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ASSOCIATION BETWEEN DIABETES AND COGNITION IN OLDER ADULTS WITHOUT DEMENTIA

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Abstract: *Objectives:* Data from the Canadian Study of Health and Aging (CSHA) evaluated cognition and depression in a sample of older adults with diabetes and compared them with those without diabetes. *Design:* Neuropsychological test scores from a comprehensive clinical assessment were contrasted for the two groups and test scores from CSHA-1 in 1991 used to predict test scores five years later from CSHA-2 with diabetes and depression as additional predictors. *Results:* There were no differences at CSHA-1 between those with diabetes and those without after adjusting for covariates of age, education, and gender. Older adults with diabetes at CSHA-2 scored lower on a measure of short-term memory, with age, education and CSHA-1 test scores as significant covariates in hierarchical regression analyses. Diabetes and depression were both associated with a measure of verbal short term memory. *Conclusions:* In this relatively healthy community sample, diabetes appears to have modest influences upon cognition, with verbal short-term memory being the most sensitive to the effects of diabetes.

Key words: Aging, diabetes, depression, neuropsychological assessment, memory.

Diabetes, particularly poorly controlled Type 1 diabetes, is associated with multiple health problems, including cognitive changes (1-4). An auto-immune condition, Type 1 diabetes may develop early in life and often leads to cognitive impairment (5). In contrast, Type 2 diabetes is associated with reduced sensitivity to insulin, and is associated with increased body mass in later life. Type 2 diabetes has also been associated with impaired cognitive functioning (6-11) and the conversion of mild cognitive impairment to dementia (12), possibly through the effects of diabetes on blood vessels (13). Both forms of diabetes vary in severity and carry much the same range of health risks. Among elderly people with diabetes in the Canadian Study of Health and Aging (CSHA) there was an increased risk of vascular dementia (14), as well as an increased risk of institutional placement (15).

There are several factors that are important in addressing the association of diabetes with changes in cognitive processes in older adults (16). First, high levels of circulating blood glucose affect the vascular system throughout the body, including the brain. Therefore, the extent to which the diabetes is controlled is important. The worst performance on cognitive tests was obtained by individuals with undiagnosed, and therefore untreated, diabetes (17). Second, increasing age is known to be a risk factor for Type 2 diabetes, which may remain undiagnosed and untreated for longer than desirable. Third, levels of physical activity, education, gender, and other personal characteristics may moderate both the time at which individuals first become aware of their diabetes and the extent to which they maintain effective methods of controlling circulating glucose levels (2).

The presence of diabetes increases the risk of cognitive decline (18, 19). There is, however, less agreement on which domains of cognitive functioning are more susceptible to poor control of blood glucose levels. There has been speculation that prefrontal cortex and executive functions are particularly prone to deterioration with diabetes (20, 21), but other reports have indicated that other functions, such as memory and processing speed, may be affected (17, 22, 23). Construction skills and measures of processing speed and memory were impaired in a group with diabetes (20), with others (23-26) noting lower scores on measures of global cognitive functioning. On a positive note, if confounding factors are controlled, essentially normal cognitive functioning can be expected if glucose levels are well controlled (27).

Several chronic diseases, including diabetes, are known to be associated with increased levels of emotional distress and depression (28, 29). Depression itself can be associated with impaired cognitive processing (30-32), developing independently of any

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chronic medical condition as well as in reaction to illness. Depression has also been associated specifically with diabetes (33-36). Having diabetes doubled the risk of depression (37), but the mechanism for the association remains unknown. For example, neither biochemical factors associated with glucose metabolism nor psychosocial demands of demands of managing the disease were related to the increased prevalence of depression in people with diabetes (36). In contrast, negative life events and poor control of glycated hemoglobin independently predicted the development of depression (35). It is not known whether depression in people with diabetes affects some areas of cognition more than others.

Here we explore the relationship of diagnosed diabetes with neuropsychological tests and with symptoms of depression. We use a representative community sample of older Canadians who were all evaluated to confirm that there was no significant cognitive impairment from any cause, i.e. we look at variation in cognitive function, but exclude those with low functioning, whether this low function may or may not be associated with diabetes. We do not differentiate Type 1 and Type 2 diabetes because both are believed to affect some domains of cognition similarly (19).

Given the existing evidence that diabetes is associated with cognitive impairment (4), it is important to determine when changes in cognition first become apparent and what domains of cognitive function are most affected. This study also assesses the development of cognitive changes in individuals who could not be regarded as cognitively impaired at baseline. We also evaluate the influence of depression upon neuropsychological test scores in several domains of cognition five years later (at the second CSHA evaluation). Previous reports (14, 15, 38) have provided information on the prevalence and incidence of diabetes and its influence as a risk factor for the development of dementia using the CSHA data.

Our first prediction was that measures of abstract reasoning, comprehension, memory, and visuospatial functions would be more affected than other cognitive domains among individuals with diabetes relative to their non-diabetic peers, and that depression would have an association with several domains of cognition. In the second stage of the analyses, we predicted that diabetes would be associated with poorer performance on tests of specific cognitive functions five years later, and that depression would remain associated with scores on the neuropsychological tests 5 years later. We also predicted that depression would be associated with cognitive function independently of the presence of diabetes.

Materials and Methods

Participants

The first stage of the CSHA (CSHA-1) involved 10,263 people from across Canada over 64 years of age; 9008 were living in the community (39). The initial interview included a screen for dementia (3MS; 40); those who scored below 78/100 on the 3MS plus a sample of those scoring above that cut point underwent more detailed assessment including a comprehensive medical and social history from an informant, medical history and examination, laboratory tests, and a neuropsychological examination (39). The project was reviewed and approved by the ethics review bodies at all 18 participating study centers. The second stage of the CSHA in 1996 (CSHA-2) recontacted as many as possible (87.5%) of the original sample. Similar screening and diagnostic procedures were used (41).

A total of 921 people completed the neuropsychological assessment battery at CSHA-1 and were confirmed by diagnostic consensus among the clinical examiners as not having any cognitive impairment. Of this group, 744 people (59% female) had information recorded by the medical history and examination as to whether or not they had diabetes. The mean age at baseline (CSHA-1) was 78.8 years (SD = 6.85), and mean 9.2 years of education (SD = 4.12).

The medical history enquired about various chronic conditions, including any known diabetes, together with information on its treatment and complications. Using this self-report information, a total of 83 individuals were identified during the medical assessment at CSHA-1 as having diabetes within the larger group independently determined by neuropsychological assessment to be without cognitive impairment. Comparisons between the group with and the group without diabetes had power of .80 to detect a difference of .28 standard deviations, with a Type I error rate of .05 as calculated by Pittenger's (42) program. Rockwood (38) summarizes the CSHA procedures to uncover cases of diabetes and reports a value of kappa of .85 for the agreement between self-reported diabetes and a physician assessment that included blood tests of glucose metabolism. Of those with diabetes evaluated at CSHA-1 by the clinical assessment, 33 people with diabetes and 303 without diabetes could still be contacted, remained cognitively intact five years later at CSHA-2, and were also assessed by a neuropsychologist on both occasions. Comparisons between these smaller groups had a power of .80 to detect a difference of .45 standard deviations with a Type 1 error rate of .05 (42). Causes of loss to follow up at CSHA-2 included death (n = 625), development of some form of diagnosed cognitive impairment, refusal to participate (n = 314), or lost from contact (n = 64).

Measures

Tuokko (43) has described the neuropsychological battery that was used in the CSHA in detail. The tests were selected to assess long-and short-term memory, abstract reasoning, judgment, language, gnosis, and construction skills. Long-term memory was assessed by the WAIS-R Vocabulary subtest, with short-term memory by the free recall trial of the Buschke Selective Reminding Test and trial 6 of the Rey Auditory Verbal Learning Test. Short forms of the WAIS-R Comprehension and Similarities subtests assessed judgment and abstract reasoning, respectively, while gnosis was assessed by object and color naming. Block Design was used as the measure of construction skills. The short Token Test evaluated language comprehension, while executive functions were evaluated through a verbal fluency test.

Depression was assessed in CSHA-1 using a 13-item clinical rating scale for the Criterion A symptoms of depression according to DSM-III-R (44). Østbye (45) used the same data to report on the prevalence of depression in older Canadian adults, but, unlike that report, the present paper uses the total number of endorsed symptoms (to a maximum of 13, including the two-week's duration of symptoms variable).

Procedure

The analysis proceeded in two stages. In the first comparison using CSHA-1 data, age, gender, and education were used as the first level in a series of hierarchical logistic regressions to contrast the group with diabetes with the group that did not have diabetes, one analysis for each neuropsychological test score. The second level tested whether or not depression symptoms added to the differentiation. The second set of analyses used the measure of cognition (neuropsychological test scores at CSHA-2) as the dependent outcomes in a hierarchical linear regression with the corresponding test score from CSHA-1 as an additional measure to the same set of demographic variables as in the first analysis. The number of symptoms of depression and diabetes status were added at the second stage. In this second analysis, we could thus evaluate whether depression might alter the relationship between diabetes and the cognitive measures.

Results

There was no significant difference in age between the group in this study with diabetes and those without ($t = 0.25$, $p = .80$), nor in years of education ($t = 0.84$, $p = .40$) or in gender (X^2, 1 df = .06, $p = .81$), previous occupation (X^2 5 df =3.09, p - .69), marital status (X^2 5 df = 3.96, $p = .56$), or in number living alone (X^2 1 df = .10, $p = .75$). Blood glucose levels were assessed in 35 of the individuals with diabetes and in 232 without. The group with diabetes had significantly higher circulating blood levels of glucose (M = 1.5 mmol/L vs 0.6 mmol/L, $t = 4.6$, $p < .001$, 95% CI = .56 to 1.41). Information on Body Mass Index (BMI) was available for 76 individuals with diabetes and 616 individuals without. The group with diabetes had a significantly higher BMI ($M = 26.4$ kg/m^2 vs 24.7 kg/m^2, t 690 df, $p = .001$, 95% CI = 0.72 to 2.79).

Table 1

Hierarchical logistic regression results: CSHA 1 estimated means and odds ratios for groups with diabetes and without diabetes with age, gender and education as covariates

	Diabetes (n = 83)		No Diabetes (n = 661)							
Measure	**Mean**	**Std. Error**	**Mean**	**Std. Error**	**n**	**Odds Ratio (95% Confidence Interval)**	**AuC**	**n**	**Odds Ratio with Depression Added (95% Confidence Interval)**	**AuC**
Vocabulary	5.1	.11	5.2	.04	638	.97 (.76-1.25)	.567	636	1.02 (.87-1.18)	.559
Buschke Recall	7.7	.68	8.5	.25	638	.96 (.87-1.06)	.565	636	1.01 (.87-1.18)	.568
Rey Trial 6	7.3	.39	6.7	.14	533	1.06 (.98-1.15)	.601	533	1.06 (.90-1.23)	.603
Similarities	6.5	.40	6.4	.151	637	1.02 (.95-1.09)	.559	636	1.02 (.87-1.18)	.562
Comprehension	8.8	.35	8.5	.13	636	1.03 (.95-1.12)	.561	635	1.02 (.87-1.18)	.558
Token Test	37.1	.86	36.9	.32	628	1.00 (.97-1.04)	.566	627	1.03 (.88-1.20)	.561
Verbal Fluency	23.3	1.07	24.3	.39	603	.99 (.96-1.02)	.588	602	1.02 (.87-1.18)	.584
Object Naming	11.9	.71	12.7	.26	638	.95 (.84-1.08)	.570	636	1.01 (.87-1.18)	562
Color Naming	5.0	.03	5.0	.01	630	1.61 (.65-4.02)	.579	628	1.03 (.88-1.20)	.574
Block Design	9.2	1.14	11.4	.42	637	.96 (.92-1.01)	.576	635	1.01 (.87-1.18)	.574

Note: n = sample size for that analysis. AuC = Area under the Receiver Operating Characteristic Curve

Table 2

Results of hierarchical least squares regression to predict CSHA-2 cognitive test scores from age, gender, education and CSHA-1 test scores at level 1 with depression and diabetes added at level 2

Measure	n	R^2	B	β	SEβ	95% Confidence Interval
Vocabulary: Level 1 Model	360	.274				
Level 2 Model	311					
CSHA-1 Score		.266	.666	.423	.080	(.51 - .82*)
Gender			-.068	-.023	.151	(-.37 - .23)
Age			-.043	-.186	.012	(-.07 - 02)*
Education			.040	.115	.018	(.01 - .08)*
Diabetes			-.355	-.073	.239	(-.83 - .12)
Depression Symptoms			-.108	-.093	.058	(-.22 - .01)
Buschke Recall: Level 1 Model	354	.256				
Level 2 Model	306	.307				
CSHA-1 score			.559	.394	.069	(.42 - .70)*
Gender			.123	.027	1.223	(-.52 - .56)
Age			-.101	-.287	.018	(-.14 - -.07)*
Education			.004	.007	.026	(-.05 - .06)
Diabetes			-1.185	-.162	.353	(-1.88 - -.49)*
Depression Symptoms			-.188	-.107	.086	(-.36 - -.02)*
Rey Trial 6: Level 1 Model	306	.290				
Level 2 Model	247	.311				
CSHA-1 Score			.502	.450	.064	(.38 - .63)
Gender			.317	.042	.430	(-.53 – 1.16)
Age			-.083	-.138	.034	(-.15 - -.02)*
Education			.156	.175	.050	(.06 - .25)*
Diabetes			-.715	-.058	.668	(-2.03 - .60)
Depression Symptoms			.059	.017	.183	(-.30 - .42)
Similarities: Level 1 Model	358	.529				
Level 2 Model	309	.550				
CSHA-1 Score			.645	.596	.048	(.55 - .74)*
Gender			.159	.018	.354	(-.54 - .86)
Age			-.070	-.101	.028	(-.13 - -.02)*
Education			.237	.226	.047	(.14 - .33)*
Diabetes			-.474	-.033	.560	(-1.58 - .63)
Depression Symptoms			-.110	-.031	.138	(-.38 - .16)
Comprehension: Level 1 Model	358	.370				
Level 2 Model CSHA-1	309	.390				
Score			.453	.469	.049	(.36 - .55)*
Gender			.024	.004	.306	(-.58 - .63)
Age			-.038	-.074	.024	(-.09 - .01)
Education			.198	.254	.040	(.12 - .28)*
Diabetes			.248	.023	.490	(-.72 – 1.21)
Depression Symptoms			-.124	-.047	.119	(-.36 - .11)
Token Test: Level 1Model	346	.435				
Level 2 Model	301	.438				
CSHA-1 Score			.527	.526	.048	(.43 - .62)*
Gender			.758	.054	.625	(-.47 – 1.99)
Age			-.094	-.086	.049	(-.19 - .001)
Education			.383	.235	.079	(.23 - .54)*
Diabetes			-.435	-.019	.983	(-2.37 – 1.50)
Depression Symptoms			-.294	-.053	.244	(-.78 - .19)
Verbal Fluency: Level 1 Model	347	.674				
Level 2 Model	299	.713				
CSHA-1 Score			.858	.822	.039	(.78 - .94)*
Gender			.646	.024	.849	(-1.02 – 2.32)
Age			-.182	-.089	.065	(-.31 - -.05)*
Education			.107	.034	.118	(-.13 - .34)
Diabetes			-1.967	-.047	1.321	(-4.57 - .63)
Depression Symptoms			-.492	-.047	.331	(-1.14 - .16)
Object Naming: Level 1 Model	355	.069				
Level 2 Model	307	.060				
CSHA-1 Score			.116	.098	.067	(-.02 - .25)
Gender			.136	.115	.067	(.004 - .27)*
Age			-.010	-.111	.005	(-.02 - .00)
Education			.024	.178	.008	(.01 - .04)*
Diabetes			-.027	-.015	.106	(-.24 - .18)

Depression Symptoms			-.009	-.019	.026	(-.06 - .04)
Block Design: Level 1 Model	348	.417				
Level 2 Model	303	.407				
CSHA-1 Score			.472	.480	.049	(.38 - .57)*
Gender			.030	.003	.431	(-.82 - .88)
Age			-.129	-.179	.034	(-.20 - -.06)*
Education			.244	.227	.052	(.14 - .35)*
Diabetes			-.201	-.014	.665	(-1.51 – 1.11)
Depression Symptoms			-.260	-.073	.161	(-.58 - .06)
Color Naming: Level 1 Model	347	.002				
Level 2 Model CSHA-1	301	.006				
Score			-.006	-.015	.025	(-.06 - .04)
Gender			.002	.013	.010	(-.02 - .02)
Age			.000	.021	.001	(-.001 - .002)
Education			-.001	-.044	.001	(-.003 - .001)
Diabetes			.007	.025	.016	(-.02 - .04)
Depression Symptoms			.003	.051	.004	(-.004 - .01)

Note: n = sample size foor that analysis; * = 95% confidence interval does not include zero

Table 1 reports the results of the first set of analyses. Numbers reported in the table are the least squares adjusted mean estimates for the logistic regression model, together with the accompanying standard errors, as well as the relative odds ratio (and 95% CI) of diabetes given a one unit increase in the cognitive measure. The main effect for the comparison of the two groups was not significant for any neuropsychological test score. There were significant covariate effects for education (odds ratio .93, 95% confidence interval (CI) .86 - .99) for the recall trial of the Rey Auditory Verbal Learning Test. In no other cases were the covariates significantly associated with the neuropsychological test scores. Adding depression to the equations did not improve the prediction of diabetes status for any of the neuropsychological measures.

Table 2 reports the results of the second set of analyses, hierarchical linear regressions for each of the ten cognitive tests using performance on the tests at CSHA-2 as the outcome. At the first level, gender, age, education and test scores from CSHA-1 were used as a baseline. Table 2 reports only the overall squared multiple correlations for this level. The second level added whether or not the person had diabetes and the number of symptoms of depression at CSHA-1. The CSHA-1 test score was the most common significant predictor, having predictive ability for all measures except the two naming tests. Age and years of education each predicted six of the ten test scores. The scores not predicted by age were for Similarities, Comprehension, and the two naming tests. The scores not predicted by years of education were Vocabulary, Buschke Free Recall, Verbal Fluency, and color naming. Gender predicted only Object Naming performance. The addition of the measures of depression and diabetes status produced significance for the Buschke recall measure (odds ratio for depression -.188, 95% CI -.36 to -.02; -1.195 for diabetes status, 95% CI -1.88 to -.49).

Of the neuropsychological tests, the color naming test was not predicted by any variable and had very little variance to predict as performance was at the maximum for most participants (ceiling effect). All the other test scores had at least two predictive measures being associated with the outcome at the conventional significance level of .05.

Discussion

The initial set of analyses showed that the presence of diabetes was not associated with lowered levels of performance on any cognitive test. The predictions that abstract reasoning, judgment, memory, and visuospatial functions would be lower in people with diabetes were not supported. Our results thus are consistent with (27) that found no or minimal differences between normal older adults and those with diabetes. It is important to note that the present sample excludes those who had developed dementia or a specific form of cognitive change that met the criteria for Cognitive Impairment, No Dementia (CIND; 46). Further, possible roles for influential demographic factors such as education were minimized by controlling them statistically. Bruce (47) addresses a different question from those raised here with their recent report that over 15% of their sample of people with diabetes developed cognitive impairment within a follow-up period of 1.6 years, a notably shorter follow-up period than in our analyses. Other studies (22) that did not screen for cases of dementia or other cognitive impairment at all may be more likely to find cognitive impairment among people with diabetes. At the same time, our measures may have lacked sensitivity for detecting change because they did not include any measures of processing speed, which has been found to be associated with diabetes by others (6, 48, 49).

In the second set of analyses, once again there was little evidence of the influence of diabetes upon the predicted measures. Therefore even with the passage of time, there is little evidence of deterioration in those specific functions. Indeed, associations with diabetes were

evident only on a sensitive measure of memory, the free recall score from the Buschke selective reminding test (50). This finding is consistent with other reported results (17, 18, 51).

As for the association with depression, this too was only associated with the Buschke recall score at CSHA-2. The Buschke is neither timed nor do the instructions stress working quickly, so lower processing speed is unlikely to be a factor in the relatively poor performance of the group with diabetes. Various scores from the Buschke were sensitive to levels of impairment (52), so our findings suggest that it is particularly sensitive to the early stages of memory impairment in people with diabetes.

Individuals with diabetes may thus show relatively few signs of changes in cognition, with some evidence for episodic memory problems as one early sign of changes in cognitive processes. Over a period of five years, only a test of episodic verbal memory was associated with the presence of diabetes. Interestingly, this measure was also the only one associated with the presence of depression. Andersohn (54) provides additional evidence on the complexity of the association with their report of the linkage of the use of antidepressant medication with the incidence of diabetes.

One of the strengths of this paper is the large national sample, with two sets of analyses complementing and supporting one another over time. Screening the sample for cases with forms of pre-existing cognitive impairment or existing dementia and controlling statistically for the influence of demographic factors means that major confounding sources have been controlled, unlike some other studies.

A limitation is that the main focus of the CSHA was on the epidemiology of dementia and the cognitive processes relevant to the diagnosis of dementia. Consequently diabetes may have been underdiagnosed during the medical assessment, and more detailed information on the severity of diabetes was not recorded. A further weakness of this study is that the medical assessment in CSHA did not record the distinction between Type 1 and Type 2 diabetes. A further consideration is the rate of Type 1 errors because across both sets of analyses, only two statistical tests of the 20 regression analyses that were performed showed any differences between groups with diabetes or association with the presence of diabetes. The small sample size of those with diabetes who were tested on both occasions also limits the generalizability of the findings.

In conclusion, our predictions of cognitive impairment and cognitive decline associated with diabetes were not supported. At the same time, we specifically excluded persons with significant existing impairment from our sample. Only measures of episodic memory differed between those with diabetes and those without, suggesting that such memory problems may be among the earliest cognitive functions to be affected by diabetes. Depression also did not appear to be strongly associated with diabetes, which again may be a function of the generally good cognitive functioning in the present sample that was carefully examined to exclude notable cognitive impairment. Future studies will help to elucidate factors accounting for good outcomes and thereby improve the prospects for the other elderly people with diabetes. Our study does suggest that some people with diabetes do very well cognitively and psychologically as they age.

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