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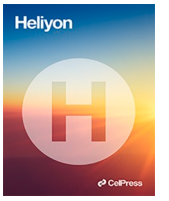

Cognitive decline in elderly patients with type 2 diabetes is associated with glycated albumin, ratio of Glycated Albumin to glycated hemoglobin, and concentrations of inflammatory and oxidative stress markers

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ABSTRACT

Objective: To investigate the correlations of cognitive function with glycated albumin (GA), the ratio of GA to glycated hemoglobin (GA/HbA_{1c}), and the concentrations of interleukin-6 (IL-6) and superoxide dismutase (SOD) in elderly patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 44 elderly T2DM patients were evaluated for cognitive function using the mini-mental state examination (MMSE) and the Montreal cognitive assessment (MoCA). Patients were then divided into two groups based on the MMSE and MoCA scores: a cognitive dysfunction group and a normal cognitive function group. The correlations of the MMSE and MoCA scores with GA/HbA_{1c}, GA, IL-6, and SOD were analyzed. Logistic regression analysis was used to identify independent influential factors for cognitive dysfunction. The predictive value of GA and GA/HbA_{1c} for cognitive dysfunction in elderly T2DM patients was evaluated by receiver operating characteristic (ROC) curve analysis.

Results: Among these patients, 28 had cognitive impairment. They had significantly higher GA/HbA_{1c}, increased GA and IL-6 levels, and lower SOD concentrations than the normal cognitive function group (all $P < 0.05$). GA/HbA_{1c} was negatively correlated with the MMSE ($r = -0.430$, $P = 0.007$) and MoCA ($r = -0.432$, $P = 0.007$) scores. SOD was positively correlated with the MMSE ($r = 0.585$, P=0.014) and MoCA ($r = 0.635$, P=0.006) scores. IL-6 was negatively correlated with the MoCA score ($r = -0.421$, P=0.015). Age and GA/HbA_{1c} were independent factors contributing to cognitive dysfunction. The areas under the ROC curves of GA and GA/HbA_{1c} for the diagnosis of cognitive dysfunction were 0.712 and 0.720, respectively.

Conclusions: GA and GA/HbA_{1c} are related to cognitive dysfunction in elderly patients with T2DM.

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1. Introduction

The incidence of central nervous system disorders, such as cognitive dysfunction, is significantly higher in patients with type 2 diabetes mellitus (T2DM) than in non-diabetic people [1]. With an increased prevalence of T2DM in the elderly population, the risk of developing cognitive dysfunction in this group is also significantly higher. Cognitive dysfunction in diabetic patients is related to oxidative stress [2] and inflammation [3]. Previous evidence has shown that elevated plasma interleukin-6 (IL-6) levels are associated with the lower cognitive ability [4]. The activity of superoxide dismutase (SOD) in the brain of T2DM rats with cognitive dysfunction was considerably lower than that in model animals with normal cognitive function [5]. Acute blood glucose fluctuations are significantly correlated with cognitive function in elderly patients with T2DM [6]. Glycated albumin (GA) reflects blood glucose fluctuations over 2–3 weeks [7]. The ratio of GA to glycated hemoglobin (GA/HbA_{1c}) reflects blood glucose fluctuations over a shorter period than GA [8] and can better reflect such fluctuations [9]. Both GA and HbA_{1c} levels can be easily obtained from routine examinations in the hospital. A previous study suggested hippocampal atrophy is associated with elevated serum GA and GA/HbA_{1c} in elderly people [10]. Additionally, cognitive decline in elderly women may be associated with increased GA levels [11]. However, no studies have evaluated the predictive value of GA and GA/HbA_{1c} for cognitive dysfunction in elderly patients with T2DM.

The mini-mental state examination (MMSE) and the Montreal cognitive assessment (MoCA) are widely used assessment tools for cognitive function. The MMSE results may be affected by an individual's education level and, therefore, cannot be used to diagnose different types of cognitive dysfunction. MoCA applies to elderly people who have received secondary or higher education. The MoCA is more sensitive than MMSE in diagnosing mild cognitive impairment (MCI) but less sensitive in diagnosing moderate or severe Alzheimer's disease. MMSE and MoCA have limitations, and not all clinicians have received standard training for using these scales in elderly patients.

In this study, we aimed to explore the correlation of cognitive function with GA and GA/HbA_{1c} in elderly patients with T2DM and to determine whether oxidative stress and inflammation are involved in cognitive impairment in this population.

2. Methods

2.1. Study subjects

Of the 78 invitations sent, 56 individuals initially agreed to participate in this study. Ultimately, 44 (56 %) participants were successfully recruited. A total of 44 elderly patients with T2DM who were admitted to the Department of Geriatric Comprehensive, Xuanwu Hospital Capital Medical University, between January 2019 and December 2019 were recruited, comprising 23 men and 21 women. The inclusion criteria were as follows: ① aged 60 years or over; ② diagnosed with T2DM according to the American Diabetes Association [12]. Patients were excluded if they: ① had a significant hearing or visual impairment that may affect the cognitive function test; ② had acute complications including diabetic ketoacidosis, lactic acidosis, hypertonic coma, and hypoglycemia; ③ had a history of chronic alcoholism or drug abuse; ④ had a previous brain injury, stroke, cerebral hemorrhage, epilepsy, or brain tumor; ⑤ had confirmed Alzheimer's disease, Parkinson's disease, and mental illness; ⑥ had co-infection, poisoning, or other diseases that may affect cognitive function; ⑦ had severe heart, lung, liver, or renal dysfunction; ⑧ took drugs that may affect cognitive function. All enrolled patients agreed to participate in this study and provided written informed consent. This study was performed after approval by the Ethics Committee of the Xuanwu Hospital of Capital Medical University (approval number: [2018] No. 112).

2.2. Demographic data collection

Demographic data, including gender, age, height, weight, years of education, years of T2DM, and history of smoking and drinking, were collected from the medical records. Body mass index (BMI) was calculated.

2.3. Biochemical data collection

Patients were fasting for at least 10 h, and the venous blood was collected the next morning on an empty stomach. Fasting blood samples were used to measure the levels of fasting plasma glucose (FPG), fasting insulin (FINS), cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). The serum HbA_{1c} levels were determined with high-performance liquid chromatography using Bole P1201 (Heb Biotechnology Co., Xi'an, China). The serum GA levels were measured by turbidimetric immunoassay using the Hitachi 7180 analyzer (Hitachi Instruments Service, Shanghai, China). The IL-6 levels were determined using the electrochemical luminescence method (Roche, Shanghai, China). The SOD concentrations were measured with the colorimetric method using a commercially available kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). GA/HbA_{1c} was calculated, and the insulin resistance index homeostasis model assessment-insulin resistance (HOMA-IR) was obtained using a steady-state model.

2.4. Cognitive function assessment

The MMSE and MoCA, scored from 0 to 30, were used to evaluate cognitive function. The MMSE consists of 30 questions, including the directional ability (10 points), language immediate memory (3 points), attention and calculation (5 points), memory capacity (3 points), language functions (8 points), and evaluation of space perception (1 point). The MoCA evaluates eight domains of cognitive function: memory, visuospatial function, attention, executive function, calculation, language, time, and orientation. For subjects with

an education level of junior high school or above, a MMSE score of ≤24 indicated cognitive dysfunction. For those with an education level of primary school, a MMSE score of ≤20 indicated cognitive dysfunction. For illiterate subjects, a MMSE score of ≤17 indicated cognitive dysfunction [13]. A MoCA score of <26 indicated cognitive dysfunction [14]. If the educational time is less than 12 years, 1 point will be added to the total MMSE score to correct the education level. A total of 7 Patients failed on MMSE and 27 failed on MoCA. Patients were then divided into two groups based on the results of MMSE and MoCA: a cognitive dysfunction group (n = 28) and a normal cognitive function group (n = 16).

2.5. Statistical analysis

The SPSS 22.0 software was used for statistical analysis. Normally distributed variables were expressed as mean ± standard deviation and compared using the independent sample *t*-test. Variables that did not meet the normal distribution assumption were expressed as the median and interquartile range and compared using the Mann Whitney *U* test. Categorical variables were compared using the Chi-square test. Correlations among GA, GA/HbA1c, HbA1c, IL-6, SOD, and cognitive function were analyzed by Spearman's correlation coefficient. The risk factors associated with cognitive dysfunction were assessed by univariate and multiple logistic regression analyses. The risk was estimated using odds ratio (OR), adjusted odds ratio (aOR), and 95 % confidence interval (CI). The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of GA and GA/HbA_{1c} for cognitive dysfunction in elderly patients with T2DM. The Youden index was used to determine the optimal cut-off points. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of demographic and clinical data

There were no significant differences in gender, years of T2DM, years of education, BMI, cholesterol, triglycerides, HDL, LDL, FPG, HOMA-IR, or HbA_{1c} between the normal cognitive function and cognitive dysfunction groups (all $P > 0.05$). Age and IL-6 levels in the cognitive dysfunction group were higher, while GA, GA/HbA_{1c}, and SOD were lower than those in the normal cognitive function group (all $P < 0.05$) (Table 1).

3.2. Correlations of cognitive function with GA, GA/HbA_{1c}, and HbA_{1c}

The MMSE and MoCA scores were negatively associated with GA/HbA_{1c} ($r = -0.430$, $P = 0.007$; $r = -0.432$, $P = 0.007$) (Table 2).

3.3. Correlations of cognitive function with the levels of IL-6 and SOD

The MoCA score was positively correlated with the SOD levels while negatively correlated with the IL-6 levels ($r = 0.635$, $P = 0.006$; $r = -0.421$, $P = 0.015$). The MMSE score was positively correlated with the SOD levels ($r = 0.585$, $P = 0.014$) (Table 3).

Table 1
Demographic and clinical data of the two groups.

	Normal cognitive function group (n = 16)	Cognitive dysfunction group (n = 28)	*P*-value
Age (years)	68.0 (63.0,71.8)	75.0 (67.3,83.0)	0.014
Gender (male/female)	9/7	14/14	0.690
Years of T2DM	13.0 (8.0,19.0)	10.0 (6.5,20.0)	0.479
Years of Education	14.0 (13.0,15.0)	14.0 (13.0,15.0)	0.862
BMI (kg/m^2)	25.8 ± 3.8	26.0 ± 3.5	0.855
Cholesterol (mmol/L)	3.82 ± 1.12	4.29 ± 0.95	0.146
Triglycerides (mmol/L)	1.16(0.93,1.54)	1.45 (1.11,2.43)	0.077
LDL (mmol/L)	2.22 ± 0.88	2.55 ± 0.73	0.182
HDL (mmol/L)	1.33 (1.08,1.46)	1.08 (0.92,1.48)	0.133
FPG (mmol/L)	6.29 (4.86,7.90)	6.92 (5.23,8.75)	0.464
HOMA-IR	3.66 (2.76,9.52)	2.56 (1.53,5.04)	0.102
HbA_{1c} (%)	6.96 ± 1.32	7.59 ± 1.59	0.195
GA (%)	15.0 (14.2,18.1)	19.05 (15.80,22.83)	0.033
GA/HbA_{1c}	2.39 ± 0.42	2.78 ± 0.52	0.028
MMSE score	30.00 (29.00,30.00)	27.00 (24.25,28.75)	0.000
MoCA score	28.00 (27.25,29.75)	22.50 (16.25,24.00)	0.000
IL-6 (pg/mL)	3.34 (2.37,4.81)	7.24 (3.05,10.22)	0.031
SOD (U/mL)	101.45 ± 5.46	88.20 ± 14.28	0.016

Data are expressed as mean ± SD or median (interquartile range) if they are not normally distributed.
Abbreviations: T2DM: type 2 diabetes mellitus; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FPG: fasting plasma glucose; HOMA-IR: homeostasis model assessment-insulin resistance; HbA_{1c}: glycated hemoglobin; GA: glycated albumin; GA/HbA_{1c}: the ratio of GA to glycated hemoglobin; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; IL-6: interleukin-6; SOD: superoxide dismutase.

Table 2
Spearman's correlation of cognitive function with GA, GA/HbA_{1c}, and HbA_{1c}.

	MMSE *r*(*P*-value)	MoCA *r*(*P*-value)
GA	−0.086 (0.601)	−0.292 (0.071)
GA/HbA_{1c}	−0.430 (0.007)	−0.432 (0.007)
HbA_{1c}	0.211 (0.174)	−0.056 (0.723)

Abbreviations: MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; HbA_{1c}: glycated hemoglobin; GA: glycated albumin; GA/HbA_{1c}: the ratio of GA to glycated hemoglobin.

Table 3
Spearman's correlation of cognitive function with IL-6 and SOD.

	MMSE *r*(*P*-value)	MoCA *r*(*P*-value)
IL-6	−0.234(0.190)	−0.421 (0.015)
SOD	0.585 (0.014)	0.635 (0.006)

Abbreviations: MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; IL-6: interleukin-6; SOD: superoxide dismutase.

3.4. Independent factors contributing to cognitive dysfunction

Next, we performed univariate and multiple logistic regression analyses to identify independent predictors of cognitive dysfunction. The results showed that age and GA/HbA_{1c} were independent factors contributing to cognitive dysfunction (Table 4).

3.5. The predictive value of GA and GA/HbA_{1c} for cognitive dysfunction in elderly patients with T2DM

The areas under the ROC curves of GA and GA/HbA_{1c} were 0.712 and 0.720, respectively (both $P < 0.05$) (Fig. 1 and Table 5). The Youden index was used to identify the optimal cut-offs.

4. Discussion

Cognitive dysfunction and dementia are major chronic complications of diabetes [15]. Diabetic patients have a 1.2- to 1.5-fold increased risk of cognitive dysfunction and a 1.6-fold increased risk of dementia compared with non-diabetic populations [16]. The progression of cognitive dysfunction is faster in elderly diabetic patients than in normal people [17], and cognitive dysfunction, in turn, aggravates the development of T2DM. In our study, 63.6 % of the elderly T2DM patients had cognitive impairment. Therefore, early detection and standardized management of cognitive dysfunction are of great importance in improving the clinical outcomes of these patients [18].

HbA_{1c} is the gold standard measure of average blood glucose levels over the preceding 8–12 weeks [19]. It is closely related to the cognitive function of diabetic patients [20]. However, patients with similar HbA_{1c} values may have different risks of complications [21]. Glycemic fluctuation is also an important indicator of glycemic control. Diabetic patients with large blood glucose fluctuations have a high risk of complications [22]. Existing evidence also indicates that blood glucose fluctuations substantially impact microglial activity. The greater the blood glucose levels fluctuate, the more cognitive function declines [23]. Compared to HbA_{1c}, GA/HbA_{1c} and GA can better reflect blood glucose fluctuations in patients with type 1 diabetes or T2DM [24,25]. GA/HbA_{1c} is associated with the onset of Alzheimer's disease [26]. It has also been identified as an independent risk factor for cognitive impairment in elderly patients with T2DM [27]. In this study, we found that the GA and GA/HbA_{1c} of the cognitive dysfunction group were higher than those of the normal cognitive function group, indicating that patients with cognitive dysfunction had larger blood glucose fluctuations and poorer blood glucose control. The HbA_{1c} values were not different between the two groups.

Table 4
Univariate and multiple logistic regression analyses.

Variables	β	S.E.	OR (95%CI)	*P*-value	m_β	m_S.E	aOR (95 % CI)	m_*P*-value
Age	0.11	0.05	1.12 (1.02–1.23)	0.016	0.14	0.06	1.15(1.01–1.30)	0.030
HbA1c	0.31	0.24	1.37 (0.85–2.20)	0.198				
GA	0.15	0.09	1.17 (0.99–1.38)	0.072				
GA/HbA_{1c}	3.03	1.32	20.79 (1.57–275.42)	0.021	3.13	1.48	22.82(1.25–417.27)	0.035
IL-6	0.28	0.15	1.33 (0.98–1.79)	0.065				
SOD	−0.13	0.08	0.87 (0.75–1.02)	0.085				

Abbreviations: OR: odds ratio; CI: confidence interval; aOR: adjusted odds ratio; HbA_{1c}: glycated hemoglobin; GA: glycated albumin; GA/HbA_{1c}: the ratio of GA to glycated hemoglobin; IL-6: interleukin-6; SOD: superoxide dismutase.

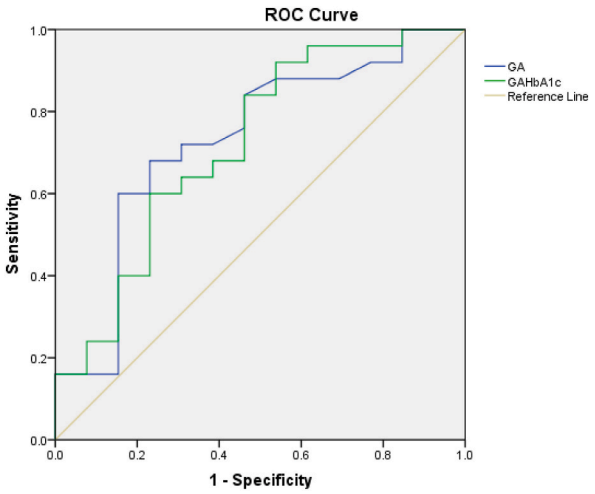

Fig. 1. ROC curve analysis of GA and GA/HbA_{1c} for the diagnosis of cognitive dysfunction in elderly patients with T2DM
Abbreviations: ROC: receiver operating characteristic; GA: glycated albumin; GA/HbA_{1c}: the ratio of GA to glycated hemoglobin.

Table 5
The predictive efficacy of GA and GA/HbA_{1c} for cognitive dysfunction in elderly patients with T2DM.

Factors	Area under the ROC curve	*P*-value	Progressive 95 % CI	The best cut-off value	Specificity (%)	Sensitivity (%)
GA	0.712	0.033	0.534–0.889	17.70 %	65.4	76.9
GA/HbA_{1c}	0.720	0.028	0.541–0.899	2.23	92.0	46.2

Abbreviations: ROC: receiver operating characteristic; CI: confidence interval; GA: glycated albumin; GA/HbA_{1c}: the ratio of GA to glycated hemoglobin.

Additionally, univariate regression analysis showed that HbA_{1c} was not correlated with the MMSE or MoCA score. These findings were consistent with a previous study [28] showing that GA and GA/HbA_{1c} were risk factors for cognitive impairment in elderly patients with T2DM, independent of HbA_{1c}. We further found that GA/HbA_{1c} was negatively correlated with the MMSE and MoCA scores in elderly patients with T2DM, which was in line with previous findings that GA/HbA_{1c} was negatively correlated with cognitive function in elderly people [29,30]. Logistic regression analysis revealed that age and GA/HbA_{1c} were independent factors contributing to cognitive dysfunction, suggesting that blood glucose fluctuations are independently correlated with cognitive function in elderly patients with T2DM. Additionally, there was no significant correlation between age, GA, and GA/HbA1c in univariate analysis. We further divided the subjects into tertiles or quartile based on their age, and observed no significant difference in the GA and GA/HbA1c among these groups.

The MoCA is best used for detecting mild cognitive dysfunction, while the MMSE has greater sensitivity in detecting cognitive impairment and functional decline. In the present study, both assessment tools were used to screen patients with cognitive dysfunction. MMSE distinguished fewer patients with cognitive dysfunction, possibly because the MMSE is less sensitive than the MoCA [31].

We further performed ROC curve analysis using cognitive dysfunction as the observational indicator. The results revealed that GA and GA/HbA_{1c} had a predictive value for detecting cognitive dysfunction in elderly patients with T2DM. The best cut-off value for GA and GA/HbA_{1c} was 17.70 % and 2.23, respectively, suggesting that patients with a GA value of >17.70 % or a GA/HbA_{1c} value of >2.23 should be screened for cognitive dysfunction. GA exhibited a certain level of sensitivity, indicating its potential use in screening high-risk patients. GA/HbA1c demonstrated high specificity, enabling us to effectively exclude individuals who were considered within the normal range.

Oxidative stress and inflammation are important pathophysiological mechanisms of diabetes and its complications. Compared with long-term sustained hyperglycemia, blood glucose fluctuations often lead to more severe oxidative stress and inflammation [32], contributing to cognitive impairment [33]. Maintaining normal blood glucose levels for a long period can reduce oxidative stress and inflammation, thereby decreasing the incidence of both macrovascular and microvascular events in diabetic patients [34]. IL-6 is elevated in patients with T2DM-associated cognitive impairment [35]. Serum IL-6 levels are associated with the risk of MCI in Chinese T2DM patients [36]. In this study, the cognitive dysfunction group showed increased IL-6 levels and reduced SOD levels compared with the normal cognitive function group, indicating increased inflammatory responses and oxidation/anti-oxidation imbalance in patients with cognitive dysfunction. OurOur previous study showed that elderly T2DM patients had higher IL-6 levels than middle-aged people [37]. Inflammation and oxidative stress are closely related to the occurrence of cognitive impairment [38]. Our data showed that the MMSE and MoCA scores increased with the SOD levels. In contrast, the MoCA score decreased with the IL-6 levels, implying that upregulated inflammatory factors and reduced antioxidant capacity may contribute to cognitive decline in elderly patients with T2DM

[39]. More inflammation- and oxidative stress-related factors need to be explored in future studies.

There are several limitations in this study. Firstly, the sample size was relatively small, and we lacked information on blood pressure, medication use, and complications. Additionally, the variation in age between the two groups might have influenced the impact of GA and GA/HbA_{1c}. Thirdly, the cross-sectional design of this study prevents the establishment of causal relationships among the correlated factors. To clarify whether glucose fluctuations, oxidative stress, and inflammation play causal roles in the development of cognitive dysfunction, further prospective studies with a large and diverse cohort and a wide range of ages and relevant clinical endpoints are needed. These studies could also assess the effects of therapies targeting glucose fluctuations, anti-inflammatory interventions, and antioxidant treatments on the development of dementia. Furthermore, *in vivo* animal studies are essential to elucidate the molecular mechanisms through which glucose fluctuations, oxidative stress, and inflammation contribute to the pathogenesis of cognitive dysfunction.

5. Conclusions

In conclusion, the cognitive function of elderly patients with T2DM is significantly related to GA, GA/HbA_{1c}, IL-6, and SOD. GA and GA/HbA_{1c} may be used to detect cognitive dysfunction in this population. Inflammation and oxidative stress are involved in the development of cognitive impairment. These data provide a scientific basis for early recognition and identification of therapeutic targets for cognitive dysfunction in elderly patients with T2DM.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Xuanwu Hospital of Capital Medical University (approval number: [2018] No. 112). All procedures performed in studies involving human participants were per the ethical standards of the institutional and national research committees and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All enrolled patients agreed to participate in this study and provided written informed consent.

Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Si-Cong Si: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Investigation. **Wei Yang:** Data curation, Project administration, Supervision, Writing – original draft, Writing – review & editing, Funding acquisition. **Hong-Yu Luo:** Data curation, Investigation, Writing – original draft. **Yi-Xin Ma:** Data curation, Investigation, Writing – original draft. **Huan Zhao:** Data curation, Investigation, Writing – original draft. **Jia Liu:** Data curation, Investigation, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

List of abbreviations

GA	glycated albumin
GA/HbA1c	the ratio of GA to glycated hemoglobin
IL-6	interleukin-6
SOD	superoxide dismutase
T2DM	type 2 diabetes mellitus
MMSE	mini-mental state examination
MoCA	Montreal cognitive assessment
ROC:	receiver operating characteristic
MCI	mild cognitive impairment

BMI	body mass index
FPG	fasting plasma glucose
FINS	fasting insulin
HDL:	cholesterol, triglycerides, high-density lipoprotein
LDL:	low-density lipoprotein
HOMA-IR	homeostasis model assessment-insulin resistance
OR	odds ratio
aOR	adjusted odds ratio
CI	confidence interval

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