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Papers

Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years

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Abstract

Objective To examine the association of type 2 diabetes with baseline cognitive function and cognitive decline over two years of follow up, focusing on women living in the community and on the effects of treatments for diabetes.

Design Nurses' health study in the United States. Two cognitive interviews were carried out by telephone during 1995-2003.

Participants 18 999 women aged 70-81 years who had been registered nurses completed the baseline interview; to date, 16 596 participants have completed follow up interviews after two years.

Main outcome measures Cognitive assessments included telephone interview of cognitive status, immediate and delayed recalls of the East Boston memory test, test of verbal fluency, delayed recall of 10 word list, and digit span backwards. Global scores were calculated by averaging the results of all tests with z scores.

Results After multivariate adjustment, women with type 2 diabetes performed worse on all cognitive tests than women without diabetes at baseline. For example, women with diabetes were at 25-35% increased odds of poor baseline score (defined as bottom 10% of the distribution) compared with women without diabetes on the telephone interview of cognitive status and the global composite score (odds ratios 1.34, 95% confidence interval 1.14 to 1.57, and 1.26, 1.06 to 1.51, respectively). Odds of poor cognition were particularly high for women who had had diabetes for a long time (1.52, 1.15 to 1.99, and 1.49, 1.11 to 2.00, respectively, for ≥ 15 years' duration). In contrast, women with diabetes who were on oral hypoglycaemic agents performed similarly to women without diabetes (1.06 and 0.99), while women not using any medication had the greatest odds of poor performance (1.71, 1.28 to 2.281, and 1.45, 1.04 to 2.02) compared with women without diabetes. There was also a modest increase in odds of poor cognition among women using insulin treatment. All findings were similar when cognitive decline was examined over time.

Conclusions Women with type 2 diabetes had increased odds of poor cognitive function and substantial cognitive decline. Use of oral hypoglycaemic therapy, however, may ameliorate risk.

Introduction

Several population based studies have shown that type 2 diabetes increases the risk of dementia.[1–5] Cognitive decline is an intermediate stage between normal ageing and dementia.[6] As dementia may be most effectively delayed in its initial stages, identifying diabetes as a modifiable risk factor for early cognitive decline could be of major public health importance. Estimates in the United States indicate that delaying onset of dementia by one year could lead to 800 000 fewer cases after 50 years.[7]

Though many investigations have examined diabetes in relation to early cognitive decline,[5 8–19] only one large prospective study has focused on women.[8] Type 2 diabetes disproportionately affects older women and is a stronger risk factor for cardiovascular disease in women than in men.[20] As cardiovascular disease is an independent risk factor for cognitive decline, we need to determine the impact of diabetes on cognition in women.[20] Moreover, few studies have evaluated the influence of different treatments for diabetes on the association between type 2 diabetes and cognition.

We assessed the associations between type 2 diabetes, different treatments for diabetes, and cognitive function in more than 16 000 women.

Methods

The nurses' health study is a prospective cohort of 121 700 US female registered nurses, who were aged 30-55 years in 1976, when the study began. Participants' health information has been updated with biennial mailed questionnaires. Over 90% of the original cohort have been followed up to date.

From 1995-2001, participants aged 70 years and older who had not had a stroke were given baseline cognitive assessments by telephone. Overall, 93% completed the interview. Interviewers were blinded to participants' health status (including diabetes). For the baseline analyses of cognitive function, we included 18 999 women with complete information on education and without type 1 diabetes, gestational diabetes, or unconfirmed diabetes (see below).

The follow up cognitive assessment began about two years after the baseline interview. After the exclusion of the 3% who died, calls have been attempted for 98% to date. Of these, 92% (n = 16 596) completed the interview, 5% (n = 967) refused, 3% (n = 526) were unreachable. For analyses of cognitive decline, we included 16 596 participants who completed both assessments and excluded women in whom diabetes had been newly diagnosed between the baseline and second interviews.

Assessment of cognitive function

Our cognitive assessment has been previously described.[21] Briefly, we initially administered only the telephone interview for cognitive status (TICS) (n = 18 999)[22] but gradually added more tests: immediate (n = 18 295) and delayed recalls of the East Boston memory test (n = 18 268), test of verbal fluency (naming animals, n = 18 285), digit span backwards (n = 16 591), and delayed recall of a 10 word list (n = 16 582). To summarise performance,

we calculated a global score averaging results of the six tests using z scores (16 563 women completed all six tests).

We have established high validity ($r=0.81$ comparing the global score from our telephone interview to an in-person exam) and high reliability ($r=0.70$ for two administrations of the TICS, 31 days apart)[21] for these telephone interviews in highly educated women.

Ascertainment of type 2 diabetes

We identified women who reported that diabetes had been diagnosed by a physician before the baseline cognitive interview. We then confirmed reports based on responses to a supplementary questionnaire including complications, diagnostic tests, and treatment; confirmations conformed to guidelines of the National Diabetes Data Group[23] until 1997, and revised criteria of the American Diabetes Association from 1998.[24] Validation studies found 98% concordance of our nurse participants' reports of type 2 diabetes with medical records.[25] We estimated duration of diabetes by subtracting date of diagnosis from date of baseline cognitive interview. We obtained information on recent drug treatment for diabetes from the biennial questionnaire before the baseline interview.

Statistical analyses

Baseline analyses—We examined the relation between type 2 diabetes and cognitive performance by comparing "poor scorers" to remaining women. "Poor scorers" on the TICS were those who scored <31 points (a pre-established cut off point[21]); on other tests, we defined poor scorers as those below the lowest 10th centile (≤7 for immediate recall and ≤6 for delayed recall on Boston memory test, ≤11 for verbal fluency test, ≤0 for delayed recall of the TICS 10 words list, and ≤3 for digit span backwards). Multivariate adjusted odds ratios of a poor score and 95% confidence intervals were calculated with logistic regression models. We also analysed scores continuously using multiple linear regression to obtain adjusted differences in mean score between women with and without diabetes.

Analyses of cognitive decline—We used logistic regression to calculate odds ratios of "substantial decline," defined as the worst 10% of the distribution of change from the baseline to the second interview (with cut off points for decline of ≥4 on the TICS, ≥6 on the category fluency test, and ≥3 on the other tests). We also used linear regression to estimate adjusted mean differences in decline by diabetes status.

Potential confounding factors—Data on potential confounders were identified from information provided as of the questionnaire immediately before the baseline cognitive assessment. All potential confounding variables were selected a priori based on risk factors for cognitive function in the existing literature (see tables 3 and 4). In analyses of cognitive decline, we adjusted for baseline performance.[26]

Results

At baseline interview 7.3% (n=1394) of the women had type 2 diabetes, with a mean duration of 12 years since diagnosis. Of the 1248 women with diabetes who completed the most recent questionnaire, 901 reported recent medication for management of diabetes (294 (33%) insulin, 607 (67%) oral hypoglycaemic agents). As expected, women with diabetes had higher prevalence of several comorbid conditions (hypertension, high cholesterol, heart disease, obesity, depression) than women without diabetes (table 1), and used hormone therapy less and drank less alcohol. On every cognitive test, mean baseline scores were lower for women with diabetes (table 2).

Table 1 Characteristics of women aged 70-81 years, according to type 2 diabetes. Figures are percentage of respondents unless stated otherwise*

	Without diabetes	With diabetes
No of participants	17 605	1394
Mean age (years)	74.2	74.2
Masters or doctorate degree	5.8	5.0
History of hypertension	53.2	78.1
History of hypercholesterolaemia	64.0	75.5
History of heart disease	5.2	15.2
Obesity (body mass index ≥30 kg/m^2)	15.3	38.8
Self perceived low energy (<55 in SF-36 energy-fatigue index)	13.4	24.7
Self perceived depression (<52 in SF-36 mental health index)	2.6	5.0
Current antidepressant use	5.3	7.9
Current regular aspirin use	37.8	42.0
Current regular use of other non-steroidal inflammatory drugs	17.1	18.2
Current use of vitamin E	41.9	37.2
Current use of postmenopausal hormone	32.6	22.0
Mean (SD) age at menopause in years	48.3 (6.4)	47.7 (6.8)
Median physical activity in metabolic equivalents/week (25th-75th centile)	9.8 (3.2-21.9)	4.3 (1.0-14.0)
Current smoking	8.7	6.0
Median alcohol intake in g/day (25th-75th centile)	1.0 (0.0-6.4)	0.0 (0.0-0.9)

*Characteristics from questionnaire immediately before baseline cognitive test. Type 2 diabetes defined as diagnosis at any time before baseline cognitive test.

We focused analyses on two measures of general cognitive function: the TICS and the global score (table 3). After we adjusted for potential confounding factors, women with diabetes were at 25-35% increased odds of poor baseline score compared with women without diabetes (odds ratio 1.34, 95% confidence interval 1.14 to 1.57, for TICS and 1.26, 1.06 to 1.51, for global score). Findings were consistent when we examined mean differences in scores; the mean score for women with diabetes was lower by –0.42 points, –0.58 to –0.27 points, on the TICS and by –0.09 units, –0.12 to –0.05 units, on the global score compared with women without diabetes. Associations became stronger with longer duration of diabetes. For those with diabetes for ≥15 years the odds of poor cognitive performance was 50% higher than for women without diabetes (1.52, 1.15 to 1.99, and 1.49, 1.11 to 2.00, respectively).

Odds of poor performance also seemed to differ across treatment groups (table 3). Compared with women without diabetes, we found high odds of poor performance for women

Table 2 Mean cognitive test scores at baseline in women aged 70-81, according to type 2 diabetes. Figures are means (SD)

Test (range of scores)	Without diabetes	With diabetes
TICS (8-41 points)	33.8 (2.8)	33.2 (2.9)
TICS 10 word list—delayed (0-10 points)	2.3 (2.0)	2.0 (1.9)
Global score (–4-2 standard units)	0.005 (0.6)	–0.1 (0.6)
East Boston memory test—immediate recall (0-12 points)	9.4 (1.7)	9.3 (1.8)
East Boston memory test—delayed (0-12 points)	9.0 (2.0)	8.9 (2.1)
Verbal fluency test (0-38 points)	16.9 (4.7)	16.3 (4.6)
Digit span backwards (0-12)	6.7 (2.4)	6.4 (2.4)

TICS=telephone interview of cognitive status.

Table 3 Diabetes, duration of diabetes, and use of medication for diabetes in women aged 70-81 in relation to baseline cognitive function

	% of women	Odds ratio of poor cognitive performance (95% CI)		Mean difference in cognitive performance (95% CI)	
		TICS (n=18 999)	Global score* (n=16 563)	TICS (n=18 999)	Global score* (n=16 563)
Diagnosis					
No diabetes	92.7	1.00	1.00	0	0
Diabetes:					
Adjusted for age and education	7.3	1.44 (1.24 to 1.69)	1.37 (1.16 to 1.63)	−0.55 (−0.70 to −0.41)	−0.11 (−0.15 to −0.08)
Multivariate adjusted†	7.3	1.34 (1.14 to 1.57)	1.26 (1.06 to 1.51)	−0.42 (−0.58 to −0.27)	−0.09 (−0.12 to −0.05)
Duration of diabetes (years)					
No diabetes	92.7	1.00	1.00	0	0
Adjusted for age and education:					
≤4	1.5	1.35 (0.97 to 1.88)	1.53 (1.08 to 2.18)	−0.37 (−0.69 to −0.06)	−0.10 (−0.17 to −0.03)
5-9	2.1	1.16 (0.86 to 1.58)	0.91 (0.64 to 1.31)	−0.51 (−0.79 to −0.24)	−0.09 (−0.15 to −0.03)
10-14	1.6	1.59 (1.17 to 2.16)	1.44 (1.03 to 2.02)	−0.68 (−1.00 to −0.37)	−0.12 (−0.19 to −0.05)
≥15	2.1	1.69 (1.30 to 2.21)	1.68 (1.27 to 2.24)	−0.63 (−0.91 to −0.36)	−0.14 (−0.21 to −0.08)
P for trend		<0.0001	<0.0001	<0.0001	<0.0001
Multivariate adjusted†:					
≤4	1.5	1.27 (0.91 to 1.79)	1.48 (1.03 to 2.11)	−0.27 (−0.59 to 0.04)	−0.08 (−0.16 to −0.01)
5-9	2.1	1.10 (0.81 to 1.50)	0.86 (0.60 to 1.25)	−0.41 (−0.69 to −0.14)	−0.07 (−0.13 to −0.01)
10-14	1.6	1.48 (1.08 to 2.02)	1.31 (0.93 to 1.85)	−0.53 (−0.84 to −0.22)	−0.09 (−0.16 to −0.02)
≥15	2.1	1.52 (1.15 to 1.99)	1.49 (1.11 to 2.00)	−0.46 (−0.73 to −0.18)	−0.11 (−0.17 to −0.04)
P for trend		0.0002	0.007	<0.0001	<0.0001
Medication‡					
No diabetes	92.7	1.00	1.00	0	0
Adjusted for age and education:					
Insulin	1.5	1.27 (0.91 to 1.78)	1.48 (1.06 to 2.08)	−0.55 (−0.86 to −0.23)	−0.14 (−0.20 to −0.07)
Oral medication	3.2	1.05 (0.82 to 1.36)	0.99 (0.74 to 1.31)	−0.40 (−0.62 to −0.18)	−0.06 (−0.11 to −0.01)
No reported treatment	1.8	1.70 (1.28 to 2.26)	1.43 (1.03 to 1.98)	−0.42 (−0.71 to −0.13)	−0.09 (−0.16 to −0.02)
Multivariate adjusted†:					
Insulin	1.5	1.20 (0.85 to 1.70)	1.38 (0.97 to 1.95)	−0.40 (−0.72 to −0.09)	−0.11 (−0.18 to −0.03)
Oral medication	3.2	1.06 (0.81 to 1.37)	0.99 (0.74 to 1.33)	−0.35 (−0.58 to −0.13)	−0.06 (−0.11 to −0.01)
No reported treatment	1.8	1.71 (1.28 to 2.28)	1.45 (1.04 to 2.02)	−0.38 (−0.67 to −0.09)	−0.08 (−0.15 to −0.01)

TICS=telephone interview of cognitive status.
*Global score combines TICS, test of verbal fluency, delayed recall of TICS 10 word list, digit backwards test, immediate and delayed recalls of East Boston memory test.
†Adjusted for age at interview (years), highest attained education (registered nurse diploma, Bachelor's degree, Master's or Doctoral degree), history of high cholesterol (yes, no), history of high blood pressure (yes, no), use of vitamin E supplement (currently yes, no), age at menopause (<50, 50-52, ≥53 years), body mass index (<22, 22-24.9, 25-29.9, ≥30 kg/m^2), cigarette smoking (current, past, never), antidepressant use (yes, no), alcohol intake (0, 1-4, 5-14, ≥15 g/day), use of aspirin (current use 1-5 times/week, use ≥6 times/week, no), use of other NSAID (current use, no), postmenopausal hormone use (currently yes, no), mental health index (0-52, 52-100), and energy-fatigue index (0-54, 55-100) from SF-36.
‡Data on medication use from questionnaire immediately before baseline cognitive assessment. Percentages do not total 100% as 0.8% who did not respond to medication question are not presented.

with diabetes who did not report pharmaceutical treatment (1.71, 1.28 to 2.28, and 1.45, 1.04 to 2.02, respectively). Those taking insulin also had modestly increased odds of poor cognition (1.20, 0.85 to 1.70, and 1.38, 0.97 to 1.95, respectively). In the more powerful analyses of mean differences, the worst performance was among women using insulin (mean differences −0.40, −0.72 to −0.09, and −0.11, −0.18 to −0.03, respectively). In contrast, those taking oral medications had similar odds of poor cognitive performance as those without diabetes (odds ratios 1.06, 0.81 to 1.37, and 0.99, 0.74 to 1.33, respectively) and had the smallest mean difference in score (mean differences −0.35, −0.58 to −0.13, and −0.06, −0.11 to −0.01, respectively).

As cognitive impairment may be a cause rather than a consequence of not taking medications, we also examined use of medication at time of diagnosis (average of 12 years before cognitive assessment). However, results were similar: the odds ratios for poor score were 1.61, 1.19 to 2.16, and 1.43, 1.02 to 2.00, respectively, for women with diabetes who were not taking medication at diagnosis compared with women without diabetes.

In addition, as duration of diabetes, medication use, and level of control are correlated we conducted additional analyses to try to assess their independent effects. The results for duration of diabetes were largely similar after we adjusted for medication use, and results for medication use were largely unchanged after we included a term for duration in the model or stratified by duration of diabetes. For example, among women with diabetes, those not taking medication had a higher risk of poor cognitive performance on the TICS compared with those taking oral medication both in the group with duration of diabetes <10 years (1.73, 1.01 to 2.98) and ≥ 10 years (1.90, 1.04 to 3.48). Furthermore, although we did not have detailed information on level of control (for example, data on haemoglobin A_{1c} concentration), all results were generally unchanged when we excluded data from women with metabolic complications (for instance, those with severely uncontrolled disease).

Finally, we restricted analyses to participants who did not report any difficulty with hearing (n=12 099) to reduce confounding by hearing status. The results were similar when we compared women with and without diabetes (1.45, 1.18 to 1.78, and 1.37, 1.10 to 1.71, respectively).

Prospective analyses of decline

Although cognitive decline was measured over just a two year period, we observed a significantly increased odds of substantial decline on the TICS (1.26, 1.03 to 1.54) for women compared with women without type 2 diabetes (table 4). However, we observed little overall relation between diabetes and decline on the global score (1.11, 0.90 to 1.37). Similarly, mean decline was greater among women with diabetes by −0.17 points (−0.33 to −0.01) on the TICS but was comparable in the two groups on

Table 4 Diabetes, duration of diabetes, use of medication for diabetes in women aged 70-81 in relation to cognitive decline over two years

	%	Odds ratio of substantial decline (95% CI)		Mean difference in cognitive decline (95% CI)	
		TICS (n=16 596)	Global score* (n=14 470)	TICS (n=16 596)	Global score* (n=14 470)
Diagnosis					
No diabetes	92.9	1.00	1.00	0	0
Diabetes:					
Adjusted for age and education	7.1	1.36 (1.12 to 1.65)	1.20 (0.97 to 1.47)	–0.29 (–0.44 to –0.13)	–0.03 (–0.06 to 0.00)
Multivariate adjusted†	7.1	1.26 (1.03 to 1.54)	1.10 (0.89 to 1.37)	–0.17 (–0.33 to –0.01)	–0.01 (–0.04 to 0.02)
Duration of diabetes (years)					
No diabetes	92.9	1.00	1.00	0	0
Adjusted for age and education:					
≤4	1.6	1.25 (0.83 to 1.88)	0.68 (0.40 to 1.17)	0.04 (–0.28 to 0.35)	0.05 (–0.01 to 0.12)
5-9	2.0	1.08 (0.74 to 1.59)	1.08 (0.73 to 1.59)	–0.10 (–0.38 to 0.18)	0.01 (–0.05 to 0.06)
10-14	1.6	1.35 (0.90 to 2.02)	1.53 (1.03 to 2.27)	–0.36 (–0.67 to –0.04)	–0.09 (–0.15 to –0.03)
≥15	1.9	1.77 (1.27 to 2.47)	1.51 (1.05 to 2.15)	–0.68 (–0.97 to –0.40)	–0.08 (–0.13 to –0.02)
P for trend		0.0004	0.005	<0.0001	0.001
Multivariate adjusted:					
≤4	1.6	1.15 (0.76 to 1.74)	0.65 (0.38 to 1.12)	0.14 (–0.18 to 0.46)	0.07 (0.01 to 0.13)
5-9	2.0	1.00 (0.68 to 1.47)	1.01 (0.68 to 1.49)	–0.01 (–0.29 to 0.27)	0.02 (–0.04 to 0.07)
10-14	1.6	1.26 (0.83 to 1.90)	1.40 (0.94 to 2.09)	–0.23 (–0.55 to 0.09)	–0.07 (–0.13 to 0.00)
≥15	1.9	1.64 (1.17 to 2.30)	1.35 (0.93 to 1.94)	–0.54 (–0.83 to –0.25)	–0.05 (–0.11 to 0.01)
P for trend		0.005	0.05	0.0004	0.05
Medication‡					
No diabetes	92.9	1.00	1.00	0	0
Adjusted for age and education:					
Insulin	1.5	1.49 (0.99 to 2.25)	1.22 (0.79 to 1.89)	–0.59 (–0.92 to –0.26)	–0.08 (–0.15 to –0.01)
Oral medication	3.1	1.12 (0.82 to 1.51)	0.82 (0.58 to 1.14)	0.00 (–0.22 to 0.23)	0.02 (–0.03 to 0.06)
No reported treatment	1.8	1.35 (0.93 to 1.95)	1.67 (1.18 to 2.37)	–0.27 (–0.56 to –0.03)	–0.02 (–0.08 to 0.04)
Multivariate adjusted:					
Insulin	1.5	1.39 (0.91 to 2.10)	1.08 (0.69 to 1.68)	–0.44 (–0.77 to –0.11)	–0.05 (–0.12 to 0.02)
Oral medication	3.1	1.09 (0.80 to 1.48)	0.77 (0.54 to 1.08)	0.07 (–0.16 to 0.30)	0.03 (–0.02 to 0.08)
No reported treatment	1.8	1.31 (0.90 to 1.90)	1.62 (1.13 to 2.30)	–0.23 (–0.53 to 0.06)	–0.02 (–0.08 to 0.05)

TICS=telephone interview of cognitive status.
*Global score combines TICS, test of verbal fluency, delayed recall of TICS 10 word list, digit backwards test, immediate and delayed recalls of East Boston memory test.
†Adjusted for age at interview (years), highest attained education (registered nurse diploma, Bachelor's degree, Master's or Doctoral degree), history of high cholesterol (yes, no), history of high blood pressure (yes, no), use of vitamin E supplement (currently yes, no), age at menopause (<50, 50-52, ≥53 years), body mass index (<22, 22-24.9, 25-29.9, ≥30 kg/m^2), cigarette smoking (current, past, never), antidepressant use (yes, no), alcohol intake (0, 1-4, 5-14, ≥15 g/day), use of aspirin (current use 1-5 times/week, use ≥6 times/week, no), use of other NSAID (current use, no), postmenopausal hormone use (currently yes, no), mental health index (0-52, 52-100), and energy-fatigue index (0-54, 55-100) from SF-36.
‡Data on medication use from questionnaire immediately before baseline cognitive assessment. Percentages do not total 100% as 0.8% who did not respond to medication question are not presented.

the global score (mean difference in decline −0.01, −0.04 to 0.03). In addition, qualitative relations with longer duration diabetes and use of medication were generally similar to those observed with baseline cognitive function.

Discussion

In this large prospective study of women aged 70-81 years with type 2 diabetes who were living in the community we found that they had marginally worse baseline cognitive performance and greater cognitive decline than women without diabetes. Longer duration of diabetes resulted in larger associations. However, women who said they were on hypoglycaemic treatment seemed to have a similar likelihood of poor cognition as women without diabetes, while women not taking medication for diabetes or those taking insulin had worse performance.

A major strength of our study is the large sample size for assessing the relations between type 2 diabetes, duration, treatment, and cognition. Other strengths are the prospective assessment of diabetes and potential confounders over 25 years of follow up and the relative homogeneity of the sample in terms of education and access to health care, which should minimise confounding.

Limitations

Limitations should be considered. Firstly, as we relied on the women reporting their own diabetes status, we may have included some women with undiagnosed diabetes in the reference group, which could have led to underestimation of the true associations. However, undiagnosed diabetes was probably rare in these nurses. Among a random sample of those with no reported diabetes, plasma samples indicated just 2% had diagnostic signs of type 2 diabetes. Secondly, as in all studies of cognitive decline, there is regression to the mean on the repeat cognitive assessment. As women with type 2 diabetes had worse cognitive performance at baseline, regression to the mean would probably have attenuated the true magnitude of cognitive decline associated with diabetes.

In addition, there are important issues to consider in interpreting our findings regarding pharmaceutical treatment of diabetes. Participants who were not taking any treatment for diabetes probably included a heterogeneous group of women with untreated diabetes and diabetes controlled through diet. Diabetes that can be controlled through diet may not be associated with poor cognition.[14] Thus, we have probably underestimated the effect of untreated diabetes. However, the increased odds of poor cognition associated with no treatment was similar across those with shorter and longer duration of diabetes (and

What is already known on this topic

Many epidemiological studies have shown that type 2 diabetes increases the risk of cognitive decline, though most studies have been in men

Type 2 diabetes is associated with greater risk of cardiovascular disease in women than in men, and cardiovascular disease may increase the risk of cognitive decline

What this study adds

Women with type 2 diabetes have about 30% greater odds of poor cognitive function than those without diabetes, with a 50% increase after 15 years' of diabetes

Women with diabetes who did not report medical treatment had the highest risk of poor cognitive function and substantial cognitive decline

Women with diabetes who reported taking oral medication had a similar risk of cognitive decline as women without diabetes

duration is probably a good indicator of prevalence of dietary control), suggesting that our underestimate may be minimal.

Though our finding that insulin treatment was associated with poor cognitive performance is consistent with results of other studies of cognition,[8 14] it is difficult to draw conclusions; people with diabetes who use insulin all have longer duration of diabetes, worse control, and higher prevalence of hypoglycaemic attacks, rendering it hard to adjust appropriately for confounding. None the less, there is growing evidence directly linking insulin to cognitive impairment: chronic hyperinsulinaemia[10] and incremental increases in serum insulin concentration after a glucose load[13] predict diminished cognition in the absence of diabetes or glucose intolerance. Moreover, insulin degrading enzyme regulates concentrations of both insulin and amyloid β in the brain[27] and infusion of insulin into healthy humans increases amyloid β concentrations in the cerebrospinal fluid,[28] further supporting a direct association between insulin and cognition.

Finally, consistent with our findings of similar cognitive performance among women taking oral medication and those without diabetes, in a controlled trial of participants with type 2 diabetes, Testa and Simonson noted that improved glucose control with oral medications resulted in better cognitive acuity, memory, and orientation.[29] In addition, an observational study of Mexican-Americans with diabetes reported significantly less cognitive decline in those with medical treatment than without.[30] Thus, although physicians may avoid prescribing oral therapy for diabetes in older people, it may be important to their cognitive health.

Conclusions

In conclusion, we found worse cognitive function and accelerated cognitive decline among women with type 2 diabetes, which seemed to be ameliorated with oral hypoglycaemic treatment. Studies have established that, in apparently healthy people, even modest differences in cognition result in substantially increased risks of dementia over several years.[6] Prevention and control of type 2 diabetes in women could have critically important public health consequences.

Contributors: GL and FG led the study design; GL, JHK, and FG contributed to the interpretation and the analysis of the data; JHK conducted the analysis of the data. FG was responsible for obtaining funding for the study. All authors contributed to writing the manuscript and are joint guarantors.

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Competing interests: During the last five years GL has received honorariums for lectures from Pfeizer and Lilly Pharmaceutical. During the past five years FG has received honorariums or temporary consulting fees from Novo Nordisk, Schering-Plough, Novartis, Orion Pharma, and Wyeth Ayerst.

Ethical approval: This study was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, MA.

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