Association between depressive symptoms and pulse wave velocity is mediated by increased adiposity in older adults with type 2 diabetes

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Background: Studies investigating the association between depression and aortic stiffness in older patients with type 2 diabetes are lacking. We postulated an association between depressive symptoms and aortic stiffness, and this relationship may be mediated by increased adiposity. Methods: We analyzed participants with type 2 diabetes aged 55 years or older (n = 958). We measured aortic stiffness using carotid–femoral pulse wave velocity (cut-off ≥ 12 m/s) using the tonometry method. We defined depressive symptoms as a score of greater than 5 on the Geriatric Depression Scale–15 (GDS-15). Adiposity indices we assessed were body mass index, waist circumference, waist-to-height ratio, visceral fat area and fat mass. Results: Among the participants, 27.2% had aortic stiffness, of whom 6.5% had depressive symptoms. Score on the GDS-15 was correlated with pulse wave velocity, and both variables were correlated with the adiposity markers we analyzed (all p < 0.05). Depressive symptoms were associated with pulse wave velocity (B = 1.79, 95% confidence interval [CI] 0.83–2.75) or aortic stiffness (risk ratio 1.60, 95% CI 1.10–2.33) in the unadjusted model. The association persisted after controlling for demographics, duration of diabetes, glycated hemoglobin, comorbidities and medications. Further adjustment for visceral fat area and fat mass in separate models reduced the association between depressive symptoms and pulse wave velocity or aortic stiffness. Mediation models revealed that the mediation proportions of fat mass and visceral fat area on the association between depressive symptoms and pulse wave velocity were 11.8% and 9.7%, respectively. A preliminary analysis of longitudinal data (n = 184) showed similar findings. Limitations: Causality cannot be inferred from the associations we observed. Conclusion: Depressive symptoms are associated with elevated pulse wave velocity in older people with type 2 diabetes, and this relationship may be partially mediated by increased adiposity.

Introduction

The leading cause of morbidity and mortality in type 2 diabetes (T2D) is cardiovascular disease. Mounting evidence supports increased arterial stiffness as a powerful risk factor for cardiovascular disease. Arterial stiffening increases with aging and is further exacerbated by T2D. As the aorta stiffens, the velocity of the pressure waves augments and the reflected pressure waves return to the heart earlier, leading to a rise in systolic blood pressure and pulse pressure, along with an increased left ventricular afterload. Carotid–femoral pulse wave velocity (PWV) is the gold-standard evaluation of aortic stiffness and a marker of vascular disease.

Depressive symptoms have been commonly linked to poorer cardiovascular outcomes in older adults. Less well-documented is the reverse association between cardiovascular disease and development of late-life depression. Existing literature, albeit sparse, has revealed a relationship between depression and risk of aortic stiffness in population-based cohorts of older people. However, this association has not been demonstrated in older people with T2D. It is likely that geriatric depression may accelerate arterial stiffening in older people with T2D (compared to their healthy counterparts), resulting in a more pronounced risk of cardiovascular disease.

A recent population-based retrospective analysis of middle-aged adults revealed that a history of depression was associated with peripherally assessed arterial stiffness index. This association was mediated by metabolic syndrome, most strongly by waist circumference and inflammatory processes. The findings suggest that accumulation of adiposity (which is known to trigger chronic low-grade inflammation) may contribute to the relationship between depression and PWV. We postulated a triangulated relationship between geriatric...
depressive symptoms and aortic stiffening mediated by increased adiposity. Different anthropometric measures have been developed to define adiposity, and inconsistencies in risk prediction exist, possibly due to limitations of the indices. Therefore, it is important to assess the predictive performance of different adiposity measures. We aimed to assess the association between depressive symptoms and PWV in older people with T2D, and to examine the potential mediating role of various global and abdominal adiposity metrics.

Methods

Study population

Adults diagnosed with T2D (aged 21 to 89 years) who attended the Diabetes Mellitus Centre or a primary care polyclinic in the northern region of Singapore were recruited by the Singapore Study of Macroangiopathy and Microvascular Reactivity in Type 2 Diabetes (SMART2D) study between August 2011 and March 2014 as described previously (phase 1, n = 2057). Assessment of depressive symptoms was incorporated into phase 2 of the cohort study (September 2014 to October 2017; Fig. 1). Given that vascular stiffness is pronounced after the age of 54 and depressive symptoms have been described in those aged 55 years or older, the final cohort analyzed involved older adults (aged ≥ 55 years) who returned in phase 2 (baseline, n = 958). We have recently entered into the phase 3 study, and mean 3-year follow-up data for a small subset of SMART2D participants (aged ≥ 55 at phase 2, n = 184) are available for an interim longitudinal analysis. Information on participants’ demographics, medical history and medications were collected. The study protocol and the process for obtaining informed consent were approved by our institution’s domain-specific ethics review board. Written informed consent was obtained from all patients.

Measurement of pulse wave velocity

The direct carotid–femoral PWV of participants resting in a supine position was assessed using applanation tonometry (SphygmoCor) to detect the pulse waveform at the carotid and femoral arteries. We calculated PWV using the travel distance between the 2 recording sites divided by the transit time, expressed in metres per second. The inter- and intra-observer coefficients of variation for the PWV readings were 5.7% and 5.9%, respectively.

Questionnaires

We administered the Geriatric Depression Scale short 15-item version (GDS-15) in our cohort. This questionnaire is the
instrument used most extensively for screening and assessing depressive symptoms in older adults,20 and has been widely validated and translated into multiple languages.18,21–23 Each of the 15 items has a “yes” or “no” answer, and the highest possible score is 15. Scores denote the following: normal, 0 to 4; mild depression, 5 to 8; moderate depression, 9 to 11; and severe depression, 12 to 15. Previous studies have reported the use of the GDS-15 in our local population aged 55 years and older.16,24 We also administered the locally translated and validated version of the standard Mini-Mental State Examination questionnaire to evaluate global cognitive performance.25 Questions were read to the participants, and their responses were recorded by trained research nurses.

Assessment of clinical parameters

We measured height and weight using standard procedures, and calculated body mass index as weight (in kg) divided by height (in m²). We determined waist circumference, waist-to-height ratio, visceral fat area and fat mass using the tetrapolar multifrequency bioelectrical impedance method (InBody-S10; BioSpace) as described previously.26 We measured blood pressure with patients in a seated position using an automated blood pressure monitor (Dinamap Pro 100V2; GE Medical Systems). We measured glycated hemoglobin (HbA1c) using a point-of-care immunoassay analyzer certified by the National Glycohemoglobin Standardization Program (DCA Vantage Analyzer; Siemens Healthcare Diagnostics). We quantified lipids using enzymatic assays with Ektachem clinical chemistry slides (Eastman Kodak). We calculated estimated glomerular filtration rate using a formula developed by the Chronic Kidney Disease Epidemiology Collaboration.27 We assessed urinary albumin from spot urine samples using a solid phase competitive chemiluminescent enzymatic immunoassay (Immulite; Siemens Healthcare Diagnostics) and calculated the urinary albumin-to-creatinine ratio.

Definitions

We classified depressive symptoms as a GDS-15 score of 5 or above, a threshold that has been reported to have high sensitivity and specificity (> 90%) for detecting major depressive disorder.28 A Mini-Mental State Examination score of less than 24 denoted cognitive impairment.25 Hypertension was diagnosed if a patient had a systolic blood pressure of 140 mm Hg or above, a diastolic blood pressure of 90 mm Hg or above or was taking antihypertensive medication. Dyslipidemia was defined as having high triglycerides (> 1.7 mmol/L) or taking lipid-lowering medication. Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m². People with an albumin-to-creatinine ratio of 30 mg/g or higher were regarded as having albuminuria. The PWV cut-off value to define aortic stiffness (obtained through direct distances) was 12 m/s or greater, according to the 2007 European Society of Hypertension–European Society of Cardiology guidelines for the management of hypertension.29

Statistical analysis

We performed statistical analysis using SPSS version 22 (IBM Corp.) and STATA version 14 (Stata Corp.). As shown in Figure 1, we excluded observations with missing data from the analysis. We presented continuous variables as mean ± standard deviation or median and interquartile range, and we presented categorical data as n (%). In the cross-sectional analysis of the baseline data, we analyzed the associations between depressive symptoms (exposure) and PWV/aortic stiffness (outcome) using Pearson correlation, linear regression, quantile regression and modified Poisson regression (to estimate the risk ratio for common binary outcome).30 We selected the covariates entered into the multiple regression model (including age, sex, education, natural log-transformed diabetes duration, HbA1c, hypertension, chronic kidney disease, albuminuria, insulin, renin–angiotensin system antagonists and adiposity indices) based on a univariate level of significance of p < 0.05. We examined the mediatory effect of the adiposity metrics (mediator) on the relationship between depressive symptoms and PWV using the STATA “sgmediation” command with bootstrapping (500 replications). We defined statistical significance as p < 0.05. The statistical methods used to analyze the longitudinal data are described in Appendix 1, available at jpn.ca/200080-a1.

Results

table 1 shows the characteristics of the participants with T2D (n = 958). Compared to patients without aortic stiffness, those with aortic stiffness (PWV ≥ 12 m/s) were older and had greater global and central adiposity, a poorer metabolic profile and worse renal function. The distributions of sex, education and use of medications (including insulin and renin–angiotensin system antagonists) were statistically different between the 2 groups. In addition, depressive symptoms (GDS-15 score ≥ 5) were more prevalent in the aortic stiffness group (6.5% vs. 3.3%).

Pearson correlation analysis showed that PWV was correlated with GDS-15 score (r = 0.135; p < 0.001). It was also correlated with body mass index (r = 0.198; p < 0.001), fat mass (r = 0.189; p < 0.001), waist circumference (r = 0.139; p < 0.001), waist-to-height ratio (r = 0.104; p = 0.001) and visceral fat area (r = 0.165; p < 0.001). We also observed a significant correlation between GDS-15 score and body mass index (r = 0.067; p = 0.037), fat mass (r = 0.091; p = 0.005), waist-to-height ratio (r = 0.073; p = 0.023) and visceral fat area (r = 0.110; p < 0.001), but not waist circumference.

As shown in Table 2, depressive symptoms were associated with PWV in the unadjusted model (model 1; B = 1.79, 95% confidence interval [CI] 0.83–2.75). In addition, depressive symptoms increased the risk of aortic stiffness by 60% (model 1; 95% CI 1.10–2.33). The relationship between depressive symptoms and PWV (B = 1.54, 95% CI 0.64–2.43) or between depressive symptoms and aortic stiffness (risk ratio 1.50, 95% CI 1.10–2.33) persisted after adjustment for age, sex, education, natural log-transformed diabetes duration, HbA1c, comorbidities (hypertension, chronic kidney disease, albuminuria) and use of...
medications (insulin, renin–angiotensin system antagonists; model 3). Further adjustment for the adiposity indices in separate models (models 4–8) resulted in a reduced association between depressive symptoms and PWV, and between depressive symptoms and aortic stiffness. All adiposity markers were independently associated with the study outcomes (PWV and aortic stiffness). The interaction term between sex and depressive symptoms was not significant for the outcomes of PWV ($p = 0.30$) or aortic stiffness ($p = 0.26$), suggesting that the association between depressive symptoms and PWV was not significantly different between men and women.

We used quantile regression to investigate the relationship between depressive symptoms and PWV under different percentiles (Appendix 1, Table S1). As shown in model 1, depressive symptoms had an increasingly significant effect on PWV in the higher percentiles (60% to 90%; all $p < 0.05$). We observed a weakened association between depressive symptoms and PWV in the 60th percentile and higher after accounting for the adiposity metrics (models 2 to 6).

We assessed the cross-sectional mediation effect of the adiposity indices in the relationship between depressive symptoms and PWV (Table 3). Fat mass and visceral fat area

| Table 1: Baseline characteristics of participants by aortic stiffness* |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Variable                        | Total ($n = 958$)         | No aortic stiffness ($n = 697$) | Aortic stiffness ($n = 261$) | $p$ value |
| Age, yr                         | $64 \pm 7$                | $64 \pm 6$                  | $66 \pm 7$                  | $< 0.001$ |
| Sex, n (%)                      |                             |                             |                             |            |
| Male                            | 481 (50.2)                 | 336 (48.2)                  | 145 (55.6)                  | 0.043      |
| Female                          | 477 (49.8)                 | 361 (51.8)                  | 116 (44.4)                  |            |
| Ethnicity, n (%)                |                             |                             |                             |            |
| Chinese                         | 544 (56.8)                 | 381 (54.7)                  | 163 (62.5)                  | 0.16       |
| Malay                           | 165 (17.2)                 | 124 (17.8)                  | 41 (15.7)                   |            |
| Indian                          | 218 (22.8)                 | 167 (24.0)                  | 51 (19.5)                   |            |
| Other                           | 31 (3.2)                   | 25 (3.6)                    | 6 (2.3)                     |            |
| Diabetes duration, yr           | 15 (9 to 22)               | 14 (8 to 20)                | 19 (12 to 27)               | $< 0.001$ |
| Body mass index, kg/m²          | 26.8 ± 4.8                 | 26.3 ± 4.5                  | 28.0 ± 5.3                  | $< 0.001$ |
| Waist circumference, cm²        | 89.9 ± 11.7                | 89.1 ± 11.4                 | 92.0 ± 12.3                 | $< 0.001$ |
| Waist:height ratio              | 0.6 ± 0.1                  | 0.6 ± 0.1                   | 0.6 ± 0.1                   | 0.013      |
| Visceral fat area, cm²          | 129.7 ± 37.5               | 126.8 ± 35.9                | 137.4 ± 40.5                | $< 0.001$ |
| Fat mass, kg                    | 35.6 ± 9.4                 | 24.8 ± 8.8                  | 27.8 ± 10.4                 | $< 0.001$ |
| Systolic blood pressure, mm Hg  | 145.3 ± 19.1               | 142.0 ± 17.9                | 153.9 ± 19.2                | $< 0.001$ |
| Diastolic blood pressure, mm Hg | 77.3 ± 8.4                 | 77.2 ± 8.4                  | 77.7 ± 6.6                  | 0.33       |
| Hypertension, n (%)             | 820 (85.6)                 | 577 (82.8)                  | 243 (93.1)                  | $< 0.001$ |
| HbA₁c, %                        | 7.8 ± 1.5                  | 7.7 ± 1.5                   | 8.0 ± 1.6                   | 0.021      |
| Total cholesterol, mmol/L       | 4.3 ± 0.9                  | 4.3 ± 0.9                   | 4.3 ± 0.9                   | 0.99       |
| High-density lipoprotein cholesterol, mmol/L | 1.3 ± 0.4          | 1.3 ± 0.4                   | 1.3 ± 0.4                   | 0.13       |
| Low-density lipoprotein cholesterol, mmol/L | 2.6 ± 0.8         | 2.6 ± 0.8                   | 2.6 ± 0.8                   | 0.45       |
| Triglycerides, mmol/L           | 1.3 (1.0 to 1.8)           | 1.3 (1.0 to 1.7)            | 1.5 (1.1 to 2.0)            | $< 0.001$ |
| Dyslipidemia, n (%)             | 890 (92.9)                 | 642 (92.1)                  | 248 (95.0)                  | 0.12       |
| Chronic kidney disease, n (%)   | 266 (27.8)                 | 151 (21.7)                  | 115 (44.1)                  | $< 0.001$ |
| Albuminuria, n (%)              | 477 (49.8)                 | 299 (42.9)                  | 178 (68.2)                  | $< 0.001$ |
| Pulse wave velocity, m/s        | 10.6 ± 3.0                 | 9.1 ± 1.6                   | 14.5 ± 2.5                  | $< 0.001$ |
| Geriatric Depression Scale (15-item), score | 0 (0 to 2)         | 0 (0 to 1)                  | 1 (0 to 2)                  | 0.013      |
| Depressive symptoms, n (%)      | 40 (4.2)                   | 23 (3.3)                    | 17 (6.5)                    | 0.027      |
| Cognitive impairment, n (%)     | 46 (4.8)                   | 29 (4.2)                    | 17 (6.5)                    | 0.13       |
| Education years, n (%)          |                             |                             |                             | 0.001      |
| 0                               | 66 (6.9)                   | 36 (5.2)                    | 30 (11.5)                   |            |
| 1–6                             | 304 (31.7)                 | 213 (30.6)                  | 91 (34.9)                   |            |
| 7–10                            | 415 (43.3)                 | 312 (44.8)                  | 103 (39.5)                  |            |
| > 10                            | 173 (18.1)                 | 136 (19.5)                  | 37 (14.2)                   |            |
| Medications, n (%)              |                             |                             |                             |            |
| Insulin                         | 301 (31.4)                 | 175 (25.1)                  | 126 (48.3)                  | $< 0.001$ |
| Oral hypoglycemic agent         | 867 (90.5)                 | 638 (91.5)                  | 229 (87.7)                  | 0.07       |
| Renin–angiotensin system antagonist | 667 (69.6)           | 471 (67.6)                  | 196 (75.1)                  | 0.024      |
| Statin                          | 849 (88.6)                 | 612 (87.8)                  | 237 (90.8)                  | 0.19       |

HbA₁c = glycated hemoglobin.  
*Data for qualitative variables are expressed as n (%), and for quantitative variables as mean ± standard deviation or median (interquartile range).
emerged as potential mediators, explaining 11.8% (95% CI 11.1–12.5) and 9.7% (95% CI 9.1–10.2) of the effects of depressive symptoms on PWV in the covariate-adjusted models (model 2), respectively. On the other hand, the conditions for mediation were not fulfilled when evaluating the association between the exposure and outcome through body mass index, waist circumference and waist-to-height ratio.

To strengthen the validity of the cross-sectional mediation analysis, we have presented preliminary results from an interim analysis of our longitudinal subcohort (n = 184) in Appendix 1.

Discussion

In the cross-sectional analysis, we found that 4.2% of our participants with T2D displayed depressive symptoms, and we observed a higher prevalence among people with aortic stiffness. Our findings also showed that depressive symptoms were associated with PWV and aortic stiffness. For the first time, we also presented a potential partial mediatery role of fat mass and visceral fat area in the relationship between depressive symptoms and PWV among older people with T2D. On the other hand, proxy measures of adiposity, including body mass index, waist circumference and waist-to-height ratio, were not significant mediators. It may be reasoned that both fat mass and visceral fat area provide more precise estimates of body fatness than proxy indices, which are limited by their inability to discriminate fat mass from lean mass. The follow-up data (Appendix 1) provided an indication of a relationship between baseline depressive symptoms and PWV at follow-up, mediated by visceral fat area (suggesting a detrimental effect of visceral adiposity). However, acknowledging the relatively small sample size of the longitudinal subcohort (and limited number of participants with depressive symptoms), the preliminary findings warrant future validation in larger prospective cohorts. Apart from increased adiposity, other factors such as sleep disturbance, mental stress and reduced physical activity may influence the relationship between depressive symptoms and aortic stiffness.

It has been suggested that the relationship between depression and arterial stiffness is bidirectional. The mechanism(s) underlying depression and arterial stiffness remain elusive. Depression may elevate the risk of arterial stiffness through inflammation, endothelial dysfunction, autonomic nerve system impairments and unhealthy behavioural factors. In reverse, it is also plausible that stiffening of the arteries may result in transmission of excessive pressure and flow pulsatility in the microvasculature, stimulating

| Variable             | Pulse wave velocity B (95% CI), p value | Aortic stiffness Risk ratio (95% CI), p value |
|----------------------|----------------------------------------|----------------------------------------------|
| Model 1†             |                                        |                                              |
| Depressive symptoms  | 1.79 (0.83 to 2.75), < 0.001            | 1.60 (1.10 to 2.33), 0.015                    |
| Model 2‡             |                                        |                                              |
| Depressive symptoms  | 1.88 (0.95 to 2.82), < 0.001            | 1.67 (1.16 to 2.39), 0.005                    |
| Model 3§             |                                        |                                              |
| Depressive symptoms  | 1.54 (0.64 to 2.43), 0.001              | 1.50 (1.03 to 2.19), 0.036                    |
| Model 4¶             |                                        |                                              |
| Depressive symptoms  | 1.47 (0.58 to 2.35), 0.001              | 1.46 (1.00 to 2.14), 0.050                    |
| Body mass index      | 0.12 (0.08 to 0.15), < 0.001            | 1.05 (1.03 to 1.08), < 0.001                  |
| Model 5††            |                                        |                                              |
| Depressive symptoms  | 1.36 (0.47 to 2.24), 0.003              | 1.37 (0.93 to 2.00), 0.11                     |
| Fat mass             | 0.06 (0.04 to 0.08), < 0.001            | 1.03 (1.01 to 1.04), < 0.001                  |
| Model 6**            |                                        |                                              |
| Depressive symptoms  | 1.42 (0.53 to 2.31), 0.002              | 1.39 (0.94 to 2.05), 0.10                     |
| Waist circumference  | 0.32 (0.16 to 0.48), < 0.001            | 1.15 (1.05 to 1.26), 0.002                    |
| Model 7††            |                                        |                                              |
| Depressive symptoms  | 1.46 (0.56 to 2.35), 0.001              | 1.42 (0.97 to 2.10), 0.07                     |
| Waist:height ratio   | 4.04 (1.45 to 6.63), 0.002              | 6.49 (1.60 to 26.38), 0.009                   |
| Model 8‡‡            |                                        |                                              |
| Depressive symptoms  | 1.39 (0.50 to 2.28), 0.002              | 1.38 (0.94 to 2.04), 0.10                     |
| Visceral fat area     | 0.10 (0.05 to 0.15), < 0.001            | 1.04 (1.01 to 1.07), 0.003                    |

CI = confidence interval; HbA1c = glycated hemoglobin.

1Model 1: unadjusted.
†Model 2: model 1 adjusted for age, sex, education, natural log-transformed diabetes duration.
‡Model 3: model 2 adjusted for HbA1c, hypertension, chronic kidney disease, albuminuria, insulin, renin-angiotensin system antagonists.
§Model 4: model 3 adjusted for body mass index.
¶Model 5: model 3 adjusted for fat mass.
**Model 6: model 3 adjusted for waist circumference.
††Model 7: model 3 adjusted for waist:height ratio.
‡‡Model 8: model 3 adjusted for visceral fat area.
Association between depressive symptoms and pulse wave velocity

Similarly, Mut-Vicu and colleagues demonstrated that older adults. The varied observations may be explained by no association between obesity and depressive symptoms in for every increase of 1 kg/m² in body mass index, the association, inverse association, U-shaped association or association,38 inverse association,39 U-shaped association40 or

Our preliminary longitudinal data showed that depressive symptoms predicted risk of increased PWV. However, because of the observational nature of this study, we could not make causal inferences about the association between depressive symptoms and aortic stiffening. Nevertheless, it is plausible that shared cardiovascular and/or lifestyle risk factors, as well as common pathophysiological mechanisms, contribute to the relationship.

Depression is associated with unhealthy eating and a sedentary lifestyle, which lead to weight gain. Late-life depression has been linked to adiposity, but conflicting findings have been reported. Studies have revealed a positive association, inverse association, U-shaped association or no association between obesity and depressive symptoms in older adults. The varied observations may be explained by heterogeneity in study populations and study design. Less is known about the relationship in older people with T2D. A significant correlation between GDS-15 score and body mass index has been observed in older people with T2D. Similarly, Mut-Vicu and colleagues demonstrated that for every increase of 1 kg/m² in body mass index, the odds of depression (evaluated using the Patient Health Questionnaire) increased by 10.1% in older adults with T2D. In contrast, Cardenas and colleagues revealed no association between body mass index and major depression (evaluated using the Patient Health Questionnaire) among community-dwelling older Latino adults diagnosed with T2D and mild to moderately severe depression. To our knowledge, studies assessing the utility of other metrics of adiposity beyond body mass index for determining geriatric depression in T2D are lacking. In the present study, we showed significant correlations between measures of global and abdominal adiposity — particularly visceral fat area — and depressive symptoms. Notably, pharmacological treatment for depression may inadvertently provoke the orexigenic signal, promoting weight gain and aggravating arterial injury; health care providers should use caution when prescribing antidepressants. People who exhibit excessive weight gain while on antidepressants should be considered for weight management intervention.

Existing literature suggests that increased adiposity is associated with aortic stiffness both cross-sectionally and longitudinally. Consistent with this, we found an independent association between adiposity metrics and PWV, and between adiposity metrics and aortic stiffness. It is conceivable that accumulation of white adipose tissue — particularly in the visceral fat compartment — stimulates the secretion of a wide variety of adipokines and inflammatory cytokines, resulting in chronic low-grade inflammation. The activation of inflammatory signalling pathways may contribute to aortic stiffening. In addition, adipokines (specifically leptin) have been implicated in enhancing neointimal and medial thickening of injured carotid artery vascular walls; inducing the proliferation and migration of aortic smooth muscle cells; stimulating the renin–angiotensin–aldosterone system; and elevating oxidative stress in endothelial cells, all of which are linked to vascular stiffness.

**Limitations**

The strength of this study is the relatively large cohort of older people with T2D. Measurements were robust, using the gold-standard PWV method and the well-validated GDS-15 to assess depressive symptoms among older adults. However, a causal relationship between depression, increased adiposity and PWV cannot be inferred from the associations we observed. Strong evidence generated from well-designed epidemiological and experimental studies are needed to confidently establish causality. We did not record data on lifestyle factors such as physical activity, dietary intake and sleep quality in this study. We estimated fat mass and visceral fat area using tetrapolar multifrequency bioimpedance instead of dual-energy x-ray absorptiometry or computed tomography. However, considerable correlations have been reported between fat mass measured by bioimpedance and dual-energy x-ray absorptiometry and between visceral fat

| Mediated pathway                                      | Model* | Total effect (95% CI) | Direct effect (95% CI) | Indirect effect (95% CI) | Sobel z | Sobel p value | Proportion mediated, % |
|------------------------------------------------------|--------|-----------------------|------------------------|--------------------------|---------|---------------|------------------------|
| Depressive symptoms → body mass index → pulse wave velocity | 1      | 1.79 (0.32 to 3.25)   | 1.66 (0.21 to 3.12)    | 0.12 (−0.06 to 0.31)    | 1.278   | 0.20          | 7.0                    |
|                                                      | 2      | 1.54 (0.19 to 2.88)   | 1.47 (0.16 to 2.77)    | 0.07 (−0.11 to 0.25)    | 0.850   | 0.40          | 4.8                    |
| Depressive symptoms → fat mass → pulse wave velocity  | 1      | 1.79 (0.37 to 3.21)   | 1.55 (0.18 to 2.92)    | 0.24 (0.03 to 0.44)     | 2.428   | 0.015         | 13.3                   |
|                                                      | 2      | 1.54 (0.16 to 2.92)   | 1.36 (0.02 to 2.69)    | 0.18 (−0.00 to 0.37)    | 2.067   | 0.039         | 11.8                   |
| Depressive symptoms → waist circumference → pulse wave velocity | 1      | 1.79 (0.32 to 3.26)   | 1.65 (0.17 to 3.14)    | 0.13 (−0.01 to 0.28)    | 1.856   | 0.06          | 7.5                    |
|                                                      | 2      | 1.54 (0.17 to 2.91)   | 1.42 (−0.05 to 2.79)   | 0.12 (−0.02 to 0.26)    | 1.855   | 0.06          | 7.9                    |
| Depressive symptoms → waist:height ratio → pulse wave velocity | 1      | 1.79 (0.33 to 3.24)   | 1.69 (0.23 to 3.15)    | 0.10 (−0.03 to 0.23)    | 1.729   | 0.08          | 5.6                    |
|                                                      | 2      | 1.54 (0.12 to 2.96)   | 1.46 (0.03 to 2.89)    | 0.08 (−0.04 to 0.20)    | 1.546   | 0.12          | 5.3                    |
| Depressive symptoms → visceral fat area → pulse wave velocity | 1      | 1.79 (0.40 to 3.18)   | 1.56 (0.18 to 2.94)    | 0.23 (0.07 to 0.40)     | 2.580   | 0.010         | 12.9                   |
|                                                      | 2      | 1.54 (0.19 to 2.88)   | 1.39 (0.06 to 2.72)    | 0.15 (0.02 to 0.28)     | 2.175   | 0.030         | 9.7                    |

CI = confidence interval; HbA1c = glycated hemoglobin.

*Model 1: unadjusted; model 2: adjusted for covariates including age, sex, education, natural log-transformed diabetes duration, HbA1c, hypertension, chronic kidney disease, albuminuria, insulin, renin–angiotensin system antagonists.
area measured by bioimpedance and computed tomography ($r = 0.76$). Because our cohort constituted mainly multiethnic Asians in Singapore, the generalizability of the data beyond this study population warrants further investigation.

**Conclusion**

We demonstrated that depressive symptoms are associated with elevated PWV in older people with T2D, and this relationship may be partially mediated by increased adiposity, particularly visceral adiposity. Because late-life depression tends to be under-recognized and under-treated, greater attention on the part of health care professionals to the management of mental health and associated weight issues in older patients with T2D may have promising benefits for vascular health and reduced risk of adverse cardiovascular outcomes.

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