Eight-Year Longitudinal Associations of the Onset of Prediabetes and Diabetes with Cognitive Function Decline Among Chinese Adults Aged 45 Years or Older

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Research

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Abstract

Background

With the population aging, diabetes and cognitive function decline are increasingly common among older adults worldwide. However, the evidence about the effects and mechanism of prediabetes and diabetes on cognitive function is still limited. The purposes of this longitudinal study were to estimate the longitudinal associations of the onset of prediabetes and diabetes status with cognitive function among Chinese adults aged 45 years or older during an 8-year period; to estimate the clinical risk factors associated with cognitive function among patients with prediabetes and diabetes.

Methods

Participants were enrolled between 2011 and 2012, and followed up between 2018 and 2019 in the China Health and Retirement Longitudinal Study. In this study, we focused on newly diagnosed diabetic status, and those diagnosed with diabetes before or not providing fasting blood samples were excluded. Diabetic status was assessed according to the 2010 American Diabetes Association (ADA) guidelines. The general cognitive function, demographic characteristics, and clinical and biochemical factors were also measured.

Results

At baseline, 849 (21.3%) participants were first diagnosed with prediabetes, and 444 (11.1%) were diabetes patients. After adjusting for age, gender, marital status, education level, ever smoking, ever drinking, self-comment about health, hypertension, dyslipidemia, depressive symptoms, cognitive function, and clinical and biochemical measurements at baseline, diabetes status was a significant risk factor for subsequent cognitive decline (unstandardized β estimate=-0.47, 95% CI=-0.91~-0.04). Further stratification analyses found that only triglyceride concentrations were negatively associated with cognitive function among prediabetes patients (unstandardized β estimate=-0.004, 95% CI=-0.007~-0.001), and only creatine reactive protein was significantly associated with cognitive decline among diabetes patients (unstandardized β estimate=-0.065, 95% CI=-0.122~-0.009).

Conclusions

There is a positive longitudinal association between the onset of diabetes and cognitive decline among middle-aged and elderly Chinese. The management of triglycerides through lifestyle modification for prediabetes and specific adjunctive anti-inflammatory therapy for diabetes could benefit cognitive performance.

Background

With the population aging, diabetes mellitus is one of the most common problems among older adults worldwide [1]. China is one of the top three countries globally with the diabetes epidemic, which continues to increase with the demographic and social transitions due to rapid aging, urbanization, and lifestyle change [2]. Moreover, prediabetes, an intermediate metabolic state of hyperglycemia higher than normal but lower than the clinical diabetes threshold, may progress to diabetes as high as 74% [3]. According to recent data from a nationally representative cross-sectional survey in China, diabetes prevalence in Chinese adults is 10.9%, and prediabetes prevalence is nearly 35.7% [4]. As a disorder of glucose metabolism, prediabetes and diabetes have already been known to be associated with a variety of clinical sequelae, including vascular and nonvascular diabetic-related complications, resulting in elevated risk of death and health costs [5, 6]. Moreover, diabetes has been reported to be a risk factor for cognitive function decline, cognitive function impairment, or even dementia (i.e., the most serious stages in the development of cognitive dysfunction) [7, 8].

Cognitive function decline or impairment significantly elevates the risk of poor quality of life in older adults and most possibly occurs with aging [9]. However, although cognitive decline among older adults is common, it is often overlooked for the early identification or even progress to dementia, which has brought a heavy burden to individual families and society [10]. Especially in Chinese culture, older adults have culturally various perspectives on cognitive function decline or impairment than their counterparts in Western culture, and cognitive function impairment is culturally stigmatized or socially discriminated [11]. Although previous evidence from western countries showed that prediabetes or diabetes in midlife was associated with a more significant cognitive decline [12], there is little research that explores the effects of the onset of prediabetes and diabetes on subsequent cognitive function among Chinese adults, especially considering the differences in the associations between diabetes and cognitive function decline with the various demographic characteristics. Moreover, previous evidence showed that there might be shared inflammatory pathways in relation to insulin resistance and cognitive impairment [13]; a prior study also reported that elevated triglycerides (TG) were associated with smaller brain volume (i.e., correlated with general cognitive ability), even in patients without diabetes [14]; suggesting that there might be different mechanisms in the association of prediabetes and diabetes with cognitive function decline, respectively. Therefore, this study using data from the China Health and Retirement Longitudinal Study (CHARLS), aimed to estimate the longitudinal associations of the onset of prediabetes and diabetes status with cognitive function among Chinese adults aged 45 years or older during an 8-year period, with a particular focus on different demographic characteristics; to estimate the clinical risk factors associated with cognitive function among patients with prediabetes and diabetes.

Methods

Study design and participants

Data were obtained from the CHARLS, which used a multistage probability sampling method to recruit Chinese residents aged 45 and older from 28 of the overall provinces in China. The details of the study sampling method have been reported elsewhere [15]. At baseline survey, a total of 17708 participants were enrolled in the CHARLS through face-to-face household interviews between 2011 and 2012. The current study was the secondary analysis of the baseline data and the fifth wave follow-up data between 2018 and 2019. As shown in Fig. 1, among the 17708 participants at baseline, 8974 participants providing fasting blood samples, not diagnosed with diabetes or high blood sugar before, and completing the cognitive function examination were selected. After excluding 258 individuals aged < 45 years and those who have been diagnosed with a stroke, emotional/nervous/psychiatric problems, memory-related disease, vision/hearing problems, or speech impediment, 8716 participants at baseline survey were included in the study, and 6125 participants completing the cognitive function examination were eligible at the follow-up survey over an 8-year period (between 2018 and 2019; retention rate: 70.3%) [16].

Data Collection

Questionnaire

A standard questionnaire administered by trained staff was used to collect information. Sociodemographic characteristics including sex, age, marital status (1 = married, 2 = separated or divorced, 3 = widowed, 4 = never married), education level (1 = primary school or below, 2 = middle school, 3 = high school or above), ever smoking (1 = yes, 2 = no), and ever drinking (1 = yes, 2 = no) were collected. Self-comment about health was assessed by asking how about your health status comparing your peers or friends (responses were classified into 1 = good, 2 = fair, 3 = poor)? Hypertension was assessed by asking, “have you been told that you have hypertension by a doctor before 2011 (responses included 1 = yes and 2 = no)”? Dyslipidemia was measured by asking, “have you been told that you have dyslipidemia by a doctor before 2011 (responses included 1 = yes and 2 = no)”?

Depressive symptoms were measured by the 10-item Center for Epidemiology Scale for Depression (CESD-10) in Chinese [17], which has been validated and extensively used among Chinese adults [18]. The sum of scores ranges from 0 to 30, with higher scores indicating a higher level of depressive symptoms severity.

In the CHARLS study, primary outcomes were general cognition functioning. The Telephone Interview of Cognitive Status (TICS-10; orientation and attention), word recall (episodic memory), and figure drawing (visual-spatial abilities) were used to assess cognitive functioning, with an overall cognition score incorporating these assessments. The overall cognitive functioning score ranged from 0 to 21, and a higher score indicated better cognitive performance [19, 20]. The TICS-10 used in this study consists of ten mental status questions: the orientation of date (month, day, year), the orientation of day of the week, the orientation of season of the year, and serial subtraction of 7 from 100 (up to five times) [21]. The TICS-10 score was the total number of the correct answers and ranged from 0 to 10 [20]. Regarding word

recall, participants were first given about two minutes to immediately recall as many words as they could in any order after interviewers read a list of 10 Chinese words (immediate recall). About four to ten minutes later, participants were asked to recall as many original words as possible (delayed recall). The word recall score consisted of the average number of immediate and delayed word recalls and ranged from 0 to 10 [20]. Regarding figure drawing, participants were asked to draw a similar figure of two pentagons overlapped with each other Participants who completed this task received a score of 1, and 0 if they failed to do so [22].

Clinical And Biochemical Measurements

A 4-mL sample of whole blood was collected to obtain plasma and buffy coat, and another 2-mL sample of whole blood was collected for HbA_{1c} analysis. All blood samples were stored in a local laboratory at 4 ℃ and were transported at -80 ℃ to the China Center of Disease Control (CDC) in Beijing within two weeks. High-sensitivity CRP, HbA_{1c}, a lipid panel (total, HDL, LDL cholesterol, and TG), glucose, blood urea nitrogen (BUN), creatinine, and cystatin C from frozen plasma or whole blood samples were measured. High-sensitivity CRP level was assessed by immunoturbidimetric assay. HbA_{1c} levels were determined using Boronate affinity high-performance liquid chromatography (HPLC). Total cholesterol, HDL cholesterol (HDL-c), LDL cholesterol (LDL-c), TG, FBG concentrations were measured using enzymatic colorimetric tests. Blood urea nitrogen (BUN) level was assessed enzymatic UV method with urease. Creatinine concentration was measured using the rate-blanked and compensated Jaffe creatine method. Cystatin C level was assessed by using particle-enhanced turbidimetric assay [23].

Diabetic Status

Participants were first assessed by asking the question, “have you been told that you have diabetes by a doctor before 2011?”. Considering cognitive functioning might be influenced by a long-term disease or treatment, in this study, we focused on newly diagnosed diabetic status, and those diagnosed with diabetes before or not providing fasting blood samples were excluded. Diabetic status was assessed according to the 2010 American Diabetes Association (ADA) guidelines. Prediabetes is defined as fasting blood glucose (FBG) level of 100–125 mg/dL or glycated hemoglobin HbA_{1c} level of 5.7–6.4%; diabetes is defined as an FBG level ≥ 126 mg/dL, or a HbA_{1c} levels≥6.5% [24].

Statistical analysis

Baseline sample characteristics were described in both the total adults and based on the diabetic status separately. Categorical data were reported as frequencies (%); normally distributed continuous variables were presented as mean (± SD), and skewed data were presented as medians (interquartile ranges). The Rao-Scott chi-square test for categorical variables and the one-way ANOVA test for continuous variables were used to assess the differences between different diabetic statuses. Univariable generalized mixed-

effects linear regression models were performed to estimate the baseline factors associated with subsequent cognitive function scores. Multivariable generalized mixed-effects linear regression models were conducted to estimate the longitudinal associations of prediabetes and diabetes with cognitive function decline. In addition, to estimate whether the associations of prediabetes and diabetes with cognitive function scores were robust in the presence of potential confounders, subgroup analyses were performed according to sample characteristics. Further, multivariable generalized mixed-effects linear regression models stratified by diabetic status were performed to investigate the clinical factors associated with cognitive function among patients with prediabetes or diabetes. All statistical analyses were conducted using Stata 16.0 SE (StataCorp, Houston, Texas, USA). Statistical significance was evaluated at the < 0.05 level (two-tailed).

Results

Baseline characteristics of participants with different diabetic status

Table 1 summarizes the baseline characteristics of the 8716 participants. The mean age of the participants was 58.93 (SD: 9.76) years, and 3987 (45.7%) were males. Notably, a total of 849 (21.3%) participants were first diagnosed with prediabetes at baseline, and 444 (11.1%) were diabetes patients. The differences between the different diabetic groups were statistically significant in the distribution of age, marital status, ever smoking, ever drinking, self-comment about health, hypertension, dyslipidemia, cognitive function, BUN, creatine, total cholesterol, TG, HDL-c, LDL-c, CRP, and hemoglobin ($P < 0.05$).

Table 1
Baseline characteristics of participants with different diabetic status

Variables	Baseline survey (n = 8716)	Baseline diabetic status [a]			*P*-value [b]
		Prediabetes (n = 1802)	Diabetes (n = 935)	Others (n = 5979)	
Gender					
Male	3987 (45.7)	849 (21.3)	444 (11.1)	2694 (67.6)	0.165
Female	4717 (54.1)	952 (20.2)	489 (10.4)	3276 (69.5)	
Missing data	12 (0.1)				
Age*, year	58.93 (9.76)	59.70 (9.53)	60.39 (10.00)	58.48 (9.76)	< 0.001
Marital status					
Married	7690 (88.2)	1559 (20.3)	815 (10.6)	5316 (69.1)	0.029
Separated or divorced	95 (1.1)	19 (20.0)	7 (7.4)	69 (72.6)	
Widowed	869 (10.0)	208 (23.9)	107 (12.3)	554 (63.8)	
Never married	52 (0.6)	15 (28.8)	4 (7.7)	33 (63.5)	
Missing data	10 (0.1)				
Education level					
Primary school or below	5953 (68.3)	1236 (20.8)	641 (10.8)	4076 (68.5)	0.945

Abbreviation: the 10-item Center for Epidemiology Scale for Depression (CESD-10); blood urea nitrogen, BUN; triglyceride, TG; HDL cholesterol, HDL-c; LDL cholesterol, LDL-c; creatine reactive protein; CRP.

*: Data was presented in mean (SD).

#: Data was described in median (interquartile range).

[a]: Diabetic status was the first diagnosis of prediabetes or diabetes assessed according to the 2010 American Diabetes Association (ADA) guidelines.

[b]: The Rao-Scott chi-square test for categorical variables and one-way ANOVA test for continuous variables were used to assess the differences between the groups.

Variables	Baseline survey (n = 8716)	Baseline diabetic status [a]			*P*-value [b]
		Prediabetes (n = 1802)	Diabetes (n = 935)	Others (n = 5979)	
Middle school	1797 (20.6)	375 (20.9)	192 (10.7)	1230 (68.4)	
High school or above	948 (10.9)	188 (19.8)	98 (10.3)	662 (69.8)	
Missing data	18 (0.2)				
Ever smoking					
Yes	3352 (38.5)	728 (21.7)	381 (11.4)	2243 (66.9)	0.028
No	5362 (61.5)	1074 (20.0)	554 (10.3)	3734 (69.6)	
Missing data	2 (0)				
Ever drinking					
Yes	5357 (61.5)	1073 (20.0)	550 (10.3)	3734 (69.7)	0.018
No	3359 (38.5)	729 (21.7)	385 (11.5)	2245 (66.8)	
Self-comment about health					
Table 1. **Baseline characteristics of participants with different diabetic status (continued)**					
Good	1664 (19.1)	298 (17.9)	208 (12.5)	1158 (69.6)	0.004

Abbreviation: the 10-item Center for Epidemiology Scale for Depression (CESD-10); blood urea nitrogen, BUN; triglyceride, TG; HDL cholesterol, HDL-c; LDL cholesterol, LDL-c; creatine reactive protein; CRP.

*: Data was presented in mean (SD).

#: Data was described in median (interquartile range).

[a]: Diabetic status was the first diagnosis of prediabetes or diabetes assessed according to the 2010 American Diabetes Association (ADA) guidelines.

[b]: The Rao-Scott chi-square test for categorical variables and one-way ANOVA test for continuous variables were used to assess the differences between the groups.

Variables	Baseline survey (n = 8716)	Baseline diabetic status [a]			*P*-value [b]
		Prediabetes (n = 1802)	Diabetes (n = 935)	Others (n = 5979)	
Fair	5484 (62.9)	1168 (21.3)	552 (10.1)	3764 (68.6)	
Poor	1568 (18.0)	336 (21.4)	175 (11.2)	1057 (67.4)	
Hypertension					
Yes	2034 (23.3)	500 (24.6)	275 (13.5)	1259 (61.9)	< 0.001
No	6651 (76.3)	1298 (19.5)	658 (9.9)	4695 (70.6)	
Missing data	31 (0.4)				
Dyslipidemia					
Yes	689 (7.9)	178 (25.8)	95 (13.8)	416 (60.4)	< 0.001
No	7894 (90.6)	1591 (20.2)	831 (10.5)	5472 (69.3)	
Missing data	133 (1.5)				
Depressive symptoms* (CESD-10)	9.06 (5.37)	9.05 (5.42)	8.72 (5.46)	9.12 (5.33)	0.105
Cognitive functioning* (Overall)	9.71 (5.07)	9.64 (5.08)	9.30 (5.17)	9.80 (5.04)	0.023
TICS*	5.56 (3.83)	5.55 (3.82)	5.31 (3.93)	5.59 (3.82)	0.109

Abbreviation: the 10-item Center for Epidemiology Scale for Depression (CESD-10); blood urea nitrogen, BUN; triglyceride, TG; HDL cholesterol, HDL-c; LDL cholesterol, LDL-c; creatine reactive protein; CRP.

*: Data was presented in mean (SD).

#: Data was described in median (interquartile range).

[a]: Diabetic status was the first diagnosis of prediabetes or diabetes assessed according to the 2010 American Diabetes Association (ADA) guidelines.

[b]: The Rao-Scott chi-square test for categorical variables and one-way ANOVA test for continuous variables were used to assess the differences between the groups.

Variables	Baseline survey (n = 8716)	Baseline diabetic status [a]			*P*-value [b]
		Prediabetes (n = 1802)	Diabetes (n = 935)	Others (n = 5979)	
Word recall*	3.09 (2.00)	3.03 (1.96)	2.83 (2.05)	3.15 (2.00)	< 0.001
Complete figure drawing	5267 (60.4)	1082 (20.5)	534 (10.1)	3651 (69.3)	0.192
FBG (mg/dL)	106.81 (29.11)	113.25 (7.92)	160.78 (60.33)	96.42 (8.50)	< 0.001 (60.33)
HBA_{1c} (%)	5.21 (0.66)	5.34 (0.47)	6.03 (1.42)	5.04 (0.34)	< 0.001
BUN* (mg/dL)	15.66 (4.55)	16.02 (4.90)	16.00 (4.79)	15.50 (4.39)	< 0.001
Creatinine* (mg/dL)	0.78 (0.24)	0.80 (0.35)	0.79 (0.21)	0.77 (0.19)	< 0.001
Total Cholesterol* (mg/dL)	193.75 (38.86)	200.56 (40.38)	204.21 (46.96)	190.06 (36.35)	< 0.001
TG* (mg/dL)	129.66 (103.6)	147.04 (100.97)	207.56 (217.60)	112.24 (61.86)	< 0.001
HDL-c* (mg/dL)	51.54 (15.15)	50.52 (15.90)	47.01 (16.65)	52.56 (14.51)	< 0.001
LDL-c* (mg/dL)	117.21 (34.74)	120.49 (37.10)	114.28 (41.13)	116.67 (32.81)	< 0.001
CRP[#] (mg/dL)	1.01 (1.57)	1.15 (1.81)	1.40 (2.31)	0.90 (1.37)	< 0.001
Hemoglobin* (g/dL)	14.41 (2.25)	14.57 (2.11)	14.57 (2.36)	14.33 (2.27)	< 0.001

Abbreviation: the 10-item Center for Epidemiology Scale for Depression (CESD-10); blood urea nitrogen, BUN; triglyceride, TG; HDL cholesterol, HDL-c; LDL cholesterol, LDL-c; creatine reactive protein; CRP.

*: Data was presented in mean (SD).

#: Data was described in median (interquartile range).

[a]: Diabetic status was the first diagnosis of prediabetes or diabetes assessed according to the 2010 American Diabetes Association (ADA) guidelines.

[b]: The Rao-Scott chi-square test for categorical variables and one-way ANOVA test for continuous variables were used to assess the differences between the groups.

Variables	Baseline survey (n = 8716)	Baseline diabetic status [a]			*P*-value [b]
		Prediabetes (n = 1802)	Diabetes (n = 935)	Others (n = 5979)	
Cystatin C* (mg/L)	1.02 (0.28)	1.02 (0.35)	1.01 (0.28)	1.02 (0.26)	0.855
Abbreviation: the 10-item Center for Epidemiology Scale for Depression (CESD-10); blood urea nitrogen, BUN; triglyceride, TG; HDL cholesterol, HDL-c; LDL cholesterol, LDL-c; creatine reactive protein; CRP.					
*: Data was presented in mean (SD).					
#: Data was described in median (interquartile range).					
[a]: Diabetic status was the first diagnosis of prediabetes or diabetes assessed according to the 2010 American Diabetes Association (ADA) guidelines.					
[b]: The Rao-Scott chi-square test for categorical variables and one-way ANOVA test for continuous variables were used to assess the differences between the groups.					

Factors Associated With Cognitive Function At Follow-up

Without adjusting for other variables, diabetes status was a risk factor for subsequent cognitive decline (unstandardized β estimate=-0.60, 95% CI=-1.05~-0.16), while the association between baseline prediabetes and subsequent cognitive function was not significant (**Supplementary Table 1**). Other variables associated with subsequent cognitive function were also presented in **supplementary Table 1**.

Eight-year associations between baseline diabetic status and subsequent cognitive function

As shown in Table 2, after adjusting for age, gender, marital status, education level, ever smoking, ever drinking, self-comment about health, hypertension, dyslipidemia, and depressive symptoms at baseline, patients with diabetes were at a higher risk of cognitive decline at follow-up (unstandardized β estimate=-0.49, 95% CI=-0.97~-0.10, model 1). However, after adjusting for variables in model 1 plus cognitive function at baseline, the significant association vanished ($P > 0.05$, model 2). After adjusting for the variables in model 2 plus BUN, creatinine, TG, HDL-c, LDL-c, CRP, hemoglobin, and Cystatin C, diabetes status was a significant risk factor for subsequent cognitive decline (unstandardized β estimate=-0.47, 95% CI=-0.91~-0.04, model 3).

Table 2
Eight-year associations between baseline diabetic status and subsequent cognitive function (multivariable analyses)

Baseline diabetic status	Cognitive Function (follow-up, n = 6125)					
	Model 1*		Model 2*		Model 3*	
	Unstandardized β estimate (95% CI)	P-value	Unstandardized β estimate (95% CI)	P-value	Unstandardized β estimate (95% CI)	P-value
Others	Ref.		Ref.		Ref.	
Prediabetes	0.05 (-0.23 ~ 0.34)	0.720	0.04 (-0.23 ~ 0.30)	0.781	0.002 (-0.31 ~ 0.31)	0.988
Diabetes	-0.49 (-0.87~-0.10)	0.014	-0.28 (-0.63 ~ 0.08)	0.124	-0.47 (-0.91~-0.04)	0.032
Abbreviation: 95% confidence interval, 95% CI; reference, Ref.						
Model 1: Adjusting for age, gender, marital status, education level, ever smoking, ever drinking, self-comment about health, hypertension, dyslipidemia, and depressive symptoms at baseline.						
Model 2: Adjusting for the variables in Model 1 plus cognitive function at baseline.						
Model 3: Adjusting for the variables in Model 2 plus clinical variables including blood urea nitrogen, creatinine, triglycerides, HDL cholesterol, LDL cholesterol, C-Reactive Protein, hemoglobin, and Cystatin C.						
*: Adjusted variables entered in the models were examined by the collinearity diagnostics, and total cholesterol was excluded.						

As shown in Fig. 2, participants were divided based on the demographic characteristics, and the subgroup analyses results found that the differences between males and females in the longitudinal associations of prediabetes and diabetes with cognitive decline were statistically significant ($P < 0.05$). Only for females, the association of prediabetes (unstandardized β estimate=-0.50, 95% CI=-0.96~-0.03) and diabetes (unstandardized β estimate=-1.13, 95% CI=-1.77~-0.49) with cognitive decline were statistically significant.

Clinical Characteristics Associated With Cognitive Function

Table 3 shows that after adjusting for age, gender, marital status, education level, ever smoking, ever drinking, self-comment about health, hypertension, dyslipidemia, depressive symptoms, and cognition function at baseline, only TG concentrations were negatively associated with cognitive function among prediabetes patients (unstandardized β estimate=-0.004, 95% CI=-0.007~-0.001), and only CRP was significantly associated with cognitive decline among diabetes patients (unstandardized β estimate=-0.065, 95% CI=-0.122~-0.009).

Table 3
Clinical characteristics associated with cognitive function among patients with different diabetic status

Baseline characteristics	Cognitive Function (follow-up, n = 6125)					
	Prediabetes		Diabetes		Others	
	Unstandardized β estimate (95% CI)#	P-value	Unstandardized β estimate (95% CI)#	P-value	Unstandardized β estimate (95% CI)#	P-value
BUN (mg/dL)*	0.048 (-0.015 ~ 0.112)	0.136	-0.002 (-0.097 ~ 0.094)	0.971	0.013 (-0.024 ~ 0.050)	0.488
Creatinine (mg/dL)*	0.064 (-2.002 ~ 2.130)	0.952	0.209 (-2.539 ~ 2.956)	0.881	0.649 (-0.514 ~ 1.811)	0.274
TG (mg/dL)*	**-0.004 (-0.007~-0.001)**	**0.038**	0.000 (-0.003 ~ 0.003)	0.897	0.001 (-0.002 ~ 0.004)	0.382
HDL-c (mg/dL)*	-0.006 (-0.026 ~ 0.014)	0.538	0.000 (-0.028 ~ 0.028)	0.999	-0.003 (-0.015 ~ 0.008)	0.573
LDL-c (mg/dL)*	0.001 (-0.007 ~ 0.008)	0.855	0.003 (-0.008 ~ 0.014)	0.542	0.000 (-0.005 ~ 0.004)	0.922
CRP (mg/dL)*	-0.023 (-0.067 ~ 0.021)	0.314	**-0.065 (-0.122~-0.009)**	**0.023**	0.008 (-0.017 ~ 0.033)	0.529
Hemoglobin (g/dL)*	-0.049 (-0.192 ~ 0.094)	0.501	0.001 (-0.201 ~ 0.203)	0.991	0.042 (-0.028 ~ 0.112)	0.238
Cystatin C (mg/L)*	-0.197 (-1.696 ~ 1.302)	0.797	1.195 (-1.149 ~ 3.539)	0.317	-0.761 (-1.525 ~ 0.003)	0.051

Abbreviation: blood urea nitrogen, BUN; triglyceride, TG; HDL cholesterol, HDL-c; LDL cholesterol, LDL-c; creatine reactive protein; CRP.

*: Continuous variable with 1-unit increase.

#: Models were adjusted for age, gender, marital status, education level, ever smoking, ever drinking, self-comment about health, hypertension, dyslipidemia, depressive symptoms, and cognition function at baseline. All variables entered in the models were examined by the collinearity diagnostics, and total cholesterol was excluded.

Discussion

The baseline survey of the longitudinal study observed that the prevalence of the first diagnosis of prediabetes and diabetes among Chinese adults aged 45 years or older was 21.3% and 11.1%, respectively. This finding was consistent with previous studies [4, 25], suggesting that prediabetes or diabetes has been a significant public health problem among Chinese adults. In this 8-year longitudinal study, we first found that patients with the onset of diabetes can predict the cognitive decline at 8-year follow-up; nevertheless, baseline prediabetes status was not significantly associated with subsequent

cognitive function decline. Similarly, previous studies have suggested that diabetes status was associated with a higher risk of cognitive decline among adults or older adults [8, 26], prediabetes was not related to poorer cognitive performance among general older adults or patients after stroke [27, 28]. Moreover, the univariable analyses also found that males, age, widowed or never married, ever smoking, poor self-comment about health, having hypertension, having dyslipidemia, and depressive symptoms scores at baseline were negatively associated with subsequent cognitive function, and these findings might be helpful to identify a profile of adults who at a higher risk of cognitive decline and provide potential confounders that may have effects on the association between diabetes status and cognitive function. Furthermore, subgroup analyses based on demographic characteristics showed that without adjusting for other variables, in females, prediabetes or diabetes was a risk factor for subsequent cognitive decline. Similarly, Chatterjee et al. reported that for vascular dementia (not for nonvascular dementia), the additional risk of diabetes is greater in women [29].

By extensively adjusting for age, gender, marital status, education level, ever smoking, ever drinking, self-comment about health, hypertension, dyslipidemia, and depressive symptoms at baseline, this longitudinal study observed the onset of diabetes status at baseline predicted subsequent cognitive decline. Several possible biological explanations have been proposed, including the indirect effects of diabetes on cognition through subclinical or clinical vascular disease for diabetes can cause the damage of cerebral microvascular and macrovascular contributing to cognitive decline [30, 31]. Another explanation might be related to the abnormal insulin modification in diabetes patients. In the central nervous system, insulin plays critical regulatory roles. At the same time, hyperglycemia can lead to accumulation of advanced glycation and products (i.e., the primary contributor to insulin resistance in diabetic cells), and brain insulin resistance is a key factor in the pathogenesis of Alzheimer's disease for interacting with key proteins affected in the neurodegenerative conditions (e.g., amyloid-beta precursor protein) [32, 33]. Further adjusting for cognitive function at baseline, the significant association disappeared, indicating that the baseline cognitive function was the most vital factor associated with subsequent cognitive function. Nevertheless, further including clinical and biochemical factors (e.g., BUN, creatinine, TG, HDL-c, LDL-c, CRP, hemoglobin, and Cystatin C) as the control variables, we observed that the onset of diabetes status at baseline was associated with a 0.47-fold increase in the risk of cognitive function decline, suggesting that there might be various clinical and biochemical factors associated with cognitive function among individuals with different diabetic status.

Our further stratification analyses found that only higher triglyceride concentration was a risk factor for cognitive function among prediabetes patients. Similarly, Power et al. reported that elevated serum TGs were associated with a greater 20-year decline in cognitive function by using a cohort study of persons recruited at ages 45 to 65 years from U.S. communities [34]; He et al. found a significant association between high plasma TG levels and mild cognitive impairment among participants aged > 65 years [35]. A possible explanation was that higher levels of TG might increase global cerebral amyloid-beta deposition affecting cognitive function transition, and another explanation may be that higher TG level was a risk factor for cerebrovascular disease, which may cause cognitive decline through hypoperfusion [36]. Furthermore, the stratification analyses also revealed that among diabetes patients, CRP level was

negatively associated with subsequent cognitive function. These findings were consistent with previous longitudinal studies, which suggests that CRP levels were positively related to future cognitive impairment and decline in elderly individuals with cardiovascular disease [37] and euthymic patients with bipolar disorder [38]. These findings might be related to that CRP is a vital biomarker for systemic inflammation, and elevation of peripheral inflammation may activate central nervous system including brain microglia, the serotonin transporter expression, oxidative stress, and decreased neuroplasticity, all potentially contributing to structural and functional brain changes, which all with accumulation can cause cognitive performance related disease [39]. Besides, evidence also suggested that there might be shared inflammatory pathways concerning insulin resistance and cognitive impairment [13]. To sum up, this study suggested that the management of TG through lifestyle modification (e.g., suitable physical activity and healthy diet) or specific therapy could bring benefits to cognitive performance among prediabetes patients; another potential clinical implication is that the adjunctive anti-inflammatory treatments may improve cognitive function among diabetes patients.

The strengths of the current study included adopting the large-scale, 8-year longitudinal study design, using the onset diagnosis of prediabetes and diabetes as exposure, and the use of questionnaires and clinical and biochemical measurements to collect information.

Limitations

Several potential limitations should also be notable. First, although data about cognitive function was measured by self-report, which may lead to biased reporting, self-reports remain a common and accepted method for assessing cognitive performance. Second, the study sample only included adults aged 45 years or older, and then the generalization of the findings may not be applicable to all Chinese adults. Third, although this study adopted an eight-year longitudinal study design, associations still should be interpreted cautiously due to they were generated from an interval that might not be long enough to uncover apparent cognitive decline.

Conclusions

In conclusion, this longitudinal study identified that baseline diabetes status could predict cognitive decline at 8-year follow-up among Chinese adults aged 45 years or older. Although this study did not reveal a significant association between baseline prediabetes status and subsequent cognitive function, it observed that TG level was negatively associated with cognitive function among prediabetes patients, and higher CRP levels predicted elevated risk of cognitive decline among diabetes patients.

Declarations

Ethics approval and consent to participate

Each participant provided a written informed consent before participating in this study. Ethics approval for the data collection of CHARLS study was obtained from the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). Ethics approval for the use of CHARLS data was obtained from the University of Newcastle Human Research Ethics Committee.

Consent for publication

All the authors listed have approved the manuscript for submission and have provided consent for publication.

Availability of data and materials

The original datasets analyzed during the current study are available at the CHARLS website (http://forum.charls.pku.edu.cn).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LG conceptualized and designed this article. XJW drafted the manuscript and made substantial contributions to conception and deign and interpretation of the data. WXW performed the statistical analyses. GDJS, RPW, and CYL acquired data, developed the database. All of the authors revised the manuscript critically and provided final approval of the submission.

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Figures

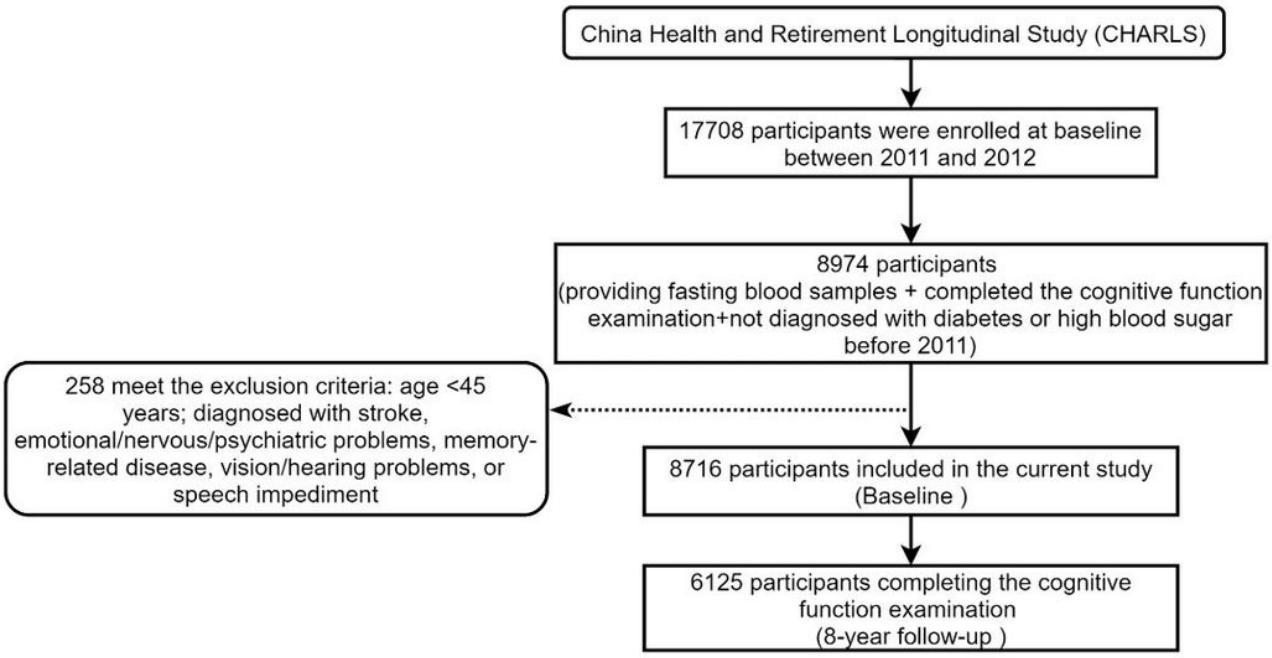

Figure 1

Flowchart of the study using data from the China Health and Retirement Longitudinal Study

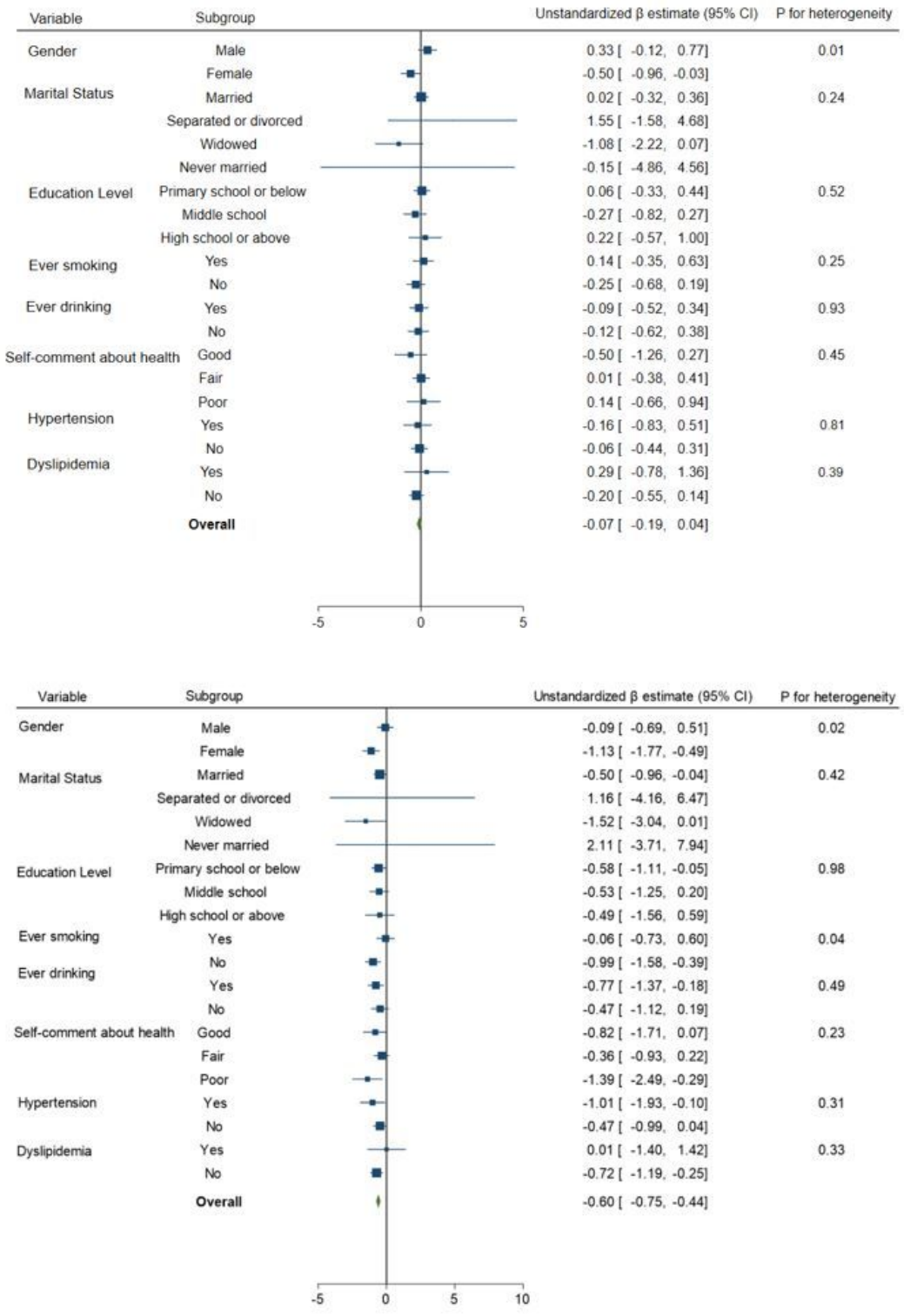

Figure 2

Subgroup analyses of the longitudinal associations of prediabetes and diabetes with cognitive function

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- SupplementaryTable.docx