms and moderate to severe depressive symptoms, and the independent relationships of these indicators with baPWV were examined in multivariate linear and logistic regression models.
3. Various subgroup analyses were conducted to explore whether any interacting factors existed in the connection between depressive symptoms and arterial stiffness.
4. A clinical diagnosis of major depressive disorder (MDD) in the subjects with moderate to severe depressive symptoms were not performed by diagnostic interviews according to DSM-IV criteria.

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

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychological disorders that affects health-related quality of life.[1] The global prevalence of MDD is 4.7%, and the lifetime rates of MDD vary greatly across different races, cultures and regions, ranging from 3.3% in mainland China to 18.6% in the United States.[2-4] Furthermore, the prevalence of MDD in patients with cardiovascular disease (CVD) is much higher:[5] 26.8% in hypertensive subjects,[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 depressed middle-aged and older adults also reported a diagnosis of comorbid CVD.[10] Therefore, there exist manifold interrelations between MDD and CVD in which 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 one of the markers of hypertension-mediated organ damage, and should be assessed among hypertensive patients according to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) hypertension guidelines.[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 concerning the relationship between depression and arterial stiffness are limited, and the results remain controversial. The Rotterdam Study (n=3704, ≥60 years) and the 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 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] In addition, the Netherlands Study of Depression and Anxiety Study (n=635, aged 20-66 years) also failed to identify the association between depression sensitivity and central arterial stiffness assessed by augmentation index.[22]

The main reasons for the abovementioned diverse findings might be the differences in the enrolled population, the assessment methods of arterial stiffness, and the criteria

for defining depression. We noticed 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 associations (if present) differed among subgroups according to various factors; this type of analysis was seldom performed in previous studies.

METHODS

Study subjects

The current study followed a cross-sectional design, and a general Chinese population was recruited. We collected the medical information of consecutive participants who received routine health physical examinations 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: an age of <18 or ≥80 years; a history of myocardial infarction, heart failure, stroke, cancer, 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 of 47.1 ± 11.7 years) were ultimately analysed in this study. Our study protocol was approved by the Ethics Committee of Xiangya Hospital, Central South University, and all participants provided written informed consent.

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 past medical histories of hypertension and diabetes mellitus. Height was measured while the participants were without shoes to the nearest 0.1 cm, and weight was measured with the participants in light indoor clothing and without shoes to the nearest 0.1 kg. Then, 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 minutes of rest. The means of two separate readings of blood pressure with an interval of 3-5 minutes between measurements were used. Fasting blood samples were collected from antecubital veins after an 8-hour overnight fast in the morning of the health check-up days. Fasting blood glucose (FBG), 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.

Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, a self-reported history of diagnosed hypertension, or current anti-hypertensive treatment. Diabetes mellitus was defined as FBG ≥7.0 mmol/L, a self-reported history of diagnosed

diabetes mellitus, or current hypoglycaemic therapy. The diagnosis of hypertension and diabetes mellitus was based on current relevant guidelines.

The PHQ-9, which consists of 9 items that are each scored from 0-3 points, was used in our study to assess depressive symptoms. Subjects were defined as having no depressive symptoms if their PHQ-9 score was less than 5, mild depressive symptoms if they had a PHQ-9 score between 5 and 9 and moderate to severe depressive symptoms if their PHQ-9 score was equal to or greater than 10. And a cut-off value of 10 on the PHQ-9 has been widely used in epidemiological studies for diagnosing MDD with a high sensitivity (85%) and specificity (89%).[23] Thus, in the present study, the PHQ-9 was used as both continuous variable and categorical variable. Specifically, the subjects were divided by the presence of depressive symptoms and moderate to severe depressive symptoms, and the latter hinted a clinical diagnosis of MDD might exist.

BaPWV was automatically measured using baPWV instruments (model BP-203RPE, Colin, Komaki City, Japan) by trained staff following the standard procedure. Participants were measured in the supine position after 10 minutes of rest in a quiet room with a comfortable temperature. Bilateral measurements of baPWV were recorded, and the higher reading was used for analysis. The validation of this automatic device and its reproducibility have been previously demonstrated. We defined a high baPWV as more than the 80th percentile of all subjects (which was 1576 cm/s).

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. Actually, in the final analysis after exclusion, all baseline characteristics were acquired from the entire population, so no missing data existed in our study. All subjects were divided into three groups according to their degrees of depressive symptoms determined by the PHQ-9 score. Continuous variables are presented as the means and standard deviations, while categorical variables are presented as frequencies and percentages. Comparisons between groups were performed using analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. The independent association between PHQ-9 and baPWV (both as continuous variable) was examined by multivariate linear regression. Multivariate linear regression and multivariate logistic regression models were used to assess the associations of depressive symptoms and moderate to severe depressive symptoms with baPWV and a high baPWV, respectively. Analyses were also stratified to examine any possible interactions of depressive symptoms and moderate to severe depressive symptoms with baPWV and a high baPWV using multiple clinically meaningful cut-off values of baseline parameters: SBP divided by 120 mmHg and DBP divided by 80 mmHg which were cut-off values of an optimal blood pressure for all ages from 16 years;[12] a FBG level of 5.6 and 6.1 mmol/L for diagnosing elevated blood glucose and impaired fasting glucose (IFG), respectively, as recommended by the 2005 National Cholesterol Education Program (NCEP) ATP3 and the World Health Organization (WHO) 1999 criteria;

abnormal lipid profiles based on the Korean guideline of dyslipidaemia for the general population;[24] and BMIs of 24 or 28 kg/m^2 were used to identify overweight and obesity, respectively, for the Chinese population. All baseline factors were included in the adjusted models, unless the variable was used to classify the subgroup. All analyses were conducted using the statistical software packages R (R 3.4.3, http://www.R-project.org, The R Foundation) and EmpowerStats (www.empowerstats.com, X&Y solutions, Inc., Boston, MA). 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 the interpretation of the results of the current study.

RESULTS

Baseline characteristics

After exclusion, a total of 1334 subjects were finally included in our final analysis (mean age 41.7 ± 11.7 years, 64.5% male). The detailed baseline characteristics of all subjects by degrees of depressive symptoms are described in table 1. The results indicated that fewer male participants were present across increasing degrees of depressive symptoms (67.8%, 52.9% and 48.1%, p<0.001), as well as a decreasing proportion of participants who smoked (46.5%, 43.2% and 29.6%, p=0.040). There was no significant difference in

terms of age, comorbidities of hypertension or diabetes mellitus, levels of SBP or DBP, BMI, FBG, or lipid profiles. As expected, a higher baPWV was found in subjects with more severe depressive symptoms (1343.6 ± 264.4, 1372.9 ± 312.3 and 1436.5 ± 314.4 cm/s, p=0.025).

PHQ-9 and baPWV

An independent and significant association existed between the score of PHQ-9 and baPWV in the multivariate linear regression analysis (beta-coefficient: 5.73; 95% confidence interval [CI]: 2.07-9.40; p=0.002), in which all baseline factors were adjusted.

Depressive symptoms and baPWV

Then, we performed multivariate linear regressions for the association between depressive symptoms and baPWV among all subjects and in subgroups. Interaction analyses were also conducted for any possible interactive effect. Table 2 shows a significant association between depressive symptoms and baPWV in both crude and adjusted models (adjusted model: beta-coefficient: 46.3; 95% CI: 17.0-75.7; p=0.002). In addition, the associations between depressive symptoms and baPWV were stronger in subgroups of individuals whose age was ≥47 years (the median of all subjects, beta-coefficient: 77.0 versus 22.9, interaction p=0.030), subjects with diabetes mellitus (beta-coefficient: 124.9 versus 24.8, interaction p=0.005), subjects with a SBP ≥120 mmHg (beta-coefficient: 64.0 versus 2.75, interaction p=0.049), and subjects with FBG ≥6.1

mmol/L (beta-coefficient: 105.2 versus 31.5, interaction p=0.038). However, no significant interactions were identified for subgroups of sex, smoking status, hypertension or DBP with a cut-off of 80 mmHg. Similarly, no significant results were shown for subgroups of age (grouped by 40 and 60 years), FBG (5.6 mmol/L), lipid parameters or BMI (presented in supplemental table 1).

Moderate to severe depressive symptoms and baPWV

We also conducted multivariate linear regressions for the association between moderate to severe depressive symptoms and baPWV among all subjects and in subgroups, and for a consistent format, we presented the results of subgroups in table 3 in the same way as in table 2. The results revealed a significant correlation between moderate to severe depressive symptoms and baPWV in the crude model (beta-coefficient: 87.7; 95% CI: 12.7-162.7; p=0.022); however, the association was attenuated and statistically nonsignificant after adjusting for confounders (beta-coefficient: 57.6; 95% CI: -3.0 to 118.2; p=0.063). Subgroup analyses showed that a significant association existed among female subjects (beta-coefficient: 133.6, 95% CI: 53.5-213.8, p=0.001) and non-smokers (beta-coefficient: 91.0, 95% CI: 25.8-156.2, p=0.006), but only the interaction analysis for subgroup by sex reached statistical significance (interaction p=0.022). No meaningful results were obtained in subgroups of age, smoking status, hypertension, diabetes mellitus, SBP, DBP and FBG. Subgroup analyses based on other classification methods of age, FBG, lipid profiles and BMI are described in supplemental table 2, and none of the

interaction results were significant.

Depressive symptoms, moderate to severe depressive symptoms and a high baPWV

As described hereinbefore, we defined a high baPWV by the 80th percentile of baPWV among all subjects. Then, we conducted multivariate logistic regression analysis with depressive symptoms, moderate to severe depressive symptoms and a high baPWV among all subjects and in the subgroups, and the results including the forest plots of odds ratios (ORs) are presented in figure 1 and figure 2, respectively. As shown in figure 1, the crude OR of depressive symptoms and a high baPWV was 1.53 (95% CI: 1.12-2.08, p=0.008), and the result was similar after adjusting for all baseline factors (OR: 1.61, 95% CI: 1.12-2.31, p=0.011). For subgroup analyses, a significant interaction between depressive symptoms and a high baPWV existed in subgroups of age divided by a cut-off of 47 years (OR: 2.16 [1.40-3.34] versus 0.91 [0.45-1.84], interaction p=0.019), SBP grouped by a cut-off of 120 mmHg (OR: 1.95 [1.29-2.97] versus 0.79 [0.32-1.94], interaction p=0.041) and FBG classified by a cut-off of 6.1 mmol/L (OR: 3.58 [1.68-7.63] versus 1.31 [0.88-1.94], interaction p=0.029). Significant ORs were also obtained among female subjects (OR: 2.53, 95% CI: 1.36-4.37, p=0.004), but further interaction analysis was not significant (interaction p=0.160). For the relationship between moderate to severe depressive symptoms and a high baPWV, a significant correlation was obtained only in the crude model (OR: 1.90; 95% CI: 1.05-3.43, p=0.033), and the result lost statistical

significance after adjusting for confounders as described in figure 2 (OR: 1.59, 95% CI: 0.79-3.21, p=0.198). With respect to subgroup analyses, significant ORs were obtained only among females (OR: 5.54; 95% CI: 2.05-14.97, p<0.001), and the interaction effect was significant (interaction p=0.003). In the same manner as in table 2 and table 3, we also divided all participants into subgroups to examine the interactive effects of other baseline parameters in the relationship of depressive symptoms, moderate to severe depressive symptoms and a high baPWV, but none of the results were significant (shown in supplemental table 3 and supplemental table 4).

DISCUSSION

In the current cross-sectional study, we established an independent association between depressive symptoms and arterial stiffness in a general population. Subgroup analyses indicated that the abovementioned association was most important in those older than 47 years, whose SBP was ≥120 mmHg or whose FBG was ≥6.1 mmol/L; the association was examined both in linear and logistic regressions. While the correlation between moderate to severe depressive symptoms and arterial stiffness lost significance after adjusting for confounding factors, this association remained notable among females, and the interaction was statistically significant.

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 the association

between depressive symptoms and arterial stiffness reflected by cfPWV.[21] The association between moderate to severe depressive symptoms and arterial stiffness lost statistical significance after adjusting for baseline factors in the present study, which was not consistent with the results of previous studies.[16,17] Interestingly, the Maastricht Study revealed that the independent association between depressive symptoms, MDD and arterial stiffness examined by cfPWV existed in only the middle-aged male subgroup (aged 40-60 years).[20] In contrast, our results indicated that the link between moderate to severe depressive symptoms and arterial stiffness was present only in females (interaction $p<0.05$), which had not been described before. The prevalence of MDD among females largely exceeds that among males, which is a difference that has been reported worldwide.[25] This sex difference was also exhibited in specific depressive symptoms; for instance, more depressed females tended to gain weight than males.[26] Moreover, an age-sex interaction was found in regard to the increase in carotid arterial stiffness.[27] It is possible that sex might have an interaction effect on the relationship between depression and arterial stiffness, but which gender is more vulnerable to the influence of depression on arterial stiffness seems conflicting according to our findings.

With respect to age, which was divided according to the median age of the entire sample in our study, we provided new information that subjects older than 47 years were more vulnerable to the impact of depressive symptoms on arterial stiffness, but the same results were not found for moderate to severe depressive symptoms. Indeed, only the Maastricht Study performed a subgroup analysis by age, and they found that the

association of depressive symptoms and MDD with arterial stiffness was notable in subjects younger than 60 years, especially among males.[20] We covered a wider range of ages (22-77 years) than the Maastricht Study (45-75 years). We also divided the sample according to the age of 60 years as in the Maastricht Study and evaluated the interaction between age and sex, but the results remained nonsignificant. It should be noted that the cohort of the Maastricht Study included diabetic individuals according to their study design.[28] The prevalence of diabetes mellitus was 27% among subjects without depressive disorder and 49% among participants with MDD in the Maastricht Study;[20] these figures were higher than those in other cohorts including ours (16.3%). Importantly, the age range in the Maastricht Study was relatively limited compared to that in ours. Therefore, the large demographic difference might explain the different results, and future studies with subjects with a wide range of ages are needed to verify the role of age and sex in the connection between depression and arterial stiffness.

Another novel finding of the current study was that FBG ≥6.1 mmol/L affected the relationship between depressive symptoms and arterial stiffness. Undoubtedly, diabetes mellitus or elevated plasma glucose is a well-known traditional risk factor for CVD and can accelerate the progression of arterial stiffness. Meta-analyses have indicated that type 2 diabetes mellitus (T2DM) is a risk factor for new-onset depression and that depression is also inversely associated with incident T2DM.[29,30] However, one recent study implied that the association between T2DM and MDD, which was examined at the epidemiologic and genetic levels, does not exist, leading to controversial results.[31] Therefore, whether

diabetes mellitus or FBG ≥6.1 mmol/L is a reliable interaction factor between depression and arterial stiffness still needs further investigation to be verified.

We also classified the subjects by a SBP of 120 mmHg and a DBP of 80 mmHg, which were cut-off values for an optimal blood pressure for all individuals older than 16 years of age according to the current hypertension guidelines.[12] And a significant interactive effect was obtained for SBP divided by 120 mmHg in the association between depressive symptoms and arterial stiffness. Elevated SBP is a traditional risk factor for CVD and affects the increase in arterial stiffness that occurs with ageing;[32] one longitudinal investigation revealed that in addition to SBP >140 mmHg, SBP between 120 and 139 mmHg was also associated with an increase in PWV compared with the PWV associated with SBP <120 mmHg.[32] However, longitudinal studies have obtained inconsistent results regarding the association between hypertension and depression.[33,34] In addition, one study inferred that subjects with low blood pressure (SBP <120 mmHg or DBP <75 mmHg) were at increased risk of incident depression compared with those with normal blood pressure among the elderly.[33] Another study revealed that anxiety or depression at baseline was associated with low blood pressure during follow-up.[35] The interaction role of SBP with depressive symptoms and arterial stiffness was first reported in our study. Limited by the cross-sectional study design, we could not fully elucidate the causality or the underlying mechanism, but one plausible explanation is that increased SBP and depressive symptoms might jointly promote the development of arterial stiffness. We also noticed that older subjects with depressive symptoms tended to have a lower night-time

SBP fall,[36] and subjects with white coat hypertension (WCH) or masked hypertension (MH) examined by ambulatory blood pressure monitoring (ABPM) had greater arterial stiffness.[37] Besides, older subjects with depression were associated with increased prevalence of left ventricular hypertrophy (LVH), which was independent of blood pressure levels.[38] 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.

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,[39] a chronic and mild inflammatory response participates in the emergence of depression from childhood to adulthood, and a variety of proinflammatory cytokines are involved in this process.[40] In addition, endothelial dysfunction is independently associated with depressive disorders.[41] Endothelial damage is modulated by selective serotonin reuptake inhibitor (SSRI) treatment in patients with MDD and in vitro cell models.[42] Dysregulation of the ANS, especially sympathetic over-activity, and activated proinflammatory cytokines can cause imbalances in the kynurenine pathway, leading to MDD.[43,44] 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.[45,46] Finally, depressed patients are vulnerable to the adoption of unhealthy lifestyle behaviours such

as smoking, overeating (leading to obesity, dyslipidaemia) and a stressful emotional state, all of which are risk factors for coronary artery disease (CAD).[47]

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 from our study. In addition, in some studies, standard diagnostic interviews according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were performed to achieve the diagnosis of MDD,[16,19,20] while in others, certain diagnostic scale was used instead.[16,17,20,21,48,49] 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 the PHQ-9 to screen MDD was both highly sensitive (85%) and specific (89%),[23] further studies with optimal designs are still needed. In addition, the covariate data we collected were limited, and we did not have information regarding socioeconomic level,[50,51] education level, physical activity level, dietary habits, assessment of cognitive impairment[52] and medications taken by participants as different anti-depressant medications might have opposite impact on arterial stiffness,[53] all of which might have influenced our results. Finally, a lack of statistical power might still existed although we had a relatively large sample size. Specially, distinguished trends emerged among subgroups of hypertension in the association between depressive symptoms and baPWV and subgroups of diabetes mellitus in the relationship between depressive symptoms and a high baPWV, however, the results of interaction were non-significant on the borderline.

CONCLUSION

Our findings suggested that depressive symptoms were independently associated with arterial stiffness, and further interaction analysis showed that subjects with depressive symptoms who were older than 47 years and who had a SBP ≥120 mmHg or FBG ≥6.1 mmol/L were more susceptible to advanced arterial stiffness. However, the independent relationship between moderate to severe depressive symptoms and arterial stiffness or severe arterial stiffness was restricted to only female subjects. Our results suggest that specific populations might need extra attention in regard to the prevention of arterial stiffness due to the effect of depression.

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REFERENCES

1. Cao Y, Li W, Shen J, Malison RT, Zhang Y, Luo X. Health-related quality of life and symptom severity in Chinese patients with major depressive disorder. *Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists.* 2013;5(4):276-283.
2. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological medicine.* 2013;43(3):471-481.
3. Gu L, Xie J, Long J, et al. Epidemiology of major depressive disorder in mainland china: a systematic review. *PloS one.* 2013;8(6):e65356.
4. Gonzalez HM, Tarraf W, Whitfield KE, Vega WA. The epidemiology of major depression and ethnicity in the United States. *Journal of psychiatric research.* 2010;44(15):1043-1051.
5. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *European heart journal.* 2014;35(21):1365-1372.
6. Li Z, Li Y, Chen L, Chen P, Hu Y. Prevalence of Depression in Patients With Hypertension: A Systematic Review and Meta-Analysis. *Medicine.* 2015;94(31):e1317.
7. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology.* 2006;48(8):1527-1537.
8. Osler M, Martensson S, Wium-Andersen IK, et al. Depression After First Hospital Admission for Acute Coronary Syndrome: A Study of Time of Onset and Impact on Survival. *American journal of*

epidemiology. 2016;183(3):218-226.

9. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation.* 2014;129(12):1350-1369.
10. Gonzalez HM, Tarraf W. Comorbid cardiovascular disease and major depression among ethnic and racial groups in the United States. *International psychogeriatrics.* 2013;25(5):833-841.
11. Tomiyama H. Arterial Stiffness: Is This a Marker for the Current Status or Future? *Journal of atherosclerosis and thrombosis.* 2016;23(9):1026-1027.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal.* 2018;39(33):3021-3104.
13. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *Journal of the American College of Cardiology.* 2014;63(7):636-646.
14. Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. *Hypertension (Dallas, Tex. : 1979).* 2017;69(6):1045-1052.
15. Vlachopoulos C, Aznaouridis K, Terentes-Printzios D, Ioakeimidis N, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with brachial-ankle elasticity index: a systematic review and meta-analysis. *Hypertension (Dallas, Tex. : 1979).* 2012;60(2):556-562.
16. Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. *Journal of the American Geriatrics Society.* 2003;51(8):1105-1110.
17. van Sloten TT, Mitchell GF, Sigurdsson S, et al. Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. *Journal of psychiatry & neuroscience : JPN.* 2016;41(3):162-168.
18. Dietz LJ, Matthews KA. Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2011;48(6):579-584.
19. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Depression, anxiety, and arterial stiffness. *Biological psychiatry.* 2011;69(8):795-803.
20. Onete V, Henry RM, Sep SJS, et al. Arterial stiffness is associated with depression in middle-aged men - the Maastricht Study. *Journal of psychiatry & neuroscience : JPN.* 2018;43(2):111-119.
21. Lewis TT, Sutton-Tyrrell K, Penninx BW, et al. Race, psychosocial factors, and aortic pulse wave velocity: the Health, Aging, and Body Composition Study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2010;65(10):1079-1085.
22. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Sensitivity to depression or anxiety and subclinical cardiovascular disease. *Journal of affective disorders.* 2013;146(1):126-131.
23. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2012;184(3):E191-196.
24. 2015 Korean Guidelines for the Management of Dyslipidemia: Executive Summary (English

Translation). *Korean circulation journal.* 2016;46(3):275-306.

25. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological bulletin.* 2017;143(8):783-822.
26. Schuch JJ, Roest AM, Nolen WA, Penninx BW, de Jonge P. Gender differences in major depressive disorder: results from the Netherlands study of depression and anxiety. *Journal of affective disorders.* 2014;156:156-163.
27. Vermeersch SJ, Rietzschel ER, De Buyzere ML, et al. Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population. *Journal of hypertension.* 2008;26(7):1411-1419.
28. Schram MT, Sep SJ, van der Kallen CJ, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *European journal of epidemiology.* 2014;29(6):439-451.
29. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia.* 2006;49(5):837-845.
30. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia.* 2010;53(12):2480-2486.
31. Samaan Z, Garasia S, Gerstein HC, et al. Lack of association between type 2 diabetes and major depression: epidemiologic and genetic evidence in a multiethnic population. *Translational psychiatry.* 2015;5:e618.
32. AlGhatrif M, Strait JB, Morrell CH, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension (Dallas, Tex. : 1979).* 2013;62(5):934-941.
33. Godin O, Elbejjani M, Kaufman JS. Body mass index, blood pressure, and risk of depression in the elderly: a marginal structural model. *American journal of epidemiology.* 2012;176(3):204-213.
34. Zimmerman JA, Mast BT, Miles T, Markides KS. Vascular risk and depression in the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE). *International journal of geriatric psychiatry.* 2009;24(4):409-416.
35. Hildrum B, Mykletun A, Holmen J, Dahl AA. Effect of anxiety and depression on blood pressure: 11-year longitudinal population study. *The British journal of psychiatry : the journal of mental science.* 2008;193(2):108-113.
36. Scuteri A, Spalletta G, Cangelosi M, et al. Decreased nocturnal systolic blood pressure fall in older subjects with depression. *Aging clinical and experimental research.* 2009;21(4-5):292-297.
37. Scuteri A, Morrell CH, Orru M, et al. Gender specific profiles of white coat and masked hypertension impacts on arterial structure and function in the SardiNIA study. *International journal of cardiology.* 2016;217:92-98.
38. Scuteri A, Castello L, Coluccia R, Modestino A, Nevola E, Volpe M. Depression is associated with increased occurrence of left ventricle concentric geometry in older subjects independently of blood pressure levels. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2011;21(12):915-921.
39. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC medicine.* 2013;11:200.

40. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin.* 2014;140(3):774-815.
41. van Dooren FE, Schram MT, Schalkwijk CG, et al. Associations of low grade inflammation and endothelial dysfunction with depression - The Maastricht Study. *Brain, behavior, and immunity.* 2016;56:390-396.
42. Lopez-Vilchez I, Diaz-Ricart M, Navarro V, et al. Endothelial damage in major depression patients is modulated by SSRI treatment, as demonstrated by circulating biomarkers and an in vitro cell model. *Translational psychiatry.* 2016;6(9):e886.
43. Won E, Kim YK. Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression. *Current neuropharmacology.* 2016;14(7):665-673.
44. Wang SY, Duan KM, Tan XF, et al. Genetic variants of the kynurenine-3-monooxygenase and postpartum depressive symptoms after cesarean section in Chinese women. *Journal of affective disorders.* 2017;215:94-101.
45. Whelton SP, Blankstein R, Al-Mallah MH, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension (Dallas, Tex. : 1979).* 2013;62(3):477-484.
46. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. *Diabetes care.* 2013;36(8):2351-2358.
47. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological psychiatry.* 2003;54(3):216-226.
48. van Sloten TT, Boutouyrie P, Tafflet M, et al. Carotid Artery Stiffness and Incident Depressive Symptoms: The Paris Prospective Study III. *Biological psychiatry.* 2018.
49. Lin IM, Lu HC, Chu CS, Lee CS, Lu YH, Lin TH. The Relationship between Brachial-Ankle Pulse Wave Velocity and Depressive Symptoms among Patients with Coronary Artery Disease. *Acta Cardiologica Sinica.* 2017;33(3):303-309.
50. Wiernik E, Lemogne C, Thomas F, et al. Perceived stress, common carotid intima media thickness and occupational status: The Paris Prospective Study III. *International journal of cardiology.* 2016;221:1025-1030.
51. Cho Y, Lim TH, Kang H, Lee Y, Lee H, Kim H. Socioeconomic status and depression as combined risk factors for acute myocardial infarction and stroke: A population-based study of 2.7 million Korean adults. *Journal of psychosomatic research.* 2019;121:14-23.
52. Scuteri A, Wang H. Pulse wave velocity as a marker of cognitive impairment in the elderly. *Journal of Alzheimer's disease : JAD.* 2014;42 Suppl 4:S401-410.
53. Scuteri A, Modestino A, Fedullo F, Assisi AP, Gianni W. Depression treatment selectively modifies arterial stiffness in older participants. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2013;68(6):719-725.

Figure legends

Figure 1 Multivariate logistic regression analysis between depressive symptoms and a high brachial-ankle pulse wave velocity among all subjects and subgroups.

CI, confidence interval; FBG, fasting blood glucose; SBP, systolic blood pressure.

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

Figure 2 Multivariate logistic regression analysis between moderate to severe depressive symptoms and a high brachial-ankle pulse wave velocity among all subjects and subgroups.

CI, confidence interval; FBG, fasting blood glucose; SBP, systolic blood pressure.

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

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

Variables	No depressive symptoms	Mild depressive symptoms	Moderate to severe depressive symptoms	P value
No. (%)	1053 (78.9)	227 (17.0)	54 (4.0)	
Males (%)	714 (67.8)	120 (52.9)	26 (48.1)	**<0.001**
Age, years	46.9 ± 11.8	47.5 ± 11.2	48.5 ± 11.7	0.523
Smoking (%)	490 (46.5)	98 (43.2)	16 (29.6)	**0.040**
Hypertension (%)	248 (23.6)	39 (17.2)	13 (24.1)	0.109
Diabetes mellitus (%)	165 (15.7)	40 (17.6)	13 (24.1)	0.225
SBP, mmHg	126.1 ± 16.6	125.0 ± 16.5	127.9 ± 14.7	0.445
DBP, mmHg	75.0 ± 10.5	74.4 ± 9.7	73.8 ± 8.5	0.513
BMI, kg/m^2	24.7 ± 3.8	24.9 ± 4.3	23.8 ± 3.5	0.147
FBG, mmol/L	5.30 ± 1.58	5.32 ± 1.42	5.64 ± 1.92	0.300
Total cholesterol, mmol/L	5.00 ± 1.04	5.07 ± 1.04	5.27 ± 1.17	0.134
Triglycerides, mmol/L	2.12 ± 1.58	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
PHQ-9 score	1.28 ± 1.39	6.47 ± 1.36	13.20 ± 3.22	**<0.001**
baPWV, cm/s	1343.6 ± 264.4	1372.9 ± 312.3	1436.5 ± 314.4	**0.025**

Data are presented as the mean ± standard deviation or n (percentage) as appropriate.

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PHQ-9, the Patient Health Questionnaire-9; SBP, systolic blood pressure.

Table 2 Multivariate linear regression analysis between depressive symptoms and brachial-ankle pulse wave velocity among all subjects and subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
All subjects	Crude	1334	41.5 (5.3, 77.8)	**0.025**	
	Adjusted	1334	46.3 (17.0, 75.7)	**0.002**	
Sex	Male	860	49.5 (9.5, 89.6)	**0.016**	0.956
	Female	474	46.4 (4.1, 88.7)	**0.032**	
Age, years	< 47	672	22.9 (-14.4, 60.2)	0.229	**0.030**
	≥ 47	662	77.0 (27.9, 126.1)	**0.002**	
Smoking	No	730	34.6 (-0.7, 69.8)	0.055	0.212
	Yes	604	63.9 (14.2, 113.6)	**0.012**	
Hypertension	No	1034	32.1 (1.0, 63.3)	**0.044**	0.055
	Yes	300	91.2 (14.6, 167.8)	**0.020**	
Diabetes mellitus	No	1116	24.8 (-6.9, 56.4)	0.124	**0.005**
	Yes	218	124.9 (46.4, 203.4)	**0.002**	
SBP, mmHg	< 120	512	2.75 (-41.3, 46.8)	0.903	**0.049**
	≥ 120	822	64.0 (24.6, 103.5)	**0.002**	
DBP, mmHg	< 80	935	44.6 (11.0, 78.2)	**0.010**	0.591
	≥ 80	399	63.4 (2.1, 124.6)	**0.043**	
FBG, mmol/L	< 6.1	1134	31.5 (-0.1, 63.1)	0.051	**0.038**
	≥ 6.1	200	105.2 (22.7, 187.7)	**0.013**	

The results were adjusted for age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, body mass index, fasting blood glucose and lipid profiles if the variable was not stratified. CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; SBP, systolic blood pressure.

Table 3 Multivariate linear regression analysis between moderate to severe depressive symptoms and brachial-ankle pulse wave velocity among all subjects and subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
All subjects	Crude	1334	87.7 (12.7, 162.7)	**0.022**	
	Adjusted	1334	57.6 (-3.0, 118.1)	0.063	
Sex	Male	860	-13.7 (-101.8, 74.5)	0.762	**0.022**
	Female	474	133.6 (53.5, 213.8)	**0.001**	
Age, years	< 47	672	41.4 (-42.0, 124.9)	0.331	0.542
	≥ 47	662	54.3 (-39.5, 148.1)	0.257	
Smoking	No	730	91.0 (25.8, 156.2)	**0.006**	0.138
	Yes	604	-21.3 (-142.1, 99.4)	0.729	
Hypertension	No	1034	29.6 (-36.8, 96.0)	0.383	0.150
	Yes	300	129.7 (-11.6, 271.0)	0.073	
Diabetes mellitus	No	1116	36.2 (-30.8, 103.2)	0.290	0.178
	Yes	218	130.3 (-16.0, 276.5)	0.082	
SBP, mmHg	< 120	512	27.3 (-72.5, 127.1)	0.592	0.376
	≥ 120	822	74.9 (-2.9, 152.7)	0.060	
DBP, mmHg	< 80	935	52.4 (-14.5, 119.3)	0.125	0.690
	≥ 80	399	68.3 (-76.3, 212.8)	0.355	
FBG, mmol/L	< 6.1	1134	56.7 (-10.1, 123.4)	0.097	0.788
	≥ 6.1	200	78.8 (-73.2, 230.7)	0.331	

The results were adjusted for age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, body mass index, fasting blood glucose and lipid profiles if the variable was not stratified. CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; SBP, systolic blood pressure.

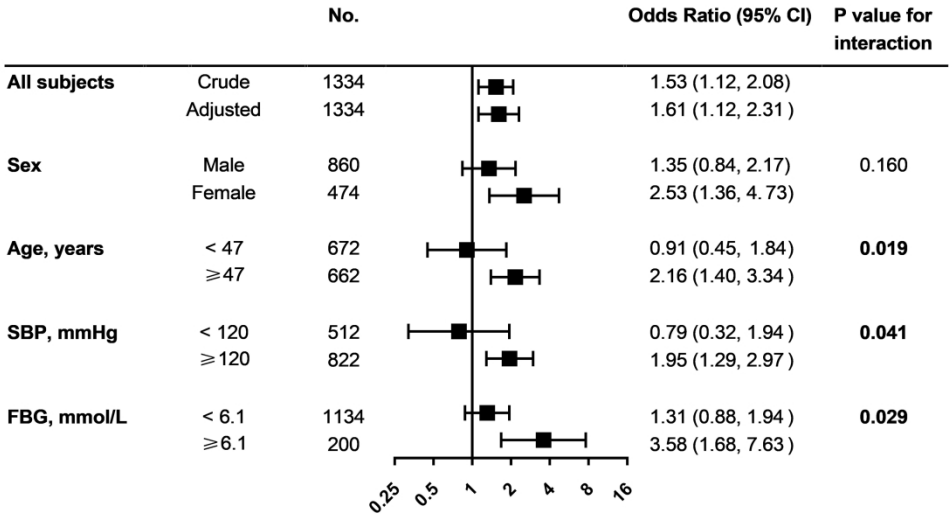

Figure 1

167x92mm (600 x 600 DPI)

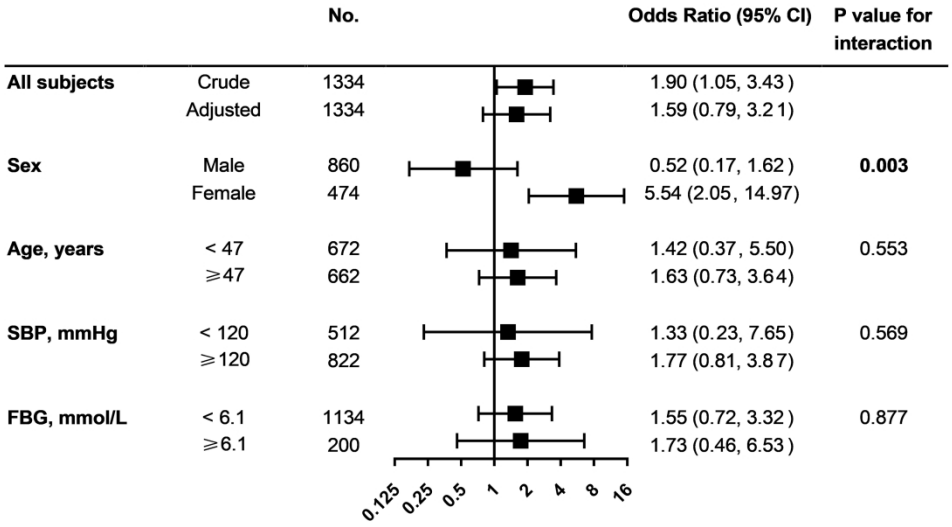

Figure 2

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Supplemental table 1 Multivariate linear regression analysis between depressive symptoms and brachial-ankle pulse wave velocity among subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
Age, years	< 40	404	27.5 (-22.1, 77.1)	0.278	0.532
	40-60	719	63.3 (21.9, 104.7)	**0.003**	
	≥ 60	211	73.6 (-17.6, 164.7)	0.115	
FBG, mmol/L	< 5.6	1039	31.1 (-1.5, 63.7)	0.062	0.083
	≥ 5.6	295	85.3 (17.4, 153.2)	**0.014**	
Total cholesterol, mmol/L	< 5.2	812	19.5 (-18.0, 56.9)	0.309	0.067
	≥ 5.2	522	83.4 (35.8, 131.0)	**<0.001**	
Triglycerides, mmol/L	< 1.7	659	37.1 (-10.8, 85.0)	0.130	0.838
	≥ 1.7	675	50.5 (4.9, 96.1)	**0.030**	
HDL-C, mmol/L	< 1.0	85	20.6 (-90.6, 131.8)	0.718	0.382
	≥ 1.0	1249	43.7 (13.2, 74.2)	**0.005**	
LDL-C, mmol/L	< 3.4	1136	37.6 (6.0, 69.2)	**0.020**	0.209
	≥ 3.4	208	97.0 (15.9, 178.1)	**0.020**	
BMI, kg/m^2	< 24	592	32.1 (-13.6, 77.7)	0.169	0.659
	24-28	492	58.1 (5.5, 110.7)	**0.031**	
	≥ 28	250	62.5 (5.7, 119.4)	**0.032**	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplemental table 2 Multivariate linear regression analysis between moderate to severe depressive symptoms and brachial-ankle pulse wave velocity among subgroups

		No.	Beta-coefficient (95% CI)	P value	P value for interaction
Age, years	< 40	404	82.7 (-24.4, 189.8)	0.131	0.647
	40-60	719	79.9 (-2.4, 162.3)	0.057	
	≥ 60	211	-0.06 (-202.4, 202.3)	0.999	
FBG, mmol/L	< 5.6	1039	38.0 (-29.1, 105.1)	0.267	0.086
	≥ 5.6	295	147.8 (8.66, 286.9)	**0.038**	
Total cholesterol, mmol/L	< 5.2	812	28.2 (-48.7, 105.2)	0.472	0.288
	≥ 5.2	522	107.8 (8.5, 207.0)	0.034	
Triglycerides, mmol/L	< 1.7	659	72.3 (-30.0, 174.6)	0.167	0.815
	≥ 1.7	675	94.8 (3.8, 185.8)	**0.042**	
HDL-C, mmol/L	< 1.0	85	21.5 (-171.2, 214.1)	0.828	0.545
	≥ 1.0	1249	53.8 (-10.1, 117.7)	0.099	
LDL-C, mmol/L	< 3.4	1136	45.6 (-24.4, 115.6)	0.202	0.547
	≥ 3.4	208	107.8 (-25.9, 241.6)	0.116	
BMI, kg/m^2	< 24	592	34.7 (-54.8, 124.3)	0.447	0.226
	24-28	492	52.0 (-54.9, 158.9)	0.341	
	≥ 28	250	198.7 (60.0, 337.4)	**0.005**	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressure, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplemental table 3 Multivariate logistic regression analysis between depressive symptoms and a high brachial-ankle pulse wave velocity among subgroups

		No.	Odd ratios (95% CI)	P value	P value for interaction
Age, years	< 40	404	1.76 (0.68, 4.56)	0.248	0.477
	40-60	719	1.46 (0.91, 2.36)	0.119	
	≥ 60	211	3.09 (1.40, 6.80)	**0.005**	
Hypertension	No	1034	1.56 (1.01, 2.42)	**0.044**	0.726
	Yes	300	1.76 (0.85, 3.65)	0.127	
Diabetes mellitus	No	1116	1.31 (0.86, 2.01)	0.207	0.085
	Yes	218	3.37 (1.48, 7.64)	**0.004**	
FBG, mmol/L	< 5.6	1039	1.50 (0.97, 2.21)	0.066	0.540
	≥ 5.6	295	1.98 (0.97, 4.06)	0.063	
Total cholesterol, mmol/L	< 5.2	812	1.23 (0.75, 2.04)	0.412	0.157
	≥ 5.2	522	2.50 (1.41, 4.43)	**0.002**	
Triglycerides, mmol/L	< 1.7	659	1.21 (0.72, 2.04)	0.466	0.192
	≥ 1.7	675	1.94 (1.25, 3.01)	**0.003**	
HDL-C, mmol/L	< 1.0	85	1.05 (0.14, 7.99)	0.964	0.926
	≥ 1.0	1249	1.63 (1.12, 2.37)	**0.011**	
LDL-C, mmol/L	< 3.4	1136	1.36 (0.90, 2.06)	0.140	0.082
	≥ 3.4	208	4.09 (1.60, 10.5)	**0.003**	
BMI, kg/m^2	< 24	592	1.25 (0.75, 2.08)	0.396	0.265
	24-28	492	2.70 (1.38, 5.29)	**0.004**	
	≥ 28	250	1.98 (0.76, 5.14)	0.163	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Supplemental table 4 Multivariate logistic regression analysis between moderate to severe depressive symptoms and a high brachial-ankle pulse wave velocity among subgroups

		No.	Odd ratios (95% CI)	P value	P value for interaction
Age, years	< 40	404	6.25 (1.34, 29.2)	**0.020**	0.415
	40-60	719	1.32 (0.54, 3.26)	0.544	
	≥ 60	211	2.62 (0.38, 18.0)	0.328	
Hypertension	No	1034	1.46 (0.63, 3.40)	0.380	0.774
	Yes	300	2.24 (0.56, 8.93)	0.251	
Diabetes mellitus	No	1116	1.48 (0.64, 3.42)	0.353	0.678
	Yes	218	2.09 (0.46, 9.49)	0.337	
FBG, mmol/L	< 5.6	1039	1.52 (0.67, 3.45)	0.322	0.478
	≥ 5.6	295	2.48 (0.55, 11.1)	0.237	
Total cholesterol, mmol/L	< 5.2	812	0.96 (0.37, 2.50)	0.932	0.111
	≥ 5.2	522	4.35 (1.49, 12.7)	**0.007**	
Triglycerides, mmol/L	< 1.7	659	0.94 (0.32, 2.83)	0.918	0.096
	≥ 1.7	675	2.77 (1.33, 5.81)	**0.007**	
HDL-C, mmol/L	< 1.0	85	4.22 (0.16, 109.5)	0.386	0.296
	≥ 1.0	1249	1.47 (0.70, 3.06)	0.308	
LDL-C, mmol/L	< 3.4	1136	1.14 (0.47, 2.72)	0.774	0.166
	≥ 3.4	208	6.09 (1.38, 26.8)	**0.017**	
BMI, kg/m^2	< 24	592	1.03 (0.42, 2.57)	0.943	0.190
	24-28	492	2.62 (0.65, 10.6)	0.177	
	≥ 28	250	9.16 (1.49, 56.4)	**0.017**	

The results were adjusted for sex, age, smoking status, hypertension, diabetes mellitus, systolic and diastolic blood pressures, fasting blood glucose, lipid profiles and body mass index if the variable was not stratified.

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	8-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	8-10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8-10
		(*e*) Describe any sensitivity analyses	8-10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	10-13
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	10-13
Outcome data	15*	Report numbers of outcome events or summary measures	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

Objective: To determine the independent relationship between depressive symptoms and arterial stiffness in the general Chinese population and explore possible interactive factors in the above relationship.

Design: A cross-sectional study.

Settings and participants: Consecutive participants who received routine health physical examinations in an affiliated hospital of a comprehensive university in Hunan Province, China, between September 2013 and March 2014 were examined. After exclusion, a total of 1334 subjects aged 22-77 years were recruited for the final analysis.

Measures: The Patient Health Questionnaire-9 (PHQ-9) was applied to assess the degrees of depressive symptoms as follows: 0-4 none depressive symptoms, 5-9 mild depressive symptoms, 10-27 moderate to severe depressive symptoms. Brachial-ankle pulse wave velocity (baPWV) was performed to reflect 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 to none depressive symptoms after adjusting for baseline confounders (beta-coefficient: 40.3; 95% CI: 6.6 to 74.1; and beta-coefficient: 87.7; 95% CI: 24.0 to 151.5; respectively). Further stratified analyses indicated that the relationships between degrees of depressive symptoms and baPWV were 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, significant association between moderate to severe depressive symptoms and baPWV was also obtained in female subjects who were younger than 60 years after adjustment, though the interactive effect was not significant (p for interaction=0.566).

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

Strengths and limitations of this study

1. The current study first analysed the association between depressive symptoms and arterial stiffness in the general Chinese population which covered a wide range of ages (22-77 years).
2. The extent of depression was reflected by mild depressive symptoms and moderate to severe depressive symptoms, and the independent relationships of these indicators with baPWV were examined in multivariate linear regression models.
3. Various subgroup analyses were conducted to explore whether any interacting factors existed in the connection between depressive symptoms and arterial stiffness.
4. A clinical diagnosis of major depressive disorder (MDD) in the subjects with moderate to severe depressive symptoms were not performed by diagnostic interviews according to DSM-IV criteria.
5. Due to the cross-sectional design of the study, no clear cause-effect conclusion could

be directly drawn.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychological disorders that affects health-related quality of life.[1] The global prevalence of MDD is 4.7%, and the lifetime rates of MDD vary greatly across different races, cultures and regions, ranging from 3.3% in mainland China to 18.6% in the United States.[2-4] Furthermore, the prevalence of MDD in patients with cardiovascular disease (CVD) is much higher:[5] 26.8% in hypertensive subjects,[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 depressed middle-aged and older adults also reported a diagnosis of comorbid CVD.[10] Therefore, there exist manifold interrelations between MDD and CVD in which 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 one of the markers of hypertension-mediated organ damage, and should be assessed among hypertensive patients according to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) hypertension guidelines.[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 concerning the relationship between depression and arterial stiffness are limited, and the results remain controversial. The Rotterdam Study (n=3704, ≥60 years) and the 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 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] In addition, the Netherlands Study of Depression and Anxiety Study (n=635, aged 20-66 years) also failed to identify the association between depression sensitivity and central arterial stiffness assessed by augmentation index.[22]

The main reasons for the abovementioned diverse findings might be the differences in the enrolled population, the assessment methods of arterial stiffness, and the criteria for defining depression. We noticed 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 associations (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 a general Chinese population was recruited. We collected the medical information of consecutive participants who received routine health physical examinations 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: an age of <18 or ≥80 years; a history of myocardial infarction, heart failure, stroke, cancer, 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 of 47.1 ± 11.7 years) were ultimately analysed in this study. Our study protocol was approved by

the Ethics Committee of Xiangya Hospital, Central South University, and all participants provided written informed consent.

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 past medical histories of hypertension and diabetes mellitus. Height was measured while the participants were without shoes to the nearest 0.1 cm, and weight was measured with the participants in light indoor clothing and without shoes to the nearest 0.1 kg. Then, 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 minutes of rest. The means of two separate readings of blood pressure with an interval of 3-5 minutes between measurements were used. Fasting blood samples were collected from antecubital veins after an 8-hour overnight fast in the morning of the health check-up days. Fasting blood glucose (FBG), 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 blood pressure: optimal

blood pressure, normal and high normal blood pressure, and hypertension, which was referred to the ESC and ESH hypertension guidelines.[12] An optimal blood pressure was defined as SBP <120 mmHg and DBP <80 mmHg; a normal and high normal blood pressure was defined as SBP between 120-139 mmHg and/or DBP between 80-89 mmHg; hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, a self-reported history of diagnosed hypertension, or under current anti-hypertensive treatment. Diabetes mellitus was defined as FBG ≥7.0 mmol/L, a self-reported history of diagnosed diabetes mellitus, or under current hypoglycaemic therapy. The diagnosis of dyslipidemia was made based on the Korean guideline of dyslipidaemia for the general population.[23] BMIs of 24 or 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 it consists of 9 items that are each scored from 0-3 points depending on the frequency of the listed problems in the last 2 weeks and a total PHQ-9 score ranges from 0 to 27. Scores are categorised as the following: 0-4 none depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression, and 20-27 severe depression.[24] And a cut-off value of 10 on the PHQ-9 has been widely used in epidemiological studies for diagnosing MDD with a high sensitivity (85%) and specificity (89%).[25] Referring to previous relevant studies and in consideration of the limited sample size of the subjects with a PHQ-9 score ≥10 (n=54), in the current study we classified the entire population into 3 groups according to PHQ-9 score: none

depressive symptoms (0-4), mild depressive symptoms (5-9), moderate to severe depressive symptoms (10-27).

BaPWV was automatically measured using baPWV instruments (model BP-203RPE, Colin, Komaki City, Japan) by trained staff following the standard procedure. Participants were measured in the supine position after 10 minutes of rest in a quiet room with a comfortable temperature. Bilateral measurements of baPWV were recorded, and the higher reading was used for analysis. The validation of this automatic device and its reproducibility have been previously demonstrated.

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. Actually, in the final analysis after exclusion, all baseline characteristics were acquired from the entire population, so no missing data existed in our study. All subjects were divided into three groups according to the degrees of depressive symptoms determined by the PHQ-9 score. Continuous variables are presented as the means and standard deviations, while categorical variables are described as frequencies and percentages. Comparisons between groups were performed using analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. The relationships between degrees of depressive symptoms and baPWV were examined in linear regressions with 3 models. Model 1 was

the crude model; model 2 adjusted for gender and age categories; model 3 further adjusted for smoking status, categories of blood pressure or BMI, comorbidities of diabetes mellitus or dyslipidemia. Besides, stratified analyses of baseline factors including gender, categories of age, blood pressure or BMI, smoking status, histories of diabetes mellitus or dyslipidemia were performed to test whether any potential interactive effects existed in the relationship between degrees of depressive symptoms and baPWV, and each stratification adjusted for all other factors except the stratification factor itself. And the group of none depressive symptoms was considered as reference in the above regression models. Finally, we specially explored the roles of age and gender in the association between moderate to severe depressive symptoms and baPWV divided by its standard deviation (275.8 cm/s). All analyses were conducted using the statistical software packages R (R 3.4.3, http://www.R-project.org, The R Foundation) and EmpowerStats (www.empowerstats.com, X&Y solutions, Inc., Boston, MA). 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 the interpretation of the results of the current study.

RESULTS

Baseline characteristics

After exclusion, a total of 1334 subjects were finally included in our final analysis (mean age 41.7 ± 11.7 years, 64.5% male). The detailed baseline characteristics of all subjects by degrees of depressive symptoms are described in table 1. The results indicated that fewer male participants were present 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 a 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 dyslipidemia, 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, 1372.9 ± 312.3 and 1436.5 ± 314.4 cm/s, p=0.025).

Depressive symptoms and baPWV

We assessed the associations between degrees of depressive symptoms and baPWV in linear regression models, and beta-coefficients and 95% confidence interval (CI) of both crude and adjusted models were shown in table 2, in which subjects with none depressive symptoms were considered as reference. In the 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 gender and age categories, significant results were observed for both mild depressive symptoms and moderate to severe depressive symptoms with baPWV. And

the results remained significant in model 3 which further adjusted for smoking status, blood pressure categories, diabetes mellitus, dyslipidemia and BMI categories (beta-coefficient: 40.3; 95% CI: 6.6 to 74.1; and beta-coefficient: 87.7; 95% CI: 24.0 to 151.5; for mild depressive symptoms, moderate to severe depressive symptoms, respectively).

Subgroup analysis of baseline factors

We also analysed the associations between degrees of depressive symptoms and baPWV in subgroups of gender, age, smoking status, blood pressure categories, diabetes mellitus, dyslipidemia and BMI categories in table 3, and the group of none depressive symptoms was still considered as reference. In stratified analysis of blood pressure categories, significant associations between mild depressive symptoms and baPWV were obtained in 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 significant association between moderate to severe depressive symptoms and baPWV was observed only in hypertension subgroup (beta-coefficient: 222.1; 95% CI: 57.1 to 387.1); and the result of interactive analysis was also significant (p for interaction=0.016). In subgroups of diabetes mellitus, significant associations in mild depressive symptoms, moderate to severe depressive symptoms with baPWV were obtained in those with diabetes mellitus (beta-coefficient: 154.1; 95% CI: 45.0 to 263.2; and beta-coefficient: 216.4; 95% CI:38.1 to 394.8; p for trend<0.001) and interactive analysis was also significant (p for interaction=0.004). For other subgroups of gender, age

categories, smoking status, dyslipidemia and BMI categories, none significant interactions were obtained (p for interaction>0.05 for all).

Subgroups of age and gender

The association between moderate to severe depressive symptoms and baPWV stratified by age and gender was presented in figure 1. There were significant associations between moderate to severe depressive symptoms and baPWV divided by its standard deviation in female subjects who were younger than 40 years (beta-coefficient: 0.76; 95% CI: 0.15 to 1.37) and aged 40-60 years (beta-coefficient: 0.66; 95% CI: 0.28 to 1.04) after adjusting for smoking status, blood pressure categories, diabetes mellitus, dyslipidemia, and BMI categories, although the interactive analysis was not significant (p for interaction=0.566).

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 degrees 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 moderate to severe depressive symptoms and arterial stiffness existed only in females who were younger than 60 years in stratified analysis of age and gender, however, the interactive

effect was not significant.

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 the association between depressive symptoms and arterial stiffness reflected by cfPWV.[21] In addition, it was remarkable that the Maastricht Study revealed that the independent associations between depressive symptoms, MDD and arterial stiffness examined by cfPWV existed in only the middle-aged male subgroup (aged 40-60 years),[20] hinting the potential interactive roles of age and gender. Noticing that the range of ages in the Maastricht Study was 40-75 years, and their study subjects were divided by the age of 60 years, we grouped our population by age of 40 and 60 years. Specially, we analysed the influence of age and gender in a similar manner which was used in the Maastricht Study. On the contrary, our results indicated that the significant associations between moderate to severe depressive symptoms and arterial stiffness were present only in females who were younger than 60 years, although the interaction effect was not statistically significant.

Actually, the prevalence of MDD among females largely exceeds that among males, which is a difference that has been reported worldwide.[26] This sex difference was also exhibited in specific depressive symptoms; for instance, more depressed females tended to gain weight than males.[27] Moreover, an age-sex interaction was found in regard to the increase in carotid arterial stiffness.[28] It is reasonable that sex might have an interaction effect on the relationship between depression and arterial stiffness, but which gender is

more vulnerable to the influence of depression on arterial stiffness seems conflicting according to our findings and the results in the Maastricht Study. It should be noted that the cohort of the Maastricht Study specially included diabetic individuals according to their study design.[29] And the prevalence of diabetes mellitus was 27% among subjects without depressive disorder and 49% among participants with MDD in the Maastricht Study,[20] 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 roles of age and gender in the connection between depression and arterial stiffness.

We also classified the whole population into 3 subgroups based on blood pressure as follows: optimal blood pressure; hypertension; and the rest which indicated normal or high normal blood pressure, which was referred to the current hypertension guidelines.[12] And a significant interactive effect was obtained for blood pressure categories in the association between degrees of depressive symptoms and arterial stiffness. One previous study showed that severe arterial stiffness was independently associated with the progression of blood pressure categories (for example, 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 SBP >140 mmHg, SBP between 120 and 139 mmHg was also associated with an increase in PWV compared with the PWV associated with SBP <120 mmHg.[31] However, longitudinal studies have obtained inconsistent results regarding the association between

hypertension and depression.[32,33] In addition, one study inferred that subjects with low blood pressure (SBP <120 mmHg or DBP <75 mmHg) were at increased risk of incident depression compared with those with normal blood pressure among the elderly.[32] Another study revealed that anxiety or depression at baseline was associated with low blood pressure during follow-up.[34] The interaction role of blood pressure with 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, but one plausible explanation is that elevated blood pressure and advanced depressive symptoms might jointly promote the development of arterial stiffness. We also noticed that older subjects with depressive symptoms tended to have a lower night-time SBP fall,[35] and subjects with white coat hypertension (WCH) or masked hypertension (MH) examined by ambulatory blood pressure monitoring (ABPM) had greater arterial stiffness.[36] Besides, older subjects with depression were associated with increased prevalence of left ventricular hypertrophy (LVH), 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 the 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 epidemiologic 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 to verify.

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 participates 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 (SSRI) treatment in patients with MDD and in vitro cell models.[44] Dysregulation of the ANS, especially sympathetic over-activity, 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, depressed patients are vulnerable to the adoption of unhealthy lifestyle behaviours such as smoking, overeating (leading to obesity, dyslipidaemia) and a stressful emotional state,

all of which are risk factors for coronary artery disease (CAD).[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 from our study. In addition, in some studies, standard diagnostic interviews according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were performed to achieve the diagnosis of MDD,[16,19,20] while in others, certain diagnostic scale was used instead.[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 the PHQ-9 score to screen MDD was both highly sensitive (85%) and specific (89%),[25] further studies with optimal designs are still needed. In addition, the covariate data we collected were limited, and we did not have information regarding socioeconomic level,[52,53] education level, physical activity level, dietary habits, assessment of cognitive impairment[54] and medications taken by participants as different anti-depressant medications might have opposite impact on arterial stiffness,[55] all of which might have influenced our results. Then, a lack of statistical power might still exist in our study although we had a relatively large sample size (n=1334). For example, distinguished trends emerged among subgroups of gender in the association between increased degrees of depressive symptoms and baPWV (p for trend<0.05 for both gender), however, the result of interaction was non-significant (p for interaction=0.072). Finally, our participants were from our health management center, and although no specific restrictions existed for those who decided to receive health check-ups, it should be noticed

that the costs of the examinations were paid by themselves. So, a selection bias existed and our sample could not fully represent a general population in the real world. Therefore, it should be cautious when extrapolating our results to other populations.

CONCLUSION

Our findings suggested that the degrees of depressive symptoms were independently associated with arterial stiffness, and further stratified analysis showed that subjects with depressive symptoms whose blood pressure 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 in regard to the prevention of arterial stiffness due to the effect of depression.

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval Our study protocol was approved by the Ethics Committee of Xiangya

Hospital, Central South University, and all the procedures were conducted in accordance with the ethical standards.

Provenance and peer review Not commissioned; externally peer reviewed.

Data-sharing statement The data from the current study are available from the corresponding author at chenglongzhang@csu.edu.cn upon reasonable request.

REFERENCES

1. Cao Y, Li W, Shen J, Malison RT, Zhang Y, Luo X. Health-related quality of life and symptom severity in Chinese patients with major depressive disorder. *Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists.* 2013;5(4):276-283.
2. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological medicine.* 2013;43(3):471-481.
3. Gu L, Xie J, Long J, et al. Epidemiology of major depressive disorder in mainland china: a systematic review. *PloS one.* 2013;8(6):e65356.
4. Gonzalez HM, Tarraf W, Whitfield KE, Vega WA. The epidemiology of major depression and ethnicity in the United States. *Journal of psychiatric research.* 2010;44(15):1043-1051.
5. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *European heart journal.* 2014;35(21):1365-1372.
6. Li Z, Li Y, Chen L, Chen P, Hu Y. Prevalence of Depression in Patients With Hypertension: A Systematic Review and Meta-Analysis. *Medicine.* 2015;94(31):e1317.
7. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic

review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology.* 2006;48(8):1527-1537.

8. Osler M, Martensson S, Wium-Andersen IK, et al. Depression After First Hospital Admission for Acute Coronary Syndrome: A Study of Time of Onset and Impact on Survival. *American journal of epidemiology.* 2016;183(3):218-226.
9. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation.* 2014;129(12):1350-1369.
10. Gonzalez HM, Tarraf W. Comorbid cardiovascular disease and major depression among ethnic and racial groups in the United States. *International psychogeriatrics.* 2013;25(5):833-841.
11. Tomiyama H. Arterial Stiffness: Is This a Marker for the Current Status or Future? *Journal of atherosclerosis and thrombosis.* 2016;23(9):1026-1027.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal.* 2018;39(33):3021-3104.
13. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *Journal of the American College of Cardiology.* 2014;63(7):636-646.
14. Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. *Hypertension (Dallas, Tex. : 1979).* 2017;69(6):1045-1052.
15. Vlachopoulos C, Aznaouridis K, Terentes-Printzios D, Ioakeimidis N, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with brachial-ankle elasticity index: a systematic review and meta-analysis. *Hypertension (Dallas, Tex. : 1979).* 2012;60(2):556-562.
16. Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. *Journal of the American Geriatrics Society.* 2003;51(8):1105-1110.
17. van Sloten TT, Mitchell GF, Sigurdsson S, et al. Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. *Journal of psychiatry & neuroscience : JPN.* 2016;41(3):162-168.
18. Dietz LJ, Matthews KA. Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2011;48(6):579-584.
19. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Depression, anxiety, and arterial stiffness. *Biological psychiatry.* 2011;69(8):795-803.
20. Onete V, Henry RM, Sep SJS, et al. Arterial stiffness is associated with depression in middle-aged men - the Maastricht Study. *Journal of psychiatry & neuroscience : JPN.* 2018;43(2):111-119.
21. Lewis TT, Sutton-Tyrrell K, Penninx BW, et al. Race, psychosocial factors, and aortic pulse wave velocity: the Health, Aging, and Body Composition Study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2010;65(10):1079-1085.
22. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Sensitivity to depression or anxiety and subclinical cardiovascular disease. *Journal of affective disorders.* 2013;146(1):126-131.

23. 2015 Korean Guidelines for the Management of Dyslipidemia: Executive Summary (English Translation). *Korean circulation journal.* 2016;46(3):275-306.
24. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine.* 2001;16(9):606-613.
25. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2012;184(3):E191-196.
26. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological bulletin.* 2017;143(8):783-822.
27. Schuch JJ, Roest AM, Nolen WA, Penninx BW, de Jonge P. Gender differences in major depressive disorder: results from the Netherlands study of depression and anxiety. *Journal of affective disorders.* 2014;156:156-163.
28. Vermeersch SJ, Rietzschel ER, De Buyzere ML, et al. Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population. *Journal of hypertension.* 2008;26(7):1411-1419.
29. Schram MT, Sep SJ, van der Kallen CJ, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *European journal of epidemiology.* 2014;29(6):439-451.
30. Yambe M, Tomiyama H, Yamada J, et al. Arterial stiffness and progression to hypertension in Japanese male subjects with high normal blood pressure. *Journal of hypertension.* 2007;25(1):87-93.
31. AlGhatrif M, Strait JB, Morrell CH, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension (Dallas, Tex. : 1979).* 2013;62(5):934-941.
32. Godin O, Elbejjani M, Kaufman JS. Body mass index, blood pressure, and risk of depression in the elderly: a marginal structural model. *American journal of epidemiology.* 2012;176(3):204-213.
33. Zimmerman JA, Mast BT, Miles T, Markides KS. Vascular risk and depression in the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE). *International journal of geriatric psychiatry.* 2009;24(4):409-416.
34. Hildrum B, Mykletun A, Holmen J, Dahl AA. Effect of anxiety and depression on blood pressure: 11-year longitudinal population study. *The British journal of psychiatry : the journal of mental science.* 2008;193(2):108-113.
35. Scuteri A, Spalletta G, Cangelosi M, et al. Decreased nocturnal systolic blood pressure fall in older subjects with depression. *Aging clinical and experimental research.* 2009;21(4-5):292-297.
36. Scuteri A, Morrell CH, Orru M, et al. Gender specific profiles of white coat and masked hypertension impacts on arterial structure and function in the SardiNIA study. *International journal of cardiology.* 2016;217:92-98.
37. Scuteri A, Castello L, Coluccia R, Modestino A, Nevola E, Volpe M. Depression is associated with increased occurrence of left ventricle concentric geometry in older subjects independently of blood pressure levels. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2011;21(12):915-921.

38. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia.* 2006;49(5):837-845.
39. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia.* 2010;53(12):2480-2486.
40. Samaan Z, Garasia S, Gerstein HC, et al. Lack of association between type 2 diabetes and major depression: epidemiologic and genetic evidence in a multiethnic population. *Translational psychiatry.* 2015;5:e618.
41. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC medicine.* 2013;11:200.
42. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin.* 2014;140(3):774-815.
43. van Dooren FE, Schram MT, Schalkwijk CG, et al. Associations of low grade inflammation and endothelial dysfunction with depression - The Maastricht Study. *Brain, behavior, and immunity.* 2016;56:390-396.
44. Lopez-Vilchez I, Diaz-Ricart M, Navarro V, et al. Endothelial damage in major depression patients is modulated by SSRI treatment, as demonstrated by circulating biomarkers and an in vitro cell model. *Translational psychiatry.* 2016;6(9):e886.
45. Won E, Kim YK. Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression. *Current neuropharmacology.* 2016;14(7):665-673.
46. Wang SY, Duan KM, Tan XF, et al. Genetic variants of the kynurenine-3-monooxygenase and postpartum depressive symptoms after cesarean section in Chinese women. *Journal of affective disorders.* 2017;215:94-101.
47. Whelton SP, Blankstein R, Al-Mallah MH, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension (Dallas, Tex. : 1979).* 2013;62(3):477-484.
48. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. *Diabetes care.* 2013;36(8):2351-2358.
49. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological psychiatry.* 2003;54(3):216-226.
50. van Sloten TT, Boutouyrie P, Tafflet M, et al. Carotid Artery Stiffness and Incident Depressive Symptoms: The Paris Prospective Study III. *Biological psychiatry.* 2018.
51. Lin IM, Lu HC, Chu CS, Lee CS, Lu YH, Lin TH. The Relationship between Brachial-Ankle Pulse Wave Velocity and Depressive Symptoms among Patients with Coronary Artery Disease. *Acta Cardiologica Sinica.* 2017;33(3):303-309.
52. Wiernik E, Lemogne C, Thomas F, et al. Perceived stress, common carotid intima media thickness and occupational status: The Paris Prospective Study III. *International journal of cardiology.* 2016;221:1025-1030.
53. Cho Y, Lim TH, Kang H, Lee Y, Lee H, Kim H. Socioeconomic status and depression as combined risk factors for acute myocardial infarction and stroke: A population-based study of 2.7 million Korean adults. *Journal of psychosomatic research.* 2019;121:14-23.

54. Scuteri A, Wang H. Pulse wave velocity as a marker of cognitive impairment in the elderly. *Journal of Alzheimer's disease : JAD.* 2014;42 Suppl 4:S401-410.

55. Scuteri A, Modestino A, Fedullo F, Assisi AP, Gianni W. Depression treatment selectively modifies arterial stiffness in older participants. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2013;68(6):719-725.

Figure legends

Figure 1 Beta-coefficients and 95% CI for the association between moderate to severe depressive symptoms and baPWV stratified by age and gender. baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; SD, standard deviation. The results were adjusted for smoking, blood pressure categories, diabetes mellitus, dyslipidemia, and BMI categories.

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

Variables	Depressive symptoms			P value
	None	Mild	Moderate to severe	
	n=1053	n=227	n=54	
Males, n (%)	714 (67.8)	120 (52.9)	26 (48.1)	<0.001
Age, years	46.9 ± 11.8	47.5 ± 11.2	48.5 ± 11.7	0.523
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
Dyslipidemia, n (%)	686 (65.1)	165 (72.7)	37 (68.5)	0.088
SBP, mmHg	126.1 ± 16.6	125.0 ± 16.5	127.9 ± 14.7	0.445
DBP, mmHg	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	24.7 ± 3.8	24.9 ± 4.3	23.8 ± 3.5	0.147
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 ± standard deviation 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, the Patient Health Questionnaire-9; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

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, 68.8)	38.6 (1.5, 75.6) ***	40.3 (6.6, 74.1) ***
Moderate to severe	92.9 (17.6, 168.2) ***	104.6 (34.1, 175.0) **	87.7 (24.0, 151.5) **
Males		74.1 (45.0, 103.1) *	47.7 (14.9, 80.5) **
Age, years			
<40		Reference	Reference
40-60		142.9 (111.6, 174.2) *	133.5 (104.6, 162.3) *
≥60		281.2 (238.4, 324.0) *	265.7 (226.0, 305.3) *
Smoking			46.7 (15.4, 78.1) **
BP categories			
Optimal			Reference
Normal and high normal			131.9 (103.4, 160.5) *
Hypertension			260.6 (226.7, 294.6) *
Diabetes mellitus			110.1 (75.8, 144.4) *
Dyslipidemia			48.6 (20.4, 76.7) *
BMI, kg/m^2			
<24			Reference
24-28			-20.9 (-49.9, 8.1)
≥28			-91.8 (-128.3, -55.3) *

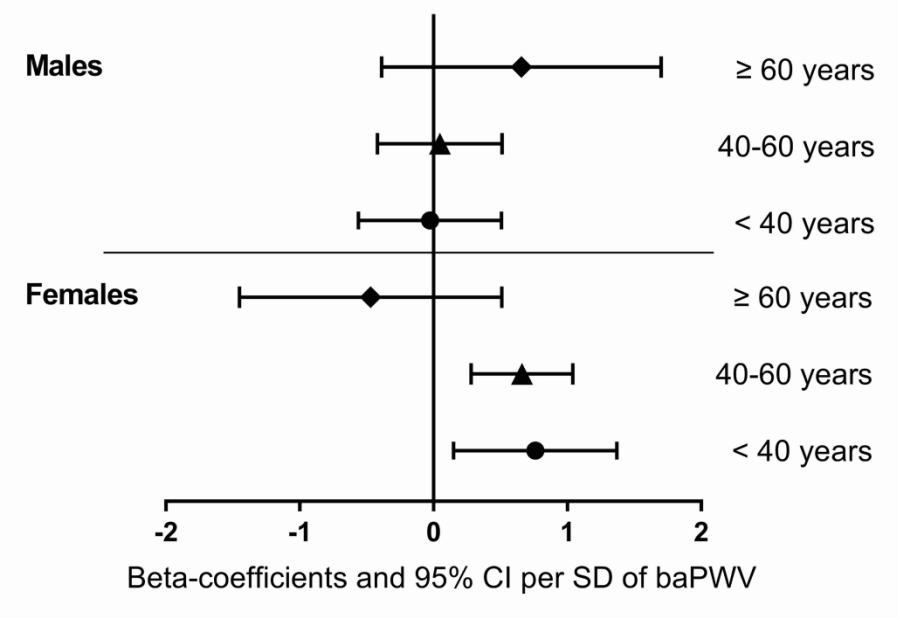
baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; CI, confidence interval.

*P<0.001, **P<0.01, ***P<0.05.

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

Subgroups	Beta-coefficient (95% CI)			P for trend	P for interaction
	None	Mild	Moderate to severe		
Gender					0.072
Male	Reference	65.6 (12.6, 118.6) ***	39.3 (-68.0, 146.6)	0.032	
Female	Reference	11.5 (-47.1, 70.1)	170.1 (66.2, 274.0) **	0.012	
Age, years					0.242
<40	Reference	-19.2 (-79.4, 40.9)	45.9 (-76.4, 168.2)	0.948	
40-60	Reference	28.4 (-24.5, 81.2)	109.0 (13.6, 204.5) ***	0.024	
≥60	Reference	112.3 (16.1, 208.4) ***	88.8 (-113.0, 290.7)	0.031	
Smoking					0.162
Yes	Reference	69.9 (13.7, 126.2) ***	22.8 (-105.9, 151.6)	0.047	
No	Reference	24.4 (-17.4, 66.2)	109.8 (39.4, 180.3) **	0.003	
BP categories					0.016
Optimal	Reference	-34.6 (-92.9, 23.7)	2.2 (-112.1, 116.4)	0.452	
Normal and high normal	Reference	55.8 (3.4, 108.2) ***	77.6 (-26.6, 181.7)	0.017	
Hypertension	Reference	109.0 (9.1, 208.9) ***	222.1 (57.1, 387.1) **	0.001	
Diabetes mellitus					0.004
Yes	Reference	154.1 (45.0, 263.2) **	216.4 (38.1, 394.8) ***	<0.001	
No	Reference	0.6 (-40.6, 41.8)	44.5 (-37.2, 126.3)	0.455	
Dyslipidemia					0.615
Yes	Reference	40.0 (-7.4, 87.4)	95.3 (3.1, 187.6) ***	0.013	
No	Reference	-3.9 (-76.0, 68.1)	85.9 (-44.4, 216.1)	0.389	
BMI, kg/m^2					0.201
<24	Reference	3.1 (-56.5, 62.6)	115.3 (9.3, 221.2) ***	0.111	
24-28	Reference	45.8 (-24.6, 116.2)	-9.4 (-139.6, 120.7)	0.468	
≥28	Reference	72.0 (-5.0, 149.1)	208.0 (26.7, 389.3) ***	0.007	

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



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	8-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	8-10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8-10
		(*e*) Describe any sensitivity analyses	8-10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	10-13
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	10-13
Outcome data	15*	Report numbers of outcome events or summary measures	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

Objective: To determine the independent relationship between depressive symptoms and arterial stiffness in the general Chinese population and explore possible interactive factors in the above relationship.

Design: A cross-sectional study.

Settings and participants: Consecutive participants who received routine health physical examinations in an affiliated hospital of a comprehensive university in Hunan Province, China, between September 2013 and March 2014 were examined. After exclusion, a total of 1334 subjects aged 22-77 years were recruited for the final analysis.

Measures: The Patient Health Questionnaire-9 (PHQ-9) was applied to assess the degrees of depressive symptoms as follows: 0-4 none depressive symptoms, 5-9 mild depressive symptoms, 10-27 moderate to severe depressive symptoms. Brachial-ankle pulse wave velocity (baPWV) was performed to reflect 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 to none depressive symptoms after adjusting for baseline confounders (beta-coefficient: 40.3; 95% CI: 6.6 to 74.1; and beta-coefficient: 87.7; 95% CI: 24.0 to 151.5; respectively). Further stratified analyses indicated that the relationships between degrees of depressive symptoms and baPWV were 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, significant association between moderate to severe depressive symptoms and baPWV was also obtained in female subjects who were younger than 60 years after adjustment, though 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 optimal range and those combined with mellitus diabetes.

Strengths and limitations of this study

1. The current study first analysed the association between depressive symptoms and arterial stiffness in the general Chinese population which covered a wide range of ages (22-77 years).
2. The extent of depression was reflected by mild depressive symptoms and moderate to severe depressive symptoms, and the independent relationships of these indicators with baPWV were examined in multivariate linear regression models.
3. Various subgroup analyses were conducted to explore whether any interacting factors existed in the connection between depressive symptoms and arterial stiffness.
4. A clinical diagnosis of major depressive disorder (MDD) in the subjects with moderate to severe depressive symptoms were not performed by diagnostic interviews according to DSM-IV criteria.
5. Due to the cross-sectional design of the study, no clear cause-effect conclusion could

be directly drawn.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychological disorders that affects health-related quality of life.[1] The global prevalence of MDD is 4.7%, and the lifetime rates of MDD vary greatly across different races, cultures and regions, ranging from 3.3% in mainland China to 18.6% in the United States.[2-4] Furthermore, the prevalence of MDD in patients with cardiovascular disease (CVD) is much higher:[5] 26.8% in hypertensive subjects,[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 depressed middle-aged and older adults also reported a diagnosis of comorbid CVD.[10] Therefore, there exist manifold interrelations between MDD and CVD in which 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 one of the markers of hypertension-mediated organ damage, and should be assessed among hypertensive patients according to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) hypertension guidelines.[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 concerning the relationship between depression and arterial stiffness are limited, and the results remain controversial. The Rotterdam Study (n=3704, ≥60 years) and the 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 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] In addition, the Netherlands Study of Depression and Anxiety Study (n=635, aged 20-66 years) also failed to identify the association between depression sensitivity and central arterial stiffness assessed by augmentation index.[22]

The main reasons for the abovementioned diverse findings might be the differences in the enrolled population, the assessment methods of arterial stiffness, and the criteria for defining depression. We noticed 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 associations (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 a general Chinese population was recruited. We collected the medical information of consecutive participants who received routine health physical examinations 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: an age of <18 or ≥80 years; a history of myocardial infarction, heart failure, stroke, cancer, 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 of 47.1 ± 11.7 years) were ultimately analysed in this study. Our study protocol was approved by

the Ethics Committee of Xiangya Hospital, Central South University, and all participants provided written informed consent.

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 past medical histories of hypertension and diabetes mellitus. Height was measured while the participants were without shoes to the nearest 0.1 cm, and weight was measured with the participants in light indoor clothing and without shoes to the nearest 0.1 kg. Then, 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 minutes of rest. The means of two separate readings of blood pressure with an interval of 3-5 minutes between measurements were used. Fasting blood samples were collected from antecubital veins after an 8-hour overnight fast in the morning of the health check-up days. Fasting blood glucose (FBG), 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 blood pressure: optimal

blood pressure, normal and high normal blood pressure, and hypertension, which was referred to the ESC and ESH hypertension guidelines.[12] An optimal blood pressure was defined as SBP <120 mmHg and DBP <80 mmHg; a normal and high normal blood pressure was defined as SBP between 120-139 mmHg and/or DBP between 80-89 mmHg; hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, a self-reported history of diagnosed hypertension, or under current anti-hypertensive treatment. Diabetes mellitus was defined as FBG ≥7.0 mmol/L, a self-reported history of diagnosed diabetes mellitus, or under current hypoglycaemic therapy. The diagnosis of dyslipidemia was made based on the Korean guideline of dyslipidaemia for the general population.[23] BMIs of 24 or 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 it consists of 9 items that are each scored from 0-3 points depending on the frequency of the listed problems in the last 2 weeks and a total PHQ-9 score ranges from 0 to 27. Scores are categorised as the following: 0-4 none depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression, and 20-27 severe depression.[24] And a cut-off value of 10 on the PHQ-9 has been widely used in epidemiological studies for diagnosing MDD with a high sensitivity (85%) and specificity (89%).[25] Referring to previous relevant studies and in consideration of the limited sample size of the subjects with a PHQ-9 score ≥10 (n=54), in the current study we classified the entire population into 3 groups according to PHQ-9 score: none

depressive symptoms (0-4), mild depressive symptoms (5-9), moderate to severe depressive symptoms (10-27).

BaPWV was automatically measured using baPWV instruments (model BP-203RPE, Colin, Komaki City, Japan) by trained staff following the standard procedure. Participants were measured in the supine position after 10 minutes of rest in a quiet room with a comfortable temperature. Bilateral measurements of baPWV were recorded, and the higher reading was used for analysis. The validation of this automatic device and its reproducibility have been previously demonstrated.

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. Actually, in the final analysis after exclusion, all baseline characteristics were acquired from the entire population, so no missing data existed in our study. All subjects were divided into three groups according to the degrees of depressive symptoms determined by the PHQ-9 score. Continuous variables are presented as the means and standard deviations, while categorical variables are described as frequencies and percentages. Comparisons between groups were performed using analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. The relationships between degrees of depressive symptoms and baPWV were examined in linear regressions with 3 models. Model 1 was

the crude model; model 2 adjusted for sex and age categories; model 3 further adjusted for smoking status, categories of blood pressure or BMI, comorbidities of diabetes mellitus or dyslipidemia. Besides, stratified analyses of baseline factors including sex, categories of age, blood pressure or BMI, smoking status, histories of diabetes mellitus or dyslipidemia were performed to test whether any potential interactive effects existed in the relationship between degrees of depressive symptoms and baPWV, and each stratification adjusted for all other factors except the stratification factor itself. And the group of none depressive symptoms was considered as reference in the above regression models. Finally, we specially explored the joint roles of age and sex in the association between mild, moderate to severe depressive symptoms and baPWV in adjusted models. All analyses were conducted using the statistical software packages R (R 3.4.3, http://www.R-project.org, The R Foundation) and EmpowerStats (www.empowerstats.com, X&Y solutions, Inc., Boston, MA). 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 the interpretation of the results of the current study.

RESULTS

Baseline characteristics

After exclusion, a total of 1334 subjects were finally included in our final analysis (mean age 41.7 ± 11.7 years, 64.5% male). The detailed baseline characteristics of all subjects by degrees of depressive symptoms are described in table 1. The results indicated that fewer male participants were present 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 a 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 dyslipidemia, 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, 1372.9 ± 312.3 and 1436.5 ± 314.4 cm/s, p=0.025). We also presented the baseline characteristics of all subjects according to tertiles of baPWV (<1203 cm/s, 1203-1430 cm/s, ≥1430 cm/s) in supplemental table 1. Results showed that across increasing tertiles of baPWV, more subjects were males, aged ≥60 years, had smoking histories, hypertension, diabetes mellitus, dyslipidemia, and moderate to severe depressive symptoms. Besides, levels of SBP, DBP, FBG, total cholesterol, LDL-C and PHQ-9 score were increased with increasing tertiles of baPWV. While the proportion of subjects whose BMI ≥28 kg/m^2 was 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 associations between degrees of depressive symptoms and baPWV in linear regression models, and beta-coefficients and 95% confidence interval (CI) of both crude and adjusted models were shown in table 2, in which subjects with none depressive symptoms were considered as reference. In the 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 categories, significant results were observed for both mild depressive symptoms and moderate to severe depressive symptoms with baPWV. And the results remained significant in model 3 which further adjusted for smoking status, blood pressure categories, diabetes mellitus, dyslipidemia and BMI categories (beta-coefficient: 40.3; 95% CI: 6.6 to 74.1; and beta-coefficient: 87.7; 95% CI: 24.0 to 151.5; for mild depressive symptoms, moderate to severe depressive symptoms, respectively).

Subgroup analysis of baseline factors

We also analysed the associations between degrees of depressive symptoms and baPWV in subgroups of sex, age, smoking status, blood pressure categories, diabetes mellitus, dyslipidemia and BMI categories in table 3, and the group of none depressive symptoms was still considered as reference. In stratified analysis of blood pressure categories, significant associations between mild depressive symptoms and baPWV were obtained in 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 significant association between moderate to severe depressive symptoms and baPWV was observed only in hypertension subgroup (beta-coefficient: 222.1; 95% CI: 57.1 to 387.1); and the interaction was also significant (p for interaction=0.016). In subgroups of diabetes mellitus, significant associations in mild depressive symptoms, moderate to severe depressive symptoms with baPWV were obtained in those with diabetes mellitus (beta-coefficient: 154.1; 95% CI: 45.0 to 263.2; and 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 categories, smoking status, dyslipidemia and BMI categories, none significant interactions were obtained (p for interaction>0.05 for all).

Subgroups of age and sex

The beta-coefficients and the 95% CI of mild depressive symptoms with baPWV divided by age and sex were described in figure 1. Smoking history, blood pressure categories, diabetes mellitus, dyslipidemia, and BMI categories were adjusted in the regression models. 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 was presented in figure 2. There were significant associations between moderate to severe depressive symptoms and baPWV in female subjects who were

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 degrees 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 with arterial stiffness were observed in male subjects aged 40-60 years, and female subjects younger than 60 years, respectively, in 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 the association between depressive symptoms and arterial stiffness 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 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 obtained for subgroups of sex or age separately in the associations between depressive symptoms and baPWV. And we further divided all subjects by age and sex concurrently to examine whether the associations differed according to age and sex. On the contrary with the findings in the Maastricht Study, our results indicated that the significant associations between moderate to severe depressive symptoms and arterial stiffness were present only in females who were younger than 60 years, although the interactive effect was not statistically significant. And 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.

Actually, the prevalence of MDD among females largely exceeds that among males, which is a difference that has been reported worldwide.[26] This sex difference was also exhibited in specific depressive symptoms; for instance, more depressed females tended to gain weight than males.[27] Moreover, an age-sex interaction was found in regard to the 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 in the Maastricht Study. It should be noted that the cohort of the Maastricht Study specially included diabetic individuals according to their study design.[29] And the prevalence of diabetes mellitus was 27% among subjects without depressive disorder and 49% among participants with MDD in the Maastricht Study,[20]

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 roles of age and sex in the connection between depression and arterial stiffness.

We also classified the whole population into 3 subgroups based on blood pressure as follows: optimal blood pressure; hypertension; and the rest which indicated normal or high normal blood pressure, which was referred to the current hypertension guidelines.[12] And a significant interactive effect was obtained for blood pressure categories in the association between degrees of depressive symptoms and arterial stiffness. One previous study showed that severe arterial stiffness was independently associated with the progression of blood pressure categories (for example, 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 SBP >140 mmHg, SBP between 120 and 139 mmHg was also associated with an increase in PWV compared with the PWV associated with SBP <120 mmHg.[31] However, longitudinal studies have obtained inconsistent results regarding the association between hypertension and depression.[32,33] In addition, one study inferred that subjects with low blood pressure (SBP <120 mmHg or DBP <75 mmHg) were at increased risk of incident depression compared with those with normal blood pressure among the elderly.[32] Another study revealed that anxiety or depression at baseline was associated with low blood pressure during follow-up.[34] The interaction role of blood pressure with 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, but one plausible explanation is that elevated blood pressure and advanced depressive symptoms might jointly promote the development of arterial stiffness. We also noticed that older subjects with depressive symptoms tended to have a lower night-time SBP fall,[35] and subjects with white coat hypertension (WCH) or masked hypertension (MH) examined by ambulatory blood pressure monitoring (ABPM) had greater arterial stiffness.[36] Besides, older subjects with depression were associated with increased prevalence of left ventricular hypertrophy (LVH), 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 the 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 epidemiologic 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 to verify.

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 participates 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 (SSRI) treatment in patients with MDD and in vitro cell models.[44] Dysregulation of the ANS, especially sympathetic over-activity, 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, depressed patients are vulnerable to the adoption of unhealthy lifestyle behaviours such as smoking, overeating (leading to obesity, dyslipidaemia) and a stressful emotional state, all of which are risk factors for coronary artery disease (CAD).[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 from our study. In addition, in some studies, standard diagnostic interviews according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

(DSM-IV) criteria were performed to achieve the diagnosis of MDD,[16,19,20] while in others, certain diagnostic scale was used instead.[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 the PHQ-9 score to screen MDD was both highly sensitive (85%) and specific (89%),[25] further studies with optimal designs are still needed. In addition, the covariate data we collected were limited, and we did not have information regarding socioeconomic level,[52,53] education level, physical activity level, dietary habits, assessment of cognitive impairment[54] and medications taken by participants as different anti-depressant medications might have opposite impact on arterial stiffness,[55] all of which might have influenced our results. Then, a lack of statistical power might still exist in our study although we had a relatively large sample size (n=1334). For example, distinguished trends emerged among subgroups of sex in the association between increased degrees of depressive symptoms and baPWV, however, the result of interaction was non-significant (p for interaction=0.072). Finally, our participants were from our health management center, and although no specific restrictions existed for those who decided to receive health check-ups, it should be noticed that the costs of the examinations were paid by themselves. So, a selection bias existed and our sample could not fully represent a general population in the real world. Therefore, it should be cautious when extrapolating our results to other populations.

CONCLUSION

Our findings suggested that the degrees of depressive symptoms were independently associated with arterial stiffness, and further stratified analysis showed that subjects with depressive symptoms whose blood pressure 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 in regard to the prevention of arterial stiffness due to the effect of depression.

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REFERENCES

1. Cao Y, Li W, Shen J, Malison RT, Zhang Y, Luo X. Health-related quality of life and symptom severity in Chinese patients with major depressive disorder. *Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists.* 2013;5(4):276-283.
2. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological medicine.* 2013;43(3):471-481.
3. Gu L, Xie J, Long J, et al. Epidemiology of major depressive disorder in mainland china: a systematic review. *PloS one.* 2013;8(6):e65356.
4. Gonzalez HM, Tarraf W, Whitfield KE, Vega WA. The epidemiology of major depression and ethnicity in the United States. *Journal of psychiatric research.* 2010;44(15):1043-1051.
5. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *European heart journal.* 2014;35(21):1365-1372.
6. Li Z, Li Y, Chen L, Chen P, Hu Y. Prevalence of Depression in Patients With Hypertension: A Systematic Review and Meta-Analysis. *Medicine.* 2015;94(31):e1317.
7. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology.* 2006;48(8):1527-1537.
8. Osler M, Martensson S, Wium-Andersen IK, et al. Depression After First Hospital Admission for Acute Coronary Syndrome: A Study of Time of Onset and Impact on Survival. *American journal of epidemiology.* 2016;183(3):218-226.
9. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation.* 2014;129(12):1350-1369.
10. Gonzalez HM, Tarraf W. Comorbid cardiovascular disease and major depression among ethnic and racial groups in the United States. *International psychogeriatrics.* 2013;25(5):833-841.

11. Tomiyama H. Arterial Stiffness: Is This a Marker for the Current Status or Future? *Journal of atherosclerosis and thrombosis.* 2016;23(9):1026-1027.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal.* 2018;39(33):3021-3104.
13. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *Journal of the American College of Cardiology.* 2014;63(7):636-646.
14. Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. *Hypertension (Dallas, Tex. : 1979).* 2017;69(6):1045-1052.
15. Vlachopoulos C, Aznaouridis K, Terentes-Printzios D, Ioakeimidis N, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with brachial-ankle elasticity index: a systematic review and meta-analysis. *Hypertension (Dallas, Tex. : 1979).* 2012;60(2):556-562.
16. Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. *Journal of the American Geriatrics Society.* 2003;51(8):1105-1110.
17. van Sloten TT, Mitchell GF, Sigurdsson S, et al. Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. *Journal of psychiatry & neuroscience : JPN.* 2016;41(3):162-168.
18. Dietz LJ, Matthews KA. Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2011;48(6):579-584.
19. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Depression, anxiety, and arterial stiffness. *Biological psychiatry.* 2011;69(8):795-803.
20. Onete V, Henry RM, Sep SJS, et al. Arterial stiffness is associated with depression in middle-aged men - the Maastricht Study. *Journal of psychiatry & neuroscience : JPN.* 2018;43(2):111-119.
21. Lewis TT, Sutton-Tyrrell K, Penninx BW, et al. Race, psychosocial factors, and aortic pulse wave velocity: the Health, Aging, and Body Composition Study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2010;65(10):1079-1085.
22. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Sensitivity to depression or anxiety and subclinical cardiovascular disease. *Journal of affective disorders.* 2013;146(1):126-131.
23. 2015 Korean Guidelines for the Management of Dyslipidemia: Executive Summary (English Translation). *Korean circulation journal.* 2016;46(3):275-306.
24. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine.* 2001;16(9):606-613.
25. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2012;184(3):E191-196.
26. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological bulletin.* 2017;143(8):783-822.
27. Schuch JJ, Roest AM, Nolen WA, Penninx BW, de Jonge P. Gender differences in major depressive

disorder: results from the Netherlands study of depression and anxiety. *Journal of affective disorders.* 2014;156:156-163.

28. Vermeersch SJ, Rietzschel ER, De Buyzere ML, et al. Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population. *Journal of hypertension.* 2008;26(7):1411-1419.
29. Schram MT, Sep SJ, van der Kallen CJ, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *European journal of epidemiology.* 2014;29(6):439-451.
30. Yambe M, Tomiyama H, Yamada J, et al. Arterial stiffness and progression to hypertension in Japanese male subjects with high normal blood pressure. *Journal of hypertension.* 2007;25(1):87-93.
31. AlGhatrif M, Strait JB, Morrell CH, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension (Dallas, Tex. : 1979).* 2013;62(5):934-941.
32. Godin O, Elbejjani M, Kaufman JS. Body mass index, blood pressure, and risk of depression in the elderly: a marginal structural model. *American journal of epidemiology.* 2012;176(3):204-213.
33. Zimmerman JA, Mast BT, Miles T, Markides KS. Vascular risk and depression in the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE). *International journal of geriatric psychiatry.* 2009;24(4):409-416.
34. Hildrum B, Mykletun A, Holmen J, Dahl AA. Effect of anxiety and depression on blood pressure: 11-year longitudinal population study. *The British journal of psychiatry : the journal of mental science.* 2008;193(2):108-113.
35. Scuteri A, Spalletta G, Cangelosi M, et al. Decreased nocturnal systolic blood pressure fall in older subjects with depression. *Aging clinical and experimental research.* 2009;21(4-5):292-297.
36. Scuteri A, Morrell CH, Orru M, et al. Gender specific profiles of white coat and masked hypertension impacts on arterial structure and function in the SardiNIA study. *International journal of cardiology.* 2016;217:92-98.
37. Scuteri A, Castello L, Coluccia R, Modestino A, Nevola E, Volpe M. Depression is associated with increased occurrence of left ventricle concentric geometry in older subjects independently of blood pressure levels. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2011;21(12):915-921.
38. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia.* 2006;49(5):837-845.
39. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia.* 2010;53(12):2480-2486.
40. Samaan Z, Garasia S, Gerstein HC, et al. Lack of association between type 2 diabetes and major depression: epidemiologic and genetic evidence in a multiethnic population. *Translational psychiatry.* 2015;5:e618.
41. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC medicine.* 2013;11:200.
42. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal

transduction theory of depression. *Psychological bulletin.* 2014;140(3):774-815.

43. van Dooren FE, Schram MT, Schalkwijk CG, et al. Associations of low grade inflammation and endothelial dysfunction with depression - The Maastricht Study. *Brain, behavior, and immunity.* 2016;56:390-396.
44. Lopez-Vilchez I, Diaz-Ricart M, Navarro V, et al. Endothelial damage in major depression patients is modulated by SSRI treatment, as demonstrated by circulating biomarkers and an in vitro cell model. *Translational psychiatry.* 2016;6(9):e886.
45. Won E, Kim YK. Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression. *Current neuropharmacology.* 2016;14(7):665-673.
46. Wang SY, Duan KM, Tan XF, et al. Genetic variants of the kynurenine-3-monooxygenase and postpartum depressive symptoms after cesarean section in Chinese women. *Journal of affective disorders.* 2017;215:94-101.
47. Whelton SP, Blankstein R, Al-Mallah MH, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension (Dallas, Tex. : 1979).* 2013;62(3):477-484.
48. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. *Diabetes care.* 2013;36(8):2351-2358.
49. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological psychiatry.* 2003;54(3):216-226.
50. van Sloten TT, Boutouyrie P, Tafflet M, et al. Carotid Artery Stiffness and Incident Depressive Symptoms: The Paris Prospective Study III. *Biological psychiatry.* 2018.
51. Lin IM, Lu HC, Chu CS, Lee CS, Lu YH, Lin TH. The Relationship between Brachial-Ankle Pulse Wave Velocity and Depressive Symptoms among Patients with Coronary Artery Disease. *Acta Cardiologica Sinica.* 2017;33(3):303-309.
52. Wiernik E, Lemogne C, Thomas F, et al. Perceived stress, common carotid intima media thickness and occupational status: The Paris Prospective Study III. *International journal of cardiology.* 2016;221:1025-1030.
53. Cho Y, Lim TH, Kang H, Lee Y, Lee H, Kim H. Socioeconomic status and depression as combined risk factors for acute myocardial infarction and stroke: A population-based study of 2.7 million Korean adults. *Journal of psychosomatic research.* 2019;121:14-23.
54. Scuteri A, Wang H. Pulse wave velocity as a marker of cognitive impairment in the elderly. *Journal of Alzheimer's disease : JAD.* 2014;42 Suppl 4:S401-410.
55. Scuteri A, Modestino A, Fedullo F, Assisi AP, Gianni W. Depression treatment selectively modifies arterial stiffness in older participants. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2013;68(6):719-725.

Figure legends

Figure 1 Beta-coefficients and 95% CI for the association between mild depressive symptoms and baPWV stratified by age and sex. baPWV, brachial-ankle pulse wave velocity; CI, confidence interval. The results were adjusted for smoking history, blood pressure categories, diabetes mellitus, dyslipidemia, and BMI categories.

Figure 2 Beta-coefficients and 95% CI for the association between moderate to severe depressive symptoms and baPWV stratified by age and sex. baPWV, brachial-ankle pulse wave velocity; CI, confidence interval. The results were adjusted for smoking history, blood pressure categories, diabetes mellitus, dyslipidemia, and BMI categories.

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

Variables	Depressive symptoms			P value
	None	Mild	Moderate to severe	
	n=1053	n=227	n=54	
Males, 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
Dyslipidemia, n (%)	686 (65.1)	165 (72.7)	37 (68.5)	0.088
SBP, mmHg	126.1 ± 16.6	125.0 ± 16.5	127.9 ± 14.7	0.445
DBP, mmHg	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 ± standard deviation 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, the Patient Health Questionnaire-9; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

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, 68.8)	38.6 (1.5, 75.6) ***	40.3 (6.6, 74.1) ***
Moderate to severe	92.9 (17.6, 168.2) ***	104.6 (34.1, 175.0) **	87.7 (24.0, 151.5) **
Males		74.1 (45.0, 103.1) *	47.7 (14.9, 80.5) **
Age, years			
<40		Reference	Reference
40-60		142.9 (111.6, 174.2) *	133.5 (104.6, 162.3) *
≥60		281.2 (238.4, 324.0) *	265.7 (226.0, 305.3) *
Smoking			46.7 (15.4, 78.1) **
BP categories			
Optimal			Reference
Normal and high normal			131.9 (103.4, 160.5) *
Hypertension			260.6 (226.7, 294.6) *
Diabetes mellitus			110.1 (75.8, 144.4) *
Dyslipidemia			48.6 (20.4, 76.7) *
BMI, kg/m^2			
<24			Reference
24-28			-20.9 (-49.9, 8.1)
≥28			-91.8 (-128.3, -55.3) *

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

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

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

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

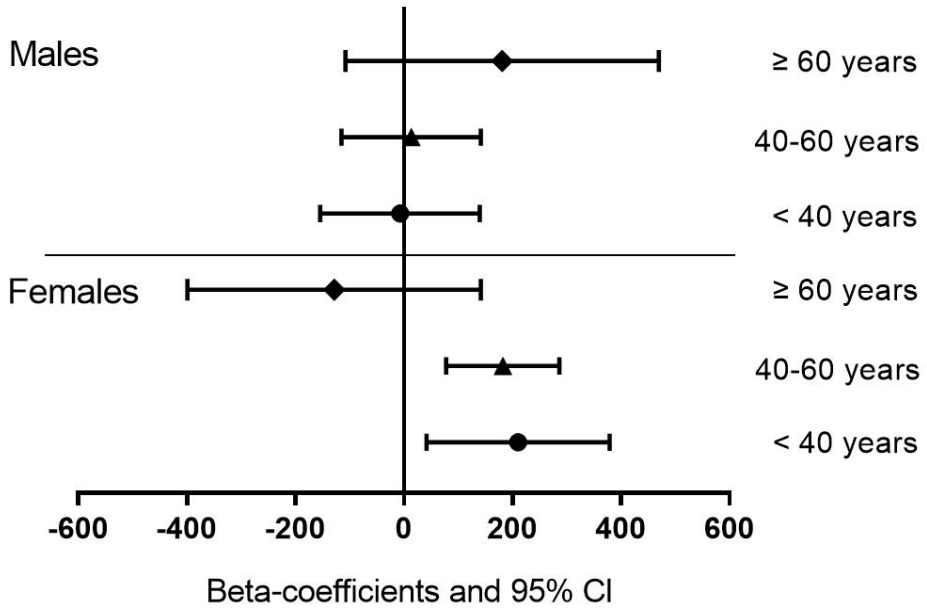

Figure 1

90x58mm (300 x 300 DPI)

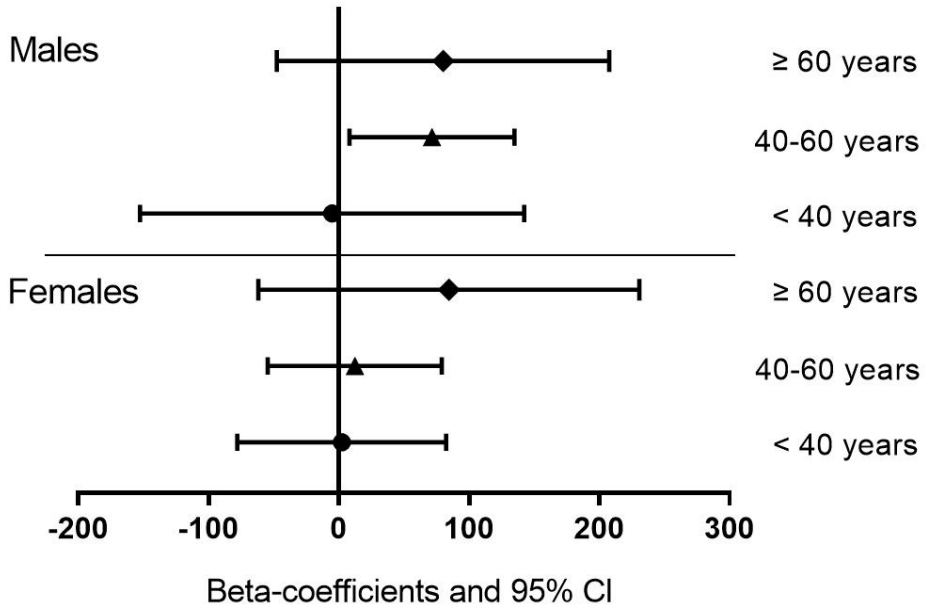

Figure 2

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Supplemental table 1 Baseline characteristics of all subjects according to tertiles of brachial-ankle pulse wave velocity

Variables	baPWV			P value
	Tertile 1 (n=445) <1203 cm/s	Tertile 2 (n=443) 1203-1430 cm/s	Tertile 3 (n=446) ≥1430 cm/s	
Males, n (%)	250 (56.2)	300 (67.7)	310 (69.5)	<0.001
Age, years, n (%)				<0.001
<40	206 (46.3)	132 (29.8)	67 (15.0)	
40-60	218 (49.0)	240 (54.2)	261 (58.5)	
≥60	21 (4.7)	71 (16.0)	118 (26.5)	
Smoking, n (%)	170 (38.2)	202 (45.6)	232 (52.0)	<0.001
BP categories, n (%)				<0.001
Optimal	234 (52.6)	143 (32.3)	83 (18.6)	
Normal and high normal	170 (38.2)	201 (45.4)	203 (45.5)	
Hypertension	41 (9.2)	99 (22.4)	160 (35.9)	
Diabetes mellitus, n (%)	54 (12.1)	64 (14.5)	100 (22.4)	<0.001
Dyslipidemia, n (%)	294 (66.1)	276 (62.3)	318 (71.3)	0.017
SBP, mmHg	118.3 ± 14.3	126.2 ± 15.2	133.5 ± 16.3	<0.001
DBP, mmHg	73.3 ± 9.4	74.9 ± 10.4	76.5 ± 10.8	<0.001
FBG, mmol/L	5.07 ± 1.13	5.24 ± 1.45	5.65 ± 1.96	<0.001
TC, mmol/L	5.01 ± 1.04	4.93 ± 1.03	5.14 ± 1.07	0.010
TG, mmol/L	2.10 ± 1.53	2.05 ± 1.47	2.18 ± 1.49	0.436
HDL-C, mmol/L	1.46 ± 0.37	1.51 ± 0.37	1.51 ± 0.38	0.051
LDL-C, mmol/L	2.66 ± 0.72	2.57 ± 0.75	2.72 ± 0.76	0.010
BMI, kg/m^2, n (%)				<0.001
<24	160 (36.0)	211 (47.6)	221 (49.7)	
24-28	181 (40.7)	151 (34.1)	160 (36.0)	
≥28	104 (23.4)	81 (18.3)	64 (14.4)	
PHQ-9 score	2.54 ± 3.04	2.37 ± 3.10	2.99 ± 3.64	0.016
Depressive symptoms				0.013
None	349 (78.4)	368 (83.1)	336 (75.3)	
Mild	84 (18.9)	59 (13.3)	84 (18.8)	
Moderate to severe	12 (2.7)	16 (3.6)	26 (5.8)	

Data are presented as mean ± standard deviation 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, the Patient Health Questionnaire-9; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	8-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	8-10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8-10
		(*e*) Describe any sensitivity analyses	8-10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	10-13
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	10-13
Outcome data	15*	Report numbers of outcome events or summary measures	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.