Association between pre-diabetes or diabetes and cognitive impairment in a -community dwelling older population: Bushehr Elderly Health (BEH) program

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Abstract

Background

Uncontrolled hyperglycemia is one of the risk factors for cognitive disorders. By this finding, both type 1 and type 2 diabetes may predispose to cognitive impairment in poorly controlled cases. The current large-scale study is aimed at cognitive impairments in diabetic and non-diabetic older adults separately.

Methods

This is a cross-sectional study from phase 2 of the Bushehr elderly health program (BEHP). Mini-cog and categorical verbal fluency tests (CFTs) were used to assess cognitive function. Patients were classified as non-diabetics, pre-diabetics, or diabetics based on the diagnostic criteria for diabetes mellitus (DM). To compare the means of the two groups, we used the t-test or the Mann-Whitney test. Multivariable logistic regression models were also used to determine the association between pre-diabetes or DM and cognitive impairment.

Results

Six hundred and ninety-three (45.2%) out of 1533 participants were ascertained to be cognitively impaired. The average hemoglobin A1C was higher in diabetic patients with cognitive impairment compared to those without cognitive impairment. (5.8 ± 1.6% vs. 5.5 ± 1.4%, P = 0.004). Besides, the mean blood glucose levels were found to be more elevated in cognitively impaired cases (108.0 ± 47.4 mg/dL vs. 102.1 ± 0.35 mg/dL, P = 0.002). After adjusting for age, gender, body mass index(BMI), waist circumference, amount of physical activity, and smoking, the multivariable logistic regression model, declared an association between diabetes and cognitive impairment (OR = 1.48, P = 0.003). Older patients, females, widows, and patients with elevated LDL-Cs and blood pressure are also more vulnerable to cognitive impairment.

Conclusion

In the BEHP, there is a positive association between cognitive impairment and DM, notably in long-term, poorly controlled cases, whereas no association was found among pre-diabetics in our elderly study populations.

Introduction

Diabetes and cognitive disorders have become more prevalent in the last decade as a result of lifestyle and demographic changes[1]. Dementia is a clinical syndrome characterized by progressive declines in cognitive and functional ability [2]. It is estimated that approximately 50 million people worldwide suffer from dementia, with the figure expected to nearly double every 20 years to approximately 115 million by 2050.[3]. According to the 2015 diabetes prevalence figures, approximately 415 million people worldwide suffer from diabetes. This number will increase to an expected number of 642 million by 2040 [4]. Evidence suggests a strong link between the progression of cognitive impairment, and impaired blood glucose or other metabolic disorders [5, 6]. Among the various components of metabolic syndrome, hyperglycemia has the strongest association with the incidence of cognitive impairment[7]. Type 2 diabetes mellitus (T2DM), in particular, has been associated with a risk of cognitive impairment, including attention disorder, decreased speed of movements, decision-making problems, and incompetent speech memory[8, 9]. Diabetes is associated with a 19% increased risk of midlife cognitive decline over 20 years, compared to non-diabetic cases[10].T2DM, smoking, and obesity are all vascular and non-vascular risk factors for dementia. An analysis of 14 studies involving 2.3 million patients and the incidence of 10,000 cases of dementia in Asia, America, and Europe have shown that diabetes is associated with a 60% increased risk of dementia, with 40% escalated rates of vascular dementia, and the risk increases are about 18% higher in women[11]. The most common cause of dementia, Alzheimer's disease(AD), is induced by the development of cerebral insulin resistance and impaired glucose regulation in the brain [12, 13]. Diabetes patients treated with insulin had four times the risk of dementia than diabetic patients receiving oral therapy or lifestyle modifications. [14]. The severity of diabetes is also a risk factor in association with elevated risks of dementia. Patients with glucose intolerance have a higher risk of dementia development [15, 16]. Moreover, non-diabetics with higher mean glucose levels are also susceptible to dementia [17]. According to some studies, people with insulin resistance are more likely to develop dementia than people with high plasma glucose levels [18]. Hence, T2DM progressively increases the overall risk of dementia and AD, especially in uncontrolled cases. According to

various studies, precise control of blood glucose in diabetics has been proven to be effective in preventing cognitive impairment, but the exact quantitative association remained unknown. Diabetes-related cognitive impairment is a critical concern for us because it gradually reduces patients' quality of life, resulting in massive health and social care needs. The goal of this study is to determine the prevalence of cognitive impairment and its relationship to diabetes treatments in the diabetic population enrolled in the Bushehr elderly health cohort study.

Materials And Methods

Sampling and setting

This is a cross-sectional approach to data from the phase II Bushehr Elderly Health Program (BEHP). The BEHP is a 3000-participant community-based prospective cohort study in Bushehr, the provincial capital city in southern Iran. The sampling for this study was a multistage stratified random sampling method accomplished in the neighborhoods of Bushehr. The second phase of this study (considering musculoskeletal and cognitive outcomes) started in 2015. In this phase, more than 2400 participants from phase I have enrolled again. The study design and protocol are explained separately (Figure 1).

Data gathering

The participants were interviewed by competent interviewers to collect data, including sociodemographic factors, types of lifestyles, general health and mental health situations, medical histories, and medicinal uses. Anthropometric measurements were performed through the manual anthropometric procedures of the National Health and Nutrition Examination Survey (NHANES). Weights were measured to 0.1 kg with a Seca leverage bascule with the least wear. Height was measured to the nearest 0.1 centimeters using a fixed stadiometer without shoes and without the head being covered. Waist circumferences were measured at a point midway between the iliac crest and the lowest rib in an upright position after breathing, using a tape in a horizontal plane around the waist, with an accuracy of 0.1 centimeters. Physical activity level (PAL) was assessed by a validated self-report questionnaire defined by different metabolic equivalent (MET) levels ranging from sleep/rest (0.9 METs) to high-intensity physical activities (>6 METs) in 24 hours of sports, work, and leisure time. Over 24 hours, for each activity, MET equivalence was multiplied by the time spent on that particular physical activity. The daily MET was calculated as the sum of MET times. Cognitive function was assessed through two sorts of tools. One of the instruments used was the Mini-Cog, which is a validated tool for cognitive assessment. This test consists of two parts; the first part assesses the ability of participants to recall three different words. Anybody who could recall all of the three words was considered to have normal cognition, and those who could not recall any of the words were considered cognitively impaired. If anyone could only recall one or two words correctly, then a clock drawing test was performed, and if the participant could draw the clock, it was assumed that he or she had a normal cognitive function, and those who could not draw the clock correctly were considered cognitively impaired. The other utilized tool was the categorical verbal fluency test (CFT) which is commonly used for assessing the integrity of semantic memory in individuals with brain damage (ranging from amnesic mild cognitive impairment to dementia). The animal category was used; participants were asked to name as many examples of the category “animal” as possible within one minute. To increase the sensitivity of cognitive impairment diagnosis, participants who were positive in both diagnostic criteria were assumed to be cognitively impaired, and others who were negative in both were considered normal. To determine the values of fasting blood sugar (FBS) and hemoglobin A1C, a blood sample was obtained after overnight fasting. FBS was measured by the enzymatic glucose oxidase method using Pars Azmoon kits that are made in Iran. HbA1c was also measured through the high-performance liquid chromatographic technique. Diabetes was defined based on A1C $\geq$ 6.5% and FBS $\geq$ 126 mg/dl or, previous diagnosed history of diabetes. The normal participants were defined based on A1C < 5.7% and FBS < 100 mg/dl. Others beyond the two explained categories were considered pre-diabetics[19].

Ethical consideration

The study was approved by the Research Ethics Committee of the Endocrinology & Metabolism Research Institute (Ethical code: IR.TUMS.EMRI.REC.1394.0036). Patient consent forms are obtained from patients, and in the case of confirmation of cognitive impairment (based on the Mini-Cog test), consent forms are obtained from patients' families or legal guardians for study participation. Informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

Concerning statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using a t-test or Mann-Whitney

test whenever the data did not appear to have a normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables, on the other hand, were compared using the chi-square test. The multivariable logistic regression model was utilized to evaluate the association between pre-diabetics and cognitive impairment. For the statistical analysis, the software SPSS version 23.0 for Windows (IBM, Armonk, New York) was used.

Results

According to the definition of cognitive impairment, pre-diabetes, and diabetes, it was revealed that 693 (45.2%) of the 1533 participants were cognitively impaired, among which 47.3% (328) were normoglycemic, 16.2% (112) were pre-diabetics, and 36.5% (253) were already diagnosed as diabetics (P<0.001). The characteristics of the total participants and their classifications by normal or impaired cognition are exhibited in table 1. In our study community, cognitive impairment was more prevalent among women (64.8%) compared to men (35.2%) (P<0.001). The means of age, FBS, HbA1c, and LDL cholesterol in cognitively impaired groups were higher compared to normal cognition (P<0.05); in reverse, the mean of physical activity level was lower in the cognitively impaired group (P<0.001).

Possible related variables which might be related to cognitive function are presented separately among the normoglycemic, pre-diabetic, and diabetic groups in table 2. In all groups, the mean age was higher, and the mean physical activity level was lower in cognitively impaired participants in comparison to normal cognition (P<0.001). Among the cognitively impaired participants, the mean waist circumference was lower only in normoglycemic cases (P = 0.044), the serum LDL-C level was higher only among the diabetic group (P<0.001), and the blood hemoglobin level was lower only among pre-diabetics (P = 0.010). The mean of physical activity based on total weekly MET was slightly lower among cognitively impaired individuals in all three groups (P<0.001).

Multivariable analysis was performed to determine the association between the independent predictors such as age, sex, BMI, WC, physical activity, smoking history, FBS, triglyceride, and LDL with cognitive impairment in the three normoglycemic, pre-diabetic, and diabetic groups. Odds ratios for age differences were calculated at 1.12, 1.06, and 1.09 in normoglycemic, pre-diabetic, and diabetic participants, respectively, which indicates that the cognitively impaired patients were older in all three groups (p<0.001). Women were more likely to have cognitive impairment in all three groups (OR = 0.21; CI 95% 0.15– 0.30 P 0.001, OR = 0.33; CI 95% 0.19–0.59 P 0.001, OR = 0.33; CI 95% 0.22-0.50 P 0.001).The association between physical activity level and smoking with cognitive impairment was only significant in diabetic patients (OR = 0.94; CI 95% 0.90-0.99, P = 0.018) and normoglycemic participants (OR = 1.32; CI 95% 1.07-1.62, P = 0.007), respectively (Table 3).In logistic regression models, the association between prediabetes and diabetes with cognitive impairment demarcated by gender was assessed. In univariate models, only diabetes (but not pre-diabetes) was associated with cognitive impairment (OR = 1.54; CI 95% 1.22-1.93, P<0.001). This association was sustained in multivariate models after adjustment for associated confounders, including age, sex, BMI, WC, physical activity, serum hemoglobin A1C, and smoking (Table 4). Participants (44.9%) were cognitively impaired (64.5% female and 31.0% male, P< 0.001).

Discussion

The purpose of this study was to thoroughly assess cognitive disorders in diabetic elderly people. We concluded in our study population that diabetic patients were more vulnerable to cognitive impairment and that lower physical activity would increase the chances of diabetic patients living with cognitive impairment. It was discovered that hyperglycemia in diabetic patients predisposes them to cognitive impairment the most, and after adjustment of underlying factors such as age, gender, BMI, waist circumference, physical activity, and smoking, we estimated that the incidence of cognitive impairment in diabetic patients increases up to 1.48 times. Furthermore, characteristics such as advanced age, female gender, a positive history of hypertension, widowhood, elevated LDL-C, and even low MET energy expenditure can all be considered risk factors for cognitive impairment. Overall, given diabetics' susceptibility to cognitive impairment, it is reasonable to expect that better glycemic control can suspend the progression of cognitive impairment or even reverse it.

Our study's findings were consistent with those of previous studies. According to the study by Xue et al. [20], diabetes increased the risk of cognitive impairment by 1.25 to 1.91 times, also fasting glucose levels, HbA1C levels, and insulin resistance index had a significant linear relationship with the incidence and progression of dementia. A study by Gao et al. [21] propounded the duration from onset of diabetes as a risk factor for dementia among the diabetic population alongside other risk factors like higher levels of age, current smoking, mean waist circumference, duration of diabetes, insulin intake, systolic blood pressure, FBS, HgA1c, and, immunoreactive insulin (IRI). According to Tiwari et al. [22], cognitive impairment is expected to be 1.3 times more common in diabetics. As reported by Sun et al.[23]

age, education level, diabetes duration, FBS, and A1C levels all contribute to cognitive impairment in older T2DM. Another study by Jia et al.[24] in China considered old age, female gender, low levels of education, widowhood or divorce, smoking history, hypertension, cardiovascular diseases, and ischemic brain diseases as the risk factors for dementia among patients with diabetes. They also illustrated that the prevalence of cognitive impairment increased in diabetics 2.14 times. Consequently, T2DM, especially in poorly controlled conditions, predisposes to disparate stages of cognitive impairment, and some of the conditions associated with diabetes seem to exacerbate that impairment [24]. Several studies have been conducted about the pathophysiology and progression of cognitive impairment. Impaired insulin signaling and insulin receptor sensitivity in neurons and dendritic branches in Alzheimer's patients indicate a link between diabetes and cognitive impairment [25]. The second related consequence is mitochondrial dysfunction. Insulin is essential for increasing mitochondrial activity in hippocampal synaptosomes [26]. Cerebral mitochondrial function declines in AD patients, which has been linked to cortical hypometabolism and impaired insulin signaling in the brain. In this regard, the pattern of metabolic changes in AD patients has influenced mitochondrial bioenergetic inhibitors [27]. Hence, mitochondrial functions after the metabolic regulations are affected by insulin, manipulating cognitive functions [28]. The relationship between diabetic autonomic neuropathy and the incidence of cognitive impairment is a further considerable issue. It has been demonstrated that diabetic autonomic neuropathy is related intimately to hypertension and increased risk of cerebral stroke, both of which are associated with cognitive impairment. Neuroinflammation and brain changes are two other significant concerns raised regarding diabetic cognitive impairment. Accumulation of inflammatory cytokines in the brain has been confirmed in diabetics, which has a significant effect on neuronal damage [29]. Moreover, NF-kb regulates oxygen radicals and the expression of TNF and variegated interleukins and therefore has an unassailable influence on initiating and activating the inflammatory cascade. High TNF levels and activity inhibit the insulin signaling pathway, which leads to increased production of oxygen radicals or ROS and the progression of cognitive impairment in these individuals [30–32].

According to Sundermann's findings, even prediabetes harms brain metabolism in older men and women. In light of previous findings linking T2DM to reduced brain volume and AD pathology[33–37], the findings of this study suggest that functional changes may occur before brain volume changes in the early stages of T2DM[38]. This study also revealed that prediabetes was associated with poorer executive function overall and language performance specifically in the context of mean cognitive impairment (MCI) in women only[38]. Despite this fact that even though these findings and the sex distribution contradict our findings. Dybjer et. al[39]. discovered that pre-diabetes and newly diagnosed diabetes are linked to MCI, and that blood glucose levels, even at the upper end of the normal range, may have a marginally negative effect on cognition. As compared to a healthy individual with normal glucose tolerance, prediabetes or diabetes had slight negative effects on memory, processing speed, and executive functioning[39]. Since there is no association between prediabetics and cognitive impairment, our findings contradict this article. This could be due to different thresholds for diagnosing prediabetic patients, sample size randomization, or the cognitive impairment assessment system. This should be investigated further in future studies on the matter.

Conclusion

In conclusion, we discovered that T2DM, particularly in persistent uncontrolled conditions, has a positive association with cognitive impairment in the elderly population. Aside from diabetes' inflammatory effect on the progression of cognitive disorders, we propose that old age, female gender, history of hypertension, widowhood, increased LDL-C, and even low-calorie consumption are additional risk factors for cognitive impairment. It is also worth noting that in our study, there was no association between prediabetic patients and cognitive impairment.

Declarations

Ethics approval and consent to participate:

The study was approved by the Research Ethics Committee of the Endocrinology & Metabolism Research Institute (Ethical code: IR.TUMS.EMRI.REC.1394.0036). Patient consent forms are obtained from patients, and in the case of confirmation of cognitive impairment (based on the Mini-Cog test), consent forms are obtained from patients' families or legal guardians for study participation. Informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication:

Not Applicable

Availability of data and materials:

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Competing interest:

All authors declare that they have no conflict of interest.

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None

Author Contributions Statement:

SF,ME,AO,MP,FSH,YSH,SM and ZSH in the study design, writing of the paper, and had significant role in analyzing data. BL participated in critical review. All authors read, provided feedback, and approved the final paper.

References

1. Pal K, Mukadam N, Petersen I, Cooper C: **Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis**. *Social psychiatry and psychiatric epidemiology* 2018, **53**(11):1149–1160.
2. Moran C, Callisaya ML, Srikanth V, Arvanitakis Z: **Diabetes therapies for dementia**. Current neurology and neuroscience reports 2019, **19**(8):1–9.
3. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP: **The global prevalence of dementia: a systematic review and metaanalysis**. *Alzheimer's & dementia* 2013, **9**(1):63–75. e62.
4. Ogurtsova K: **dRF J.**, Huang Y, Linnenkamp U, Guariguata L, Cho NH, **et al**. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015:40–50.
5. Wong RHX, Scholey A, Howe PRC: **Assessing premorbid cognitive ability in adults with type 2 diabetes mellitus—a review with implications for future intervention studies**. Current diabetes reports 2014, **14**(11):547.
6. Grünblatt E, Bartl J, Riederer P: **The link between iron, metabolic syndrome, and Alzheimer's disease**. Journal of Neural Transmission 2011, **118**(3):371–379.
7. Dik MG, Jonker C, Comijs HC, Deeg DJ, Kok A, Yaffe K, Penninx BW: **Contribution of metabolic syndrome components to cognition in older individuals**. Diabetes care 2007, **30**(10):2655–2660.
8. Palta P, Schneider AL, Biessels GJ, Touradji P, Hill-Briggs F: **Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains**. Journal of the International Neuropsychological Society 2014, **20**(3):278–291.
9. Monette MC, Baird A, Jackson DL: **A meta-analysis of cognitive functioning in nondemented adults with type 2 diabetes mellitus**. Canadian journal of diabetes 2014, **38**(6):401–408.
10. Rawlings AM, Sharrett AR, Schneider AL, Coresh J, Albert M, Couper D, Griswold M, Gottesman RF, Wagenknecht LE, Windham BG: **Diabetes in midlife and cognitive change over 20 years: a cohort study**. Annals of internal medicine 2014, **161**(11):785–793.
11. Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M *et al*: **Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia**. Diabetes Care 2016, **39**(2):300–307.
12. de la Monte SM: **Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease**. Curr Alzheimer Res 2012, **9**(1):35–66.
13. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB: **Diabetes mellitus and Alzheimer's disease: shared pathology and treatment?** Br J Clin Pharmacol 2011, **71**(3):365–376.

14. Ott A, Stolk RP, van Harskamp F, Pols HAP, Hofman A, Breteler MMB: **Diabetes mellitus and the risk of dementia**. Neurology 1999, **53**(9):1937.
15. N S, Karan: **Assessment of the cognitive status in diabetes mellitus**. J Clin Diagn Res 2012, **6**(10):1658–1662.
16. Luchsinger JA: **Adiposity, hyperinsulinemia, diabetes and Alzheimer's disease: an epidemiological perspective**. Eur J Pharmacol 2008, **585**(1):119–129.
17. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, Haneuse S, Craft S, Montine TJ, Kahn SE *et al*: **Glucose levels and risk of dementia**. N Engl J Med 2013, **369**(6):540–548.
18. Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, Kanba S, Kiyohara Y: **Glucose tolerance status and risk of dementia in the community: the Hisayama study**. Neurology 2011, **77**(12):1126–1134.
19. Ika K, Suzuki E, Mitsuhashi T, Takao S, Doi H: **Shift work and diabetes mellitus among male workers in Japan: does the intensity of shift work matter?** Acta Med Okayama 2013, **67**(1):25–33.
20. Xue M, Xu W, Ou YN, Cao XP, Tan MS, Tan L, Yu JT: **Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies**. Ageing Res Rev 2019, **55**:100944.
21. Gao Y, Xiao Y, Miao R, Zhao J, Cui M, Huang G, Fei M: **The prevalence of mild cognitive impairment with type 2 diabetes mellitus among elderly people in China: A cross-sectional study**. Arch Gerontol Geriatr 2016, **62**:138–142.
22. Tiwari SC, Tripathi RK, Farooqi SA, Kumar R, Srivastava G, Kumar A: **Diabetes mellitus: A risk factor for cognitive impairment amongst urban older adults**. Ind Psychiatry J 2012, **21**(1):44–48.
23. Sun L, Diao X, Gang X, Lv Y, Zhao X, Yang S, Gao Y, Wang G: **Risk Factors for Cognitive Impairment in Patients with Type 2 Diabetes**. J Diabetes Res 2020, **2020**:4591938.
24. Jia HH, Liu L, Huo GX, Wang RQ, Zhou YQ, Yang LY: **A qualitative study of the cognitive behavioral intention of patients with diabetes in rural China who have experienced delayed diagnosis and treatment**. BMC Public Health 2020, **20**(1):478.
25. Calvo-Ochoa E, Arias C: **Cellular and metabolic alterations in the hippocampus caused by insulin signalling dysfunction and its association with cognitive impairment during aging and Alzheimer's disease: studies in animal models**. Diabetes Metab Res Rev 2015, **31**(1):1–13.
26. Heras-Sandoval D, Ferrera P, Arias C: **Amyloid-β protein modulates insulin signaling in presynaptic terminals**. Neurochemical research 2012, **37**(9):1879–1885.
27. Choi J, Malakowsky CA, Talent JM, Conrad CC, Gracy RW: **Identification of oxidized plasma proteins in Alzheimer's disease**. Biochemical and biophysical research communications 2002, **293**(5):1566–1570.
28. Lu T, Pan Y, Kao S, Li C, Kohane I: **chan**, J.; Yankner, **BA**. *Nature* 2004, **429**:883.
29. Gaspar JM, Baptista FI, Macedo MP, Ambrosio AF: **Inside the diabetic brain: role of different players involved in cognitive decline**. ACS Chemical Neuroscience 2016, **7**(2):131–142.
30. Wang J, Li G, Wang Z, Zhang X, Yao L, Wang F, Liu S, Yin J, Ling E-A, Wang L: **High glucose-induced expression of inflammatory cytokines and reactive oxygen species in cultured astrocytes**. Neuroscience 2012, **202**:58–68.
31. Sima AA: **Encephalopathies: the emerging diabetic complications**. Acta diabetologica 2010, **47**(4):279–293.
32. Kuhad A, Bishnoi M, Tiwari V, Chopra K: **Suppression of NF-κβ signaling pathway by tocotrienol can prevent diabetes associated cognitive deficits**. Pharmacology Biochemistry and Behavior 2009, **92**(2):251–259.
33. Moran C, Phan TG, Chen J, Blizzard L, Beare R, Venn A, Münch G, Wood AG, Forbes J, Greenaway TM: **Brain atrophy in type 2 diabetes: regional distribution and influence on cognition**. Diabetes care 2013, **36**(12):4036–4042.
34. Moran C, Beare R, Phan TG, Bruce DG, Callisaya ML, Srikanth V: **Type 2 diabetes mellitus and biomarkers of neurodegeneration**. Neurology 2015, **85**(13):1123–1130.
35. Biessels GJ, Reijmer YD: **Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI?** Diabetes 2014, **63**(7):2244–2252.
36. Callisaya ML, Beare R, Moran C, Phan T, Wang W, Srikanth VK: **Type 2 diabetes mellitus, brain atrophy and cognitive decline in older people: a longitudinal study**. Diabetologia 2019, **62**(3):448–458.
37. Bangen KJ, Werhane ML, Weigand AJ, Edmonds EC, Delano-Wood L, Thomas KR, Nation DA, Evangelista ND, Clark AL, Liu TT: **Reduced regional cerebral blood flow relates to poorer cognition in older adults with type 2 diabetes**. Frontiers in aging neuroscience 2018:270.

38. Sundermann EE, Thomas KR, Bangen KJ, Weigand AJ, Eppig JS, Edmonds EC, Wong CG, Bondi MW, Delano-Wood L: **Prediabetes Is Associated With Brain Hypometabolism and Cognitive Decline in a Sex-Dependent Manner: A Longitudinal Study of Nondemented Older Adults**. Frontiers in Neurology 2021, **12**.
39. Dybjer E, Nilsson PM, Engström G, Helmer C, Nägga K: **Pre-diabetes and diabetes are independently associated with adverse cognitive test results: a cross-sectional, population-based study**. BMC endocrine disorders 2018, **18**(1):1–10.

Tables

Table 1- Characteristics of the participants

	Total Participants N=1533	normal cognition N = 840	Impaired cognition N = 693	*P-value*
Age, year	69.2±6.5	67.6±5.2	71.2±7.3	**<0.001**
Sex, %				
female	750 (48.9)	301 (35.8)	449 (64.8)	**<0.001**
male	783 (51.1)	539 (64.2)	244 (35.2)	
BMI, kg/m^2	30.9±5.1			
WC, cm	98.5±11.9	98.5±11.2	98.4±12.8	0.917
Education, %				
Illiterate	563 (36.7)	320 (38.1)	243 (35.1)	
Primary School	540 (35.2)	278 (33.1)	262 (37.8)	
High School	136 (8.9)	82 (9.8)	54 (7.8)	0.173
Diploma	196 (12.8)	102 (12.1)	94 (13.6)	
Academic	98 (6.4)	58 (6.9)	40 (5.8)	
Marital status, %				
Single	13 (0.8)	6 (0.7)	7 (1.0)	
Married	1195 (77.9)	731 (87.0)	464 (67.0)	**<0.001**
Divorced	13 (0.8)	7 (0.8)	6 (0.9)	
Widow- Widower	312 (20.4)	96 (11.4)	216 (31.2)	
Smoking, %				
Occasionally smoker	66 (4.3)	30 (3.6)	36 (5.2)	0.132
Current smoker	256 (16.7)	132 (15.7)	124 (17.9)	
Glycemia, %				
Normo-glycemia	792 (51.7)	464 (55.2)	328 (47.3)	
Prediabetes	256 (16.7)	144 (17.1)	112 (16.2)	**0.001**
Diabetes	485 (31.6)	232 (27.6)	253 (36.5)	
Hypertension, %	1084 (70.7)	573 (68.2)	511 (73.7)	**0.018**
HbA1c, %	5.6±1.5	5.5±1.4	5.8±1.6	**0.004**
normal glycemia	4.7±0 .5	4.8±0 .4	4.7±0 .5	0.241
Prediabetes	5.6±0 .7	5.5±0 .7	5.6±0 .6	0.148
Diabetes	7.1± 1.8	7.1± 1.7	7.2± 1.9	0.754
FBS	105.0±41.2	102.1±35.0	108.7±47.4	**0.002**
normal glycemia	85.7±7.8	86.1±7.6	85.0±8.1	0.054
Prediabetes	101.0±14.0	101.3±14.2	100.6±13.8	0.672
Diabetes	138.9±58.2	134.5±51.5	143.1±63.6	0.103
Triglyceride, mg/dl	133.8±67.3	133.6±69.9	134.1±63.9	0.871
LDL, mg/dl	109.1±37.5	107.2±37.5	111.5±37.5	**0.028**
HDL, mg/dl	45.7±11.0	45.5±11.2	45.9±10.7	0.522

Total weekly MET (kcal/kg/day)	30.9±5.1	31.7±5.1	29.9±4.8	**<0.001**

WC: waist circumference; HbA1c: hemoglobin A1c; FBS: fasting blood sugar; LDL: low-density lipoprotein; HDL: high-density lipoprotein

Table 2- Characteristics of the participants

Variable	Normo-glycemia			Pre-diabetes			Diabetes		
	normal C N = 464	CI N = 328	*P-value*	normal C N = 144	CI N = 112	*P* value	normal C N = 232	CI N = 253	*P* value
Age, year	67.5±5.0	71.9±7.8	**<0.001**	68.6±6.4	72.2±7.3	**<0.001**	67.1±4.5	69.8± 6.4	**<0.001**
WC/cm	96.9±11.2	95.2±12.8	**0.044**	100.0±10.3	100.0±13.5	0.979	100.6±11.0	101.9±11.4	0.218
HbA1c, %	4.8±0 .4	4.7±0 .5	0.241	5.5±0 .7	5.6±0 .6	0.148	7.1± 1.7	7.2± 1.9	0.754
FBS, mg/dl	86.1±7.6	85.0±8.1	0.054	101.3±14.2	100.6±13.8	0.672	134.5±51.5	143.1±63.6	0.103
Triglyceride, mg/dl	125.8±61.0	118.3±52.1	0.072	143.6±76.4	152.0±80.6	0.391	142.8±80.1	146.7±64.9	0.559
LDL, mg/dl	114.4±34.6	116.0±35.7	0.524	111.3±44.5	118.8±38.3	0.158	90.3±32.7	102.3±37.9	**<0.001**
HDL, mg/dl	46.2±11.1	47.2±11.1	0.198	45.1±11.0	46.3±10.0	0.346	44.3± 11.3	43.8±10.1	0.618
Hemoglobin, g/dl	14.6±1.5	14.5± 1.8	0.121	14.7±1.8	14.1±2.0	**0.010**	14.2±1.7	14.2±1.7	0.785
Total weekly MET (kcal/kg/day)	31.9±5.1	30.3±5.1	**<0.001**	31.5±5.2	29.2±4.4	**<0.001**	31.3±4.9	29.5±4.5	**<0.001**

WC: waist circumference; HbA1c: hemoglobin A1c; FBS: fasting blood sugar; LDL: low-density lipoprotein; HDL: high-density lipoprotein

Table 3- Associations of possibly related variables with cognitive impairment

Variable	Normal (n=780)			Pre-diabetes (n=245)			Diabetes (n=480)		
	OR	95% CI OR	*P*-value	OR	95% CI OR	*P*-value	OR	95% CI OR	*P*-value
Age	1.12	1.09- 1.15	**<0.001**	1.06	1.01-1.11	0.007	1.09	1.05-1.13	**<0.001**
Sex	0.21	0.15- 0.30	**<0.001**	0.33	0.19-0.59	<0.001	0.33	0.22-0.50	**<0.001**
BMI	0.63	0.29- 1.36	0.248	2.15	0.58-7.89	0.248	2.39	0.83-6.81	0.103
WC	0.99	0.98-1.00	0.385	1.00	0.98-1.03	0.646	1.01	0.99-1.02	0.261
Physical activity	0.98	0.95-1.01	0.377	0.93	0.87-1.00	0.070	0.94	0.90-0.99	**0.018**
Smoking	1.32	1.07-1.62	**0.007**	0.78	0.53-1.17	0.245	1.25	0.93-1.68	0.135
FBS	0.99	0.97-1.01	0.396	1.00	0.98-1.02	0.749	1.00	1.00-1.01	0.050
Triglyceride	0.99	0.99-1.00	0.138	1.00	0.99-1.00	0.090	0.99	0.99-1.00	0.662
LDL	0.99	0.99-1.00	0.430	1.00	0.99-1.01	0.319	1.00	1.00-1.01	**0.006**

BMI: body mass index; WC: waist circumference; FBS: fasting blood sugar; LDL: low-density lipoprotein;

Table 4- Associations of pre-diabetes and diabetes with cognitive impairment

	OR	95% CI OR	*P*-value
Unadjusted model			
Pre-diabetes	1.10	0.82-1.46	0.510
Diabetes	1.54	1.22-1.93	**<0.001**
Adjusted models			
Pre-diabetes[1]	0.99	0.74-1.34	0.999
Diabetes	1.37	1.08-1.73	**0.009**
Pre-diabetes[2]	0.91	0.66- 1.24	0.554
Diabetes	1.51	1.18- 1.94	**0.001**
Pre-diabetes[3]	0.96	0.70-1.32	0.826
Diabetes	1.59	1.24-2.05	**0.000**
Pre-diabetes[4]	0.92	0.67-1.27	0.637
Diabetes	1.46	1.12-1.88	**0.004**
Pre-diabetes[5]	0.92	0.66-1.27	0.612
Diabetes	1.50	1.16-1.94	**0.002**
Pre-diabetes[6]	0.91	0.66-1.26	0.603
Diabetes	1.51	1.16-1.96	**0.002**
Pre-diabetes[7]	0.92	0.67-1.27	0.630
Diabetes	1.48	1.14-1.91	**0.003**

OR: Odds Ratio, CI: Confidence Interval

1 Adjusted for age, sex

2 Adjusted for age, sex

3 Adjusted for age, sex, BMI

4 Adjusted for age, sex, BMI, WC, physical activity

5 Adjusted for age, sex, BMI, WC, physical activity, serum hemoglobin

6 Adjusted for age, sex, BMI, WC, physical activity, serum hemoglobin, and smoking

7 Adjusted for age, sex, BMI, WC, physical activity, smoking

Figures

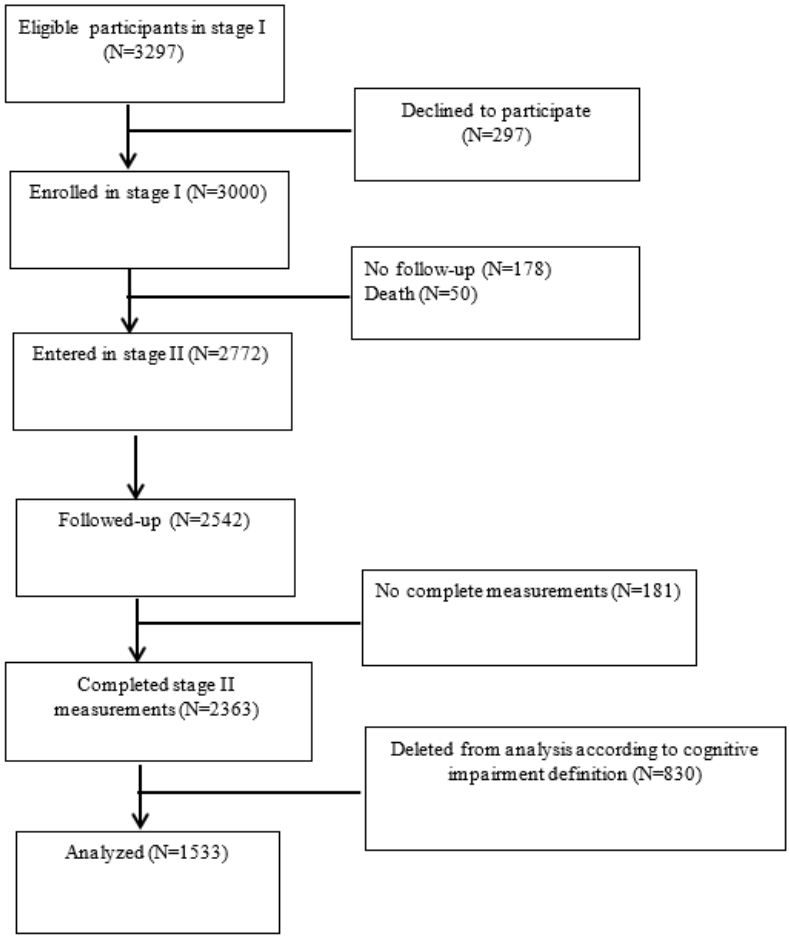

Figure 1

Flow chart of enrolments in this study