Int J Clin Exp Med 2019;12(4):4174-4183
www.ijcem.com /ISSN:1940-5901/IJCEM0077419

Original Article

The effect of metabolic factors on the post-stroke depression of ischemic stroke patients

Jiantong Jiao[1*], Long Wang[3*], Jin Huang[1*], Chao Cheng[1], Weiyi Huang[1], Kemiao Yuan[4], Suyin Feng[5], Yansong Zhang[6], Na Zhang[7], Pinggang Di[8], Shuo Feng[9], Junfei Shao[1], Fang Wang[2]

[1]Department of Neurosurgery, Wuxi People's Hospital, Wuxi, Jiangsu, China; Departments of [2]Endocrinology and Metabolism, [3]Neurosurgery, Heping Hospital Affiliated to Changzhi Medical College, Changzhi, Shanxi, China; [4]Department of Oncology, Traditional Chinese Medicine Hospital of Wuxi, Wuxi, Jiangsu, China; [5]Department of Neurosurgery, The Fourth People's Hospital of Wuxi, Wuxi, Jiangsu, China; [6]Department of Neurosurgery, Nanjing Brain Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; [7]Department of Neurology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China; [8]Department of Neurology, Wulian People's Hospital, Wulian, Shandong, China; [9]Department of Neurosurgery, Jiaonan People's Hospital, Jiaonan, Qingdao, China. [*]Co-first authors.

Received April 5, 2018; Accepted December 10, 2018; Epub April 15, 2019; Published April 30, 2019

Abstract: Objective: To investigate the relationship between metabolic syndrome (MetS) risk factors and the risk of post-stroke depression (PSD) in ischemic stroke patients. Methods: A total of 667 ischemic stroke patients participated in blood sample collection for the analysis of MetS risk factors, and in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) testing. The association between MetS risk factors and the risk of PSD was assessed using Cox regression proportional hazards models, and the Chi-squared test was used to evaluate differences in demographic variables and clinical characteristics in the subgroups. Results: In our study, the incidence of PSD in the 2-year follow-up was 35.4%. The risk of PSD was elevated with increased blood glucose levels (Hazard ratio [HR]: 2.147, 95% confidence interval [CI]: 1.331-3.463; top vs. bottom quartile) and glycosylated hemoglobin (HbA1c) (HR: 2.348, 95% CI: 1.424-3.871; top vs. bottom quartile). The hazard ratio was increased for z-scores of blood glucose and HbA1c, and for the combined metabolic syndrome score. In addition, the risk of PSD was increased in ischemic stroke patients with high blood glucose levels (≥6.0 mmol/l) and with HbA1c (≥6.5%). However, we did not find significant associations between PSD and other MetS risk factors, including body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol, and triglycerides. Conclusions: Depression is prevalent among ischemic stroke patients. Blood glucose levels and HbA1c are positively associated with the risk of PSD and might be useful bio-markers to predict its development.

Keywords: Post-stoke depression, metabolic syndrome factors, blood glucose, glycosylated hemoglobin

Introduction

Stroke is a leading cause of morbidity and mortality throughout the world. With the slow decline in mortality rates, increasing numbers of stroke survivors are left to a variety of physical, cognitive, and psychosocial impairments [1]. Depression after stroke is a common problem, distressing the patients, and a systematic review of 61 observational studies found a pooled estimate of up to 31% for its prevalence [2]. Evidence from numerous studies has established that depression is associated with a poorer outcome in stroke patients [3]. It is suggested that the association between stroke and depression is bi-directional [4]: stroke increases the risk of depression [5], and vice-versa, depression independently increases the risk of stroke [6]. Thus, neurologists and other professionals treating stroke patients must be more vigilant with regard to the assessment of their patients for the possibility of depression.

MetS involves various risk factors, such as impaired glucose levels, dyslipidemia, hypertension, and central obesity, which predispose persons to cardiovascular mortality and morbidity [7]. To date, the association of MetS or metabolic factors with psychological problems is still inconclusive. Some evidence shows a sig-

nificant association between Mets and depression [7-14], whereas the findings of other studies show none [15-17]. As for the MetS factors, metabolic dys-regulation was found to influence brain function, and the disturbance in blood glucose regulation might be associated with cognitive impairment and a depressed mood [18]. A recent systematic review indicated that previously diagnosed type 2 diabetes increases the risk of depression [19]. Some studies demonstrated that depression is decidedly relevant to obesity and glucose metabolism [20, 21]. Cholesterol was also found to be associated with mood disorder, although the relationship in other studies is unclear [22, 23]. Collectively, those findings indicate that MetS and its factors may play important roles in the development of depression.

Even though widespread research has been carried out on post-stroke depression over the past few decades, little knowledge of the true etiology has been accomplished. Up to now, few studies have focused on the association between metabolic factors and post-stroke depression. Therefore, our present study investigated whether metabolic factors contribute to and can be used to predict the risk of depression after stroke.

Methods

Subjects

The study involved 667 eligible participants with ischemic stroke, 382 males and 285 females, treated at Heping Hospital Affiliated to Changzhi Medical College, The Fourth People's Hospital of Wuxi, Wuxi People's Hospital, Nanjing Brain Hospital, The First Affiliated Hospital of Nanchang University, Wulian People's Hospital, Jiaonan People's Hospital and Traditional Chinese Medicine Hospital of Wuxi, between March 2009 and April 2015 and followed up to May 2017. The average age for the males was 56.2±9.6, and for the females, 56.9±9.8 years. The patients were enrolled by the researchers at the start of treatment. Data were collected on height, weight, SBP, DBP, and circulating levels of glucose, HbA1c, total cholesterol, and triglycerides. Information about the patients' demographic variables and clinical characteristics was also collected. The radiological diagnosis of ischemic stroke was carried out by computed tomography (CT) and magnetic resonance imaging (MRI). The ischemic stroke was located in the right hemisphere of 315, in the left hemisphere of 321, and in the cerebellum of 31 patients. The severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS) at the ward, emergency room, or clinic. If the NIHSS score was ≤3, the patients were defined as having had a minor stroke, and if the score was >3 they were defined as having had a moderate-to-severe stroke [24]. Eligible criteria included: (1) a first-ever diagnosis of ischemic stroke; (2) capability of completing questionnaires or answering questions and participating in the program; (3) no history of mental disorder; (4) no other serious diseases.

Our institution received approval for the study from the ethics committee of the review board, and informed consent was obtained from all patients.

Assessment of depression

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) test was performed to diagnose PSD in patients [25]. The patients received the DSM-IV test every 2 or 3 months during the 2-year follow-up, given by a trained physician in the out-patient department or by telephone. If depression was indicated, psychosocial intervention or general medical advice was recommended.

Quartile analysis

The MetS risk factors were categorized as quartiles. The lowest quartile was used as a reference. The relative risks of other quartiles were estimated by Cox regression analysis, compared to the lowest quartile. In the Cox regression multivariate analyses, age, gender, education, smoking, alcohol consumption, marriage, hemisphere, infarct location and NIHSS score were adjusted as covariates. The linear trend for the association was calculated in the regression model.

Standardized z-score analysis

For each MetS risk factor, a z-score was calculated. Standardized scores let each determinant to be investigated in the same scale, making a uniform comparison possible. The existing values were transformed to standardized variables (z-scores), with zero as the mean and one as the standard deviation (SD) (z=(x-m)/s).

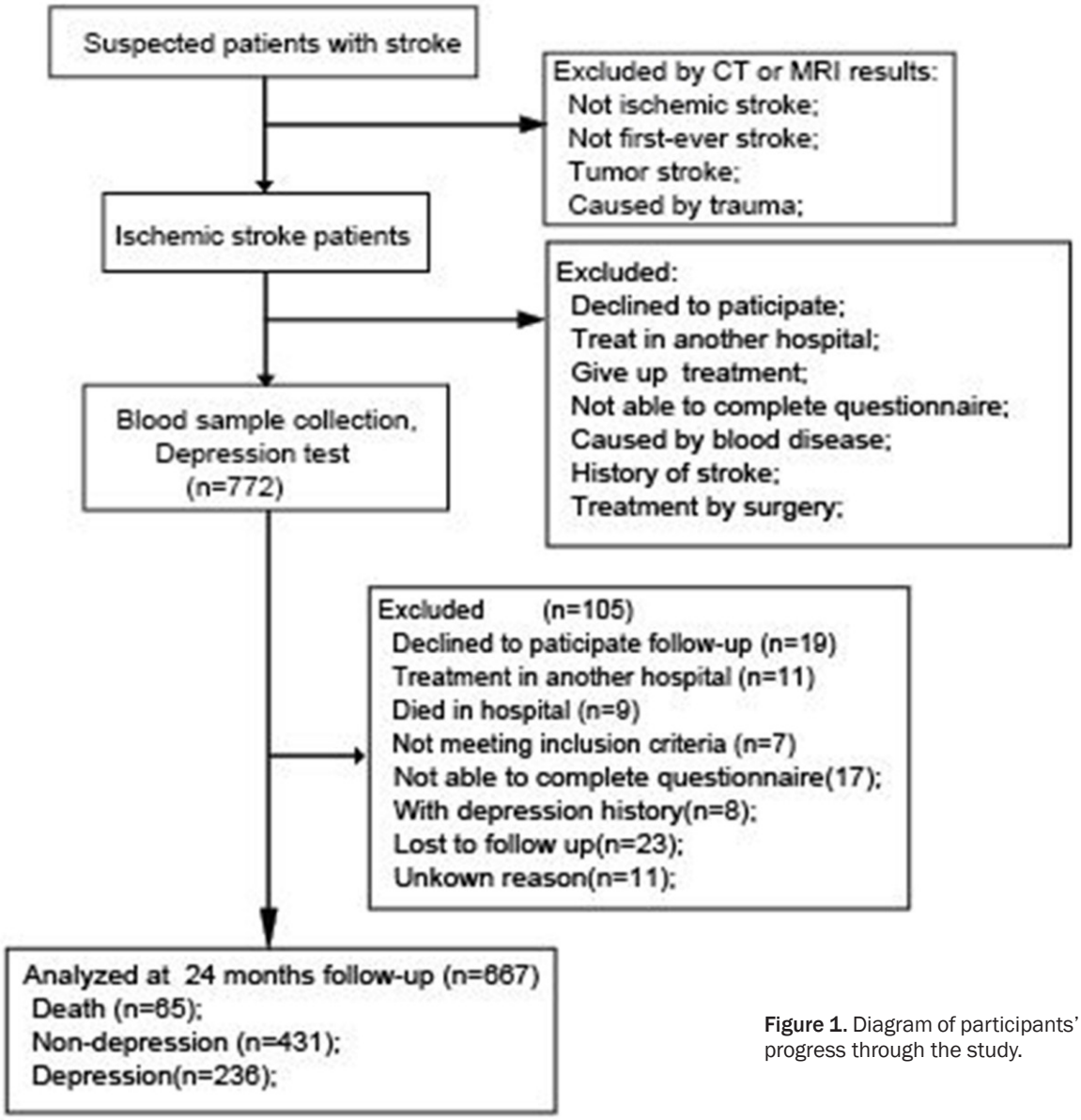

Figure 1. Diagram of participants' progress through the study.

Skewed variables (natural logarithm for blood glucose and HbA1c, a reciprocal for triglycerides) were transformed prior to standardization. In a composite analysis, the MetS risk factor score was constructed by adding the individual z-scores and further standardizing the resulting sum. The adjustments in the z-score analysis were the same as in the quartile analysis.

Analysis by WHO standards

The MetS risk factors were divided into two categories according to cut-offs defined by WHO Standards as follows: overweight (BMI 25-30 kg/m^2), obesity (BMI ≥30 kg/m^2), hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), impaired glucose tolerance (fasting glucose 6.0-6.9 mmol/l), diabetes (fasting glucose ≥7.0 mmol/l), hyper-triglyceridemia (fasting triglycerides ≥1.7 mmol/l), and hypercholesterolemia (fasting total cholesterol ≥6.2 mmol/l).

Statistical analysis

Group differences in demographic variables and clinical characteristics were treated with the Chi-squared test. Cox regression is a method used for investigating the effect of several variables upon the time a specified event takes to happen. In this study, the Cox regression proportional hazards model was used to estimate the relationship of the risk of depression with

Table 1. Baseline characteristics of the subjects

Characteristics	Depressed	Non-depressed	*P* values
Age (y), n (%)			
≥50	156 (66.1)	320 (74.2)	
<50	80 (33.9)	111 (25.8)	P=0.026
Gender, n (%)			
Male	139 (58.9)	243 (56.4)	
Female	97 (41.1)	188 (43.6)	P=0.530
Marriage, n (%)			
Married	216 (91.5)	401 (93.0)	
Unmarried	20 (8.5)	30 (7.0)	P=0.478
Education, n (%)			
Primary	67 (28.4)	104 (24.1)	
Secondary	76 (32.2)	150 (34.8)	
Advanced	93 (39.4)	177 (41.1)	P=0.475
Smoking, n (%)			
Yes	82 (34.7)	179 (41.5)	
No	154 (65.3)	252 (58.5)	P=0.094
Alcohol, n (%)			
Yes	76 (32.2)	174 (40.4)	
No	160 (67.8)	257(59.6)	P=0.037
Stroke severity			
NIHSS≤3	124 (52.5)	310 (71.9)	
NIHSS>3	112 (47.5)	121 (28.1)	P<0.001
Hemisphere, n (%)			
Left	112 (47.5)	209 (48.5)	
Right	114 (48.3)	201 (46.6)	
Cerebellum	10 (4.2)	21 (4.9)	P=0.880
Infarct location, n (%)			
Frontal	116 (49.2)	201 (46.6)	
Temporal	69 (29.2)	147 (34.1)	
Parietal	22 (9.3)	31 (7.2)	
Occipital	19 (8.1)	31 (7.2)	
Cerebellum	10 (4.2)	21 (4.9)	P=0.650

BMI, SBP, DBP, and circulating levels of glucose, HbA1c, total cholesterol, and triglycerides in ischemic stroke patients during 2-year follow-up. All statistical analyses were performed by using the SPSS statistical software (version 19.0, USA), and the results were considered statistically significant when the appropriately calculated two-tailed *p*-value was <0.05.

Results

Baseline characteristics of the patients

A total of 772 patients were identified, of which 667 (86.4%) were eligible for participation and underwent DSM-IV testing and blood sample collection for the analysis of metabolic syndrome factors. At 24 months, 23 patients were lost for follow-up, and 65 had died. In the final analysis, there were 382 males and 285 females, of whom 315, 321, and 31 had right-, left-sided, and cerebellum ischemic stroke, respectively. The reasons for non-participation are shown in **Figure 1**. During the 2-year follow-up, 236 were identified as depressed patients and 431 non-depressed by the HADS test after hospital discharge. The incidence of PSD in ischemic stroke patients was 35.4%. The baseline characteristics were compared between the depressed and non-depressed groups in terms of demographic variables and clinical characteristics (**Table 1**). Most of the demographic values for the subgroups were not statistically different, with the exceptions of a higher percentage of young people (age <50) (*P*=0.026), more serious stroke patients (P<0.001) and more alcohol consumption in the depressed group (*P*=0.037) (**Table 1**).

PSD and metabolic syndrome factors in quartile analysis

In the adjusted quartile analysis, glucose was related to the risk of PSD, which was increased more than two-fold (HR: 2.135, 95% CI: 1.326-3.436). After further adjustment for BMI, glucose was still significantly associated with the risk of PSD (HR: 2.147, 95% CI: 1.331-3.463) (**Table 2**). Similar results were found in the relationship between HbA1c and PSD. When the fourth quartile was compared with the reference, the relative risk of PSD was 2.318 (1.413-3.803), and the strength of association was not changed obviously (HR: 2.348, 95% CI: 1.424-3.871) after further adjustment for BMI (**Table 2**). However, we did not find significant associations between the risk of PSD and BMI, SBP, DBP, cholesterol, and triglycerides (**Table 2**). After further adjustment for BMI, we still did not find any significant association (**Table 2**).

PSD and metabolic syndrome factors in a composite analysis

In the adjusted multivariable cox regression analyses of z-scores, no statistically significant

Table 2. Risks of PSD in relation to quartiles of metabolic factors

				Model[1]		Model[2]	
Exposures	Q	Mean ± SD	Ca/Co	HR	95% CI	HR	95% CI
BMI	1	19.338±1.128	61/104	1.000	(reference)		
(kg/m^2)	2	21.901±0.695	56/111	0.909	0.572-1.444		
	3	24.338±0.870	58/109	0.950	0.599-1.505		
	4	27.962±1.982	61/107	0.998	0.629-1.583		
	P_{trend}			0.957			
SBP	1	120.018±8.161	59/105	1.000	(reference)	1.000	(reference)
(mmHg)	2	133.704±2.753	55/114	0.845	0.531-1.343	0.845	0.531-1.344
	3	141.899±3.190	59/110	1.001	0.632-1.585	1.001	0.631-1.588
	4	160.533±11.282	63/102	1.084	0.682-1.722	1.084	0.679-1.733
	P_{trend}			0.576		0.577	
DBP	1	62.934±5.028	59/108	1.000	(reference)	1.000	(reference)
(mmHg)	2	76.720±3.624	55/109	0.961	0.605-1.525	0.960	0.604-1.527
	3	89.077±3.872	59/109	1.004	0.636-1.586	1.004	0.635-1.587
	4	106.107±8.535	63/105	1.040	0.658-1.643	1.039	0.653-1.653
	P_{trend}			0.831		0.835	
Glucose	1	3.745±0.564	41/125	1.000	(reference)	1.000	(reference)
(mmol/l)	2	5.021±0.341	57/108	1.609	0.991-2.613	1.612	0.992-2.619
	3	6.061±0.367	64/103	1.862	1.155-3.004	1.870	1.158-3.019
	4	8.958±2.225	74/95	2.135	1.326-3.436	2.147	1.331-3.463
	P_{trend}			0.002		0.002	
HbA1c (%)	1	4.397±0.511	36/117	1.000	(reference)	1.000	(reference)
	2	5.520±0.293	64/116	1.696	1.037-2.776	1.704	1.041-2.791
	3	6.690±0.376	61/98	2.037	1.231-3.370	2.046	1.236-3.387
	4	9.421±2.014	75/100	2.318	1.413-3.803	2.348	1.424-3.871
	P_{trend}			0.001		0.001	
Cholesterol	1	3.351±0.539	62/103	1.000	(reference)	1.000	(reference)
(mmol/l)	2	4.648±0.338	54/111	0.793	0.500-1.259	0.792	0.499-1.259
	3	5.917±0.416	56/107	0.886	0.558-1.407	0.885	0.557-1.407
	4	7.713±1.238	64/110	0.957	0.608-1.506	0.955	0.605-1.507
	P_{trend}			0.972		0.967	
Triglyceride	1	1.014±0.167	59/108	1.000	(reference)	1.000	(reference)
(mmol/l)	2	1.393±0.139	55/111	0.952	0.598-1.514	0.951	0.598-1.515
	3	1.869±0.299	59/108	0.986	0.623-1.560	0.985	0.622-1.562
	4	4.155±1.939	63/104	1.046	0.661-1.657	1.045	0.657-1.663
	P_{trend}			0.821		0.825	

CI: confidence interval, *HR:* hazard ratio, *Q:* quartile, *SD:* standard deviation, *BMI:* body mass index, *SBP:* systolic blood pressure, *DBP:* diastolic blood pressure, *HbA1c:* glycosylated hemoglobin. 1: Hazard ratios were estimated from Cox regression models after adjustment for age, gender, education, smoking, alcohol consumption, marriage, hemisphere, infarct location and NIHSS. 2: Additional adjusted for BMI.

association with PSD was observed for BMI, SBP, DBP, cholesterol, and triglycerides (**Table 3**). For blood glucose and HbA1c, significant associations were found for a unit z-score increment (HR: 1.276, 95% CI: 1.081-1.506 for blood glucose; HR: 1.385, 95% CI: 1.170-1.641 for HbA1c) (**Table 3**). After further adjustment for BMI, such significant associations still existed (HR: 1.280, 95% CI: 1.084-1.511 for blood glucose; HR: 1.409, 95% CI: 1.185-1.675 for HbA1c) (**Table 3**). When all the metabolic factors were calibrated and adjusted for each other, the significant associations persisted only for glucose and HbA1c (HR: 1.204, 95% CI: 1.014-1.430 for blood glucose; HR: 1.420, 95% CI: 1.168-1.727 for HbA1c) (**Table 3**). When the

Table 3. Relative risks (95%CI) of PSD, by z-scores of metabolic factors, and of the MetS score

	Model[1]		Model[2]		Model[3]	
Exposures	HR	95% CI	HR	95% CI	HR	95% CI
BMI	0.984	0.835-1.159			0.920	0.771-1.097
SBP	1.085	0.921-1.277	1.093	0.924-1.291	1.032	0.858-1.242
DBP	1.070	0.910-1.260	1.076	0.912-1.269	0.989	0.823-1.188
Glucose[4]	1.276	1.081-1.506	1.280	1.084-1.511	1.204	1.014-1.430
HbA1c[4]	1.385	1.170-1.641	1.409	1.185-1.675	1.420	1.168-1.727
Cholesterol	0.976	0.827-1.151	0.977	0.827-1.155	0.899	0.737-1.097
Triglyceride[5]	0.972	0.824-1.146	0.968	0.819-1.145	1.058	0.869-1.290
MetS score	1.069	1.013-1.127				

CI: confidence interval, *HR:* hazard ratio, *BMI:* body mass index, *SBP:* systolic blood pressure, *DBP:* diastolic blood pressure, *HbA1c:* glycosylated hemoglobin, z=(x-m)/s (z: z-score, x: raw score, m: mean, s: standard deviation). Model[1]: Hazard ratios were estimated from Cox regression models after adjustment for age, gender, education, smoking, alcohol consumption, marriage, hemisphere, infarct location and NIHSS. Model[2]: Additional adjusted for BMI. Model[3]: Further adjusted for all the individual z-scores (except in MetS score analysis). 4: Glucose and HbA1c were logarithmically transformed. 5: Triglyceride were reciprocally transformed.

MetS z-score was calibrated by adding the z-scores of all the metabolic factors, the relative risk per unit increment of the MetS z-score was 1.069 (1.013-1.127) (**Table 3**).

PSD and metabolic syndrome factors in analysis by WHO classification

In the analysis of dichotomized categories according to the WHO classification of risk factors, increases in risk were found for individuals with impaired glucose metabolism (fasting blood glucose above versus below 6.0 mmol/l), and those with a high percentage of HbA1c (fasting HbA1c above versus below 6.5%), with a relative risk of 1.631 (1.168-2.277) and 1.685 (1.205-2.355), respectively (**Table 4**). After further adjustment for BMI, the relative risk was not changed obviously (HR: 1.622, 95% CI: 1.161-2.267 for blood glucose; HR: 1.674, 95% CI: 1.195-2.344 for HbA1c) (**Table 4**). However, we did not find any significant relationship between the risk for PSD and being overweight (BMI above versus below 25 kg/m^2), having hypertension (SBP ≥140 mmHg and/or DBP ≥90 mmHg), hypertriglyceridemia (fasting triglycerides ≥1.7 mmol/l), or hypercholesterolemia (fasting total cholesterol ≥6.2 mmol/l) (**Table 4**).

Discussion

In this study of 667 ischemic stroke patients, an analysis of single metabolic risk factors revealed that glucose and HbA1c were significantly associated with an increased risk of PSD. Further a composite metabolic syndrome score-based on BMI, blood pressure, and circulating concentrations of glucose, HbA1c, total cholesterol and triglycerides-was significantly associated with PSD.

Depression after stroke is a common, chronic and recurrent health problem [26, 27]. In our study, its prevalence was 35.4%, similar to or higher than levels in reports of other investigators [27, 28]. However, the mechanism of PSD is still unclear. MetS factors-excess weight, hypertension, cholesterol disorder and hypertriglyceridemia-have been found to play important roles in pathological changes of neurological disorders, such as abnormal signal transduction, atherosclerosis, microinfarcts and hemorrhages [29]. However, our study did not find any significant association of PSD with BMI, SBP, DBP, cholesterol and triglycerides.

Impaired glucose metabolism increases the risk of PSD. The etiology of this phenomena is the hypothalamic-pituitary-adrenal cortex (HPA) axis, which is considered as one of key mechanisms in depression-related biological alterations [30]. The insulin-like growth factors (IGFs) as essential components of the HPA axis play important roles in the development of depression [31]. The impaired glucose metabolism involves longstanding insulin resistance that is accompanied by a compensatory increase in insulin secretion. The chronic hyper-insulinemic

Table 4. Relative risks (95% CI) of PSD by WHO categories of metabolic factors

			Model[2]		Model[3]	
Exposures	Cut-off[1]	Ca/Co	HR	95% CI	HR	95% CI
BMI	<25	159/291	1.000	(reference)		
(kg/m^2)	≥25	77/140	1.130	0.795-1.607		
SBP	<140	142/257	1.000	(reference)	1.000	(reference)
(mmHg)	≥140	94/174	0.953	0.683-1.330	0.946	0.677-1.321
DBP	<90	149/287	1.000	(reference)	1.000	(reference)
(mmHg)	≥90	87/144	1.116	0.793-1.572	1.104	0.783-1.558
Glucose	<6.0	130/294	1.000	(reference)	1.000	(reference)
(mmol/l)	≥6.0	106/137	1.631	1.168-2.277	1.622	1.161-2.267
HbA1c	<6.5	119/271	1.000	(reference)	1.000	(reference)
(%)	≥6.5	117/160	1.685	1.205-2.355	1.674	1.195-2.344
Cholesterol	<6.2	150/275	1.000	(reference)	1.000	(reference)
(mmol/l)	≥6.2	86/156	1.008	0.718-1.416	0.995	0.707-1.401
Triglyceride	<1.7	149/282	1.000	(reference)	1.000	(reference)
(mmol/l)	≥1.7	87/149	1.061	0.753-1.497	1.050	0.744-1.484

CI: confidence interval, *HR:* hazard ratio, *BMI:* body mass index, *SBP:* systolic blood pressure, *DBP:* diastolic blood pressure, *HbA1c:* glycosylated hemoglobin. 1: Cut-off levels are according to WHO definition. 2: HRs were estimated from Cox regression models after adjustment for age, gender, education, smoking, alcohol consumption, marriage, hemisphere, infarct location and NIHSS. 3: Relative risks were further adjusted for BMI (except in BMI analysis).

state reduces IGF-binding proteins and increases free IGFs [32]. Insulin, IGFs, and their corresponding receptors are abundantly expressed in neuronal and glial cells throughout the brain, while the highest density of their gene expression is in the hypothalamus [33-35]. The interactions between insulin and its receptors stimulate the signaling pathway in neural cells concerned with the HPA axis, which enhances glucose transport and promotes growth, survival and energy metabolism [36].

In turn, the increased activity of the HPA axis results in an increased release of cortisol and other glucocorticoids, catecholamines, growth hormone, and glucagon. Cortisol stimulates glucose production and increases lipolysis, decreasing insulin sensitivity and hampering insulin secretion from β cells [37]. Suggestively, there may be a bi-directional association between impaired glucose metabolism and the HPA axis in the development of depression.

In addition, serotonin as the most central neurotransmitter is found to be associated with major depressive disorders. A clinical study found that most antidepressants used today increase synaptic levels of serotonin [38]. Hyperglycemia and acidosis induce changes in serotonin levels [39]. Furthermore, glutamate is also thought to play a role in the pathophysiology of major depressive disorders [40]. A high glutamate level was recently found to accompany PSD [41]. In animal models, the increase in extracellular glutamate concentrations following forebrain ischemia was observed to be more pronounced in hyperglycemic than in normoglycemic rats [42]. Thus, a PSD mechanism including high levels of glucose, serotonin and glutamate is emerging and seems interesting.

The risk of PSD is significantly associated with the MetS z-score, glucose and HbA1c in our study. This novel finding strongly indicates that PSD as a common finding after a known stroke event is not merely due to limitations imposed by manifest neurological deficits. The pathological changes induced by MetS or MetS factors put such patients at risk for developing gradual neurological deficits and cognitive decline, making them more vulnerable to depressive disorders.

It is well known that depression is associated with patients' clinical status, worsening metabolic control, poor adherence to medication, and increased health-care expenditures [43]. Furtherly, depression hinders rehabilitation of nerve function and has relevance to worse functional outcome and increased mortality [44, 45]. Although the relationship between depression and poor outcomes after a stroke is

still unclear, a number of biobehavioral mechanisms have been hypothesized to underlie the relationship: (1) depression is related to poor health behavior; (2) depression is correlated with other major comorbidities; (3) depression is accompanied by biological changes [46]. Because the depression is not identified and treated in a timely manner, PSD exerts a negative impact on cognitive function, physical recovery and post-stroke survival [47]. Given the adverse effect, we believe that it is necessary to identify depression in ischemic stroke patients and that, if needed, psychological intervention should be carried out.

There are some limitations to our study. First, the measurements of the exposure variables were not repeated, so we could not handle the dilution bias. Second, we lacked data on further covariates such as the use of medication, particularly antihypertensive, antidiabetic, and antilipemic drugs. Third, we had inadequate information about the family and social factors of the patients, which may also influence the development of depression. Forth, we did not measure the size of infarcts, which may also generate bias for the results. However, our research had a prospective design with a large number of participants and is one of the few studies to date with enough valid information to investigate the relation between MetS factors and the risk of PSD in ischemic stroke patients. In the analysis, we also measured the level of HbA1c in order to prevent the effects of blood glucose fluctuation. The data of follow-up were fairly complete due to high-quality records for endpoint determination and due to little loss for the follow-up of patients. In addition, information on several confounders was available for adjustment.

In summary, the results of the present study demonstrate a significant association of impaired glucose metabolism with the risk of PSD in ischemic stroke patients. Therefore, it is suggested that high levels of circulating glucose and HbA1c may predict PSD in ischemic stroke patients. Further studies are needed to elucidate the exact pathophysiological and biochemical mechanisms of depression associated with impaired glucose metabolism.

Disclosure of conflict of interest

None.

Address correspondence to: Junfei Shao, Department of Neurosurgery, Wuxi People's Hospital of Nanjing Medical University, Qiangyang Road 299#, Wuxi, Jiangsu, China. Tel: +86-0510-8535-0053; E-mail: wxhneurosurgery@126.com; Fang Wang, Endocrinology and Metabolism, Heping Hospital Affiliated to Changzhi Medical College, Yanan South Road 110#, Changzhi, Shanxi, China. E-mail: wangfangczmu@126.com

References

[1] Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J and Hong Y. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119: 480-486.

[2] Hackett ML and Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke 2014; 9: 1017-1025.

[3] Ayerbe L, Ayis S, Wolfe CD and Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br J Psychiatry 2013; 202: 14-21.

[4] Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, Delong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P Jr and Valvo WJ. Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry 2005; 58: 175-189.

[5] Linden T, Blomstrand C and Skoog I. Depressive disorders after 20 months in elderly stroke patients: a case-control study. Stroke 2007; 38: 1860-1863.

[6] Pan A, Sun Q, Okereke OI, Rexrode KM and Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA 2011; 306: 1241-1249.

[7] Sekita A, Arima H, Ninomiya T, Ohara T, Doi Y, Hirakawa Y, Fukuhara M, Hata J, Yonemoto K, Ga Y, Kitazono T, Kanba S and Kiyohara Y. Elevated depressive symptoms in metabolic syndrome in a general population of Japanese men: a cross-sectional study. BMC Public Health 2013; 13: 862.

[8] Rhee SJ, Kim EY, Kim SH, Lee HJ, Kim B, Ha K, Yoon DH and Ahn YM. Subjective depressive symptoms and metabolic syndrome among the general population. Prog Neuropsychopharmacol Biol Psychiatry 2014; 54: 223-230.

[9] McCaffery JM, Niaura R, Todaro JF, Swan GE and Carmelli D. Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. Psychosom Med 2003; 65: 490-497.

[10] Skilton MR, Moulin P, Terra JL and Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. Biol Psychiatry 2007; 62: 1251-1257.

[11] Nishina M, Nishina K, Ohira T, Makino K and Iso H. Associations of psychological distress with metabolic syndrome among Japanese urban residents. J Atheroscler Thromb 2011; 18: 396-402.

[12] Viinamaki H, Heiskanen T, Lehto SM, Niskanen L, Koivumaa-Honkanen H, Tolmunen T, Honkalampi K, Saharinen T, Haatainen K and Hintikka J. Association of depressive symptoms and metabolic syndrome in men. Acta Psychiatr Scand 2009; 120: 23-29.

[13] Raikkonen K, Matthews KA and Kuller LH. Depressive symptoms and stressful life events predict metabolic syndrome among middle-aged women: a comparison of World Health Organization, Adult Treatment Panel III, and International Diabetes Foundation definitions. Diabetes Care 2007; 30: 872-877.

[14] Roohafza H, Sadeghi M, Talaei M, Pourmoghaddas Z and Sarrafzadegan N. Psychological status and quality of life in relation to the metabolic syndrome: Isfahan Cohort Study. Int J Endocrinol 2012; 2012: 380902.

[15] Hildrum B, Mykletun A, Midthjell K, Ismail K and Dahl AA. No association of depression and anxiety with the metabolic syndrome: the Norwegian HUNT study. Acta Psychiatr Scand 2009; 120: 14-22.

[16] Herva A, Rasanen P, Miettunen J, Timonen M, Laksy K, Veijola J, Laitinen J, Ruokonen A and Joukamaa M. Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. Psychosom Med 2006; 68: 213-216.

[17] Akbari H, Sarrafzadegan N, Aria H, Garaei AG and Zakeri H. Anxiety but not depression is associated with metabolic syndrome: The Isfahan Healthy Heart Program. J Res Med Sci 2017; 22: 90.

[18] Hendrickx H, McEwen BS and Ouderaa F. Metabolism, mood and cognition in aging: the importance of lifestyle and dietary intervention. Neurobiol Aging 2005; 26 Suppl 1: 1-5.

[19] Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, Peyrot M and Pouwer F. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. Diabetes Care 2011; 34: 752-762.

[20] Shelton RC and Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. Prog Neurobiol 2010; 91: 275-299.

[21] Bouwman V, Adriaanse MC, van 't Riet E, Snoek FJ, Dekker JM and Nijpels G. Depression, anxiety and glucose metabolism in the general dutch population: the new Hoorn study. PLoS One 2010; 5: e9971.

[22] Serrano-Gonzalez M, McConnel C, Bokhary M, Oden J and Lopez X. Association of non-high-density lipoprotein cholesterol with psychosocial dysfunction in children and adolescents with obesity. Child Obes 2015; 11: 647-649.

[23] De Berardis D, Marini S, Piersanti M, Cavuto M, Perna G, Valchera A, Mazza M, Fornaro M, Iasevoli F, Martinotti G and Di Giannantonio M. The relationships between cholesterol and suicide: An update. ISRN Psychiatry 2012; 2012: 387901.

[24] Liu Z, Cai Y and He J. High serum levels of 8-OHdG are an independent predictor of post-stroke depression in Chinese stroke survivors. Neuropsychiatr Dis Treat 2018; 14: 587-596.

[25] Lobbestael J, Leurgans M and Arntz A. Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clin Psychol Psychother 2011; 18: 75-79.

[26] Farner L, Wagle J, Engedal K, Flekkoy KM, Wyller TB and Fure B. Depressive symptoms in stroke patients: a 13 month follow-up study of patients referred to a rehabilitation unit. J Affect Disord 2010; 127: 211-218.

[27] Ayerbe L, Ayis S, Crichton S, Wolfe CD and Rudd AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. Stroke 2013; 44: 1105-1110.

[28] Wang Z, Zhu M, Su Z, Guan B, Wang A, Wang Y, Zhang N and Wang C. Post-stroke depression: different characteristics based on follow-up stage and gender-a cohort perspective study from Mainland China. Neurol Res 2017; 39: 996-1005.

[29] Oh HM, Kim SH, Kang SG, Park SJ and Song SW. The relationship between metabolic syndrome and cognitive function. Korean J Fam Med 2011; 32: 358-366.
[30] Liyanarachchi K, Ross R and Debono M. Human studies on hypothalamo-pituitary-adrenal (HPA) axis. Best Pract Res Clin Endocrinol Metab 2017; 31: 459-473.
[31] Wang Y, Huang M, Jiao JT, Wu YL, Ouyang TH, Huang J, Liu SS and Li CL. Relationship between concentrations of IGF-1 and IGFBP-3 and preoperative depression risk, and effect of psychological intervention on outcomes of high-grade glioma patients with preoperative depression in a 2-year prospective study. Med Oncol 2014; 31: 921.
[32] Hoyer S. The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: an update. J Neural Transm (Vienna) 2002; 109: 341-360.
[33] Gasecki D, Kwarciany M, Nyka W and Narkiewicz K. Hypertension, brain damage and cognitive decline. Curr Hypertens Rep 2013; 15: 547-558.
[34] Kreier F, Kap YS, Mettenleiter TC, van Heijningen C, van der Vliet J, Kalsbeek A, Sauerwein HP, Fliers E, Romijn JA and Buijs RM. Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. Endocrinology 2006; 147: 1140-1147.
[35] Takahashi Y, Iseki C, Wada M, Momma T, Ueki M, Kawanami T, Daimon M, Suzuki K, Tamiya G and Kato T. Impaired glucose metabolism slows executive function independent of cerebral ischemic lesions in Japanese elderly: the Takahata study. Intern Med 2011; 50: 1671-1678.
[36] Pocai A, Obici S, Schwartz GJ and Rossetti L. A brain-liver circuit regulates glucose homeostasis. Cell Metab 2005; 1: 53-61.
[37] Tabak AG, Akbaraly TN, Batty GD and Kivimaki M. Depression and type 2 diabetes: a causal association? Lancet Diabetes Endocrinol 2014; 2: 236-245.
[38] Schildkraut JJ and Kety SS. Biogenic amines and emotion. Science 1967; 156: 21-37.
[39] Ramakrishnan R, Prabhakaran K, Jayakumar AR, Gunasekaran P, Sheeladevi R and Suthanthirarajan N. Involvement of Ca2+/calmodulin-dependent protein kinase II in the modulation of indolamines in diabetic and hyperglycemic rats. J Neurosci Res 2005; 80: 518-528.
[40] Hashimoto K. Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res Rev 2009; 61: 105-123.
[41] Wang X, Li YH, Li MH, Lu J, Zhao JG, Sun XJ, Zhang B and Ye JL. Glutamate level detection by magnetic resonance spectroscopy in patients with post-stroke depression. Eur Arch Psychiatry Clin Neurosci 2012; 262: 33-38.
[42] Kagansky N, Levy S and Knobler H. The role of hyperglycemia in acute stroke. Arch Neurol 2001; 58: 1209-1212.
[43] Lustman PJ and Clouse RE. Depression in diabetic patients: the relationship between mood and glycemic control. J Diabetes Complications 2005; 19: 113-122.
[44] Nickel A and Thomalla G. Post-stroke depression: impact of lesion location and methodological limitations-A topical review. Front Neurol 2017; 8: 498.
[45] Meng G, Ma X, Li L, Tan Y, Liu X and Zhao Y. Predictors of early-onset post-ischemic stroke depression: a cross-sectional study. BMC Neurol 2017; 17: 199.
[46] Ormstad H, Aass HC, Amthor KF, Lund-Sorensen N and Sandvik L. Serum levels of cytokines, glucose, and hemoglobin as possible predictors of poststroke depression, and association with poststroke fatigue. Int J Neurosci 2012; 122: 682-690.
[47] Ilut S, Stan A, Blesneag A, Vacaras V, Vesa S and Fodoreanu L. Factors that influence the severity of post-stroke depression. J Med Life 2017; 10: 167-171.