Diabetes and Function in Different Cognitive Systems in Older Individuals Without Dementia

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OBJECTIVE — To examine the relation of type 2 diabetes to the level of function in five different cognitive systems in older individuals without dementia.

RESEARCH DESIGN AND METHODS — Participants were 882 older men and women without dementia participating in the Rush Memory and Aging Project, a longitudinal clinical-pathological study of aging and dementia. They underwent uniform evaluations, which included clinical classification of dementia, and detailed cognitive function testing from which previously established summary measures of episodic memory, semantic memory, working memory, perceptual speed, visuospatial ability, and global cognition were derived. Diabetes was identified by history and direct medication inspection.

RESULTS — Diabetes was present in 116 (13%) participants. In separate linear regression models controlling for age, sex, and education, diabetes was associated with lower levels of semantic memory ($P < 0.001$) and perceptual speed ($P = 0.005$), but not with episodic memory, working memory, or visuospatial ability or with a measure of global cognition. The associations of diabetes with cognition were reduced when controlling for several vascular variables, and the associations were substantially stronger in current smokers than in individuals who never smoked or formerly smoked.

CONCLUSIONS — These results suggest that type 2 diabetes is associated with cognitive impairment, especially in semantic memory and perceptual speed and that these effects may be modified by smoking status.

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Type 2 diabetes is a common disease in older age, affecting about one in five individuals over the age of 65 years. It is associated with mortality and significant morbidity, including neurological disability. Although the effects of diabetes on the peripheral nervous system are well established, the effects of diabetes on the central nervous system have been less clear (1,2). Several studies have found that diabetes is related to dementia (3,4) and lower levels of cognitive function (5,6), whereas others have not (7,8). Further, some studies found that diabetes was associated with lower scores on some individual cognitive tests, but not on others (9,10), suggesting that diabetes may differentially affect cognition. To date, few studies have systematically examined the relation of diabetes to different cognitive domains in a large cohort of older individuals (11). Further, to our knowledge, none have identified factors that might modify this relation.

We used data from the Rush Memory and Aging Project, an ongoing epidemiologic study of neurological conditions of old age, to examine the relation of diabetes to cognitive function in nearly 900 older individuals free of dementia. We examined the relation of type 2 diabetes to summary measures of specific cognitive domains and of global cognitive function. In addition, because of the relation of diabetes to vascular disease, we examined whether selected vascular risk factors, such as smoking, or conditions, such as stroke, could explain or modify the relation of diabetes to cognition.

RESEARCH DESIGN AND METHODS

— All participants were older individuals who enrolled in the Rush Memory and Aging Project, an ongoing longitudinal clinical-pathological study of risk factors for chronic neurological conditions of old age (12,13). They were recruited from retirement facilities in the greater Chicago metropolitan area, and all provided informed consent. The study was approved by the Institutional Review Board of Rush University Medical Center.

Individuals were eligible for these analyses if they had completed a baseline clinical evaluation and were free of dementia. Clinical evaluations were structured and uniform and included a medical history, neurological examination, and a detailed assessment of cognitive function (see below). All participants were asked to bring prescription and over-the-counter medication containers, which were then visually inspected and coded using the Medi-Span system (14). Each participant was examined by a neurologist or geriatrician experienced in the evaluation of individuals with dementia who, after review of all clinical data, classified participants with respect to dementia (15). Of the 941 individuals enrolled in the study from 1 January 1997 to 1 April 2005, 59 met criteria for dementia and were excluded from analyses. In the remaining 882 individuals, age was 80.5 ± 6.9 years (mean ± SD), education was 14.4 ± 3.1 years, and the Mini-Mental State Examination score was 27.8 ± 2.2; 73.5% were women and 91.2% were white and non-Hispanic.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Assessment of diabetes

Diabetes was present if, at the baseline evaluation, the participant reported a history of diagnosis of diabetes or was taking medication (insulin or oral hypoglycemic) to treat diabetes, as determined by direct inspection of all prescription and nonprescription medication containers. A history of diabetes was identified by answering "yes" to any of three questions: *1*) "Have you ever been told by a doctor, nurse, or therapist that you had diabetes, or sugar in the urine, or high blood glucose?" *2*) "Has a doctor, nurse, or therapist ever told you to take insulin or injections for your high blood glucose?" *3*) "Has a doctor, nurse, or therapist ever told you to take medicine by mouth for your high blood glucose?" The identification of diabetes is consistent with that previously reported in the Religious Orders Study (2,11).

Assessment of cognitive function

Cognitive function tests were selected to assess a broad range of cognitive abilities commonly affected by aging (16). The Mini-Mental State Examination was used for descriptive purposes but not in analyses. The remaining 19 tests were chosen to assess five cognitive domains that may be differentially related to a variety of diseases or conditions. The grouping of tests into the five cognitive domains was supported by a factor analysis with varimax rotation (16). The agreement between the factor analytic grouping and the hypothesized grouping was assessed with the Rand's statistic, which equaled 0.79, indicating a good fit ($P < 0.001$ for the hypothesis test of no concordance). Episodic memory was evaluated using seven tests: Word List Memory, Word List Recall, and Word List Recognition from the procedures established by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (17); immediate and delayed recall of Story A from the Logical Memory subtest of the Wechsler Memory Scale–Revised (18); and immediate and delayed recall of the East Boston Story (19). Three tests assessed semantic memory: Verbal Fluency (17), an abbreviated version of the Boston Naming Test (17), and an abbreviated version of the Reading Test (20). There were three working memory tests: Digit Span Forward and Backward of the Wechsler Memory Scale–Revised (18) and Digit Ordering (21). Four tests assessed perceptual speed: the Symbol Digit Modalities Test (22), Number Comparison (23), and two indexes from a modified version of the Stroop Neuropsychological Test (16). Visuospatial ability was evaluated by two tests: items from Judgment of Line Orientation and Standard Progressive Matrices (24).

To minimize floor and ceiling effects and other sources of measurement error, we constructed summary measures of each cognitive domain for use in analyses, rather than using individual test scores. We used previously established summary measures (16) of five cognitive domains, episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability, as well as a summary measure of global cognitive function. Each cognitive domain summary measure was derived by converting the raw scores from the corresponding individual tests to *z* scores, using the mean and SD from the evaluation of all participants in the study and averaging the *z* scores. A measure of global cognitive function was formed by averaging the *z* scores of all 19 tests. Valid summary measures required valid scores on at least half of the component tests, which was the case for >98% of participants for each of the six summary measures.

Assessment of vascular risk factors and conditions

A comprehensive baseline medical history is collected on all participants in the Rush Memory and Aging Project. A variety of questions pertain to vascular risk factors, including current and former smoking, and vascular conditions, including a history of stroke, myocardial infarction, congestive heart failure, and claudication. Current smoking was based on the question, "Do you smoke cigarettes now?" and, if the participant answered "no," then he or she was asked about former smoking based on the question, "Did you ever smoke cigarettes regularly?" Questions pertaining to leg claudication were derived from the Rose questionnaire (25). Further, clinical examinations allowed for documentation of several health and disease indexes. Systolic blood pressure was obtained from the average of three measures of systolic pressure (two while sitting and one after standing 1 min), and diastolic blood pressure was similarly obtained. Other indexes collected during the examinations included measured height and weight to calculate BMI (kg/m^2), as well as signs suggestive of stroke on neurological examination. These signs included a unilateral pronator drift, focal weakness, asymmetric reflexes, and a Babinski sign. For the purpose of this study, current or former cigarette smoking history, myocardial infarction, congestive heart failure, and claudication were rated as absent or present as determined by self-report. Systolic and diastolic blood pressure and BMI were based on the examinations and were analyzed as continuous variables. Stroke was the examining physician's diagnosis based on the clinical history and neurological examination findings.

Data analyses

The relation of diabetes to cognitive function was examined in a series of linear regression models. All models were adjusted for age, sex, and education. We first examined the relation of diabetes to each measure of function in a specific cognitive domain and then to a measure of overall cognitive ability. Because there were six outcomes, we used a *P* value of 0.008 (0.05 divided by 6) for a two-sided test as a cutoff score for significance for all regression analyses presented here. In subsequent analyses of cognition, we repeated the core models with terms added separately for nine vascular risk factors or conditions that might account for the association of diabetes with cognition. We then tested in separate models whether any of these nine vascular variables modified the relation of diabetes to cognition. Finally, after identifying an interaction between diabetes and smoking, we examined the effect of three separate model terms (no diabetes, smoking; diabetes, no smoking; diabetes, smoking) on each of the six cognitive outcome measures. Models were validated graphically and analytically. Programming was done in SAS.

RESULTS

Characteristics of individuals with and without diabetes

Of the 882 study participants included in these analyses, diabetes was present in 116 (13%). Of those with diabetes, 77 (66%) were taking medication for the treatment of diabetes: 9 were taking insulin but no oral hypoglycemic drug, 57 were taking an oral hypoglycemic drug but no insulin, and 11 were taking both. Overall, individuals with diabetes were

Table 1—*Characteristics of 882 participants according to the presence or absence of diabetes*

	No diabetes	Diabetes	*P*
n	766	116	—
Age (years)	80.9 ± 6.8	78.0 ± 7.3	<0.001
Male sex (%)	25.1	36.2	0.011
Education (years)	14.5 ± 3.0	13.7 ± 3.4	0.007
MMSE score/30	27.9 ± 2.1	27.5 ± 2.7	0.185
Current smoking (%)	3.5	6.1	0.189
Former smoking (%)	35.5	36.8	0.782
Stroke (%)	9.6	13.8	0.185
Myocardial infarction (%)	11.5	16.4	0.168
Congestive heart failure (%)	4.9	15.1	<0.001
Claudication (%)	6.7	6.9	0.844
Systolic blood pressure (mmHg)	136.3 ± 15.8	139.1 ± 16.7	0.077
Diastolic blood pressure (mmHg)	72.1 ± 10.1	70.9 ± 9.9	0.242
BMI (kg/m^2)	26.9 ± 5.2	30.1 ± 6.3	<0.001

Data are means ± SD unless otherwise specified. MMSE, Mini-Mental State Examination.

younger, more likely to be men, less educated, more likely to have a history of congestive heart failure, and more likely to have an elevated BMI (Table 1).

Diabetes and cognitive function

We first examined the relation of diabetes to each of the five cognitive domains in separate linear regression models that adjusted for age, sex, and education (Table 2). Diabetes was associated with lower performance in two cognitive domains: diabetes was associated with a 0.206 lower score on the measure of semantic memory and with a 0.228 lower score on the measure of perceptual speed. The effect of diabetes on semantic memory or on perceptual speed was equivalent to the effect of ~14 and 6 years of age, respectively. Diabetes was not associated with episodic memory, working memory, or visuospatial ability.

Because of the finding of associations of diabetes and two cognitive domains, we next examined whether diabetes was related to the composite measure of global cognitive ability. We did not find a significant association, although the effect of diabetes on global cognition was in the expected direction (Table 2).

Factors that might account for the association of diabetes with cognition

We next considered the possibility that vascular risk factors or conditions might account for the relation of diabetes to semantic memory and perceptual speed.

In separate analyses, we added terms for nine vascular variables. The association of diabetes with semantic memory was unchanged in analyses that controlled for stroke, systolic blood pressure, diastolic blood pressure, myocardial infarction, claudication, former smoking, or current smoking. By contrast, after controlling for congestive heart failure (estimated coefficient −0.171; SE = 0.067, $P = 0.011$) or BMI (estimated coefficient −0.147; SE = 0.061, $P = 0.017$), the relation of diabetes to semantic memory was no longer significant.

The association of diabetes with perceptual speed was unchanged in analyses that controlled for stroke, myocardial infarction, claudication, or former smoking. However, the association was no longer significant when controlling for congestive heart failure (estimated coefficient −0.184; SE = 0.089, $P = 0.039$), BMI (estimated coefficient −0.158; SE = 0.083, $P = 0.058$), current smoking (estimated coefficient −0.190; SE = 0.080, $P = 0.018$), systolic blood pressure (estimated coefficient −0.209; SE = 0.080, $P = 0.009$), or diastolic blood pressure (estimated coefficient −0.204; SE = 0.080, $P = 0.011$).

Potential modifiers of the association of diabetes with cognition

In subsequent analyses, we tested whether each of the same vascular risk factors and conditions modified the relation of diabetes to any of the five cognitive systems or to global cognition by adding terms for the interaction of diabetes with each covariate in separate models.

There were no interactions between diabetes and any of the vascular variables, except for with current smoking. There were 34 current smokers, of whom 7 had diabetes (Table 1). We conducted separate analyses using the five cognitive domains as outcome measures to explore whether the interaction of diabetes and current smoking affected level of function in different cognitive domains (Table 3). Compared with a reference group of individuals without diabetes and who do not smoke, individuals with diabetes who smoke had significantly lower levels of semantic memory, working memory, and perceptual speed. Individuals without diabetes who smoke or those with diabetes who did not smoke did not have lower levels of function in these three cognitive domains. There was no significant interaction of diabetes and current smoking on episodic memory or visuospatial ability.

Similarly, compared with a reference group of individuals without diabetes and who do not smoke, individuals with diabetes who smoke had a significantly lower level of global cognition, whereas individuals without diabetes who smoke or those with diabetes who did not smoke did not have a lower level of function (Table 3).

Table 2—*Relation of diabetes to cognitive function in five different cognitive domains and to global cognition*

	Estimated coefficient	SE	*t*	*P**
Episodic memory	−0.073	0.064	−1.14	0.253
Semantic memory	−0.206	0.060	−3.42	<0.001
Working memory	−0.049	0.072	−0.69	0.493
Perceptual speed	−0.228	0.080	−2.84	0.005
Visuospatial ability	−0.157	0.074	−2.13	0.033
Global cognition	−0.124	0.049	−2.52	0.012

Estimated from separate linear regression models that are controlled for age, sex, and education. *The α level was set at 0.008 to account for the six outcome measures (i.e., 0.05/6 = 0.008).

CONCLUSIONS — In this study of nearly 900 older individuals free of dementia, we found that diabetes was associated with cognitive impairment. Diabetes was related to some cognitive

Table 3—*Relation of diabetes to cognition as a function of current smoking status*

	Model term	Estimated coefficient	SE	*P**
Episodic memory	No diabetes, smoking	0.099	0.123	0.421
	Diabetes, no smoking	−0.009	0.065	0.889
	Diabetes, smoking	−0.287	0.237	0.226
Semantic memory	No diabetes, smoking	−0.138	0.113	0.224
	Diabetes, no smoking	−0.141	0.061	0.021
	Diabetes, smoking	−0.614	0.219	0.005
Working memory	No diabetes, smoking	−0.015	0.139	0.917
	Diabetes, no smoking	0.007	0.074	0.922
	Diabetes, smoking	−0.783	0.270	0.004
Perceptual speed	No diabetes, smoking	−0.144	0.155	0.352
	Diabetes, no smoking	−0.155	0.083	0.061
	Diabetes, smoking	−0.900	0.300	0.003
Visuospatial ability	No diabetes, smoking	−0.083	0.143	0.563
	Diabetes, no smoking	−0.093	0.075	0.215
	Diabetes, smoking	−0.411	0.271	0.129
Global cognition	No diabetes, smoking	−0.016	0.093	0.866
	Diabetes, no smoking	−0.059	0.050	0.235
	Diabetes, smoking	−0.546	0.181	0.003

Estimated from separate linear regression models that are controlled for age, sex, and education. *The α level was set at 0.008 to account for the six outcome measures (i.e., 0.05/6 = 0.008).

domains, particularly semantic memory and perceptual speed, but not others. Consistent with a previous study (26), we found that the effect of diabetes on perceptual speed and semantic memory was equivalent to the effect of ~6–14 years of age.

Our finding of a relation of diabetes to impaired cognition is consistent with some previously published cross-sectional studies (5,6,9,27–29), but not others (7,8,10,30). Of the four studies that did not find a relation, two had <200 participants (10,30), and a third used only one brief measure of cognition (7). These factors may have limited the power to detect an association between diabetes and cognition.

The basis for the association of diabetes to cognition is uncertain. A vascular process is a plausible basis, given the associations of diabetes with vascular disease (1,31) and of vascular disease with impaired cognition, particularly perceptual speed (32,33). Our study found that diabetes was related to perceptual speed but not to episodic memory, which is typically affected earliest and most prominently in Alzheimer's disease. This dissociation suggests that diabetes may be affecting cognition through a vascular process rather than through Alzheimer's disease pathology. Indeed, the associations of diabetes to semantic memory or perceptual speed were no longer statistically significant after controlling for several vascular risk factors. However, controlling for stroke and evidence of vascular disease in other systems (e.g., myocardial infarction) did not alter the association of diabetes to cognition. This, as well as observations from published studies that controlled for some of these factors yet showed associations of diabetes to cognition (6,26,34), raises the possibility that other mechanisms may be involved.

An unexpected finding was that we found a significant interaction of diabetes with current cigarette smoking. The association of diabetes with cognitive impairment was substantially stronger in current smokers compared to those who never smoked or formerly smoked. We interpret these results with caution, as there were only seven individuals with diabetes who smoked. Nevertheless, the model assumptions were found to be adequately met. To our knowledge, no previous research has examined whether smoking or other vascular risk factors modify the relation of diabetes to cognition. The mechanisms underlying this finding remain to be elucidated. Cigarette smoking is known to be associated with several harmful biological processes in addition to its effects on blood vessels, such as atherosclerosis and other changes in vessel wall morphology and function (35). These include oncogene activation and genetic mutations (36), oxidative stress and telomere damage (37), activation of inflammatory processes (38), and metabolic imbalances (39). It is possible that one or more of these processes could interact, either directly or indirectly, with the biological effects of diabetes and result in altered central nervous system function and impaired cognition. In addition, it is possible that other unmeasured factors, vascular or nonvascular, may account for the association of diabetes to cognition.

This study has several strengths. First, data analysis of a relatively large cohort of older individuals enhanced our ability to detect the associations of interest. Second, based on structured clinical evaluations and the use of widely accepted criteria, individuals with dementia were identified and excluded from analyses, allowing the examination of the relation of diabetes to cognition in a cohort of older individuals free of dementia. Third, the use of composite measures of cognitive function, derived from extensive neuropsychological testing, reduced floor and ceiling artifacts and other sources of random variability. Further, these composite measures allowed for the examination of the relation of diabetes to separate cognitive domains. Finally, the clinical evaluations provided detailed medical information that permitted examination of risk factors that might account for or modify the associations of interest.

This study also has several important weaknesses. First, the identification of some variables, including diabetes and smoking, was based partly or wholly on self-report. Further, laboratory data supporting a diagnosis of diabetes were not available. These factors may have lead to incomplete ascertainment of some variables and underestimation of the effect of diabetes on cognitive function. Nevertheless, we found strong associations between diabetes and cognitive function. Second, because the interaction between diabetes and smoking was based on a small number of individuals, it will be important to replicate these findings. Third, data were cross-sectional, negating our ability to examine the relation of diabetes to change in cognition. Longitudinal studies of the relation of diabetes to change in cognitive function, particularly change in different cognitive systems (11), may help elucidate mechanisms underlying these relations.

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