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High normal fasting blood glucose is associated with dementia in Chinese elders

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Abstract

Background—Diabetes is a risk factor for MCI and dementia. However, the association between high normal fasting blood glucose (FBG) and dementia has not been studied.

Methods—Polytomous logistic regression was used to assess the association of dementia and MCI with FBG in an age- and sex-matched sample of 32 dementia patients, 27 amnestic MCI (aMCI) patients and 31 normal controls (NC). Analyses were repeated for those with normal FBG. Correlations between FBG and cognitive test scores were obtained.

Results—Controlling for age, sex, education, body mass index, Hachinski Ischemic Score, MRI stroke, and normalized brain, hippocampal and white matter hyperintensity MRI volumes; higher FBG was associated with dementia vs. aMCI status (OR= 3.13; 95% CI:1.28–7.69). This association remained (OR= 7.75; 95% CI:1.10–55.56) when analyses were restricted to subjects with normal FBG. When dementia patients were compared with NC adjusting for age, sex and education a significant association with FBG also was seen (OR=1.83; 95%CI:1.09–3.08), but the association was lost when vascular covariates were added to the model. FBG was not associated with aMCI status vs. NC. Higher FBG was correlated with poorer performance on the Trailmaking Test Part B (p=0.003). The percentage of dementia patients with high normal FBG (90%) was significantly higher than that of aMCI patients with high normal FBG (32.9%) (χ^2=13.9, p<0.001).

Conclusions—Higher FBG was associated with dementia (vs. aMCI) independent of vascular risk factors and MRI indicators of vascular disease, and remained a significant risk factor when analyses were restricted to subjects with normal FBG. The results of this cross-sectional study suggest that a high normal level of FBG may be a risk factor for dementia.

Keywords

dementia; Alzheimer's disease; mild cognitive impairment; fasting blood glucose; diabetes; hippocampal volume; white matter hyperintensity; magnetic resonance imaging; cognitive performance; vascular risk

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1. Introduction

Diabetes is a risk factor for dementia and MCI [1–5] as well as for cognitive decline among older adults [6–8]. The mechanisms responsible for the link between diabetes, cognitive decline and dementia are not well understood. Possible explanations include the effects of diabetes on the metabolism of beta amyloid [9] and on vascular ischemic disease [10].

Although high levels of fasting blood glucose increase the risk of dementia and MCI [11], the association between variation in normal levels of FBG and these cognitive outcomes has not been addressed. Data from cross-sectional studies suggest that variation of normal FBG may be related to scores on episodic and working memory tasks [12,13].

We report here the findings of a cross-sectional study of older adults in Shanghai, China, comparing cases of dementia with amnestic MCI (aMCI) cases and normal controls. On the basis of previous work, we hypothesized that FBG in the pre-diabetic and diabetic range would be associated with aMCI and dementia in comparison with normal controls. To determine whether the association was restricted to those with high FBG, we explored the entire range of FBG levels with respect to associations with diagnosis and cognitive performance.

2. Methods

2.1 Study population

Subjects were participants in the Shanghai Community Brain Health Initiative-Pilot (SCOBHI-P), a cross-sectional study of older persons living in Shanghai, China. Cases of dementia and MCI were identified from consecutive cases newly diagnosed in the Memory Disorders Clinic (MDC) at Huashan Hospital between May, 2007 and November, 2008. One hundred and nine cases of dementia and MCI and their informants were invited to participate; of these 58 were recruited (53.2%). Of the 51 not recruited, 42 refused, 8 were unreachable and 1 had a stroke. The principal reasons for refusal were two: they had been examined recently in the clinic and did not wish to be examined again, or they did not want to make the trip to return because either they lived too far away or it was too hot to travel. Because Huashan Hospital is a major teaching hospital, its patients represent the population of Shanghai and travel to the hospital can take considerable effort. Controls were identified using a government-maintained “name list”, which includes the name, sex, age, address and telephone number of every resident in Shanghai. For this study, we obtained the name list for the Jing’an district where Huashan Hospital is located and focused on a resident group living in five buildings in the Jingansi Temple Community. Potential controls were approached at the door to describe the study. Of 71 potential participants from the name list, 10 refused (14%). An additional three names on the name list were unreachable. The recruitment rate in the community was 81.6%. When the 58 residents in the community were clinically evaluated, two met study criteria for dementia (3.5%) and 12 met Petersen criteria for MCI (20.6%). These individuals were added to the respective case pools. Of 116 eligible cases and controls, we frequency matched 32 normal controls (NC), 34 MCI and 34 dementia cases by age and sex for analyses. Among the MCI cases, 4 (12%) were found to have the non-amnestic type (naMCI), and 30 (88%) the amnestic type (aMCI). Because there was an insufficient number to analyze separately, naMCI cases were excluded from subsequent analyses. Three participants were missing complete data on MRI volumes (one aMCI and two demented pateint) and three were missing data on fasting blood glucose (one NC and two aMCI patients), resulting in a final sample of 31 NC, 27 aMCI cases and 32 dementia cases.

The study was approved by the Huashan Hospital, Fudan University in Shanghai, China and the University of South Florida Institutional Review Boards. We obtained written informed consent from all cases and controls and their proxies.

2.2 Dementia diagnosis

All subjects received a detailed physical and neurologic evaluation by study neurologists (Q.Z and Q.G), a neuropsychological battery, MRI, and blood donation. The neuropsychological battery included the Chinese Cognitive Abilities Screening Instrument (CASI) [14], WAIS-R Digit Span [15], Bell Cancellation Test [16], WMS Logical Memory Test [17] (immediate and delayed recall), Rey-Osterrieth Complex Figure [18] (copying and recall), Stroop Test [19], Auditory Verbal Learning Test [20], Category Verbal Fluency Test, WAIS-R Similarities Test [15], Trail-making Test [21], Clock-Drawing Test [22], Boston Naming Test [23] and Mattis Dementia Rating Scale [24]. Consensus diagnostic conferences were conducted by the Chinese team (D.D., Q.Z., Q.G, Z.H.) with a subset of difficult cases also attended by members of the U.S. team (R.P., D.G., D.P.S., A.R.B., J.A.M). Dementia and its subtypes were diagnosed with DSM-IV criteria [25], NINCDS-ADRDA [26] criteria for Alzheimer's disease, and NINDS-AIREN criteria for vascular dementia [27]. Qualitative MRI assessment was used in the diagnosis and subtyping of dementia; quantitative MRI ratings were performed independently (C.D.) without knowledge of diagnostic status.

2.3 MRI volumetric measures

Brain images were obtained at Huashan Hospital with a GE 1.5T MRI. Imaging parameters were: (1) axial spin echo, T2-weighted double echo image, TE1 20 ms, TE2 90 ms, TR 2420 ms, FOV 24 cm, slice thickness 3 mm; (2) coronal 3D spoiled gradient recalled echo (IR-prepped SPGR) acquisition, T1- weighted image, TR 9.1 ms, flip angle 15 degrees, FOV 24 cm, slice thickness 1.5 mm; (3) axial FLAIR image, TE1 120 ms, TR 9000 ms, T1 2200 ms, FOV 24 cm; slice thickness 3 mm. The images were sent to the Imaging of Dementia & Aging (IDeA) Laboratory where image quantification was performed by a rater blinded to age, gender, educational achievement and diagnostic status.

Analysis of brain and white matter hyperintensity (WMH) volumes was based on a FLAIR sequence designed to enhance WMH segmentation [28]. Brain and WMH segmentation was performed in a two-step process according to previously-reported methods [29,30]. Intra- and inter-rater reliability for these methods are high and have been published [31]. Boundaries for the hippocampus were manually traced according to previously reported methods [32] that emphasize analysis of the anterior 2/3 of the hippocampus. Intra-rater reliability determined for right and left hippocampus using this method is excellent with ICCs of 0.98 for right side and 0.96 for left side.

2.4 Age and education

Age in years was reported by proxies of cases and controls, as was the highest level of education completed by the case and control. Educational level was coded as 0: no school; 1: primary school; 2: middle school; 3: high school; 4: college or university and 5: above university.

2.5 Fasting blood glucose, history of diabetes and daily physical exercise

A 15 cc blood sample was obtained from subjects when they arrived at the hospital for diagnostic evaluation in the morning. Subjects were instructed to fast after dinner the night before (12 hours). Five cc of the sample were used for assessment of fasting blood glucose

and the remainder for other studies. Fasting blood glucose was assessed using a glucose oxidase assay [33] in the HuaShan Hospital clinical laboratory.

History of diabetes was assessed by a single question: “Has a doctor ever told you that you had diabetes mellitus or high blood sugar?” The question was asked during the medical assessment with both the participant and his or her proxy present. For demented patients, the proxy was relied upon for accurate information.

As a measure of daily physical exercise, proxies for all participants provided information on minutes walked per day.

2.6 Modified Hachinski Ischemic Score

Data for the Modified Hachinski Ischemic Score were obtained from the participant’s medical record, neurological evaluation and questions posed to the participant and/or proxy during the evaluation.

2.7 Statistical analyses

Prior to analyses, WMH volume was log-transformed to produce a more normally distributed variable and all MRI volumes were subsequently converted to Z-scores.

Univariate comparisons were made between diagnostic groups for potential confounders of the association between FBG and diagnosis. Comparisons utilized Wilcoxon Rank-Sum Tests for continuous variables and chi square for dichotomous variables.

Polytomous logistic regression analyses were performed to assess associations of FBG with dementia and aMCI (with NC as the reference category) and of FBG with NC and aMCI (with dementia as the reference category). For all tables, odds ratios and 95% confidence intervals are given comparing the more impaired category with the less impaired category. Models adjusted for age, sex and education and for additional potential confounding variables were obtained. The more fully-adjusted models controlled for the Modified Hachinski Ischemic Score; normalized brain, hippocampal and WMH volumes; body mass index; and MRI evidence of stroke in addition to age, sex and education. To determine whether the effects seen were associated with differences in normal levels of FBG, a group of models was run eliminating participants with FBG in the pre-diabetic (6.1–6.9 mmol/l) and diabetic (>7.0 mmol/l) range. A final group of models was run eliminating participants who were previously diagnosed with diabetes. In addition, models were rerun with history of diabetes added as a covariate.

Additional comparisons were made between individuals with low and high normal FBG divided at the median using both World Health Organization (WHO) [34] (<6.1 mmol/l) and American Diabetes Association (ADA) [35] definitions (<5.6 mmol/l) to determine normal FBG. These comparisons utilized chi square analyses to compare frequency of low and high normal FBG across groups.

Finally, partial correlations were obtained between FBG and neuropsychological test scores for the entire sample and for the group with normal FBG.

Data were analyzed with SAS 9.2. Polytomous regression utilized Proc Logistic, while partial correlations were obtained with Proc Corr adjusting for the effects of age, sex and education level.

3. Results

3.1 Univariate comparisons

Participants with normal cognition (NC), aMCI and dementia did not differ significantly in age, sex, education, percent with FBG≥7.0 mmol/l, percent with history of diabetes, body mass index, percent with stroke identified on MRI or minutes walked per day (Table 1). However, demented participants had higher levels of FBG and modified Hachinski Ischemic Scores, larger WMH volumes, smaller brain volumes, and lower Mattis Dementia Rating Scale scores than both aMCI and NC. In addition, aMCI participants had smaller hippocampal and brain volumes than NC as well as lower Mattis Dementia Rating Scales scores than NC. The mean Mattis Dementia Rating Scale score in demented cases corresponded to a Mini-Mental State Examination (MMSE) score of about 19, consistent with mild to moderate dementia, while that for aMCI corresponded to a MMSE score of approximately 22.5 [36].

3.2 Polytomous logistic regression models

Table 2 shows four models where the dependent variable was dementia vs. aMCI. In the model adjusted only for age, sex and education (Model 1), FBG was strongly associated with dementia ($p<0.01$). This association remained in the model adjusted for the additional covariates (Model 2). In Models 3 and 4 in which the analysis was restricted to individuals with normal FBG according to WHO criteria (<6.1 mmol/l), the association between dementia and FBG was maintained.

Table 3 shows similar models in which dementia was compared to NC. In the model adjusted only for age, sex and education (Model 1), there was a significant association between FBG and dementia. However, this association was lost in the more fully adjusted model (Model 2). When the analysis was restricted to individuals with normal FBG, a significant association between dementia and FBG was seen in the model adjusted only for age, sex and education (Model 3). This association was no longer significant in the more fully adjusted model (Model 4).

When aMCI was compared with normal cognition, FBG was not associated with aMCI in any model (Table 4).

To examine whether the associations were generated by individuals with a history of diabetes all of whom were being medicated for this condition, the 17 participants with this diagnosis were eliminated and the models rerun. The pattern of significant associations with FBG was unchanged. Adding history of diabetes as a covariate to the logistic models also resulted in no change in the FBG associations with clinical outcomes.

3.3 Comparisons of high and low normal levels of FBG

Approximately equal percentages of NC (87.1%) and aMCI (89.3%) subjects had normal FBG according to the WHO guidelines, whereas the percentage of dementia cases with normal FBG was lower (73.5%). To assess the role of high and low levels of FBG within the normal range, we divided normal FBG at the median into two intervals (low: mmol/l= 3.9–5.0) and (high: mmol/l= 5.1–6.0). Figure 1 shows that among participants with normal FBG according to the WHO guidelines 64% of the dementia cases had high normal FBG, while only 32% of the aMCI cases had high normal FBG ($\chi^2=5.13$, $p<0.05$). The analyses were re-run with high FBG corresponding to the ADA guidelines for normal FBG (<5.6 mmol/l), dividing FBG at the median into low normal FBG (3.9–4.9), and high normal FBG (5.0–5.5). For these guidelines, 80.6% of NC had normal FBG, compared with 82.1% aMCI cases and 58.8% of dementia cases. Using the definition of high normal FBG for ADA guidelines,

80% of dementia cases with normal FBG had high normal readings while only 26% of the aMCI met criteria for high normal FBG (χ^2=12.4, p<0.001).

3.4 Associations of FBG with scores on neuropsychological tests

For the entire sample, when the effects of age, sex and education were partialed out, only the Trailmaking Test was associated with FBG, with higher FBG associated with worse performance (longer durations) on both the A (partial r= .25, p=0.04) and B (partial r=.36, p=0.003) forms of this test. Verbal Category Fluency for animals and vegetables showed trends of poorer performance with higher FBG (partial r=−.21, p=0.09). All other cognitive test scores, including measures of verbal and spatial memory, psychomotor speed, visual construction, attention, language and verbal reasoning, had partial Pearson correlations below 0.10 (p>0.26). When attention was restricted to participants with FBG in the normal range (<6.1 mmol/l), additional cognitive tests showed significant partial correlations, including copying of the Rey-Osterrieth Complex Figure (partial r=−0.27, p=.04) and Category Fluency for fruits (partial r=− 0.27, p=.04). The association with the Trailmaking Test – Form B was maintained (partial r=0.37, p=.003) in this group.

4. Discussion

We found that higher FBG was associated with dementia among older Shanghainese residents. This association was most evident when patients with dementia were compared with those with aMCI. Although dementia patients differed from aMCI in having higher Modified Hachinski Ischemic scores, larger mean WMH volume, and smaller mean brain volume, adjustment for these factors as well as MRI evidence of stroke led to only a small attenuation of the association with FBG, suggesting that FBG may not be acting primarily through a vascular pathway. When attention was restricted to participants with normal FBG, the association between FBG and dementia was not diminished. In models adjusted only for age, sex and education, this was true for comparisons of dementia with both aMCI and NC. When other covariates were entered, the association between FBG and dementia vs. NC was attentuated and lost significance. To our knowledge, this is the first evidence that variation of FBG in the normal range may be associated with dementia.

Previous studies have suggested that the risk of dementia and MCI may be related to diabetes and its correlates, such as hyperinsulinemia [1,2]. In our study, 21% of our dementia patients had fasting blood glucose 7.0 or above compared with 0% of the aMCI patients and 6% of the controls. Although based on relatively small numbers of participants, this finding is consistent with previous studies. A history of diabetes was reported by similar percentages of controls, aMCI and dementia patients (Table 1). All participants with previous diabetes diagnoses were reported by themselves or their proxies as still taking anti-diabetic medications (n=15) or insulin (n=2). Among the seven demented participants with a history of diabetes, five had FBG 7.0 or above and all had FBG above 6.1. None of the five aMCI participants with a history of diabetes had FBG 7.0 or above and only one had FBG above 6.1 at the time of testing. The reason for inadequate glycemic control in demented, but not in aMCI patients, is unclear. Possibilities include poorer compliance with medications among demented patients, poorer diet in demented patients compared with aMCI patients or normal controls, or worse glycemic regulation in more advanced dementia patients.

When the participants with a history of diabetes were eliminated from the models or when history of diabetes was entered as a covariate, the pattern of findings regarding associations with FBG was unchanged. The fact that none of the dementia patients previously treated for diabetes were in the high normal FBG range suggests that the associations with high normal fasting blood glucose were not a result of past treatment for this condition.

Few studies have examined the association between cognitive performance and normal variation in FBG. High normal levels of FBG have been associated with worse performance on tests of declarative and working memory in healthy adults without diagnosis of diabetes or hypertension [13] and with cognitive impairment in normoglycemic elderly [37]. FBG and diabetes have been shown to be associated with a variety of cognitive tests, although the strongest associations are generally seen with performance on timed tests [7,37–40]. In the current study, we observed significant correlations between FBG and performance on the Trailmaking Tests A and B for the entire sample and Trailmaking Test B, Rey-Osterrieth Complex Figure copy and Category Fluency for fruits for the group with normal FBG (<6.1 mmol/l). The absence of association between FBG and measures of declarative memory coupled with the associations of tests requiring speeded visual scanning is consistent with earlier findings showing associations primarily with measures of perceptual speed [37,38,41].

It is possible that part of the effect of FBG may be mediated through microvascular lesions [42,43] associated with larger white matter hyperintensity volumes in dementia (Table 1). This is particularly evident for the outcome of dementia vs. NC. Addition of the Modified Hachinski Ischemic Score and white matter hyperintensity volume to the model adjusted for age, sex and education resulted in loss of the significant association for dementia vs. NC as well as attenuation of association between FBG and dementia in the dementia-aMCI comparison.

In the ACCORD-Memory in Diabetes Study (ACCORD-MIND) [44], no association was found between baseline elevated fasting plasma glucose in Type II diabetics and performance on several cognitive measures. However, higher baseline hemoglobin A1c was associated with worse performance on the cognitive tests adminstered. It is important to note that clinical evidence of dementia was a reason for exclusion from the ACCORD-MIND Study, which would have attenuated the range of cognitive impairment in the participants and made it more difficult to find an association with fasting plasma glucose.

The association between normal FBG variation and the likelihood of dementia may be explained by increases in insulin resistance that predate the clinical onset of diabetes by more than a decade and are associated with a gradual increase in FBG within the normal range of variation. In a large longitudinal study, individuals who were destined to develop diabetes had higher mean levels of FBG within the normal range from 13 years to less than 2 years prior to diagnosis [45]. Assessment of insulin sensitivity in individuals with normal FBG may be beneficial for detecting early signs of diabetes that may have a consequence for progression of underlying Alzheimer's disease or vascular dementia.

That insulin can influence AD pathology is suggested by a recent study in which a significant correlation was seen between higher insulin levels and Aβ42 plasma levels in 71 patients with amnestic MCI [46]. Measurement of AD lesions at autopsy in the Honolulu Asia Aging Study demonstrated a significant effect of diabetes among carriers of an APOE-ε4 allele in increasing the numbers of neuritic plaques and neurofibrillary tangles in the cortex and hippocampal atrophy as well as leading to a higher risk of cerebral amyloid angiopathy [5]. Although such data provide support for an association between diabetes and AD pathology, subsequent studies have provided little support for such an association [42,47].

Another possible explanation for our findings is that the observed associations are related to differences in body mass index. However, as shown in Table 1, body mass index did not differ among the three groups. Also, addition of body mass index to the models did not change any of the findings.

Studies of the association of diabetes with WMH have generated variable results. Although one study demonstrated a significant association between diabetes and the severity of deep WMHs [48], others have shown no association [49] or non-significant trends [50]. In the present study, there was a non-significant trend for FBG to be associated with greater WMH volume in both the entire sample ($r=0.20$, $p=0.06$) and in the sample with FBG <6.1 ($r=0.22$, $p=0.07$). Like other studies [51], we found higher FBG to be associated with poorer cognitive performance independently of the severity of WMH. Adjustment for WMH and brain volume led to only a slight decrease in the odds ratio associated with FBG in the comparison of dementia and aMCI and a larger attenuation in the dementia-NC comparison. These findings suggest that the effect of higher FBG may be mediated in part through these lesions. WMH, although frequently thought to be a marker of microvascular damage, may also reflect retrograde degeneration of axons secondary to an Alzheimer's disease process [52]

This study has significant strengths. Data were available not only for clinical outcomes, but for performance on a variety of neuropsychological tests. In addition, information was available on vascular risk factors that could confound the association and quantitative MRI volumetric indices that could help explain the findings. The study also has important limitations. Cases were identified largely from a Memory Disorders Clinic, while controls were identified from a community sample. The identification of cases in an outpatient setting has the potential to increase the frequency of diabetes among aMCI and dementia cases relative to the community. However, it is unlikely to bias the percentage of individuals with high and low FBG in the normal range. Aside from a single measure of FBG, we did not have data on fasting insulin levels or glucose tolerance tests, which could provide measures of hyperinsulinemia and insulin sensitivity. Data also were not collected for hemoglobin A1c. The cross-sectional nature of the study also prohibits testing of causal associations between FBG and MRI, clinical and cognitive outcomes. Therefore, the issue of reverse causation must be considered. It is conceivable that more demented patients may adopt a diet with higher carbohydrate intake, leading to higher FBG in the normal range, or may participate in less physical activity leading to a similar outcome. However, minutes walked per day did not differ between the groups (Table 1). Study of the potential causative associations between variations in normal levels of FBG and cognitive outcomes requires a longitudinal design with acquisition of multiple indicators of glucose regulation, preferably with repeated MRI scans and neuropsychological testing to assess change over time.

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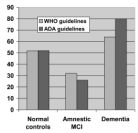

Figure 1.

Percentages of subjects in different diagnostic categories with fasting blood glucose in the high normal range (WHO guidelines: 5.1–6.0 mmol/l; ADA guidelines: 4.8–5.5 mmol/l) among those with normal FBG according to the guidelines (WHO guidelines: < 6.1 mmol/l; ADA guidelines <5.6 mmol/l).

Percent with high fasting blood glucose was higher for dementia vs. amnestic MCI (WHO: χ^2= 5.13, p <0.05; ADA χ^2=12.4, p < 0.001). Comparisons between demented patients and normal controls were not significant (WHO: χ^2=0.78, p=0.38; ADA: χ^2=3.80, p=.051).

Table 1

Univariate comparisons between diagnostic groups

Diagnosis	Normal cognition (n= 31)	Amnestic MCI (aMCI) (n=27)	Dementia (n=32)	Statistically significant differences*
Age in years [mean (sd)]	73.4 (5.6)	74.7 (4.1)	74.6 (5.7)	None
Sex (% female)	48.4	48.1	50.0	None
Educational level [mean (sd)]	2.7 (1.4)	2.8 (1.4)	2.2 (1.7)	None
Fasting blood glucose (mmol/l) [mean (sd)]	5.3 (1.0)	5.0 (0.7)	6.1 (1.6)	Dementia>normal (p<0.05) Dementia>aMCI (p<0.001)
Percent with FBG ≥7.0	5.8	0	21.9	None
Percent with history of diabetes	16.1	18.5	21.9	None
Modified Hachinski Ischemic score [mean (sd)]	1.1 (1.6)	1.2 (1.8)	2.8 (2.8)	Dementia>normal(p<0.01) Dementia>aMCI (p<0.05)
Brain volume [mean (sd)]	0.51 (0.75)	0.02 (0.78)	−0.59 (1.06)	Dementia < normal (p<0.0001) Dementia < aMCI (p<.0.05) aMCI < normal (p<0.05)
Hippocampal volume [mean(sd)]	0.49 (0.75)	−0.15 (0.82)	−0.45 (1.17)	Dementia < normal (p<0.001) aMCI < normal (p<.01)
Log of white matter hyper-intensity volume [mean (sd)]	−0.32 (0.95)	−0.08 (1.2)	0.55 (0.75)	Dementia >normal (p<0.001) Dementia>aMCI (p<0.001)
Mattis Dementia Rating Scale score [mean(sd)]	135.0 (6.3)	123.3 (11.3)	103.3(17.4)	Dementia<aMCI(p<0.0001) aMCI< normal (p<0.0001) Dementia<normal (p<0.0001)
Body mass index [mean(sd)]	25.09 (4.07)	23.68 (3.73)	25.00 (3.63)	None
Stroke on MRI (%)	16.13	22.22	34.38	None
Minutes walked per day [mean(sd)]	32.0 (35.4)	39.2 (24.3)	31.6 (32.9)	None

*Wilcoxon Rank-Sum Test for continuous variables, chi-square for discrete variables.

Table 2

Odds ratios and 95% confidence intervals for dementia (vs. amnestic MCI) from polytomous logistic regression models adjusted for age, gender and education.†

	Model 1 (n=59)	Model 2 (n=59)	Model 3 (n=48)	Model 4† (n=48)
Fasting blood glucose (mmol/l)	3.30 (1.50–7.30)**	3.13 (1.28–7.69)*	7.87 (1.91–32.26)**	7.75 (1.10–55.56)*
Modified Hachinski Ischemic Score		1.33 (0.87–2.04)		1.34(0.85–2.13)
Hippocampal volume		0.57(0.25–1.32)		0.54(0.23–1.30)
Brain volume		0.35 (0.13–0.97)*		0.34 (0.11–1.02)
White matter hyperintensity volume		2.74 (1.06–7.04)*		1.81 (0.64–5.18)
Body mass index		0.95 (0.77–1.18)		0.90 (0.71–1.13)
Stroke on MRI		0.85 (0.14–5.08)		0.53 (0.07–3.97)

*p<0.05,

**p<0.01

†Models 1 and 3 adjust for age, sex and education. Models 2 and 4 adjust for age, sex, education and other covariates as shown in the table. Eleven participants with fasting blood glucose ≥ 6.1 mmol/l were excluded from Models 3 and 4.

Table 3

Odds ratios and 95% confidence intervals for dementia (vs. normal controls) from polytomous logistic regression models adjusted for age, gender and education.†

	Model 1 (n=63)	Model 2 (n=63)	Model 3 (n=50)	Model 4 (n=50)
Fasting blood glucose (mmol/l)	1.83 (1.09–3.08)*	1.46 (0.85–2.51)	4.78 (1.25–18.18)*	3.64 (0.44–30.30)
Modified Hachinski Ischemic Score		1.45 (0.89–2.36)		1.39 (0.82–2.36)
Hippocampal volume		0.24 (0.09–0.61)**		0.20 (0.06–0.62)**
Brain volume		0.17 (0.06–0.49)**		0.13 (0.04–0.46)**
White matter hyperintensity volume		3.22 (1.21–8.54)*		2.71 (0.91–8.11)
Body mass index		0.89 (0.71–1.10)		0.82 (0.65–1.05)
Stroke on MRI		1.16 (0.17–8.11)		0.52 (0.06–4.83)

*p<0.05

**p<0.01

†Models 1 and 3 adjust for age, sex and education. Models 2 and 4 adjust for age, sex, education and other covariates as shown in the table. Thirteen participants with fasting blood glucose ≥ 6.1 mmol/l were excluded from Models 3 and 4.

Table 4

Odds ratios and 95% confidence intervals for amnestic MCI (vs. normal controls) from polytomous logistic regression models adjusted for age, gender and education.†

	Model 1 (n=58)	Model 2 (n=58)	Model 3 (n=52)	Model 4 (n=52)
Fasting blood glucose (mmol/l)	0.55 (0.26–1.19)	0.47 (0.20–1.09)	0.61 (0.20–1.83)	0.47 (0.12–1.80)
Modified Hachinski Ischemic Score		1.09 (0.71–1.68)		1.04 (0.67–1.61)
Hippocampal volume		0.41 (0.19–0.90)*		0.37 (0.14–0.97)*
Brain volume		0.47 (0.20–1.11)		0.39 (0.15–1.02)
White matter hyperintensity volume		1.18 (0.60–2.31)		1.50 (0.67–3.32)
Body mass index		0.93 (0.79–1.10)		0.92 (0.77–1.09)
Stroke on MRI		1.37 (0.29–6.55)		0.99 (0.20–4.97)

*$p<0.05$

†Models 1 and 3 adjust for age, sex and education. Models 2 and 4 adjust for age, sex, education and other covariates as shown in the table. Six participants with fasting blood glucose ≥ 6.1 mmol/l were excluded from Models 3 and 4.