

Ethical approval: The study protocol was reviewed and approved by institutional review boards at the College of Medicine, University of Malawi, and the University of Maryland, Baltimore.

- 1 Bloland PB, Lackritz EM, Kazembe PN, Were JB, Steketee R, Campbell CC. Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa. *J Infect Dis* 1993;167:932-7.
- 2 Nzila AM, Nduati E, Mberu EK, Hopkins SC, Monks SA, Winstanley PA, et al. Molecular evidence of greater selective pressure for drug resistance exerted by the long-acting antifolate pyrimethamine/sulfadoxine compared with the shorter-acting chlorproguanil/dapsone on Kenyan *Plasmodium falciparum*. *J Infect Dis* 2000;181:2023-8.
- 3 Plowe CV, Doumbo OK, Djimde A, Kayentao K, Diourte Y, Doumbo SN, et al. Chloroquine treatment of uncomplicated *Plasmodium falciparum* malaria in Mali: parasitologic resistance versus therapeutic efficacy. *Am J Trop Med Hyg* 2001;64:242-6.
- 4 Peterson DS, Milhous WK, Wellems TE. Molecular basis of differential resistance to cycloguanil and pyrimethamine in *Plasmodium falciparum* malaria. *Proc Natl Acad Sci USA* 1990;87:3018-22.
- 5 Triglia T, Menting JGT, Wilson C, Cowman AF. Mutations in dihydropteroate synthase are responsible for sulfone and sulfonamide resistance in *Plasmodium falciparum*. *Proc Natl Acad Sci USA* 1997;94:13944-9.
- 6 Kublin JG, Dzinjalimala FK, Kamwendo DD, Malkin EM, Cortese JF, Martino LM, et al. Molecular markers for failure of sulfadoxine-pyrimethamine and chlorproguanil-dapsone treatment of *Plasmodium falciparum* malaria. *J Infect Dis* 2002;185:380-8.
- 7 Kublin JG, Cortese JF, Njunju EM, Mukadam RAG, Wirima JJ, Kazembe PN, et al. Reemergence of chloroquine-sensitive *Plasmodium falciparum* malaria following cessation of chloroquine use in Malawi. *J Infect Dis* 2003;187:1870-5.
- 8 Plowe CV, Kublin JG, Doumbo OK, P. *falciparum* dihydrofolate reductase and dihydropteroate synthase mutations: epidemiology and role in clinical resistance to antifolates. *Drug Resist Update* 1998;1:389-96.
- 9 Cortese JF, Plowe CV. Antifolate resistance due to new and known *Plasmodium falciparum* dihydrofolate reductase mutants expressed in yeast. *Mol Biochem Parasitol* 1998;94:205-14.
- 10 Sirawaraporn W, Sathikul T, Sirawaraporn R, Yuthavong Y, Santi DV. Antifolate-resistant mutants of *Plasmodium falciparum* dihydrofolate reductase. *Proc Natl Acad Sci USA* 1997;94:1124-9. (Accepted 2 December 2003)

doi 10.1136/bmj.37977.653750.EE

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

Giancarlo Logroscino, Jae Hee Kang, Francine Grodstein

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 by 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

Many investigations have examined diabetes in relation to early cognitive decline, but only one large prospective study has focused on women.¹ Type 2 diabetes disproportionately affects older women and is a stronger risk factor for cardiovascular disease in women than in men.² Cardiovascular disease is also an independent risk factor for cognitive decline. 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. From 1995-2001, participants aged 70 years and older who had not had a stroke were given baseline cognitive

Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA

Giancarlo Logroscino
associate professor of neuroepidemiology

Channing Lab, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115

Francine Grodstein
associate professor of medicine

Jae Hee Kang
instructor of medicine

Correspondence to: G Logroscino
glogrosc@hsph.harvard.edu

BMJ 2004;328:548-51



This is the abridged version of an article that was posted on bmj.com on 23 February 2004: <http://bmj.com/cgi/doi/10.1136/bmj.37977.495729.EE>

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.

The follow up cognitive assessment began about two years after the baseline interview. For analyses of cognitive decline, we included 16 596 participants who completed both assessments, excluding women who had died, refused, or were unreachable or in whom diabetes had been newly diagnosed between the baseline and second interviews.

Assessment of cognitive function

Our cognitive assessment has been previously described and has high reliability and validity.³ Briefly, we initially administered only the telephone interview for cognitive status (TICS)⁴ but gradually added more tests: immediate and delayed recalls of the East Boston memory test, test of verbal fluency, digit span backwards, and delayed recall of a 10 word list. To summarise performance, we calculated a global score averaging results of the six tests using z scores (16 563 women completed all six tests).

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. Validation studies found 98% concordance of participants' reports of type 2 diabetes with medical records.⁵ 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 of the nurses' health study 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 point³); on other tests, we defined poor scorers as those below the lowest 10th centile. 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

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/m²), 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.

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. We also used linear regression to estimate adjusted mean differences in decline by diabetes status.

Potential confounding factors—Potential confounders were identified from information provided from 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. In analyses of cognitive decline, we adjusted for baseline performance.⁶

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, and used hormone therapy less and drank less alcohol. On every cognitive test, mean baseline scores were lower for women with diabetes.

We focused analyses on two measures of general cognitive function: the TICS and the global score (table). 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. Findings were consistent when we examined mean differences in scores. For those with diabetes for ≥ 15 years the odds of poor cognitive performance were 50% higher than for women without diabetes.

Compared with the odds in women without diabetes, we found high odds of poor performance for women with diabetes who did not report pharmaceutical treatment. Those taking insulin also had modestly increased odds of poor cognition. In the more powerful analyses of mean differences, the worst performance was among women using insulin. In contrast, those taking oral medications had similar odds of poor cognitive performance as those without diabetes and had the smallest mean difference in score.

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). 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 were largely similar after we did so.

Finally, we restricted analyses to participants who did not report any difficulty with hearing (n = 12 099)

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

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

We observed a significantly increased odds of substantial decline over the two year period on the TICS (1.26, 1.03 to 1.54) for women with, compared with women without, type 2 diabetes (see bmj.com). 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 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

This large prospective study of women aged 70–81 years with type 2 diabetes found marginally worse baseline cognitive performance and greater cognitive decline than women without diabetes. Longer duration of diabetes resulted in larger associations. 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, 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.

Limitations

We relied on self reported diabetes status, so we may have included some women with undiagnosed diabetes

in the reference group. However, this was probably rare in these nurses; plasma samples from a random sample of those with no reported diabetes, indicated just 2% had diagnostic signs of type 2 diabetes.

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.

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.⁷ 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 duration is probably a good indicator of prevalence of dietary control), suggesting that our underestimate may be minimal.

There is growing evidence directly linking insulin to cognitive impairment: chronic hyperinsulinaemia⁸ and incremental increases in serum insulin concentration after a glucose load⁹ 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 brain¹⁰ and infusion of insulin into healthy humans increases amyloid β concentrations in the cerebrospinal fluid,¹¹ further supporting a direct association between insulin and cognition.

Other studies have also found less cognitive decline in those with medical treatment for their diabetes than those without.¹²⁻¹³ Thus, although physicians may avoid prescribing oral therapy for diabetes in older people, it may be important to their cognitive health.

Conclusions

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.¹⁴ Prevention and control of type 2 diabetes in women could have critically important public health consequences.

Contributors: See bmj.com

Funding: Grants AG15424 and CA87969 from the National Institutes of Health. FG is partially supported by a New Scholars in Aging award from the Ellison Medical Foundation.

Competing interests: During the last five years GL has received honorariums for lectures from Pfizer 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.

- 1 Gregg, EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160:174-80.
- 2 Coker LH, Shumaker SA. Type 2 diabetes mellitus and cognition: an understudied issue in women's health. *J Psychosom Research* 2003;54: 129-39.
- 3 Kang JH, Grodstein F. Regular use of nonsteroidal anti-inflammatory drugs and cognitive function in aging women. *Neurology* 2003;60:1591-7.
- 4 Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* 1988;1:111-7.
- 5 Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 1991;338:774-8.
- 6 Vickers A, Altman D. Analysing controlled trials with baseline and follow-up measurements. *BMJ* 2001;323:1123-4.
- 7 Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, et al. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham study. *Diabetes Care* 1997;20:1388-95.
- 8 Kalmijn S, Feskens EJ, Launer LJ, Stijnen T, Kromhout D. Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995;38:1096-102.
- 9 Stolk RP, Breteler MM, Oit A, Pols HA, Lamberts SW, Grobbee DE, et al. Insulin and cognitive function in an elderly population. The Rotterdam study. *Diabetes Care* 1997;20:792-5.
- 10 Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci USA* 2003;100:4162-7.
- 11 Watson GS, Peskind ER, Asthana S, Purganan K, Wait C, Chapman D, et al. Insulin increases CSF Abeta42 levels in normal older adults. *Neurology* 2003;60:1899-903.
- 12 Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* 1998;280:1490-6.
- 13 Wu JH, Haan MN, Liang J, Ghosh D, Gonzalez HM, Herman WH. Impact of antidiabetic medications on physical and cognitive functioning of older Mexican Americans with diabetes mellitus: a population-based cohort study. *Ann Epidemiol* 2003;13:369-76.
- 14 Bozoki A, Giordani B, Heidebrink JL, Berent S, Foster NL. Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Arch Neurol* 2001;58:411-6.

(Accepted 27 November 2003)

doi 10.1136/bmj.37977.495729.EE

A memorable consultation

A home visit in an old industrial part of Swansea left me with an indelible memory of two things—the flu pandemic of 1918, which caused an estimated 24-40 million deaths, and the way in which doctors were sometimes paid in the past. It was not uncommon for this to be in kind, and occasionally grateful patients were prepared to part with cherished family heirlooms.

I saw Mrs Davies in the early 1980s, when she herself was 85 and her faculties were failing. She lived alone, and I arranged to see her with her brother, who had travelled some distance to be present. She gave an excellent account of her early life and the tragic circumstances of her husband's death.

It was early on a Friday. Her fiancé, a soldier, had returned home on leave from the first world war. On Monday they were married, and on Tuesday he started to develop flu symptoms. Its course was

rapid and fulminating, and on the following Friday he died. Within that week her world had changed from absolute joy to tragedy. She did not remarry and bore her loss with great dignity.

The consultation took place in the living room, the middle room of a terraced house. On the sideboard was an exceptional clock. It was 18 inches tall with a jet black wooden case, presumably ebony. Inside the glass front was a brilliant white face with black Roman numerals; the pendulum shone. As I left, I said to her brother that it was difficult not to admire such an exceptional timepiece. He paused, looked at me sternly, and growled, "It's mine."

Donald D R Williams *consultant psychiatrist, Cefn Coed Hospital, Swansea*