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Original article

Associations of baseline glycemic status and its transitions with cognitive and physical functioning decline

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ABSTRACT

Objective: Evidence about the decline of cognition and physical function across glycemic status (normoglycemia, prediabetes, and diabetes) is inconsistent. We evaluated longitudinal changes in cognition and physical function according to glycemic status and also different glycemic transitions.
Study design: Population-based cohort study.
Methods: 9307 participants (mean age 59.7 years, 53.7 % women) were included from the China Health and Retirement Longitudinal Study (2011–2018). Global cognition (assessed by orientation, memory, and executive function) and physical function (calculated as the sum of impaired basic and instrumental activities of daily living) were assessed in each wave. The glycemic status was assessed in waves 2011 and 2015. Diabetes was defined as fasting blood glucose ≥7.0 mmol/L, HbA1c ≥6.5 %, self-reported diabetes, or glucose-lowering medication use. Prediabetes was defined as fasting blood glucose 5.6–6.9 mmol/L or an HbA1c of 5.7–6.4 %.
Results: Compared with normoglycemia, baseline diabetes was associated with a faster decline in orientation (−0.018 SD/year, 95%CI -0.032, −0.004) and a faster increase in physical function score (0.082 /year, 95%CI 0.038, 0.126). We did not observe any effect of prediabetes on the changing rate of cognition and physical function. Progression from normoglycemia to diabetes between waves 2011 and 2015 was associated with a significantly faster decline in global cognition, memory, executive function, and physical function compared with stable normoglycemia.
Conclusions: Baseline diabetes was associated with accelerated decline of cognition and physical function. Associations with prediabetes were not observed, suggesting an important short diagnostic window when diabetes presents de novo.

1. Introduction

Type 2 diabetes (hereinafter referred to as diabetes), characterized by hyperglycemia, constitutes a serious health burden affecting approximately 463 million adults worldwide [1]. Compared to well-known diabetes-related complications such as cardiovascular disease, the effects of hyperglycemia on cognition and physical functioning have so far been less investigated. Diabetes has been associated with a slight cognitive decline, probably starting during the prediabetic stage [2]. Nevertheless, the relationship between prediabetes and cognitive function is less clear, with results of both harmful [3–6], and null effects reported [7]; and most of these studies were conducted in Western populations. In addition, prediabetes is also related to various vascular disorders, potentiating cognitive and functional decline early before the onset of diabetes [8]. By now, only one longitudinal study, conducted among the Swedish elderly (≥60 years old), has specifically reported the accelerated physical function decline among participants with prediabetes and diabetes [9]. As such, significant knowledge gaps remain.

In China, the prevalence rate of diabetes has increased dramatically, rising from 0.67 % in 1980 to 11.2 % in 2017. Currently, Chinese patients account for 24 % of the global patients with diabetes [10]. Even more Chinese adults live with prediabetes: a shocking prevalence rate of 35.2 % has been estimated [11]. Ethnic differences substantially contribute to differences in the prevalence and health effects of

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prediabetes [12,13] and might influence the age of onset of diabetes-associated cognitive decline [14]. The latter has not been analyzed in the Asian population and in middle age (45–60 years old). Moreover, prediabetes is not a robust diagnostic entity, especially at older age (≥60 years old) [15,16]. The effects of transitions between normoglycemia, prediabetes, and diabetes during follow-up in changes of cognition and physical function have never been studied.

Therefore, we investigated the longitudinal changes in cognition and physical function across the glycemic spectrum (including normoglycemia, prediabetes, and diabetes) in the middle-aged and older Chinese population (≥45 years old) of the population-based China Health and Retirement Longitudinal Study (CHARLS). In addition, we determined the impact of the transition of glycemic statuses during follow-up.

2. Methods

2.1. Study population

The CHARLS is a community-based longitudinal survey of the Chinese population of middle-aged and elderly (≥45 years old). The detailed study design has been described elsewhere [17,18]. Briefly, the baseline survey was conducted between June 2011 and March 2012 with individuals selected through multistage probability sampling. Follow-up is performed every two years with physical measurements and blood samples. Three follow-up waves (2013, 2015, 2018) were completed after the baseline survey. The CHARLS has been approved by the Peking University Institutional Review Board. Written informed consent was obtained for all study participants.

A detailed flow chart for participants' selection is shown in ESM Fig. 1. Of the 9882 participants, who attended physical and clinical visits at baseline, 575 were excluded for the following reasons: self-reported doctor-diagnosed mental disease (n = 390) or unavailable information to define baseline glycemic statuses (n = 185). Then, from the 6553 participants who had complete cognition measurement at baseline, 1271 were excluded because of loss to follow-up (n = 1064) or missing covariates (n = 207). Hence, 5282 participants were included in the present cognition analyses. Similar to the disability analysis, from 9162 participants who had complete baseline physical function measurements, 721 were excluded because of loss to follow-up (n = 334) or missing covariates (n = 387), and 8441 participants were included in the final analysis.

2.2. Measurements

Structured questionnaires were administered by trained field workers using a face-to-face computer-assisted personal-interview system to collect demographic, lifestyle, and medical history data. Body mass index (BMI) was calculated as body weight divided by the square of height (kg/m^2). Education level was classified as no formal education, elementary school, middle school, and high school or higher level of education. Smoking status was assessed using the questions: “Have you ever chewed tobacco, smoked a pipe, smoked self-rolled cigarettes, or smoked cigarettes/cigars?” and “Do you still have the habit or have you quit?”, and was further defined as never, former, and current. Alcohol consumption was assessed using the question, “Did you drink any alcoholic beverages, such as beer, wine, or liquor in the past year? If yes, how often?”. Blood pressure was measured three times at a sitting resting position, and the mean was used for the analyses. Information about the use of blood pressure- and blood glucose-lowering drugs were collected using the question, “Are you now taking any of the following treatments to treat hypertension/diabetes? Taking Chinese traditional medicine, Western modern medicine, or other treatments?”. We defined prevalent chronic diseases as the number of self-reported doctor-diagnosed chronic diseases (heart disease, stroke, chronic lung disease, asthma, and cancer) [19].

Blood samples were available from the baseline and the wave 2015 [17,18]. Participants were asked to fast overnight before collection. Blood glucose was tested using the Hexokinase method, and glycated hemoglobin (HbA1c) was measured using the high-performance liquid chromatography method. Triacylglycerol, total cholesterol, and HDL-cholesterol (HDL) were assessed with routine clinical chemistry methods.

2.3. Definitions of prediabetes and diabetes

We defined fasting status as the participant reported fasting over 8 h before blood sample collection. According to the 2020 American Diabetes Association criteria [20], diabetes was defined as fasting blood glucose ≥7.0 mmol/L (126 mg/dL), non-fasting blood glucose ≥11.1 mmol/L (200 mg/dL), HbA1c level ≥ 47.5 mmol/mol (6.5 %), self-reported doctor-diagnosed diabetes, or current use of blood glucose-lowering medication. Prediabetes was defined as fasting blood glucose in the range of 5.6–6.9 mmol/L (100–125 mg/dL) or an HbA1c level of 38.8–46.4 mmol/mol (5.7–6.4 %). In addition, we also studied the glycemic transition statuses (normoglycemia - normoglycemia; normoglycemia - prediabetes; normoglycemia - diabetes; prediabetes - normoglycemia; prediabetes - prediabetes; and prediabetes - diabetes) between baseline and wave 2015 among baseline nondiabetic participants.

2.4. Cognitive and disability assessments

Both cognitive and disability assessments have been performed in all waves. Participants underwent a battery of three cognitive tests, for the cognitive assessment, including orientation, memory, and executive function, with higher scores indicating better cognitive function. Orientation was assessed by asking questions regarding the date (year, month, day of month, and day of week) and season, and then allocated 1 point to each correct answer with the sum score ranging from 0 to 5. Memory was determined by testing immediate and delayed recall of ten unrelated words. The sum of words, which were successfully recalled in these two recall tests, was used as the composite memory score, ranging from 0 to 20. The executive function was assessed by the figure drawing test. The participant was asked to observe and draw a picture of two overlapping pentagons and the serial seven test. The participant was asked to subtract 7 from 100 (up to five times). The executive function score was the sum of these two tests, ranging from 0 to 6. The reliability and validity of these cognitive tests have been well-documented [5,21].

The z scores were calculated to allow direct comparisons across different cognitive tests. Specifically, we standardized the follow-up score by subtracting the mean of the baseline score and then dividing it by the baseline standard deviation (SD). The global cognitive z score was estimated by averaging the z scores from the three tests and then standardizing it to baseline using the mean and SD of the global cognitive z score. Therefore, a unit of z score would mean the one SD above the mean baseline score.

Physical function was assessed by the activities of daily living (ADL: dressing, bathing, eating, getting in or out of bed, toileting, continence) and instrumental activities of daily living (IADL: doing household chores, preparing hot meals, shopping for groceries, managing money, taking medications). Each item was scored from 0 to 3 (0: no difficulty, 1: some difficulty but can still do it, 2: much difficulty and need help, 3: unable). The ADL and IADL scores were the sums of their components, and the level of physical dysfunction was assessed as the sum of these two, ranging from 0 to 33, with higher scores indicating worse ability.

2.5. Statistical analysis

Baseline characteristics are presented as mean (SD) or median (interquartile range, IQR) for continuous variables and frequency (percentage) for categorical variables. Linear mix-effect models were used to investigate the difference in annual changes in cognition and functioning between baseline glycemic statuses, using normoglycemia as the reference. We used the follow-up time (years since baseline) as a time scale. We fitted the models with the intercept and the time term as random effects accounting for inter-individual differences at baseline and changing rates in outcome variables during follow-up. For the fixed-effects part, we first included baseline glycemic status, time, glycemic status × time interaction, baseline age, and sex. The "glycemic status × time" interaction term indicated a differential changing rate. We also adjusted for possible confounders, including education level, BMI, smoking status, alcohol consumption, triacylglycerol, total cholesterol, HDL, systolic blood pressure, blood pressure-lowering medication, and prevalent chronic diseases.

To check for any possible effect modification caused by age or sex, we separately added a three-way product interaction term (glycemic status × time × baseline age; glycemic status × time × sex) into the model and further explored these by stratification. A p-value <0.10 indicated a significant interaction as a relaxation of type I error. Age stratification was based on the median age (60 years) to ensure the sample size for subgroup analysis and the comparability to the former study [9].

In addition, we used the Sankey plot to explore the impact of glycemic transition statuses between baseline and wave 2015 among baseline nondiabetic participants. Then we investigated the difference in annual changes in cognition and functioning between different glycemic transitions with the stable normoglycemia (normoglycemia - normoglycemia) used as the reference.

To deal with the missing values, we used a multiple imputation, chained-equations method to replace missing data for cognitive and functioning reassessments, respectively. Variables used in the predictive mean matching model to impute the missing values of outcomes included the baseline information (baseline age, sex, education level, body mass index, smoking status, alcohol consumption, systolic blood pressure, use of blood pressure-lowering medications, triacylglycerol, total cholesterol, high-density lipoprotein, use of lipid-lowering medications, and prevalent chronic diseases [heart disease, stroke, chronic lung disease, asthma, and cancer]) and baseline outcome measurements. For each longitudinal analysis, we created 20 imputed data sets and obtained estimates by pooling results using Rubin's rules. In addition, we included age as a spline term in a sensitivity analysis to check for any possible nonlinear effect. Data were handled and analyzed with SPSS Statistics version 25.0.0.1 (IBM Corp., Armonk, NY) and R, CRAN version 4.0.5, with packages "lme4", "lmerTest", and "mice". All analyses were performed at the significance level of 0.05 (2-tailed) unless specified otherwise.

3. Results

3.1. Baseline characteristics

Among the 5282 participants included in the cognition analysis, the

Table 1
Baseline characteristics of the study population.

	Cognition analysis (n = 5282)			Physical function analysis (n = 8441)		
	Normoglycemia (n = 2363)	Prediabetes (n = 2111)	Diabetes (n = 808)	Normoglycemia (n = 3764)	Prediabetes (n = 3402)	Diabetes (n = 1275)
Age, years	58.1 ± 8.9	58.7 ± 8.5[a]	59.7 ± 8.4[a]	58.8 ± 9.3	59.7 ± 9.1[b]	60.4 ± 8.9[b]
Women, n (%)	1091 (46.2)	983 (46.6)	392 (48.5)	2000 (53.1)	1818 (53.4)	704 (55.2)
Education						
No formal education	375 (15.9)	345 (16.3)	147 (18.2)	1069 (28.4)	988 (29.0)	370 (29.0)
Elementary school	1057 (44.7)	917 (43.4)	338 (41.8)	1575 (41.8)	1383 (40.7)	523 (41.0)
Middle school	606 (25.6)	566 (26.8)	209 (25.9)	731 (19.4)	706 (20.8)	250 (19.6)
High/vocational/university	325 (13.8)	283 (13.4)	114 (14.1)	389 (10.3)	325 (9.6)	132 (10.4)
Body mass index, kg/m^2	23.1 ± 3.8	24.0 ± 3.7[a]	25.1 ± 4.7[a]	22.9 ± 3.7	23.8 ± 3.9[b]	24.8 ± 4.5[b]
Smoking status, n (%)						
Never	1303 (55.1)	1206 (57.1)[a]	468 (57.9)[a]	2260 (60.0)	2102 (61.8)[b]	785 (61.6)[b]
Former	197 (8.3)	224 (10.6)[a]	101 (12.5)[a]	283 (7.5)	320 (9.4)[b]	137 (10.7)[b]
Current	863 (36.5)	681 (32.3)[a]	239 (29.6)[a]	1221 (32.4)	980 (28.8)[b]	353 (27.7)[b]
Alcohol consumption, n (%)						
No alcohol consumption	1474 (62.4)	1336 (63.3)	532 (65.8)	2500 (66.4)	2286 (67.2)	870 (68.2)
Less than once a month	219 (9.3)	167 (7.9)	69 (8.5)	315 (8.4)	249 (7.3)	104 (8.2)
More than once a month	670 (28.4)	608 (28.8)	207 (25.6)	949 (25.2)	867 (25.5)	301 (23.6)
Systolic blood pressure, mmHg	127.7 ± 20.6	131.1 ± 20.8[a]	134.5 ± 20.7[a]	128.0 ± 21.3	131.4 ± 21.2[b]	135.2 ± 21.4[b]
Use of blood pressure-lowering medication, n (%)	352 (14.9)	427 (20.2)[a]	255 (31.6)[a]	546 (14.5)	670 (19.7)[b]	400 (31.4)[b]
Triacylglycerol, mg/dL	97.4 (71.7, 138.1)	110.6 (77.9, 163.7)[a]	140.7 (91.2, 220.4)[a]	96.5 (70.8, 136.3)	109.3 (77.0, 160.2)[b]	137.2 (92.0, 221.3)[b]
Total cholesterol, mg/dL	187.1 ± 35.4	197.6 ± 37.8[a]	202.2 ± 44.1[a]	187.3 ± 35.6	198.0 ± 38.8[b]	202.6 ± 45.0[b]
High-density lipid cholesterol, mg/dL	52.1 ± 14.5	50.5 ± 15.0[a]	45.6 ± 15.6[a]	52.5 ± 14.6	51.4 ± 15.4[b]	46.4 ± 16.0[b]
Use of lipid-lowering medication, n (%)	81 (3.4)	106 (5.0)[a]	103 (12.7)[a]	116 (3.1)	154 (4.5)[b]	151 (11.8)[b]
Prevalent chronic disease, n (%)						
Heart disease	230 (9.7)	254 (12.0)[a]	141 (17.5)[a]	357 (9.5)	401 (11.8)[b]	208 (16.3)[b]
Stroke	39 (1.7)	32 (1.5)	22 (2.7)	67 (1.8)	51 (1.5)	36 (2.8)[b]
Chronic lung disease	237 (10.0)	206 (9.8)	95 (11.8)	378 (10.0)	338 (9.9)	153 (12.0)
Asthma	93 (3.9)	75 (3.6)	28 (3.5)	135 (3.6)	122 (3.6)	53 (4.2)
Cancer	15 (0.6)	18 (0.9)	8 (1.0)	27 (0.7)	29 (0.9)	15 (1.2)

Values are mean (standard deviation) or median (interquartile range) for continuous variables and number (percentage) for categorical variables.
[a] Significantly different from normoglycemia subgroup in the cognition analysis.
[b] Significantly different from normoglycemia subgroup in the physical function analysis.

mean (SD) age was 58.6 (8.7) years, the median (IQR) follow-up duration was 6.9 (4.0–7.0) years, 2111 (40.0 %) were classified as having prediabetes, and 808 (15.3 %) as diabetes. For the physical function analysis, 8441 participants were included, 3402 (40.3 %) were classified as having prediabetes, and 1275 (15.1 %) were classified as having diabetes. The mean (SD) age was 59.4 (9.2) years, and the median (IQR) follow-up duration was 7.0 (6.9–7.0) years. The distributions of baseline characteristics by glycemic statuses were virtually the same for these two analyses. As shown in Table 1, the participants with prediabetes or diabetes tended to be older at baseline; a larger proportion was women and had a poorer cardiovascular risk profile.

3.2. Cognition and physical function changes among various baseline glycemic statuses

Table 2 and Fig. 1 demonstrate the baseline difference and annual changes in cognition *z* scores among different glycemic statuses. Compared with normoglycemia, people with diabetes had significantly worse performance in global cognition, memory, and executive function at baseline, but no difference was observed for individuals with prediabetes. Over the follow-up period, only diabetes was associated with a faster decline in orientation (−0.018 SD/year, 95%CI -0.032, −0.004). A significant interaction was detected between age and glycemic statuses associated with orientation decline (p for interaction = 0.002). After stratification, the association between diabetes and orientation decline was only significant among older participants (≥60 years old) (ESM Table 1). No significant interaction between glycemic statuses and sex was found concerning changes in cognition function (ESM Table 2).

Table 2 and Fig. 2 provide the baseline difference and annual changes in physical function among glycemic statuses. There was no difference in physical function among different glycemic groups at baseline. Whereas during the follow-up, diabetes was associated with a faster increase in physical function score (0.082 /year, 95%CI 0.038, 0.126), ADL (0.036 /year, 95%CI 0.015, 0.056), and IADL (0.043 /year, 95%CI 0.015, 0.071), no difference was observed for prediabetes. No significant interaction was found between glycemic status and age, and sex on physical function (ESM Table 3, ESM Table 4).

3.3. Cognition and physical function changes across various glycemic transitions during follow-up

ESM Fig. 2 shows the transitions of glycemic statuses between baseline and wave 2015 among baseline nondiabetic participants, using the data from the physical function analysis. Specifically, among the 7166 nondiabetic participants (normoglycemia or prediabetes) at baseline, 5055 had available data on glycemic definition at wave 2015, which was used here. Of the 2414 baseline prediabetic participants, 358 (14.8 %) progressed to diabetes, 555 (23.0 %) regressed to normoglycemia, and 1501 (62.2 %) remained to be prediabetes. Of the 2641 baseline normoglycemic participants, 1410 (53.4 %) progressed to prediabetes, 214 (8.1 %) progressed to diabetes, 1017 (38.5 %) remained normoglycemic. Similar Sankey plot from the cognition data was shown in ESM Fig. 3.

Table 3 provides the mean difference in the rate of concomitant change in cognition and physical function comparing different glycemic transition statuses. By using the stable normoglycemia as the reference, we observed that those who progressed from normoglycemia to diabetes had a significantly faster decline in global cognition (−0.041 SD/year, 95%CI −0.074, −0.009), memory (−0.049 SD/year, 95%CI −0.084, −0.014), and executive function (−0.033 SD/year, 95%CI −0.066, −0.000). Similar trends were also found for the disability analysis; we observed that those who progressed from normoglycemia to diabetes had an accelerated increase in concomitant physical function score (0.157 /year, 95%CI 0.064, 0.250) and IADL (0.117 /year, 95%CI 0.055, 0.179); these effect sizes were even larger than prevalent diabetes.

3.4. Sensitivity/nonresponse analyses

Sensitivity analysis results using imputed data were similar to those from the main analyses (ESM Tables 5). Results remain robust after we included age as a spline term (ESM Tables 6). Of the 9307 participants, who attended physical and clinical measurements at baseline, 4025 (43.2 %) were excluded from the cognition analysis because of missing information or loss of follow-up. Compared to the included participants, those excluded participants were older, more often women, and had lower education and lower cognition scores at baseline (ESM Table 7). Similarly, 866 (9.3 %) individuals were excluded from the physical function analysis. Those excluded participants were older, had a higher proportion of blood-pressure-lowering medication use, and had a higher prevalence of chronic diseases (ESM Table 8).

4. Discussion

In this population-based middle-aged and older Chinese cohort, we

Table 2
The associations between glycemic status and baseline performance (intercept), and annual changes in cognition *z* scores (SD/year) and functioning scores, using linear mixed models.

		Glycemic status (intercept)		Time, years[a]	Glycemic status × time (years)[b]	
		Prediabetes	Diabetes		Prediabetes × time	Diabetes × time
Global cognition	Model 1	0.026 (−0.027, 0.079)	−0.030 (−0.102, 0.042)	−0.039 (−0.045, −0.032)	0.002 (−0.008, 0.012)	−0.009 (−0.022, 0.005)
	Model 2	−0.011 (−0.059, 0.037)	−0.109 (−0.176, −0.041)	−0.038 (−0.045, −0.032)	0.003 (−0.007, 0.012)	−0.008 (−0.021, 0.006)
Orientation	Model 1	0.044 (−0.010, 0.097)	0.051 (−0.022, 0.123)	−0.039 (−0.046, −0.032)	−0.001 (−0.011, 0.010)	−0.019 (−0.033, −0.005)
	Model 2	0.011 (−0.039, 0.062)	−0.021 (−0.091, 0.050)	−0.039 (−0.046, −0.032)	−0.000 (−0.010, 0.010)	−0.018 (−0.032, −0.004)
Memory	Model 1	−0.005 (−0.055, 0.045)	−0.050 (−0.118, 0.019)	−0.020 (−0.027, −0.012)	0.001 (−0.010, 0.012)	0.002 (−0.013, 0.016)
	Model 2	−0.036 (−0.084, 0.013)	−0.114 (−0.182, −0.047)	−0.020 (−0.027, −0.013)	0.002 (−0.009, 0.012)	0.002 (−0.012, 0.017)
Executive function	Model 1	0.021 (−0.030, 0.073)	−0.056 (−0.126, 0.015)	−0.034 (−0.041, −0.027)	−0.003 (−0.013, 0.007)	−0.004 (−0.017, 0.010)
	Model 2	−0.001 (−0.050, 0.048)	−0.101 (−0.169, −0.032)	−0.035 (−0.041, −0.028)	−0.003 (−0.013, 0.007)	−0.003 (−0.017, 0.011)
Physical function	Model 1	−0.018 (−0.133, 0.097)	0.150 (−0.008, 0.308)	0.176 (0.154, 0.198)	0.003 (−0.029, 0.035)	0.082 (0.038, 0.127)
	Model 2	−0.024 (−0.140, 0.091)	0.042 (−0.122, 0.205)	0.176 (0.154, 0.198)	0.003 (−0.029, 0.035)	0.082 (0.038, 0.126)
ADL	Model 1	−0.027 (−0.078, 0.023)	0.075 (0.006, 0.144)	0.062 (0.052, 0.072)	0.007 (−0.007, 0.022)	0.036 (0.016, 0.056)
	Model 2	−0.034 (−0.084, 0.017)	0.026 (−0.046, 0.098)	0.062 (0.052, 0.072)	0.007 (−0.007, 0.022)	0.036 (0.015, 0.056)
IADL	Model 1	0.004 (−0.076, 0.083)	0.070 (−0.038, 0.179)	0.111 (0.097, 0.125)	−0.004 (−0.024, 0.017)	0.043 (0.015, 0.072)
	Model 2	0.001 (−0.078, 0.081)	0.004 (−0.108, 0.116)	0.111 (0.097, 0.125)	−0.004 (−0.024, 0.017)	0.043 (0.015, 0.071)

Results were reported using normoglycemia as the reference. Model 1 was adjusted for baseline age and sex. Model 2 was further adjusted for education level, body mass index, smoking status, alcohol consumption, systolic blood pressure, use of blood pressure-lowering medications, triacylglycerol, total cholesterol, high-density lipoprotein, use of lipid-lowering medications, and prevalent chronic diseases (heart disease, stroke, chronic lung disease, asthma, and cancer) at baseline.

[a] Time (years) represents the annual change in cognition and functioning scores (slope) for the reference group.

[b] Glycemic status × time (years) represents the additional annual change in cognition and functioning scores (slope) for the prediabetes or diabetes group.

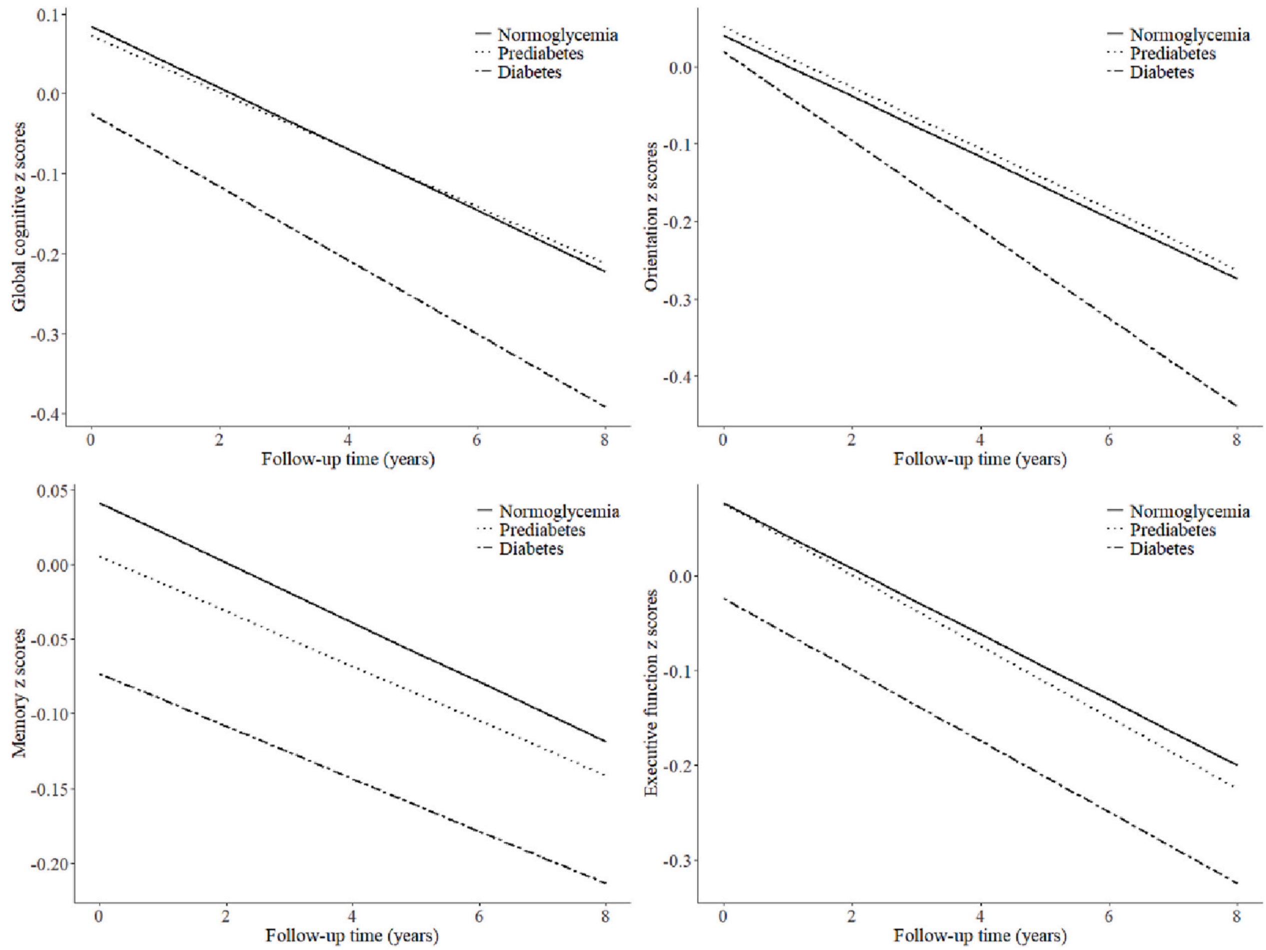

Fig. 1. Predicted trajectories of cognitive *z* scores according to baseline glycemic status
Analyses adjusted for baseline age, sex, education level, body mass index, smoking status, alcohol consumption, systolic blood pressure, use of blood pressure-lowering medications, triacylglycerol, total cholesterol, high-density lipoprotein, use of lipid-lowering medications, and prevalent chronic diseases (heart disease, stroke, chronic lung disease, asthma, and cancer).

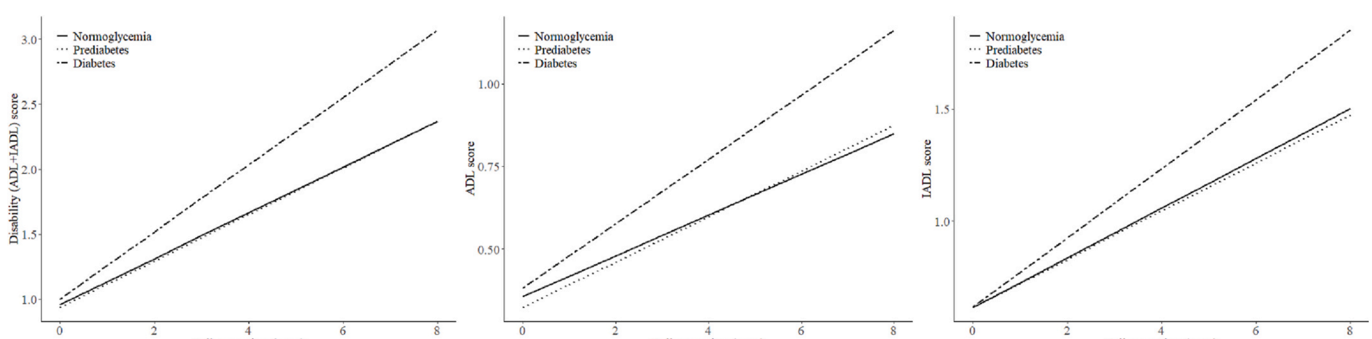

Fig. 2. Predicted trajectories of functioning scores according to baseline glycemic status
Analyses adjusted for baseline age, sex, education level, body mass index, smoking status, alcohol consumption, systolic blood pressure, use of blood pressure-lowering medications, triacylglycerol, total cholesterol, high-density lipoprotein, use of lipid-lowering medications, and prevalent chronic diseases (heart disease, stroke, chronic lung disease, asthma, and cancer).

found that prevalent diabetes was associated with an accelerated decline in cognition and physical function over time. Baseline prediabetes was not associated with the changing rate of cognition and physical function over time. The transition of normoglycemia to diabetes during follow-up was also related to an accelerated concomitant decline in cognition and physical function.

Although former studies have shown an increased risk of dementia in diabetic patients, cognition changes in people with prediabetes have been less studied [2–7]. As a prodromal feature of dementia, the accelerated cognitive decline becomes evident years before diagnosis [22]. However, the results are inconsistent among the few available longitudinal studies investigating the relationships between prediabetes/diabetes and cognition decline. Compared to normoglycemia, those with prediabetes or diabetes had faster cognitive decline [3,6], while others found that these problems were restricted to diabetes [5,7]. As for the specific cognitive domain, two studies reported that diabetes was

Table 3
Longitudinal analysis of the mean difference in the rate of concomitant change in cognition z scores (SD/year) and functioning scores comparing different glycemic transitions, using linear mixed models.

Glycemic transition (2011–2015)	Normoglycemia - normoglycemia	Normoglycemia - prediabetes	Normoglycemia - Diabetes	Prediabetes - normoglycemia	Prediabetes - prediabetes	Prediabetes - diabetes	Diabetes-
Cognition analysis							
N	659	916	119	376	947	227	808
Global cognition	Reference	−0.006 (−0.023, 0.010)	−0.041 (−0.074, −0.009)	−0.007 (−0.027, 0.014)	−0.004 (−0.020, 0.013)	−0.015 (−0.040, 0.009)	−0.017 (−0.034, 0.001)
Orientation	Reference	0.004 (−0.013, 0.021)	0.005 (−0.028, 0.039)	−0.002 (−0.023, 0.020)	−0.003 (−0.020, 0.014)	−0.009 (−0.035, 0.016)	−0.018 (−0.036, −0.001)
Memory	Reference	−0.013 (−0.030, 0.005)	−0.049 (−0.084, −0.014)	−0.005 (−0.028, 0.017)	−0.007 (−0.025, 0.010)	−0.013 (−0.040, 0.014)	−0.010 (−0.028, 0.009)
Executive function	Reference	0.001 (−0.015, 0.018)	−0.033 (−0.066, −0.000)	0.002 (−0.020, 0.022)	−0.009 (−0.025, 0.008)	−0.015 (−0.041, 0.010)	−0.005 (−0.023, 0.012)
Disability analysis							
N	1017	1410	214	555	1501	358	1275
Physical function	Reference	0.013 (−0.037, 0.064)	0.157 (0.064, 0.250)	−0.009 (−0.074, 0.056)	−0.001 (−0.051, 0.049)	0.040 (−0.036, 0.116)	0.111 (0.059, 0.164)
ADL	Reference	0.000 (−0.023, 0.023)	0.038 (−0.004, 0.080)	−0.008 (−0.037, 0.021)	0.004 (−0.018, 0.027)	0.025 (−0.009, 0.059)	0.044 (0.020, 0.068)
IADL	Reference	0.014 (−0.019, 0.048)	0.117 (0.055, 0.179)	0.001 (−0.042, 0.044)	−0.005 (−0.038, 0.028)	0.012 (−0.038, 0.063)	0.062 (0.028, 0.097)

Adjusted for baseline age, sex, education level, body mass index, smoking status, alcohol consumption, systolic blood pressure, use of blood pressure-lowering medications, triacylglycerol, total cholesterol, high-density lipoprotein, use of lipid-lowering medications, and prevalent chronic diseases (heart disease, stroke, chronic lung disease, asthma, and cancer) at baseline.

associated with a faster decline in perceptual speed and executive function tasks but not with episodic memory [3,4]. In contrast, others found a relationship with a faster memory decline but not with the executive function [7]. Associations between prediabetes and a specific cognitive domain have not been reported. Methodological discrepancies, such as the cohort characteristics (age range, ethnicity), follow-up duration, and cognitive assessment tools, may explain the differences between the findings. In particular, we did not find a significant association with prediabetes despite a relatively large sample size (2111 individuals with prediabetes). Our findings and that of Zheng et al. do not support that the sample size is responsible for the heterogeneous findings on prediabetes and cognitive decline [5].

The present study is the first prospective investigation of the trajectory of physical function among different glycemic statuses in the Chinese population. Our results are compatible with prior studies and found that diabetes is associated with a substantially increased risk of physical dysfunction. In complement to a prior meta-analysis mainly based on cross-sectional studies [8], our findings showed that despite a similar level of physical function at baseline, the rate of functioning decline during follow-up is faster for diabetic patients. Regarding the relationship between prediabetes and physical function, the literature is inconsistent and mainly based on cross-sectional studies. For example, according to a study in the UK among people aged 60–70 years, prediabetes was associated with weaker muscle strength and impaired physical function [23]. Among the Japanese elderly (mean age 71 years), however, prediabetes was not associated with walking speed and chair stand time tests [24]. In addition, the Helsinki Birth Cohort Study (mean age 70 years) indicated that only impaired glucose tolerance and not impaired fasting glucose are related to poor physical performance [25]. Only one longitudinal study, conducted among Swedish older adults over 60, has specifically investigated the physical function decline among different glycemic statuses and concluded that prediabetes (defined by HbA1c) is associated with faster functional decline and disability compared to normoglycemia [9]. Although our study had a much larger sample size, we could not confirm this relationship between prediabetes and the accelerated decline of physical function. Differences in age range, duration of follow-up, ascertainment of prediabetes, and measurements of physical function may explain the discrepancy between the two studies.

Notably, when using baseline glycemic status as a non-chronicity with possible transitions, we found that compared to stable normoglycemia, those who progressed from normoglycemia to diabetes have an accelerated decline in global cognition, memory, executive function, and physical function. The transition to prediabetes did not return such complications. Supported by former evidence [4,15], our findings indicate that prediabetes might not be a reliable high-risk entity, at least not to prevent cognitive decline or physical dysfunction.

Although the pathophysiological pathways through which baseline diabetes may cause cognitive and physical dysfunction remain to be elucidated, several mechanisms have been proposed. For example, diabetes directly causes atherosclerotic diseases, such as stroke, which contributes to cognitive decline and physical dysfunction. Prior studies based on the Swedish National Study on Ageing and Care in Kungsholmen (SNAC-K) reported that diabetes, but not prediabetes, is associated with an increased risk of ischemic stroke and post-stroke dementia [26], and the association between diabetes and functional decline is partly mediated by cardiovascular disease [9]. Another possible mechanism involves shared risk factors. Many diabetes-related risk factors, such as obesity and depression, are also related to a faster decline in cognition and physical functioning [27–30].

A major strength of our study is the large, well-designed population-based cohort with repeated outcome measurements which enabled us to generate the trajectories of cognition and physical function among different glycemic statuses. Additionally, with repeated data on glycemic status during follow-up, we explored any possible effect caused by the glycemic transition. Taken together, our study filled in a specific knowledge gap about the cognition and functioning changes across glycemic status in China. Our study has some limitations that should be acknowledged. First, although ethnicity information was not collected in the CHARLS, we still can reasonably presume that most of the participants were Han Chinese, limiting our findings' generalizability to other ethnicities and countries. Secondly, only those with complete baseline information and at least one repeated measurement were eligible for the current study, possibly leading to selection bias. Results from the nonresponse analysis show that the responding participants were relatively healthier than those excluded, which may limit the internal validity and generalization. Moreover, our analysis of responders' data may have underestimated complications by excluding nonresponders' potentially faster functioning decline, especially cognition function [31]. Also, limited by the available waves in the CHARLS, the follow-up interval was relatively short, and we could not investigate the association between glycemic transition and subsequent decline of cognition and physical function. Other studies with longer follow-up times are required to deal with the possible reverse causation. Finally, unlike performance-based measures such as walk time, ADL and IADL generally display weak validity and reproducibility, and are susceptible to ceiling effect [32]. As the emphasis has changed towards early detection in community-dwelling older adults, the measurements of physical functioning we used here may not be sensitive enough to detect the minor deficits present during its onset. A former study reported that combining self-reported and performance-based measurements can refine prognostic information, particularly among older persons with high self-reported functioning [33]. Therefore, future studies using more comprehensive physical function measurements are needed.

In conclusion, our results indicate that diabetes, but not prediabetes, is associated with an accelerated decline in cognition and physical function in middle-aged and older Chinese. Additionally, a transition from normoglycemia towards the development of diabetes was also related to a faster concomitant decline in cognition and physical function, suggesting a critical short diagnostic window when diabetes de novo presents.

Contributors

Kan Wang contributed to study concept and design, and interpreting the data, composed the statistical dataset, performed the analyses, and wrote and revised the manuscript.

Hui Gao contributed to interpreting the data and critical revision of the manuscript.

Eric J. G. Sijbrands contributed to interpreting the data and critical revision of the manuscript.

Maryam Kavousi contributed to study concept and design, interpreting the data and critical revision of the manuscript.

Fariba Ahmadizar contributed to study concept and design, interpreting the data and critical revision of the manuscript.

All authors reviewed and approved the final version and no other person made a substantial contribution to the paper.

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Ethical approval

The CHARLS was approved by the Peking University Institutional Review Board, and all participants provided written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

The original CHARLS dataset is available at http://charls.pku.edu.cn/. The full dataset used in this analysis are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2023.03.009.

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