Risk factors for cognitive impairment in older people with diabetes: a community-based study

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Abstract

Aim: The aim of this study was to investigate the risk factors for cognitive impairment in older people with diabetes.

Methods: This cross-sectional study included 2626 community-dwelling participants with diabetes aged ⩾55 years, living in Beijing, China. The participants were screened for risk factors, including smoking, obesity, hypertension, stroke, coronary heart disease, dyslipidemia, depression, apolipoprotein E (APOE) genotype, and low physical activity. Cognitive function was assessed with the scholarship-adjusted Mini-Mental State Examination (MMSE): MMSE ⩽17 for iliterate participants; MMSE ⩽20 for primary school graduates (⩾6 years of education); and MMSE ⩽24 for junior school graduates or above (⩾9 years of education).

Results: The prevalence of cognitive impairment in older people with diabetes was 9.90%. Multiple logistic regression analysis demonstrated that stroke [odds ratio (OR) = 1.71, 95% confidence interval (CI) = 1.20–2.43], less than 0.5 h exercise per day (OR = 1.89, 95% CI = 1.37–2.61), and depression (OR = 1.64, 95% CI = 1.06–2.54), but not smoking, obesity, hypertension, dyslipidemia, and coronary heart disease, were independent risks for cognitive impairment in older people with diabetes. In addition, being married (OR = 0.66, 95% CI = 0.47–0.93) and urban living (OR = 0.33, 95% CI = 0.22–0.48) could decrease the risk of cognitive impairment.

Conclusions: Stroke, depression, and less than 0.5 h exercise per day were independent risks for cognitive impairment in older people with diabetes, whereas being married and urban living were protective.

Keywords: cognitive impairment, dementia, diabetes, MMSE, risk factor, stroke

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Introduction

Dementia and diabetes are two prevalent conditions affecting older people. Comorbidity is common and with the rapid aging of the population in China, these health issues have become important public health concerns. Previous studies have shown that type 2 diabetes mellitus (T2DM) is associated with cognitive impairment and increased risk of dementia.[2,3] Because the treatment for cognitive impairment is limited, it is more important to identify the specific risk factors to delay its onset in older people with diabetes.

The risk factors for cognitive impairment in T2DM include vascular risk factors and relevant vascular diseases (e.g. smoking, hypertension, dyslipidemia, obesity, stroke, coronary heart disease), low physical activity, depression, and the apolipoprotein E (APOE) genotype.[1,4] Cardiovascular risks often occur concurrently in the older people, especially in patients with T2DM.[5] Thus far, the evidence from previous studies is mixed in supporting the association between cardiovascular risks (e.g. hypertension, hyperlipidemia, and obesity) and cognitive impairment.[6–8] Moreover, which cardiovascular risk matters most in people with diabetes is still unidentified. Other studies have shown that low physical activity is correlated with cognitive decline,[9] but these results are inconsistent. There

is evidence that suggests physical activity may not affect the risk of cognitive decline in people with T2DM.[10] Previous studies also showed an inconsistent association between depression and cognitive decline.[11,12]

To date, investigations into the risk factors for cognitive impairment in people with diabetes have been limited and many risk factors have also been assessed in isolation.[13–15] Few studies exploring the association of risk factors for cognitive impairment in people with diabetes have adequately been corrected for all of the confounders. Thus, the aim of this cross-sectional study is to investigate the risk factors for cognitive impairment in a large community-dwelling older population with diabetes.

Participants and methods

Participants

The participants in our study were from the Beijing Longitudinal Study of Aging II (BLSA II) prospective cohort. The baseline survey ran from July to November 2009. A multi-stage cluster random sampling method was performed to select a representative community cohort older than 55 years. Details of recruitment have been described previously.[16,17] A total of 10,039 long-term residents from three urban districts and one rural county were enrolled in the survey. Among which, 2626 people with diabetes and a valid Mini-Mental State Examination (MMSE) score were analyzed.

Data collection

All assessments were performed by trained physicians and nurses. Fasting blood samples were taken for measurement of the serum levels of total cholesterol (TCH), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen (BUN), serum creatinine, and serum uric acid (UA) for all subjects. The Sysmex Chemix-180 automatic biochemical analysis device (Sysmex Infosystems, Kobe, Japan) was used to examine blood samples. Fasting blood glucose (FBG) was determined by the One Touch Ultra blood sugar device (Life-Scan, Inc., Milpitas, CA, USA). The APOE genotype was examined using one-stage polymerase chain reaction (PCR) as described by Wenham *et al*.[18]

A validated Chinese version of the MMSE was administered to evaluate the cognitive function.[19] To assess depression, Geriatric Depression Scale-15 items (GDS-15) were assessed.[20]

Definitions

As validated in the previous study,[19] cognitive impairment was defined as: MMSE $\leqslant$17 for illiterates; MMSE $\leqslant$20 for primary school graduates ($\geqslant$6 years of education); MMSE $\leqslant$24 for junior school graduates above ($\geqslant$9 years of education).

People with diabetes, as defined by World Health Organization (WHO) criteria,[21] are those who are found to have a fasting plasma glucose (FPG) greater than or equal to 7.0 mmol/l (126 mg/dl) or have already been diagnosed with diabetes, or are undergoing antidiabetic therapy. Hyperuricemia was defined as a serum UA level $>$416 μmol/l in men and $>$356 μmol/l in women.[22]

Risk factors include: residency (urban living, rural living); smoking (current smoker); obesity [body mass index (BMI) $\geqslant$28 kg/m^2, as defined by Cooperative Meta-analysis Group of China Obesity Task Force criteria];[23] hypertension [systolic blood pressure (SBP) $\geqslant$140 mmHg, diastolic blood pressure (DBP) $\geqslant$90 mmHg, having already-diagnosed hypertension or using antihypertensive agents]; dyslipidemia [TCH $\geqslant$6.22 mmol/l or TG $\geqslant$2.26 mmol/l or LDL-C $\geqslant$4.14 mmol/l or HDL-C $<$1.04 mmol/L]; stroke (a self-reported history of stroke diagnosed by at least a district hospital); coronary heart disease (CHD: a history of myocardial infarction, angina, self-reported CHD or cardiac medications use); depression (a GDS score of 5 or more was used to define subjects as having depressive symptoms); low physical activity (daily exercise $<$0.5 h); high FBG ($\geqslant$7.0 mmol/l).

Statistical analyses

Chi-squared tests were employed to test between-group differences in categorical variables. For all continuous variables, the results were reported as the mean and standard deviation ($m \pm$ s.d.) and Student's *t*-test was used to compare group differences. The Pearson correlation tests were used to test the correlations among the risk factors for cognitive impairment. Potential risk factors of

cognitive impairment were analyzed using multivariate logistic regression analyses to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Demographic, genetic, and clinical variables including age, sex, residency, marital status, current smoking, alcohol drinking, daily sleep <6 h, daily exercise <0.5 h, APOEε4 carrier, obesity, hypertension, CHD and stroke, GDS >5, high UA, dyslipidemia, and high FBG were included in the multivariate logistic regression model.

The analyses of all data were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA). Statistically significant findings were determined using a two-tailed p value of 0.05.

Results

The correlations among the risk factors for cognitive impairment are presented in Table 1. For example, there were significant correlations between TG and age, BMI, DBP, FBG, TCH, LDL-C and HDL-C (the Pearson correlation coefficients were −0.10, 0.12, 0.04, 0.16, 0.28, −0.35, 0.05, respectively).

The characteristics of the participants according to cognitive function status are presented in Table 2. Of the total 2626 participants involved in the analyses, 260 of the participants were classified as having cognitive impairment. The mean cognitive function MMSE score was 26.58 ± 4.11. The prevalence of cognitive impairment was 9.90%. The average age was 71.21 ± 7.41 years, 973 (37.05%) were males.

Compared with subjects with normal cognitive function, participants with cognitive impairment were older, more likely to have less sleep and exercise, and to have hypertension, stroke, and depression. Participants with normal cognition were more likely to be married, live in an urban area than their counterparts with cognitive impairment. In addition, the SBP, DBP, and serum level of FBG were higher in participants who had cognitive impairment.

Multivariate logistic regression analysis found that daily exercise <0.5 h (OR = 1.89, 95% CI = 1.37–2.61), stroke (OR = 1.71, 95% CI = 1.20–2.43), and GDS >5 (OR = 1.64, 95% CI = 1.06–2.54) were independent risk factors for cognitive impairment. However, urban living (OR = 0.33, 95% CI = 0.22–0.48) and being married (OR = 0.66, 95% CI = 0.47–0.93) were associated with lower prevalence of cognitive impairment (Table 3). Smoking, obesity, hypertension, dyslipidemia, and CHD were not independently associated with cognitive impairment in older people with diabetes in the multivariate model.

Table 1. The correlations among the risk factors for cognitive impairment.

	Age	Education	BMI	SBP	DBP	FBG	TG	TCH	HDL	LDL	GDS	MMSE
Age (years)	**1.00**											
Education (years)	−0.20△	**1.00**										
BMI (kg/m²)	−0.11△	−0.03	**1.00**									
SBP (mmHg)	0.02	−0.09△	0.06#	**1.00**								
DBP (mmHg)	−0.21△	−0.07△	0.08△	0.41△	**1.00**							
FBG (mmol/L)	−0.08△	−0.11△	0.05*	0.03	0.09△	**1.00**						
TG (mmol/L)	−0.10△	−0.04	0.12△	0.02	0.04*	0.16△	**1.00**					
TCH (mmol/L)	−0.07△	−0.05*	−0.02	0.04	0.03	0.12△	0.28△	**1.00**				
HDL (mmol/L)	0.10△	0.02	−0.18△	−0.02	−0.10△	−0.10△	−0.35△	0.24△	**1.00**			
LDL (mmol/L)	−0.05#	−0.05*	0.02	0.06#	0.05#	0.11△	0.05#	0.87△	0.13△	**1.00**		
GDS score	0.13△	−0.04*	−0.001	0.02	−0.08△	0.005	−0.02	−0.0004	0.07△	−0.004	**1.00**	
MMSE score	−0.24△	0.39△	0.03	−0.05*	−0.04*	−0.06#	−0.009	−0.04	−0.01	−0.02	−0.14△	**1.00**

Notes: The Pearson correlation coefficients are presented in the table.
*p value <0.05; #p value <0.01; △p value <0.001.
BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; GDS, Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; TCH, total cholesterol; TG, triglycerides.

Table 2. Characteristics of the participants according to cognitive function status.

Characteristics	Total sample	Cognitive impairment	Normal cognitive function	*p*-value
n, (%)	2626	260 (9.90)	2366 (90.10)	/
MMSE score	26.58 ± 4.11	19.29 ± 4.39	27.47 ± 2.78	<0.001
Sociodemographic				
Age	71.21 ± 7.41	73.51+7.14	70.93+7.47	<0.0001
55–65, *n* (%)	627 (23.87)	37 (14.23)	590 (24.94)	<0.0001
65–75, *n* (%)	1140 (43.41)	114 (43.85)	1026 (43.36)	/
75–85, *n* (%)	808 (30.77)	94 (36.15)	714 (30.18)	/
⩾85, *n* (%)	51 (1.94)	15 (5.77)	36 (1.52)	/
Male, *n* (%)	973 (37.05)	89 (34.23)	884 (37.36)	0.32
Urban, *n* (%)	2167 (82.52)	196 (75.38)	1971 (92.56)	0.0014
Education, *n* (%)				
Illiteracy	298 (11.35)	31 (11.92)	267 (11.28)	0.61
Primary school graduates	767 (29.21)	69 (26.54)	698 (29.50)	/
Junior school graduates or above	1561 (59.44)	160 (61.54)	1401 (59.22)	/
Lifestyle, *n* (%)				
Currently married	2078 (79.13)	187 (71.92)	1891 (79.92)	0.0026
Alcohol use	220 (8.38)	19 (7.31)	201 (8.5)	0.51
Smoking, current	285 (10.85)	33 (12.69)	252 (10.65)	0.31
Sleep <6 h	467 (17.81)	63 (24.23)	404 (17.10)	0.0044
Physical activity				
Exercise <0.5 h, *n* (%)	614 (23.42)	90 (34.62)	524 (22.18)	<0.001
Genetic				
APOEε4 carrier, *n* (%)	213 (10.12)	26 (13.32)	187 (9.87)	0.26
Clinical				
BMI (kg/m^2)	25.25 ± 3.35	25.24+3.43	25.26+3.34	0.72
BMI ⩾28 kg/m^2	506 (19.36)	52 (20.16)	454 (19.28))	0.73
High UA, *n* (%)	459 (17.68)	43 (16.67)	416 (17.80)	0.65
Hypertension, *n* (%)	1832 (69.90)	197 (75.77)	1635 (69.25)	0.03
CHD*, *n* (%)	668 (25.48)	76 (29.23)	592 (25.06)	0.14
Stroke, *n* (%)	360 (17.73)	61 (23.46)	299 (12.66)	<0.001

(Continued)

Table 2. (Continued)

Characteristics	Total sample	Cognitive impairment	Normal cognitive function	*p*-value
GDS>5, *n* (%)	285 (11.70)	46 (18.25)	239 (10.94)	0.0006
TCH (mmol/l)	5.36 ± 1.11	5.31 ± 1.11	5.36 ± 1.10	0.50
TG (mmol/l)	1.73 ± 1.12	1.63 ± 0.80	1.74 ± 1.14	0.06
HDL-C (mmol/l)	1.31 ± 0.35	1.35 ± 0.54	1.30 ± 0.33	0.22
LDL-C (mmol/l)	3.280 ± 0.89	3.28 ± 0.92	3.28 ± 0.88	0.98
FBG (mmol/l)	8.08 ± 2.66	8.31 ± 3.02	8.05 ± 2.61	0.01
SBP (mmHg)	129.51 ± 12.58	131.7 ± 16.49	129.3 ± 12.04	0.02
DBP (mmHg)	77.66 ± 8.10	79.05 ± 9.79	77.50 ± 7.88	0.01

APOEε4, apolipoprotein E ε4; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; GDS, Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; TCH, total cholesterol; TG, triglycerides; UA, uric acid.
*Myocardial infarction, coronary heart disease (CHD), or angina.

Table 3. Multivariable logistic regression analysis of cognitive impairment in participants with diabetes.

	β	SE	χ^2	Adj. OR	95% CI	*p* value
Urban	−0.56	0.10	33.42	0.33	0.22–0.48	<.0001
Currently married	−0.21	0.09	5.65	0.66	0.47–0.93	0.02
Exercise <0.5 h	0.32	0.08	14.91	1.89	1.37–2.61	0.0001
Stroke	0.27	0.09	8.70	1.71	1.20–2.43	0.003
GDS >5	0.25	0.11	4.97	1.64	1.06–2.54	0.03

Notes: Analyses included the following covariates: age, gender, location, daily sleep <6 h, daily exercise <0.5 h, marital status, high UA, BMI ⩾28 kg/m^2, alcohol drinking, smoking, APOE ε4 carrier, hypertension, stroke, GDS >5, cardiovascular disease, high TCH, high TG, high LDL-C, low HDL-C, high FBG.
BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; GDS, Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TCH, total cholesterol; TG, triglycerides; UA, uric acid.

Discussion

In the large sample of community-dwelling older people with diabetes, this study showed that univariate predictors of cognitive impairment included age, less sleep and exercise, hypertension, stroke, depression, being married, and urban living. With multiple logistic regression controlling for age, education, sex, apolipoprotein E (APOE) ε4 and other risk factors, stroke, depression, and low physical activity increased the risk of cognitive impairment by 71%, 64%, and 89%, respectively, while being married and urban living reduced the risk of cognitive impairment by 34% and 67%, respectively.

An association between a lower level of cognitive function and stroke has been found in some studies in people with diabetes,[24,25] but there are several other analyses in which no such association is found.[14] A review also showed that the evidence for

a relationship between macro-vascular disease and cognitive decline in diabetes was inconsistent.[4] The result of our study is similar to the Edinburgh Type 2 Diabetes Study (ET2DS) which reported that cognitive decline was significantly associated with stroke, but not with nonstroke vascular events.[13] Evidence for an association with stroke is stronger than that for vascular sites which are more distant from the brain.[4] Stroke may be a surrogate marker for clinically significant atherosclerosis. It is speculated that an increased risk of cognitive impairment in older people with diabetes is probably contingent on many processes, such as white matter integrity, vascular lesions, and Alzheimer-type abnormalities.[1] Thus, interventions designed to reduce the incidence of stroke may also be effective in reducing the risk of cognitive impairment.

The association between depressive symptoms and diabetes-associated cognitive impairment was inconsistent.[12,26] A national population-based cohort study showed that depression and diabetes were independently associated with a greater risk for dementia, and the combined association of both exposures with the risk for dementia was stronger than the additive association.[11] Our study demonstrated that depression was associated with an increased risk for cognitive impairment. However, it is not known whether depression leads to cognitive impairment or *vice versa*.[27] A prospective population based study showed that depression seems to be a concomitant symptom of cognitive impairment rather than an independent risk factor.[28] Therefore, caregivers should pay more attention to early detection and treatment of depression in older people with cognitive impairment.

The evidence form previous studies is inconsistent in supporting the effects of exercise on cognitive function.[9,10,29,30] Our study showed that low physical activity was related to an increased risk of cognitive impairment in the multivariate analysis. Exercise-mediated physiologic mechanisms, which likely account for neuroprotective effects on brain structures, include facilitation of synaptogenesis, reduced disordered protein deposition, and improved vascularization.[30] In addition, exercise may mediate cardiovascular risk factors that are associated with cognitive decline, such as hypertension, dyslipidemia, and obesity. However, the causal relationship between physical activity and cognitive impairment is not clear. Sabia *et al.*[31] reported that physical activity in people with dementia began to decline up to 9 years before diagnosis. Previous findings showing a lower risk of dementia in physically active people may be due to a decline in physical activity levels in the preclinical phase of dementia. The cross-sectional design of this study precludes determination of cause and effect between low physical activity and cognitive impairment. Thus, further prospective studies are needed to identify the most beneficial aspects of exercise programs.

Although hypertension causes stroke, its role in cognitive impairment remains unproven.[32] Kennelly *et al.*[33] suggest the 'U-phenomenon' to characterize the relationship between blood pressure and dementia. A Cochrane review shows that blood pressure lowering in later life does not appear to prevent the development of dementia or cognitive impairment in hypertensive patients without prior cerebrovascular disease.[34] We found that participants with cognitive impairment were more likely to be affected by hypertension in the univariate analysis, but hypertension was not a risk factor for cognitive impairment after adjusting for other risk factors. The association between hypertension and cognitive function is complex, and further studies are warranted to explore hypertension management strategies for older people. The association between obesity and cognitive impairment is inconsistent. A meta-analyses showed that underweight, overweight, and obesity in midlife increase dementia risk.[35] However, other studies reported no association between BMI and cognitive impairment in older people with diabetes.[14,25] A recent prospective study showed that weight loss in later life characterized dementia, suggesting that obesity is a protective factor against dementia in older age.[36] The present study found no association between obesity and cognitive impairment. Hence, further studies are needed to clarify the association between obesity and the risk of cognitive impairment in older people with diabetes.

Our study suggests that CHD is not associated with cognitive impairment. The results have been negative in most cross-sectional studies[25,32] and in all prospective analyses.[13,14] The role of dyslipidemia in cognitive impairment in people with diabetes is also uncertain. Most studies failed to find any association between plasma lipid profiles and cognitive function.[37,38] A few studies reported that elevated levels of plasma TG, cholesterol[39] or lower mean HDL-C[8] were associated with poorer cognitive function. However, these small studies

have not adequately been corrected for all of the confounding risk factors. The most recent longitudinal study[40] and meta-analysis showed that smoking is associated with increased risk of dementia.[41] A recent large cohort study showed smoking cessation was associated with decreased risk of dementia.[42] Our study found no association between smoking and cognitive impairment. These conflicting results may be due to the different study populations examined and different study designs used.

The influence of socio-demographic and genetic factors on cognitive impairment has been investigated in several studies. Our study showed that being married and urban living were protective factors in the multivariate analysis. These results are consistent with previous studies.[17,43] A population-based study of dementia progression demonstrating that the slower rates of cognitive and functional decline in those with Alzheimer's dementia who have spouse caregivers suggest a particular importance of marital relationships in dementia care.[44] Living with a spouse meant more interactions and communications. Positive spousal interactions and high caregiver commitment were associated with delayed nursing home placement in dementia.[45] Consistent with previous studies, our study showed the prevalence of cognitive impairment was higher in rural areas than in urban ones. Low education level and low socioeconomic status in the rural population might be important reasons for the urban–rural differences.[46,47] Some studies in the general population have shown that APOE ε4 carrier status is a risk factor for dementia. However, studies in people with diabetes suggest an uncertain association between APOE ε4 carrier status and risk of cognitive impairment.[14,15,49] Our study found an increased trend for the percentage of APOE ε4 carrier status in people with cognitive impairment compared with people with normal cognition. (13.32% *versus* 9.87%, $p = 0.26$). Our logistic regression model showed that APOE ε4 carrier status was not an independent risk factor for cognitive impairment, possibly due to lack of statistical power or the inclusion of different study populations.

The strength of this study is its population-based design with a large diabetic population size. Moreover, almost all important risk factors were covered in the present study. The risk factors for cognitive impairment, such as demographics, low physical activity, laboratory data, relevant diseases, and genetic vulnerability (APOE ε4 allele) were also considered in assessing the relations between risk factors and cognitive impairment. There are a few limitations in this study. First, because this is a cross-sectional study, whether risk factors are the cause or consequence of cognitive impairment cannot be definitely determined. Second, MMSE tests were used to define cognitive impairment, which may miss out mild cognitive impairment owing to its low sensitivity, although MMSE tests are still the most commonly used tests for cognitive screening in a population study. Third, medications that potentially affect cognitive function were not included in the study. Fourth, in multiple logistic regression analyses, entering all risk factors into a single model is not always the best approach to analyzing the data. However, entering highly correlated variables into the same multivariate model can result in predictors being eliminated in the process. Thus, further well-designed prospective studies are needed to clarify the correlation between risk factors and cognitive decline in people with diabetes.

Conclusion

In this large sample of older people with diabetes, stroke, depression, and low physical activity were all independent risk factors for cognitive impairment. Prevention of stroke, early detection and treatment of depression, and more exercise are crucial to reducing the risk of cognitive impairment in older people with diabetes.

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Authors' note

Study design and manuscript preparation: PC, SX acquisition of subjects and data: SX, QL, LS; analysis and interpretation: SX, QL, LS funding and critical review: PC; final version manuscript preparation and approval: all authors.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics approval and informed consent

The study received ethical approval from the Research Ethics Boards at Xuanwu Hospital of Capital Medical University (Registration number: CTR-IPR-20-11012). Written informed consent was obtained from all participants on the provision of a complete study description.

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