

Elevated Fasting Blood Glucose Level Increases the Risk of Cognitive Decline Among Older Adults with Diabetes Mellitus: The Shanghai Aging Study

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Abstract.

Background: Several studies have demonstrated that the elevated fasting blood glucose (FBG) may increase the risk of incident dementia in older adults with or without diabetes mellitus (DM). However, similar results are rarely reported in Chinese population.

Objective: This study aimed to demonstrate the association between FBG and risk of incident cognitive decline in older Chinese adults.

Methods: We prospectively followed up 1,555 dementia-free participants with baseline FBG measurement in the Shanghai Aging Study.

Results: We identified 126 incident dementia cases across a mean of 5.2 years. Cumulative dementia incidence in type II DM participants with higher FBG (>6.1 mmol/L) increased most dramatically, second with that of non-DM participants with higher FBG, than that of participants with lower FBG (≤ 6.1 mmol/L). DM participants had a significant higher risk of incident dementia (adjusted HR 1.51, 95%CI 1.25–1.82) by every 1 mmol/L increment of FBG. Among DM participants, baseline FBG was positively related to the rate of annual decline of MMSE ($\beta = 0.10$, $p = 0.0018$).

Conclusions: Our results suggest that especially in people with type II DM, effective blood glucose control may help to prevent cognitive impairment in later life.

Keywords: Cognitive function, cohort study, dementia, diabetes mellitus, fasting glucose, incidence

INTRODUCTION

With the aging of the population, dementia has become a major threat to public health worldwide,

and the societal burden of dementia will be continually growing in the next decades [1, 2]. Prevalence of diabetes mellitus (DM) was 6.8%, 11.0%, and 10.1% in Europe, North America and the Caribbean, and South East Asia, respectively, as reported by the International Diabetes Federation. There are 425 million diabetics worldwide; among them, 104 million, aged 60 or over, have impaired glucose tolerance [3].

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The high prevalence of DM together with unrealized potential for prevention and treatment makes it one of the most important modifiable risk factors for dementia [4].

Population-based studies have demonstrated the evidence that the risk of dementia and cognitive deficits increased in people with DM [5, 6]. A systematic review from 14 longitudinal population-based studies concluded that the incidence of “any dementia” was higher in individuals with DM than in those without DM [5]. In addition, some studies reported that high glycemic index, impaired fasting glucose, pre-diabetes, borderline diabetes, and impaired glucose tolerance may associate with dementia, cognitive decline, or brain volumes change, but the findings were mostly from western populations [7–15].

About one fifth of the world’s population is Chinese. The China National Diabetes and Metabolic Disorders Study reported that prevalence of DM was rapidly increasing with age, from 3.2% in those aged 20–39 years to 20.4% among those aged 60 years and over, and in recent years, the largest increases have occurred in the oldest age groups [16]. The association between DM and cognitive impairment among Chinese older adults has been studied with cross-sectional design [17–21]. Only two prospective studies were conducted in Chinese populations in Singapore and Hong Kong [22, 23]. The significant association between DM/blood glucose and incident cognitive impairment, however, was not explored by their results. Prospective community-based studies are lacking in mainland China to understand the potential consequences of the glucose metabolism for the risk of cognitive decline.

The Shanghai Aging Study is a population-based epidemiologic cohort study conducted in China with a study design, operational procedures and diagnostic criteria similar to most cohort studies in western countries [24]. In the prospective stage, we aimed to explore the association between baseline fasting blood glucose (FBG) and risk of incident cognitive decline among older Chinese adults residing in an urban community. Our hypotheses were 1) that elevated baseline FBG level would be independently associated with an increased risk of dementia incidence; 2) that baseline FBG level would be positively correlated to global cognitive decline; and 3) that the effect of the association may be different between participants with and without type II DM.

MATERIALS AND METHODS

Recruitment of study participants

From January 2010 to September 2011, we enrolled 3,141 permanent residents aged 60 or older in the Jingansi community in downtown Shanghai. Participants were excluded if they (1) were residing in nursing homes and other institutions; 2) had severe impairments in vision, hearing, or speaking and thus could not participate in the neuropsychological evaluation; or 3) had severe schizophrenia or mental retardation based on their medical record or diagnosis by neurologists. Detailed procedure of the recruitment has been published elsewhere [24].

This study was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China. A written informed consent was obtained from all of the participants and/or their legal guardian.

Demographic characteristics and medical history

Participants were interviewed face-to-face by trained research nurses to collect information on their demographic characteristics and lifestyle factors, e.g., cigarette smoking. History of hypertension, stroke, and heart disease (including coronary artery disease and arrhythmia) were asked and confirmed from their medical records. In addition, all participants’ weight and height were measured and recorded in order to calculate body mass index (BMI) (weight in kilograms divided by the square of the height in meters). Obesity was defined as $BMI \geq 27.5 \text{ kg/m}^3$ based on WHO definition for Asian populations [25].

DM ascertainment

Participants who reported a physician diagnosed type II DM, and currently on anti-diabetic medication were defined as having DM. Verification was made by research nurses with checking the participants’ medical records and Jingansi Community diabetes registry database.

Measurement of baseline FBG

Participants were instructed to fast after dinner the night before for at least 12 hours. A 5 ml blood sample was obtained from participants when they arrived at the hospital for clinical interview in the next early morning. FBG was assessed using a glucose

oxidase assay [26] at the clinical laboratory in Huashan Hospital. The normal range of FBG was defined as 3.9–6.1 mmol/L, based on the value originated in diabetes diagnostic criteria of WHO [27].

Neuropsychological assessments

Cognitive function of each participant was assessed by a neuropsychological test battery, which covers the following domains: global cognition, executive function, spatial construction function, memory, language, and attention. The battery contained the 1) Mini-Mental State Examination; 2) Conflicting Instructions Task (Go/No Go Task); 3) Stick Test; 4) Modified Common Objects Sorting Test; 5) Auditory Verbal Learning Test; 6) Modified Fuld Object Memory Evaluation; 7) Trail-making tests A and B; and 8) RMB (Chinese currency) test. The neuropsychological tests were administered by study psychometrists according to the education level of each participant. Normative data and a detailed description of these tests are reported elsewhere [28, 29]. All tests were conducted in Chinese within 90 minutes.

Neurological examinations

Each participant was examined by neurologists for motor responses and reflexes. Center for Epidemiologic Studies Depression Scale (CESD) was administered to assess whether a participant met criteria for depressive symptoms within the past week. Depression was determined to be present if the CESD score ≥ 16 [30]. Neurologists also administered the Clinical Dementia Rating [31, 32] and Activities of Daily Living (ADL) scales to elicit memory complaints and physical activities of daily living [33].

Consensus diagnosis

A group of neurologists, neuropsychologist, and neuroepidemiologist reviewed the functional, medical, neurological, psychiatric, and neuropsychological data and reached a consensus diagnosis for dementia using DSM-IV criteria [34]. Detailed diagnostic procedures are reported elsewhere [24].

APOE Genotype Assessment

DNA was extracted from blood or saliva collected from study participants. APOE genotyping was conducted by the Taqman SNP method [35]. The

presence of at least one $\epsilon 4$ allele was considered as being APOE- $\epsilon 4$ positive.

Follow up procedure

At baseline, 156 dementia cases were detected among 3,141 participants, with an overall dementia prevalence of 5.0% (95% CI: 4.3–5.8) [24, 29]. From April 1, 2014 to December 31, 2016, as the first incidence wave, 2,985 participants without dementia at baseline were scheduled to follow-up. Research coordinators contacted them based on their contact information recorded at the baseline. Cognitive function of participants was evaluated using the same neuropsychological battery that was used at baseline. Consensus diagnosis of incident dementia was conducted by the same diagnosis group using the same diagnostic criteria as at baseline.

Statistical analysis

Continuous variables were expressed as the mean and standard deviation (SD), and categorical variables were expressed as number and frequencies (%). The Student *t*-test, Wilcoxon rank-sum test, Pearson Chi-square test, and Fisher exact test were used to compare continuous and categorical variables.

According to the normal range of FBG (3.9–6.1 mmol/L) originating in diabetes diagnostic criteria of WHO [27], 4 subgroups of participants were defined as: 1) DM participants with higher baseline FBG (>6.1 mmol/L), 2) DM participants with lower baseline FBG (≤ 6.1 mmol/L), 3) non-DM participants with higher baseline FBG (>6.1 mmol/L), and 4) non-DM participants with lower baseline FBG (≤ 6.1 mmol/L).

Incidence rate of dementia was calculated as the number of new-onset cases divided by the total person-years of follow-up and described as “per 100 person-years, 95% confidence intervals (CIs)”. Kaplan-Meier curves were used to present the cumulative incidence of dementia by follow-up time. Log-rank test and *post hoc* pairwise comparisons were used to compare the cumulative incidence rate of dementia within four subgroups.

Three Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and 95% CI for incident dementia by baseline FBG as continuous variable, in DM and non-DM groups. Model 1 was a univariate model to explore the “crude” effect of baseline FBG on incident dementia without considering other confounders. Model 2 was a multivariate

model adjusting for sex, age, education years, and APOE ϵ 4, which were the major covariates. Model 3 was also a multivariate model additionally include covariates such as obesity, cigarette smoking, heart disease, hypertension, stroke and depression, in order to adjust confounders of vascular and mental factors. The weighted Schoenfeld residual-based test was used to check the proportional hazards (PH) assumption. p values of the all variables were all greater than 0.05, indicating that each variable satisfied the PH assumption, and the global test of model satisfied the PH assumption ($\chi^2 = 6.25$, $p = 0.8563$). As a sensitivity analysis, competing risk analysis where lost to follow-up is treated as the competing risk was conducted by the Fine-Gray's model. Sex, age, years of education, APOE ϵ 4, obesity, cigarette smoking, depression, heart disease, hypertension, and stroke were included as covariates. The mean follow-up time (June 31, 2015) was considered as the time when participants who were lost to follow-up censored.

For a given participant, the "rate of annual decline of MMSE score", which indicates the worse annual change in global cognitive function across the follow-up period of evaluation, was calculated as the difference of MMSE scores (the baseline MMSE minus the follow-up MMSE) divided by follow-up years [36]. In DM and non-DM groups, multivariate linear regression model was used to examine the association of baseline FBG level and the rate of annual decline of MMSE, adjusting sex, age, years of education, APOE ϵ 4, obesity, cigarette smoking, heart disease, hypertension, stroke, depression, and baseline MMSE score. Residual plots were used to check the linearity assumption of the linear regression models.

All of the p -values and 95% CIs were estimated in a two-tailed manner. Differences were considered to be statistically significant at $p < 0.05$. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of participants with or without baseline FBG

We successfully followed and interviewed 1,659 (55.6%) participants, in which 1,555 (52.1%) had the FBG measurement at the baseline, and with a mean follow-up of 5.2 (SD 0.9) years. One hundred and four participants were not included in the analysis because they refused taking the FBG

measurement at baseline. Compared to participants with baseline FBG, they were older [82.9 (SD 5.8) versus 70.7 (SD 6.9), $p < 0.0001$], less obese (11.5% versus 20.1%, $p = 0.0337$), with higher prevalent heart disease (27.9% versus 10.6%, $p < 0.0001$), hypertension (71.2% versus 52.8%, $p = 0.0010$), stroke (19.2% versus 12.5%, $p = 0.0492$), lower MMSE score [26.2 (SD 3.0) versus 28.3 (SD 1.9), $p < 0.0001$], and more severe ADL impairment [23.6 (SD 7.7) versus 20.4 (SD 2.8), $p < 0.0001$] (Table 1).

Characteristics of participants followed up and lost-to-follow up

Individuals who were lost-to-follow up included 263 (8.8%) deceased, 271 (9.1%) who refused to be interviewed, 779 (26.1%) with whom we lost contact (due to moving to an unknown residential address, abroad, or to nursing homes), and 13 (0.4%) who suffered severe mental disorder or impairment of vision, hearing or speaking and were not able to cooperate with clinical interviews and neuropsychological testing. There were no significant differences by sex, education, stroke, APOE ϵ 4, cigarette smoking, and FBG between those followed and lost-to-follow up (Supplementary Table 1). We also compared the characteristics of participants with and without incident dementia (Supplementary Table 2).

Characteristics of participants with FBG ≤ 6.1 mmol/L and FBG > 6.1 mmol/L

As showed in Table 1, among 1,555 participants, 359 (23.1%) with FBG > 6.1 mmol/L. Comparing with FBG ≤ 6.1 mmol/L participants, those with FBG > 6.1 mmol/L were significantly older [71.9 (SD 6.6) versus 70.4 (SD 6.9), $p = 0.0001$], and with less education years [11.4 (SD 4.4) versus 12.2 (SD 3.8), $p = 0.0067$]. Participants with FBG > 6.1 mmol/L were assessed lower MMSE score at baseline [28.1 (SD 2.1) versus 28.4 (SD 1.9), $p = 0.0037$], lower MMSE score at follow-up [26.5 (SD 3.9) versus 27.0 (SD 3.8), $p = 0.0010$], higher rate of annual decline of MMSE score [0.4 (SD 0.9) versus 0.3 (SD 1.0), $p = 0.0237$] and more dementia (10.9% versus 7.3%, $p = 0.0288$). In addition, participants with FBG > 6.1 mmol/L had more obesity (28.1% versus 17.6%, $p < 0.0001$), heart disease (13.1% versus 9.8%, $p = 0.0045$), hypertension (61.8% versus 50.1%, $p < 0.0001$), and DM (5.4% versus 40.1%, $p < 0.0001$).

Table 1

Baseline characteristics of sociodemographic, health behaviors, genetics, medical history, and cognitive function of the participants who completed the incidence wave

	Completed follow-up interview without baseline FBG N = 104	Completed follow-up interview with baseline FBG N = 1,555	<i>p</i> *	FBG ≤ 6.1 mmol/L N = 1,196	FBG > 6.1 [‡] mmol/L N = 359	<i>p</i> [†]
Sex, male, n (%)	30 (28.9)	729 (46.9)	0.0004	554 (46.3)	175 (48.8)	0.4193
Age, y, mean (SD)	82.9 (5.8)	70.7 (6.9)	<0.0001	70.4 (6.9)	71.9 (6.6)	0.0001
Education, y, mean (SD)	10.1 (4.9)	12.0 (4.0)	0.0002 [#]	12.2 (3.8)	11.4 (4.4)	0.0067 [#]
Obesity, n (%)	12 (11.5)	312 (20.1)	0.0337	211 (17.6)	101 (28.1)	<0.0001
Cigarette smoking, n (%)	6 (5.8)	163 (10.5)	0.1222 ^{**}	131 (11.0)	32 (8.9)	0.2608
Heart disease, n (%)	29 (27.9)	164 (10.6)	<0.0001	117 (9.8)	47 (13.1)	0.0045
Hypertension, n (%)	74 (71.2)	821 (52.8)	0.0003	599 (50.1)	222 (61.8)	<0.0001
Diabetes mellitus type II, n (%)	12 (11.5)	209 (13.4)	0.5805	65 (5.4)	144 (40.1)	<0.0001
Stroke, n (%)	20 (19.2)	195 (12.5)	0.0492	147 (12.3)	48 (13.4)	0.5881
Depression, n (%)	13 (12.5)	232 (14.9)	0.5007	181 (15.3)	51 (14.2)	0.6653
MMSE, mean (SD)	26.2 (3.0)	28.3 (1.9)	<0.0001 [#]	28.4 (1.9)	28.1 (2.1)	0.0037 [#]
ADL, mean (SD)	23.6 (7.7)	20.4 (2.8)	<0.0001 [#]	20.3 (2.1)	20.8 (4.5)	0.0017 [#]
APOE ε4 allele positive, n (%)	7 (15.9)	250 (17.0)	0.8544 ^{**}	204 (17.1)	46 (12.8)	0.1802
Dementia, n (%)	42 (40.4)	126 (8.1)	<0.0001	87 (7.3)	39 (10.9)	0.0288
Follow-up MMSE, mean (SD)	22.8 (6.5)	26.9 (3.8)	<0.0001 [#]	27.0 (3.8)	26.5 (3.9)	0.0010 [#]
Rate of annual decline of MMSE, mean (SD)	1.1 (1.8)	0.3 (1.0)	<0.0001 [#]	0.3 (1.0)	0.4 (0.9)	0.0237 [#]

*Comparison between the groups with and without baseline FBG; [†]Comparison between the groups with FBG ≤ 6.1 mmol/L and FBG > 6.1 mmol/L; [‡]6.1 mmol/L was the fasting glucose upper normal limits; Pearson Chi-square test, Student *T* test, [#]Wilcoxon rank sum test; ^{**}Fisher exact test. FBG, Fasting blood glucose; ADL, activities of daily living scales; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; SD, standard deviation.

Incidence rate within all participants and subgroups

Dementia incidence in the DM participants with higher FBG (>6.1 mmol/L) (144 participants with 743.2 person-years) and lower FBG (≤6.1 mmol/L) (65 participants with 344.2 person-years) were 2.42 (95%CI 1.30–3.54)/100 person-years and 1.39 (95%CI 1.09–1.68)/100 person-years. Incidence rate of dementia in non-DM participants with higher FBG (215 participants with 1,078.6 person-years) and lower FBG (1,131 participants with 5992.0 person-years) were 1.93 (95%CI 1.11–2.76)/100 person-years and 1.16 (95%CI 0.02–2.30)/100 person-years

Association between FBG and incident cognitive decline

Cumulative incidence rate of dementia in DM participants with higher baseline FBG (>6.1 mmol/L) increased most dramatically, second with that of non-DM participants with higher FBG, than that of participants with lower FBG (≤6.1 mmol/L) (log-rank test, *p* = 0.0412) (Fig. 1). A significant difference of cumulative incidence rate was found between DM participants with higher FBG and non-DM participants with lower FBG (*p* = 0.0242). Similar result

was found in non-DM participants with lower FBG versus non-DM participants with higher FBG (*p* = 0.0472).

Figure 2 showed that DM participants had a 51% higher risk for incident dementia (HR = 1.51, 95%CI 1.25–1.82) for every 1 mmol/L increment of baseline FBG, adjusting for age, sex, education, APOE ε4, obesity, cigarette smoking, heart disease, hypertension, stroke, and depression (Model 3). No statistically significant association was found among non-DM participants. In a sensitivity analysis for treating the lost-to-follow up as the competing risk, we also found that DM participants had a 33% higher risk for incident dementia (HR = 1.33, 95%CI 1.15–1.54) by every 1 mmol/L increment of baseline FBG among DM participants. However, no statistically significant association was found among all participants (HR = 1.07, 95%CI 0.96–1.21) and non-DM participants (HR = 1.00, 95%CI 0.85–1.18).

Among DM participants, baseline FBG was positively related to the rate of annual decline of MMSE, after adjusted for age, sex, education, baseline MMSE scores, APOE ε4, obesity, cigarette smoking, heart disease, hypertension, stroke, and depression (β = 0.10, *p* = 0.0018). Significant relation was not found in non-DM participants (β = -0.03, *p* = 0.375) (Fig. 3).

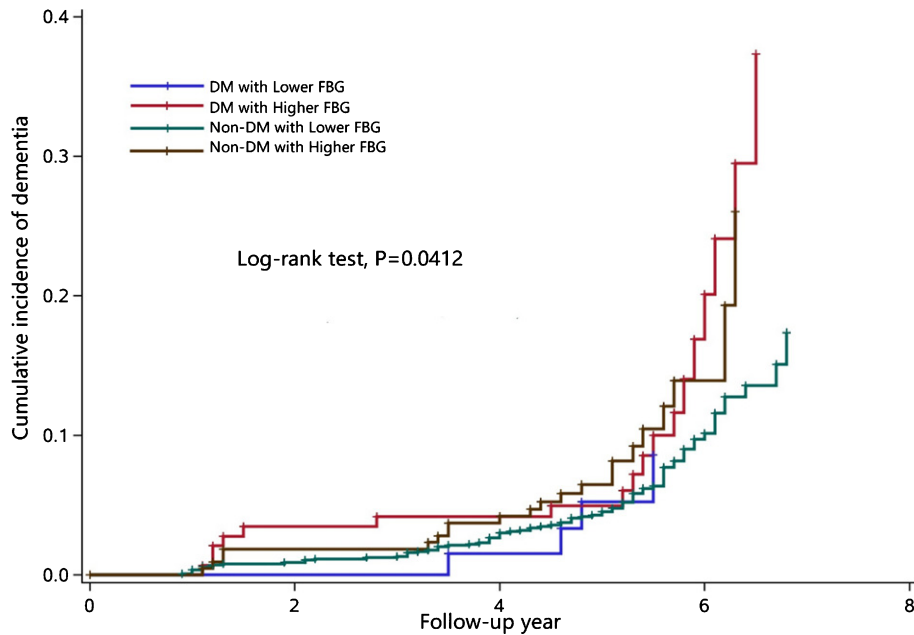


Fig. 1. Cumulative incidence of dementia in DM and non-DM subgroups by category of baseline fasting blood glucose. Note: (1) Cumulative incidence rate of dementia in DM participants with higher baseline FBG (>6.1 mmol/L) increased most dramatically, second with that of non-DM participants with higher FBG, than that of participants with lower FBG (≤ 6.1 mmol/L) (log-rank test, $p = 0.0412$); (2) DM with lower FBG: DM participants with baseline FBG ≤ 6.1 mmol/L; DM with higher FBG: DM participants with FBG > 6.1 mmol/L; Non-DM with higher FBG: non-DM participants with higher FBG > 6.1 mmol/L; Non-DM with lower FBG: non-DM participants with FBG ≤ 6.1 mmol/L. DM, diabetic mellitus; FBG, fasting blood glucose.

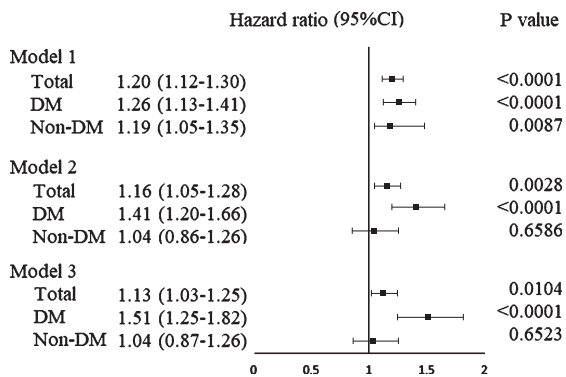


Fig. 2. Hazard ratios for incident dementia by baseline fasting blood glucose as continuous variable in total, DM and non-DM participants. Note: (1) DM participants had significantly higher risk for incident dementia by every 1 mmol/L increment of baseline FBG in 3 Cox regression model, adjusting for age, sex, education, APOE $\epsilon 4$, obesity, cigarette smoking, heart disease, hypertension, stroke, and depression. No statistically significant association was found among non-DM participants; (2) Model 1: Univariate analysis; Model 2: Multivariate Cox regression model, adjusted for sex, age, years of education, and APOE $\epsilon 4$; Model 3: Multivariate Cox regression model, adjusted for sex, age, years of education, APOE- $\epsilon 4$, obesity, cigarette smoking, depression, heart disease, hypertension, and stroke. HR, hazard ratio; CI, confidence interval; DM, diabetic mellitus; APOE, apolipoprotein E.

DISCUSSION

Our study found a positive association between baseline FBG level and risk of incident all-cause dementia and global cognitive function decline in participants with type II DM, but not in those without, after controlling for confounders of socio-demographic characteristics, health behaviors, APOE genotype, and medical conditions. These data suggest that elevated FBG may have deleterious effects on the aging brain, especially in population with DM, even a slight increase of FBG may induce a higher risk of cognitive decline. To our knowledge, this is the first prospective community-based study providing the evidence for the association between baseline FBG and risk of cognitive decline among Chinese older adults through the Shanghai Aging Study.

The association between DM and cognitive impairment among Chinese older adults has been studied. A dementia prevalence study found that, demented subjects had a greater duration of diabetes [OR 1.42, (95%CI 1.35–1.49)], and took more frequent use of diabetes medications [OR 0.94, (95%CI 0.89–0.98)]

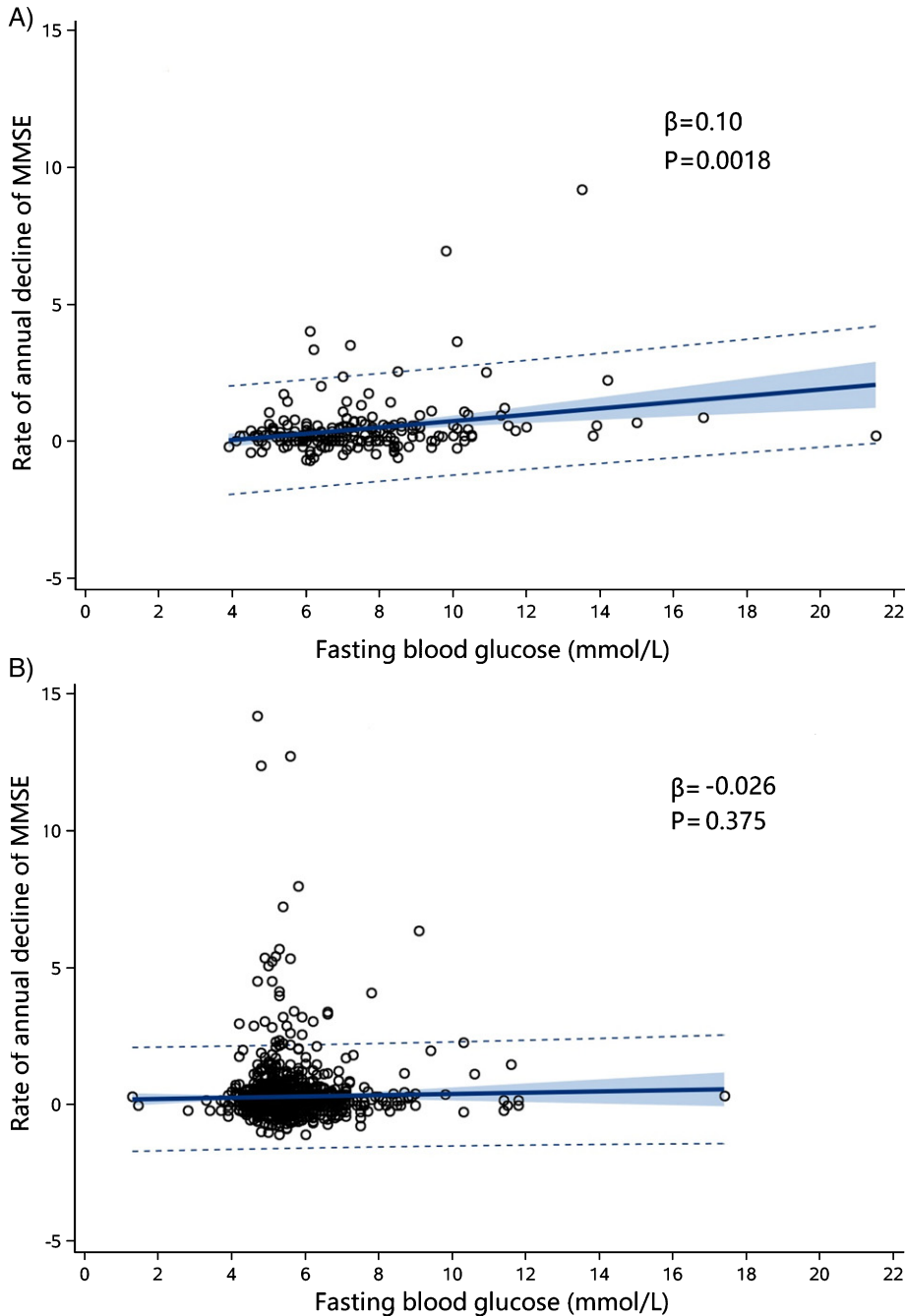


Fig. 3. Linear relation of baseline fasting blood glucose and rate of annual decline of MMSE in DM and non-DM participants. Note: (1) Among DM participants, baseline FBG was positively related to the rate of annual decline of MMSE, after adjusted for age, sex, education, APOE $\epsilon 4$, obesity, cigarette smoking, heart disease, hypertension, stroke, depression, and baseline MMSE (A); significant relation was not found in non-DM participants (B); (2) shadow represents 95% Confidence Interval (CI); dotted line represents 95% prediction limits; solid line represents regression line. MMSE: Mini-Mental State Examination; APOE, apolipoprotein E.

[17]. A cross-sectional study demonstrated that fasting plasma glucose was related to increased risk of cognitive impairment [OR 1.18, (95%CI 1.02–1.35)] among participants with Type II DM [18]. DM

was also found to be associated with mild cognitive impairment (MCI) with vascular risk factors [OR 1.48, (95%CI 1.16–1.87)] and MCI resulting from cerebrovascular disease [OR 1.38, (95%CI

1.02–1.86)] [19]. However, a study in Hong Kong reported that prevalent diabetes was not associated with cognitive impairments [OR 0.92, (95%CI 0.61–1.39)]. No significant association between incident diabetes and cognitive impairments [adjusted OR 2.6, (95%CI 0.3–23.2)] was reported after a 3-year-follow-up [21, 23]. The Epidemiology of Dementia in Singapore (EDIS) study showed that diabetes was associated with MCI [OR 1.85, (95%CI 1.11–3.05)] as well as moderate/dementia [OR 2.11, (95%CI 1.23–3.61)] [20], while the Singapore Longitudinal Ageing Studies demonstrated that elevated blood glucose was not significantly with cognitive decline [adjusted OR 0.94, (95%CI 0.64–1.38)] [22].

Our results are consistent with that from previous studies in western population. Two independent prospective studies [PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) and the Rotterdam Study] with a total 8,447 participants, aged 61–97 years demonstrated that participants with a DM history had worse cognitive decline across the majority of test compared with participants without a DM history. Higher levels of FBG were not associated with worse annual change in global cognitive function in older people without a DM history [8]. The Health, Aging, and Body Composition (Health ABC) study was a prospective cohort study with 3,069 older adults meanly aged 74.2 years. It was reported that DM and poor glucose control among individuals with DM were associated with cognitive function (assessed by Modified MMSE and Digit Symbol Substitution Test) and greater decline compared to those without DM [12]. The Sydney Memory and Ageing Study, investigating a longitudinal population-derived cohort with 1,037 adults aged 70–90years, found that glucose disorders and diabetes were associated with greater 2-year decline in total brain volume [40.0(SD 4.2) versus 46.7(SD 5.7) versus 18.1(SD 6.2) mm³, respectively, $p < 0.005$]. Incident glucose disorders, like diabetes, were associated with accelerated decline in global cognition and brain volumes in non-demented elderly, whereas stable impaired fasting glucose was not [10]. Few studies have reported the relationship between cognitive decline and FBG or insulin level in non-DM individuals. The Adults Changes in Thought (ACT) study reported that after followed 2,581 dementia-free members for a median of 6.8 years, higher average glucose levels were related to an increased risk of dementia among participants with DM [adjusted HR 1.40, (95%CI 1.12–1.76)] and participants without DM [adjusted HR 1.18, (95%CI 1.04–1.33)] [7]. The

Nurses' Health Study showed that the higher insulin levels in non-DM participants were related to faster cognitive decline [37]. These results of non-DM participants are not in agreement with ours. Reasons may include the definition of non-DM, as well as different length of follow-up.

Vascular risk factors may act as confounders or mediators in the association between FBG and dementia or cognitive decline. The Honolulu-Asia Aging study reported type II diabetes increased incidence of both AD and vascular dementia in a population-based cohort of 2,574 Japanese-American [38]. In addition, neuroimaging data have suggested that the increased risk of cognitive decline and dementia in patients with diabetes may be due to dual pathological processes involving both cerebrovascular damages and neurodegenerative changes [39].

The APOE $\epsilon 4$ allele has been confirmed to be a strong risk factor of dementia in western populations. In China, the incidence phase of the Shanghai Survey of Dementia reported a similar APOE $\epsilon 4$ risk of developing AD to that in western community studies [40]. Two case-control studies also stated that the APOE $\epsilon 4$ was associated with AD in Chinese patients [41, 42]. The frequency of the APOE $\epsilon 4$ allele in our study population is 9.3%, which is in the range of that in Asian (including Chinese) populations (6.3–9.3%) [43–45], but lower than that in Caucasian and African American populations (11–27%) [46]. Our study did not find a significant difference in the proportion of participants with APOE $\epsilon 4$ allele between the participants who developed dementia and those who did not. The inconsistent result may be due to different study design, sample representativeness, or sample size.

Elevated blood glucose levels may contribute to an increased risk of dementia and cognitive decline through several potential mechanisms. Increased blood glucose may have direct detrimental effects on vascular endothelium or atherosclerotic plaques. Obesity, insulin resistance, atherogenic dyslipidemia and hypertension may cause the blood glucose dysregulation. These factors constitute the metabolic syndrome, which are reported to be predictors of cerebrovascular disease, ischemic stroke, and accelerated cognitive decline and dementia [47–50]. Additionally, "toxic" effects of hyperglycemia can lead to slowly progressive functional and structural abnormalities in the brain. Studies demonstrated that chronic hyperglycemia may lead to cognitive impairments and abnormalities in synaptic plasticity in

rats [51, 52]. These processes could affect brain tissue directly, at the same time, could also lead to microvascular changes [51]. Furthermore, indirect neurodegeneration induced by advanced glycation end-products which are probably involved in the neurotoxic pathways of amyloid- β in the pathogenesis of Alzheimer's disease (AD). Hypofunction of the insulin-degrading enzyme which metabolizes amyloid- β and insulin is associated with greater risk of AD and cognitive impairment [53, 54].

Strengths of the current study include the prospective study design, suggesting a directional relation between baseline FBG and incident dementia, a relatively large sample size, and adjustment of relevant confounders. We defined the DM history based on self-report confirmed by medical record to avoid the miss-reporting from the participants. In addition, the diagnosis of cognitive function was based on complete clinical, neuropsychological assessments, as well as consensus diagnosis for every participant both at the baseline and follow-up interview.

There are some limitations in this study as well. Firstly, we could not distinguish subtypes of incident dementia by brain image because only part of the dementia cases undertook a CT/MRI examination. Secondly, although we measured the FBG in the early morning by a standardized protocol, a spot measured FBG may not enough represent the participants' real blood glucose level, as well as the trend of FBG changes. Thirdly, we did not include 104 participants whose baseline FBG was lacking and 1,326 participants who lost to follow-up. These participants will more likely to have cognitive decline, thus dementia incidence and effect of the association between FBG and cognitive decline might be underestimated. Fourthly, because the latency period for neurodegenerative disease lasts many years, most of the participants who were diagnosed with incident dementia might already have pre-clinical cognitive impairment at baseline. This is confirmed with the rather lower baseline MMSE score of the group eventually diagnosed with dementia. We did an additional analysis including baseline MMSE, and found a persist association between FBG and dementia (Supplementary Table 3). Besides baseline MMSE, there might be other confounding variables that have not been measured in our study. For example, participants with DM and higher FBG may well be undertreated and have a higher risk for dementia as a consequence. Efficacy of different antidiabetic drugs may influence the blood glucose control. Homocysteine was reported as a potentially important modifiable

cause of cognitive dysfunction in older adults [55, 56]. Fifthly, we did not include the clinical diagnosis and FBG assessment during the follow-up period, therefore the effect of blood glucose control to the dementia risk could not be measured. Finally, because our study participants are living in downtown Shanghai, a developed metropolis with high standard of living conditions, our results would have a limited generalizability to the whole Chinese population.

In conclusion, our results demonstrated a significantly positive association between baseline FBG level and risk of incident cognitive decline among older participants with type II DM in the Shanghai Aging Study. It suggests that, especially in people with DM, effective blood glucose control may help to prevent cognitive impairment in later life. Prospective studies with larger sample size, longer follow-up, longitudinal blood glucose monitoring and performance in domain-specific cognitive measures should be conducted to further understand the consequences of the glucose metabolism for the risk of cognitive impairment in older population.

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SUPPLEMENTARY MATERIAL

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