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Cognitive impairment in elderly people with prediabetes or diabetes: A cross-sectional study of the NHANES population

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ABSTRACT

Aim: To investigate the cognitive function in people without diabetes, with prediabetes and with diabetes.
Methods/Design: The study design used was a cross-sectional analysis of data in people above 60 years registered in NHANES from 2011 to 2014.Three assessments were used to characterize cognitive function: (a) CERAD Word Learning subtest assessing immediate and delayed learning ability, (b) The Animal Fluency test assesing categorical verbal fluency, and (c) The Digit Symbol Substitution test assessing processing speed, sustained attention, and working memory.
Results: (A) Memory recall (−0.19, [−0.34; −0.039], p = 0.014) and Delayed memory recall decline was associated with diabetes (−0.285, [−0.503; −0.067], p = 0.01), but not in an adjusted analysis. (B) Animal Fluency score decline was associated with diabetes (−1.185, [−1.688; −0.682], p < 0.001). (C) Digit Symbol score decline was associated with diabetes (−6.897, [−8.491; −5.302], p < 0.001). Prediabetes was not associated with cognitive function.
Conclusions: This study demonstrates an association between cognitive dysfunction and diabetes. Results may also indicate that cognitive decline is not yet present in people with mild impairments of glucose homeostasis.

1. Background

Cognitive health has been establishedas an important public health concern. Especially for the aging population [1,2]. Decline and impairments in cognitive functioning has been associated with quality of life, personal relationships, and increased health care needs, moreover, this puts additional pressure on healthcare providers and increases financial health costs [3]. Elderly with diabetes are heavily influenced by many different complication related to their disease and lifestyle, from heart disease, neuropathies, hearing impairments, loss of lung capacity to cognitive decline [4–8]. Cognitive decline for patients with diabetes have been reported in several studies over the years [9–11]. People with type 2 diabetes often score lower on assessments of learning, attention/executive functioning and memory [9,11]. Both hyperglycemia and microvascular disease are contributors to cognitive decline in diabetes [10]. The association of cognitive decline in people with prediabetes is more unclear [12–15].

This study sought to investigate the cognitive function in people without diabetes, with prediabetes and with diabetes. The hypothesis is that reduced cognitive function can be observed for people with prediabetes, similarly to people with diabetes.

2. Methods

2.1. Study design

The study design used was a cross-sectional analysis of data from several years of the NHANES (National Health and Nutrition Examination Survey). Data were collected by the National Center for Health Statistics from 2011 to 2014 using a complex multistage probability sample designed to represent the civilian noninstitutionalized U.S. population [16].

2.2. Participants

Participants with age < = 60 were included in this study. Participants who did not understand or read English, Spanish, Korean, Mandarin, Vietnamese, or Cantonese were not assessed. Laboratory data from HbA1c and fasting plasma glucose (FPG) were used to identify people who had diabetes and prediabetes. Participants with an HbA1c result above or equal to 6.5% (48 mmol/mol) was classified as having diabetes, whereas participants with an HbA1c level of = > 6 and <6.5% (42–48 mmol/mol) and/or fasting plasma

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Table 1
Cohort characteristics divided into groups; control (people without diabetes or prediabetes), people with prediabetes, diabetes and presented as mean (standard deviation), median [prediction interval] or as a proportion %.

	Control	Prediabetes	Diabetes
n	1981	647	678
Age, years	70.1 (7.1)	70.2 (6.9)	69.7 (6.7)
Males, %	46	52	56
Duration diabetes, y	–	–	14.2 (10.9)
HbA1c, %/mmol/mol	5.5 [5.3; 5.7]/37	6.1 [6; 6.2]/43	7.2 [6.7; 8.2]/55
BMI, kg/m^2	27.5 (5.8)	29.5 (6.1)	31.4 (6.9)
Weight, kg	74.5 (17.6)	81.3 (19.8)	85.9 (21.3)
Systolic blood pressure, mmHg	134 (21)	133 (19)	136 (20)
Diastolic blod pressure, mmHg	70 (14)	68 (14)	66(16)
LDL mmol/L	2.92 [2.35; 3.47]	2.85 [2.33; 3.57]	2.38 [1.84; 3.03]
Stroke, %	7	7	11
Memory recall	6.3 (1.7)	6.2 (1.7)	6 (1.6)
Memory delayed recall	5.9 (2.5)	6 (2.3)	5.5 (2.3)
Animal fluency	16.8 (5.8)	16.4 (5.2)	15.4 (5.2)
Digit symbol	48 (17.6)	45.4 (16.8)	40.1 (16.7)

glucose of =>6.1 and below 7 (mmol/l) was classified as having prediabetes according to the thresholds based on the World Health Organization (WHO)/International Expert Committee (IEC) criteria [17]. Participants answering yes to the question “Doctor told you have diabetes” was excluded from the prediabetes group. For participants with diabetes confirmed by HbA1c, the length of diagnosis was obtained from the NHANES questionnaire.

2.3. Cognitive assessments

Three assessments were used to characterize cognitive function in participants aged 60 or above. Each test had a specific target for assessing a specific cognitive function. We included all participants who completed the cognitive assessment. The tests are described in detail in the NHANES documentation [18], here in brief:

The *CERAD Word Learning subtest* assesses immediate and delayed learning ability for new verbal information [19]. It has been used in large epidemiologic studies [19–21]. The test comprises three consecutive learning trials, and an additional delayed recall. For the first three learning trials, participants are instructed to read aloud 10 unconnected words, one at a time, as they are presented. Immediately following the presentation of the words, participants recall as many words as possible. In each of the three learning trials, the order of the 10 words is changed. The maximum score possible on each trial is 10. The delayed word recall was conducted after the other two cognitive exercises were completed (approximately 8−10 min).

The *Animal Fluency* (AF) test asses categorical verbal fluency, a component of executive function [22]. AF scores have been shown to discriminate between persons with normal cognitive functioning compared with those with mild cognitive impairment and more severe forms of cognitive impairment (e.g. Alzheimer’s disease) [23,24]. The test demands awareness (e.g., naming different animals), irrespective of cultural context, that is not absolutely reliant on formal educational experiences of a particular culture [22]. The AF test has been used in large-scale screenings and epidemiologic studies [24–26]. In one minute, participants are asked to name as many animals as possible — for each correct animal one point was given. In NHANES protocol, participants were prior to the test asked to name three items of clothing, another verbal fluency category, as a practice test. Participants who could not name three items of clothing did not continue with the Animal Fluency exercise.

The Digit Symbol Substitution test (DSST), a performance module from the Wechsler Adult Intelligence Scale (WAIS III), relies on processing speed, sustained attention, and working memory [27]. The DSST has been used in large screenings, epidemiological and clinical studies [28,29]. The assessment is conducted using a paper form that has a key at the top containing nine numbers paired with symbols. Participants have 2 min to copy the corresponding symbols in the 133 boxes that adjoin the numbers. The score is the total number of correct matches. In the NHANES protocol a sample practice test was administered before the participants began the main test. Participants who could not correctly match the symbols with the numbers on their own during the sample test did not continue.

2.4. Statistical methods

Outcomes were all assessed in an unadjusted and in an adjusted analysis. A GLM model (type: general linear model) [30] was used to assess Memory recall, Animal Fluency, and Digit Symbol scores in relation to diabetes and prediabetes. Logarithmic transformation was applied to skewed continuous measures before analysis. Normally distributed data are presented with means ± standard deviations, and non-parametric data are presented with medians (95% prediction interval). P-value of <0.05 was considered to be statistically significant. The adjusted value was calculated with the covariates: gender, BMI, age, systolic blood pressure, educational level, stroke and, LDL).

3. Results

A total of 3287 individuals were included in this study. Of these subjects, 647 participants had prediabetes, and 678 participants had diabetes. The characteristics of the population are shown in Table 1. The relation between the three groups, age and cognitive tests is illustrated in Fig. 1. The unadjusted and adjusted estimates are presented in Table 2. Missing data for each assessment are documented in the NHANES data documentation [18]. For the cognitive test, approximately 84% did complete all three tests and 92% had Hb1Ac measurments.

3.1. Memory recall and delayed memory recall

Memory recall decline was associated with diabetes with an estimate of −0.19 ([−0.34 ; −0.039]p = 0.014). In an adjusted analysis with the covariates gender BMI, age, systolic blood pressure, educational level, stroke and, LDL the association did not remain significant. Both age, systolic blood pressure, educational level, stroke and LDL were found to be statistically significant covariates. For prediabetes no significant effect was observed, −0.001 ([−0.153; 0.15], p = 0.989), this remained non-significant in the adjusted analysis.

Delayed memory recall decline was associated with diabetes with an estimate of −0.285 ([−0.503; −0.067], p = 0.1).

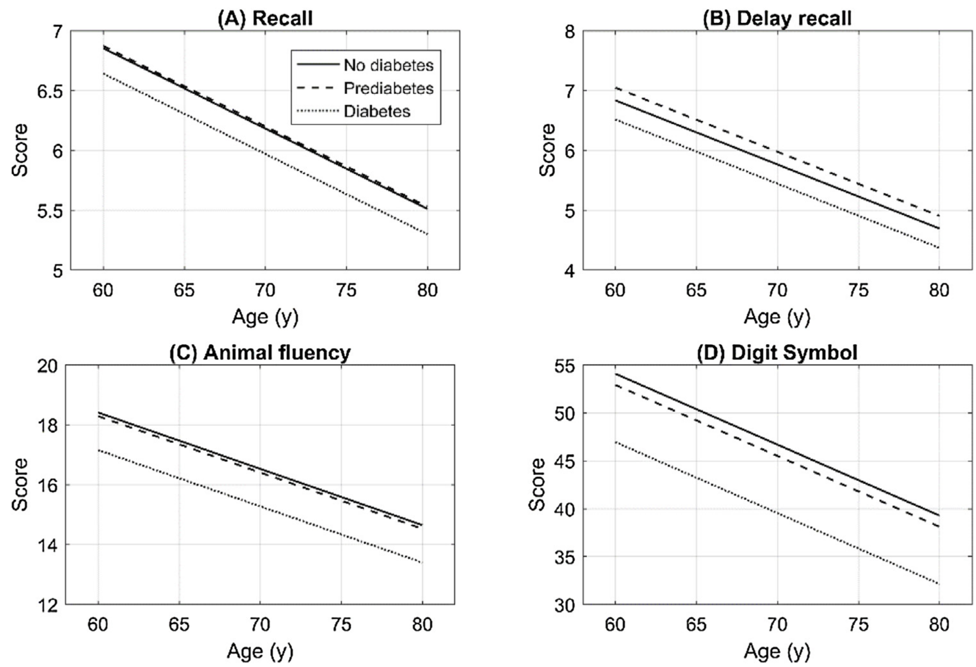

Fig. 1. The relation between age and cognitive test results in people without diabetes, prediabetes and diabetes. Model output.

Table 2
Unadjusted and adjusted* relation from diabetes and prediabetes on test results. Presented with effect estimates with 95% confidence interval of estimate and significance level. *Covariates included in the GLM (model): gender, BMI, age, systolic blood pressure, stroke, educational level and, LDL:

	Prediabetes (n = 647)	95% confidence interval	p-val	Diabetes (n = 678)	95% confidence interval	p-val
Unadjusted						
Memory recall	−0.001	[−0.153; 0.15]	0.989	−0.19	[−0.34; −0.039]	0.014
Memory delayed recall	0.18	[−0.04; 0.4]	0.109	−0.285	[−0.503; −0.067]	0.01
Animal Fluency	−0.174	[−0.68; 0.333]	0.501	−1.185	[−1.688; −0.682]	<0.001
Digit Symbol	−1.411	[−3.009; 0.187]	0.084	−6.897	[−8.491; −5.302]	<0.001
Adjusted						
Memory recall	0.09	[−0.093; 0.272]	0.337	−0.011	[−0.216; 0.195]	0.919
Memory delayed recall	0.217	[−0.049; 0.483]	0.11	−0.07	[−0.369; 0.228]	0.644
Animal Fluency	−0.569	[−1.191; 0.052]	0.073	−0.96	[−1.658; −0.263]	0.007
Digit Symbol	−1.182	[−2.89; 0.525]	0.175	−4.214	[-6.151; −2.277]	<0.001

In an adjusted analysis with the covariates BMI, age,systolic blood pressure, educational level, stroke and, LDL the association did not remain significant with the estimated effect of −0.07 ([−0.369 ; 0.228], p = 0.644). For prediabetes no significant effect was observed, 0.18 ([−0.04; 0.4], p = 0.109), this remained non-significant in the adjusted analysis.

3.2. Animal fluency

Animal Fluency score decline was associated with diabetes with an estimate of −1.185 ([−1.688; -−0.682], p < 0.001) and prediabetes with an non-significant relation with estimate of −0.174 ([−0.68; 0.333], p = 0.501). In an adjusted analysis with the covariates gender, BMI, age, systolic blood pressure, educational level, stroke and, LDL the association with diabetes did remain significant with the estimated effect of −0.96 ([−1.658 ; −0.263], p = 0.007)and prediabetes was still non-significant with the estimated effect of −0.569 ([−1.191; 0.052], p = 0.073).

3.3. Digit symbol

Digit Symbol score decline was associated with diabetes with an estimate of −6.897 ([−8.491; −5.302], p < 0.001) but no association was found for prediabetes with an estimate of −1.411 ([−3.009; 0.187], p = 0.084). In an adjusted analysis with the covariates gender, BMI, age, systolic blood pressure, educational level, stroke and, LDL the association with diabetes did remain significant with the estimated effect of −4.214 ([−6.151; −2.277], p < 0.001)and prediabetes remained non-significant with the estimated effect of −1.182 ([−2.89 ; 0.525], p = 0.175).

4. Discussion

This study investigates the cognitive function in people without diabetes, with prediabetes and with diabetes in a national representative sample of the US population above the age of 60. The results show that there is an association between cognitive decline and diabetes, but this association is not observed in people with prediabetes.

Assessment of immediate and delayed learning ability for new verbal information were reduced in people with diabetes, but the effect was not present after adjusting for covariates. However, both high blood content of LDL and high blood pressure were predicting covariates. These are hallmark traits of diabetes and could be factors for the cognitive decline observed in people with diabetes. The association between hypertension and dementia related to stroke is documented in several studies. Evidence from research shows the development of cognitive decline following stroke in patients [31]. The connection between high blood pressure and cognitive decline in the nonappearance of stroke is more controversial [32]. How-

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ever, several larger studies have confirmed an association between blood pressure and cognitive dysfunction. The Framingham Heart Study has demonstrated that cognitive dysfunction was related to blood pressure measurements [33]. Also, Kivipelto et al. demonstrated in a longitudinal study that midlife arterial hypertension or high cholesterol levels significantly increase the late-life risk of Alzheimer's disease [34]. Moreover, the accumulation of vascular risk factors as in the metabolic syndrome seems to be even more important than each single factor. A number of studies have shown that a higher vascular risk score is associated with worse cognitive performance [35,36].

In this study the Animal Fluency test score were reduced significantly for people with diabetes. AF scores have been shown to discriminate between persons with normal cognitive functioning compared with those with mild cognitive impairment and more severe forms of cognitive impairment [23,24]. The Digit Symbol Substitution test score were also reduced in people with diabetes, also after adjusting for covariates. It is well-established that in those people with type 2 diabetes degree and duration of hyperglycemia are associated to cognitive decline and dementia. More rapid cognitive decline is moreover associated with HbA1c levels and longer duration of disease [34]. Studies have suggested that the pathophysiology of cognitive decline is multifactorial and complex and may even occur at the very earliest stages of diabetes and are further worsened by the metabolic syndrome [37]. The metabolic state in-between normal glucose homeostasis and diabetes have been defined as prediabetes and the risk factors connected to prediabetes have in previous studies been associated to cognitive decline [37–39]. However, we did observe any significant relation to cognitive function and prediabetes in our cohort.

4.1. Strengths and limitations

This study used a sample from the NHANES, which is considered to be a representative section of the adult population in the United States. There is limitation; the nature of cross-sectional study cannot be used to analyze behavior over a period to time and does not determine cause and effect of the observed.

Additionally, in this study, we could not distinguish between individuals with type 1 diabetes and type 2 diabetes. Though, we know that the a larger proportion of patients had type 2 diabetes; up to 95% of diabetics in our nationally representative sample had type 2 diabetes [40]. Selection bias is also a potential limitation to most studies, we cannot rule out that people agreeing to laboratory/cognitive examination are prone to some selection bias. The definition of prediabetes was based on the World Health Organization (WHO)/International Expert Committee (IEC) HbA1c criteria, which seems to have better prediction for CVD and all-cause mortality than individuals with prediabetes identified by the ADA (American Diabetes Association) criteria [17]. Using the ADA criteria for defining prediabetes would have included a different proportion of people as prediabetes. This is important to have in mind when comparing results between studies on cognitive functioning and prediabetes.

4.2. Conclusion

This cross-sectional study demonstrates an association between diabetes and cognitive dysfunction assessed by several cognitive validated tests. Results may indicate that cognitive decline is not yet present in people with mild impairments of glucose homeostasis.

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None to report.

Conflict of interest

The authors declare that they have no competing interests.

Consent for publication

All authors gave consent for publication.

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