Research Paper

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

Mei Chung Moh, PhD; Serena Low, MBBS, MSc; Tze Pin Ng, MD; Su Fen Ang, PhD; Keven Ang, PhD; Chee Fang Sum, MBBS; Tavintharan Subramaniam, MBBS; Su Chi Lim, MBBS, PhD

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.[1] 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.[2,3] Carotid–femoral pulse wave velocity (PWV) is the gold-standard evaluation of aortic stiffness and a marker of vascular disease.[4]

Depressive symptoms have been commonly linked to poorer cardiovascular outcomes in older adults.[5,6] Less well-documented is the reverse association between cardiovascular disease and development of late-life depression.[6–8] Existing literature, albeit sparse, has revealed a relationship between depression and risk of aortic stiffness in population-based cohorts of older people.[9,10] 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.[11] 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.[12] We postulated a triangulated relationship between geriatric

Correspondence to: S.C. Lim, Diabetes Centre, Admiralty Medical Centre, Khoo Teck Puat Hospital, 676 Woodlands Drive 71 #03-01, Singapore 730676; lim.su.chi@ktph.com.sg

Submitted Apr. 26, 2020; Revised Jul. 9, 2020; Accepted Jul. 29, 2020

DOI: 10.1503/jpn.200080

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.[13] 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 mediatory 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).[14] 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[15] and depressive symptoms have been described in those aged 55 years or older,[16] 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.[17] 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.[18,19] This questionnaire is the

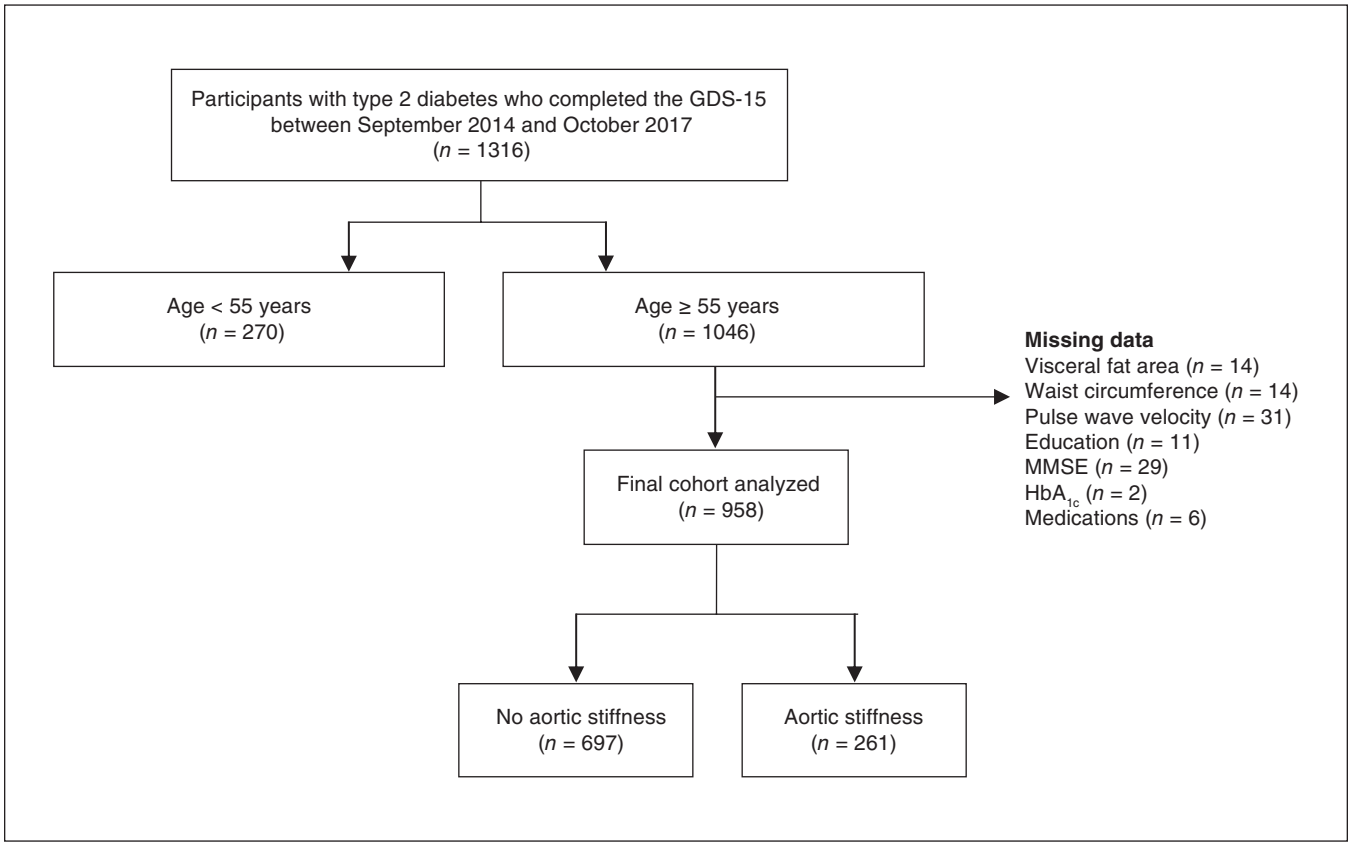

Fig. 1: Flow diagram depicting the derivation of the final cohort for cross-sectional analysis. GDS-15 = Geriatric Depression Scale (15-item); HbA_{1c} = glycated hemoglobin; MMSE = Mini-Mental State Examination.

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 m^2). 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 (HbA_{1c}) 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 m^2. 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, HbA_{1c}, 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% v. 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 1.03–2.19) persisted after adjustment for age, sex, education, natural log-transformed diabetes duration, HbA_{1c}, comorbidities (hypertension, chronic kidney disease, albuminuria) and use of

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 ± 7	64 ± 6	66 ± 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/m^2	26.8 ± 4.8	26.3 ± 4.5	28.0 ± 5.3	< 0.001
Waist circumference, cm^2	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, cm^2	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 ± 8.6	0.33
Hypertension, *n* (%)	820 (85.6)	577 (82.8)	243 (93.1)	< 0.001
HbA_{1c}, %	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 hypglycemic 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).

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 2: Association of depressive symptoms with pulse wave velocity and aortic stiffness

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 (per 10 cm)	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 (per 10 cm^2)	0.10 (0.05 to 0.15), < 0.001	1.04 (1.01 to 1.07), 0.003

CI = confidence interval; HbA_{1c} = glycated hemoglobin.
*Model 1: unadjusted.
†Model 2: model 1 adjusted for age, sex, education, natural log-transformed diabetes duration.
‡Model 3: model 2 adjusted for HbA_{1c}, 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.

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 mediatory 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,[31] mental stress[32] and reduced physical activity[33] may influence the relationship between depressive symptoms and aortic stiffness.

It has been suggested that the relationship between depression and arterial stiffness is bidirectional.[10] 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.[34] 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

Table 3: Mediation effects of adiposity metrics on the relationship between depressive symptoms and pulse wave velocity

Mediated pathway	Model*	Total effect coefficient (95% CI)	Direct effect coefficient (95% CI)	Indirect effect coefficient (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; HbA_{1c} = glycated hemoglobin.
*Model 1: unadjusted; model 2: adjusted for covariates including age, sex, education, natural log-transformed diabetes duration, HbA_{1c}, hypertension, chronic kidney disease, albuminuria, insulin, renin–angiotensin system antagonists.

cerebral microvascular damage. The damage may in turn increase the risk of depressive symptoms by disrupting the frontosubcortical neuronal circuits involved in mood regulation and executive functions ("vascular depression" hypothesis).[35,36] 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.[37] Late-life depression has been linked to adiposity, but conflicting findings have been reported. Studies have revealed a positive association,[38] inverse association,[39] U-shaped association[40] or no association between obesity and depressive symptoms in older adults.[41] 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.[42] Similarly, Mut-Vicu and colleagues[43] demonstrated that for every increase of 1 kg/m^2 in body mass index, the odds of depression (evaluated using the Patient Health Questionnaire-9[44]) increased by 10.1% in older adults with T2D. In contrast, Cardenas and colleagues[45] revealed no association between body mass index and major depression (evaluated using the Patient Health Questionnaire-9[44]) 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,[46] 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.[13,14] 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.[47] The activation of inflammatory signalling pathways may contribute to aortic stiffening.[48] In addition, adipokines (specifically leptin) have been implicated in enhancing neointimal and medial thickening of injured carotid artery vascular walls;[49] inducing the proliferation and migration of aortic smooth muscle cells;[50] stimulating the renin–angiotensin–aldosterone system;[51] and elevating oxidative stress in endothelial cells,[52] 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 (r = 0.96),[53] and between visceral fat

area measured by bioimpedance and computed tomography (r = 0.76).[54] Because our cohort constituted mainly multi-ethnic 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.

Acknowledgements: The authors thank the staff from the Singapore Clinical Research Institute (SCRI) for their contribution to the study protocol and database design. Study data were collected and managed using REDCap electronic data capture tools hosted at the SCRI.

Affiliations: From the Clinical Research Unit, Khoo Teck Puat Hospital, Singapore (Moh, Low, S. Ang, K. Ang, Subramaniam, Lim); the Diabetes Centre, Admiralty Medical Centre, Khoo Teck Puat Hospital, Singapore (Low, Sum, Subramaniam, Lim); the Gerontology Research Programme, Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore (Ng); and the Saw Swee Hock School of Public Health, National University Hospital, Singapore (Lim).

Competing interests: None declared.

Contributors: All authors designed the study. S. Low and K. Ang acquired the data, which M. Moh, S. Low and S. Lim analyzed. M. Moh wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

Funding: The SMART2D cohort is supported by the Singapore Ministry of Health's National Medical Research Council CS-IRG (MOH-000066). S. Lim is supported by the Singapore Ministry of Health's National Medical Research Council Clinical Scientist Award (NMRC/CSA-INV/0020/2017).

References

1. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010;121:505-11.
2. Lee HY, Oh BH. Aging and arterial stiffness. *Circ J* 2010;74:2257-62.
3. Fortier C, Agharazii M. Arterial stiffness gradient. *Pulse (Basel)* 2016;3:159-66.
4. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012;30:445-8.
5. Pequignot R, Dufouil C, Prugger C, et al. High level of depressive symptoms at repeated study visits and risk of coronary heart disease and stroke over 10 years in older adults: the three-city study. *J Am Geriatr Soc* 2016;64:118-25.
6. Choi NG, Kim J, Marti CN, et al. Late-life depression and cardiovascular disease burden: examination of reciprocal relationship. *Am J Geriatr Psychiatry* 2014;22:1522-9.
7. Hazuda HP, Gaussoin SA, Wing RR, et al. Long-term association of depression symptoms and antidepressant medication use with incident cardiovascular events in the Look AHEAD (Action for Health in Diabetes) clinical trial of weight loss in type 2 diabetes. *Diabetes Care* 2019;42:910-8.
8. Meng R, Yu C, Liu N, et al. Association of depression with all-cause and cardiovascular disease mortality among adults in China. *JAMA Netw Open* 2020;3:e1921043.
9. Tiemeier H, Breteler MM, van Popele NM, et al. Late-life depression is associated with arterial stiffness: a population-based study. *J Am Geriatr Soc* 2003;51:1105-10.
10. 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. *J Psychiatry Neurosci* 2016;41:162-8.
11. Dregan A, Rayner L, Davis KAS, et al. Associations between depression, arterial stiffness, and metabolic syndrome among adults in the UK Biobank population study: a mediation analysis. *JAMA Psychiatry* 2020;77:598-606.
12. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004;15:2792-800.
13. Moh MC, Sum CF, Lam BC, et al. Evaluation of body adiposity index as a predictor of aortic stiffness in multi-ethnic Asian population with type 2 diabetes. *Diab Vasc Dis Res* 2015;12:111-8.
14. Moh MC, Sum CF, Tavintharan S, et al. Baseline predictors of aortic stiffness progression among multi-ethnic Asians with type 2 diabetes. *Atherosclerosis* 2017;260:102-9.
15. Rogers WJ, Hu YL, Coast D, et al. Age-associated changes in regional aortic pulse wave velocity. *J Am Coll Cardiol* 2001;38:1123-9.
16. Feng L, Nyunt MS, Yap KB, et al. Frailty predicts new and persistent depressive symptoms among community-dwelling older adults: findings from Singapore longitudinal aging study. *J Am Med Dir Assoc* 2014;15:76.e7-76.e12.
17. Butlin M, Qasem A. Large artery stiffness assessment using SphygmoCor Technology. *Pulse (Basel)* 2017;4:180-92.
18. Burke WJ, Roccaforte WH, Wengel SP. The short form of the Geriatric Depression Scale: a comparison with the 30-item form. *J Geriatr Psychiatry Neurol* 1991;4:173-8.
19. D'Ath P, Katona P, Mullan E, et al. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. *Fam Pract* 1994;11:260-6.
20. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17:37-49.
21. Mui AC. Geriatric Depression Scale as a community screening instrument for elderly Chinese immigrants. *Int Psychogeriatr* 1996;8:445-58.
22. Sugishita K, Sugishita M, Hemmi I, et al. A validity and reliability study of the Japanese version of the Geriatric Depression Scale 15 (GDS-15-J). *Clin Gerontol* 2017;40:233-40.
23. Lucas-Carrasco R. Spanish version of the Geriatric Depression Scale: reliability and validity in persons with mild-moderate dementia. *Int Psychogeriatr* 2012;24:1284-90.
24. Ng TP, Jin A, Feng L, et al. Mortality of older persons living alone: Singapore longitudinal ageing studies. *BMC Geriatr* 2015;15:126.
25. Ng TP, Niti M, Chiam PC, et al. Ethnic and educational differences in cognitive test performance on Mini-Mental State Examination in Asians. *Am J Geriatr Psychiatry* 2007;15:130-9.
26. Moh MC, Sum CF, Tavintharan S, et al. Gain in adiposity over 3 years is associated with progressive renal decline in multi-ethnic south-east Asians with type 2 diabetes. *J Diabetes* 2019;11:316-25.
27. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604-12.
28. Ng TP, Feng L, Yap KB, et al. Long-term metformin usage and cognitive function among older adults with diabetes. *J Alzheimers Dis* 2014;41:61-8.
29. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of

Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105-87.
30. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702-6.
31. Kim CW, Chang Y, Zhao D, et al. Sleep duration, sleep quality, and markers of subclinical arterial disease in healthy men and women. *Arterioscler Thromb Vasc Biol* 2015;35:2238-45.
32. Vlachopoulos C, Kosmopoulou F, Alexopoulos N, et al. Acute mental stress has a prolonged unfavorable effect on arterial stiffness and wave reflections. *Psychosom Med* 2006;68:231-7.
33. Boreham CA, Ferreira I, Twisk JW, et al. Cardiorespiratory fitness, physical activity, and arterial stiffness: the Northern Ireland Young Hearts Project. *Hypertension* 2004;44:721-6.
34. Peng L, Bi S, Liu X, et al. Association between depressive symptoms and arterial stiffness: a cross-sectional study in the general Chinese population. *BMJ Open* 2020;10:e033408.
35. Cooper LL, Mitchell GF. Aortic stiffness, cerebrovascular dysfunction, and memory. *Pulse (Basel)* 2016;4:69-77.
36. Alexopoulos GS, Meyers BS, Young RC, et al. "Vascular depression" hypothesis. *Arch Gen Psychiatry* 1997;54:915-22.
37. Rossetti C, Halfon O, Boutrel B. Controversies about a common etiology for eating and mood disorders. *Front Psychol* 2014;5:1205.
38. Pan A, Sun Q, Czernichow S, et al. Bidirectional association between depression and obesity in middle-aged and older women. *Int J Obes* 2012;36:595-602.
39. Li ZB, Ho SY, Chan WM, et al. Obesity and depressive symptoms in Chinese elderly. *Int J Geriatr Psychiatry* 2004;19:68-74.
40. Cho J, Jin Y, Kang H. Weight status, physical activity, and depression in Korean older adults. *J Epidemiol* 2018;28:292-9.
41. Peltzer K, Phaswana-Mafuya N. Depression and associated factors in older adults in South Africa. *Glob Health Action* 2013;6:1-9.
42. de Lima Filho BF, da Nobrega Dias V, Carlos AG, et al. Factors related to depressive symptoms in older adult patients with type 2 diabetes mellitus. *Exp Gerontol* 2019;117:72-5.
43. Mut-Vitcu G, Timar B, Timar R, et al. Depression influences the quality of diabetes-related self-management activities in elderly patients with type 2 diabetes: a cross-sectional study. *Clin Interv Aging* 2016;11:471-9.
44. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606-13.
45. Cardenas V, Mausbach BT, Sommerfeld D, et al. Depression is associated with increased risk for metabolic syndrome in Latinos with type 2 diabetes. *Am J Geriatr Psychiatry* 2017;25:646-53.
46. Cassano P, Fava M. Tolerability issues during long-term treatment with antidepressants. *Ann Clin Psychiatry* 2004;16:15-25.
47. Unamuno X, Gomez-Ambrosi J, Rodriguez A, et al. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Invest* 2018;48:e12997.
48. Wang M, Monticone RE, McGraw KR. Proinflammatory arterial stiffness syndrome: a signature of large arterial aging. *J Vasc Res* 2018;55:210-23.
49. Schafer K, Halle M, Goeschen C, et al. Leptin promotes vascular remodeling and neointimal growth in mice. *Arterioscler Thromb Vasc Biol* 2004;24:112-7.
50. Oda A, Taniguchi T, Yokoyama M. Leptin stimulates rat aortic smooth muscle cell proliferation and migration. *Kobe J Med Sci* 2001;47:141-50.
51. Bornstein SR, Torpy DJ. Leptin and the renin-angiotensin-aldosterone system. *Hypertension* 1998;32:376-7.
52. Bouloumie A, Marumo T, Lafontan M, et al. Leptin induces oxidative stress in human endothelial cells. *FASEB J* 1999;13:1231-8.
53. Kim H, Kim CH, Kim DW, et al. External cross-validation of bioelectrical impedance analysis for the assessment of body composition in Korean adults. *Nutr Res Pract* 2011;5:246-52.
54. Ogawa H, Fujitani K, Tsujinaka T, et al. InBody 720 as a new method of evaluating visceral obesity. *Hepatogastroenterology* 2011;58:42-4.