

Diabetes Mellitus and Risk of Alzheimer's Disease and Dementia with Stroke in a Multiethnic Cohort

Jose A. Luchsinger,^{1,2} Ming-Xin Tang,^{1,3} Yaakov Stern,^{1,4,5} Steven Shea,^{2,6} and Richard Mayeux^{1,4-7}

Research on the relation between diabetes mellitus and dementia has produced conflicting results, and the relation has not been investigated among Blacks and Hispanics. In this study, Cox proportional hazards models were used to analyze longitudinal data from 1,262 elderly subjects without dementia at baseline (1991–1996) who were followed for an average of 4.3 years between 1992 and 1997. Outcomes were incident Alzheimer's disease and dementia associated with stroke. The prevalence of diabetes was 20% at baseline. The adjusted relative risk of Alzheimer's disease among persons with diabetes as compared with those without diabetes was 1.3 (95% confidence interval (CI): 0.8, 1.9). The adjusted relative risk for the composite outcome of Alzheimer's disease and cognitive impairment without dementia (without stroke) in subjects with diabetes was 1.6 (95% CI: 1.2, 2.1). The adjusted relative risk of stroke-associated dementia in persons with diabetes was 3.4 (95% CI: 1.7, 6.9). Among Blacks and Hispanics, approximately one third of the risk of stroke-associated dementia was attributable to diabetes (33% (95% CI: 31, 36) and 36% (95% CI: 33, 37), respectively), as compared with 17% (95% CI: 13, 22) among Whites. The finding of an association between diabetes and the composite outcome of Alzheimer's disease and cognitive impairment without dementia (without stroke) is consistent with prior reports of a modest relation between diabetes and Alzheimer's disease. *Am J Epidemiol* 2001;154:635–41.

Alzheimer disease; dementia; diabetes mellitus; survival analysis

Dementia and diabetes mellitus are two of the most prevalent problems in the elderly. More than 10 percent of people over the age of 65 years develop dementia, and the prevalence of dementia increases to more than 50 percent for people over the age of 85 (1, 2). More than 10 percent of the elderly suffer from diabetes, and the prevalence is increasing (3, 4). Dementia and diabetes are more common among Blacks and Hispanics (3–7), and there are differ-

ences in the predictive ability of known risk factors for dementia across ethnic groups (5, 8–12).

The association between diabetes and vascular dementia may depend on the presence of subclinical cerebrovascular disease or frank stroke (13–15), and it may be mediated through traditional cardiovascular disease risk factors, specifically hyperlipidemia and hypertension (16–18). The relation between diabetes and Alzheimer's disease is less obvious, although a role for glycated end products in the pathogenesis of Alzheimer's disease has been hypothesized (19, 20).

Several longitudinal studies have demonstrated an association between a history of diabetes and cognitive deficits (21, 22) and dementia (23–26). The finding of an association between diabetes and Alzheimer's disease has been inconsistent. Two reports from the Rotterdam Study showed a relation between diabetes and Alzheimer's disease, with relative risks of 1.3 (95 percent confidence interval (CI): 1.0, 1.9) and 1.9 (95 percent CI: 1.3, 2.8) (23, 26). The relative risk of Alzheimer's disease among subjects treated with insulin was higher than that among subjects treated with oral hypoglycemic agents (compared with subjects without diabetes) in one of those studies (23), while in the most recent report from the same cohort, the risk of Alzheimer's disease was elevated only among diabetic subjects treated with insulin, and risk was not elevated among subjects treated with oral hypoglycemic agents (26). One study from Rochester, Minnesota (24) reported a doubling of the risk of Alzheimer's disease among men with diabetes as compared with men without diabetes (relative risk = 2.3,

Received for publication September 18, 2000, and accepted for publication April 16, 2001.

Abbreviations: CI, confidence interval; NINCDS-ADIRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

¹ Taub Institute for Research of Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY.

² Division of General Medicine, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY.

³ Division of Biostatistics, Joseph P. Mailman School of Public Health, Columbia University, New York, NY.

⁴ Gertrude H. Sergievsky Center, Columbia University, New York, NY.

⁵ Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY.

⁶ Division of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY.

⁷ Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY.

Reprint requests to Dr. Richard Mayeux, Gertrude H. Sergievsky Center, PH-19, Columbia University, 630 West 168th Street, New York, NY 10032 (e-mail: rpm2@columbia.edu).

95 percent CI: 1.6, 3.3) and a non-statistically significant increased risk among women (relative risk = 1.37, 95 percent CI: 0.9, 2.0). Another study of a British cohort also reported a higher risk of Alzheimer's disease among subjects with diabetes compared with subjects without it, with a relative risk of 1.4 (95 percent CI: 1.1, 17.0) (25). In these studies, the relative risk of Alzheimer's disease was lower than that for overall dementia and vascular dementia, and risk was attenuated once cases with stroke were excluded.

The incidence of vascular dementia varies considerably depending on the criteria used (27); if cases of vascular dementia are classified as Alzheimer's disease, the finding of a weak relation between diabetes and Alzheimer's disease may be due to misclassification. One study that used more sensitive criteria for the detection of vascular dementia found no association between diabetes and Alzheimer's disease: The relative risks of Alzheimer's disease in subjects with diabetes as compared with subjects without diabetes were 0.98 (95 percent CI: 0.48, 1.99) and 1.0 (95 percent CI: 0.58, 1.72) when the researchers considered 25-year history of diabetes and 15-year history of diabetes, respectively (28). Thus, the finding of a relation between diabetes and dementia, specifically Alzheimer's disease and vascular dementia, may depend on the criteria used to define vascular dementia and the accuracy of the diagnostic procedures employed. None of the previous studies examining the relation between diabetes and dementia included large numbers of Blacks or Hispanics.

The objective of this study was to clarify the association between diabetes and the different types of dementia. Because the prevalence of diabetes in Blacks and Hispanics is higher than that in Whites (3, 4), we also examined whether this difference could account for the higher risk of dementia reported in non-Whites (5–7).

MATERIALS AND METHODS

Study population

Participants in the Washington Heights-Inwood Columbia Aging Project cohort were drawn by random sampling of healthy Medicare beneficiaries aged ≥ 65 years residing within a geographically defined area of northern Manhattan (New York City). The sampling procedures have been described elsewhere (5). Each subject underwent an in-person structured interview of health and function at the time of study entry, followed by the completion of a standard medical history, physical and neurologic examinations, and a battery of neuropsychological tests (29). The subjects were recruited between 1991 and 1996 and were followed annually; the evaluations used at baseline were repeated at each follow-up. Subjects were followed for an average of 4.3 years between 1992 and 1997. Persons who had completed at least 1 year of follow-up were included in the analysis. Of the 2,126 persons who underwent the baseline assessment, 327 persons were excluded because of prevalent dementia and 537 persons were not available for follow-up (141 had died and 396 refused follow-up or had moved). The 537 excluded persons were slightly older than the analytical sample (mean age = 78 years vs. 75 years),

were similar with regard to gender and ethnic distributions, and had a lower prevalence of diabetes (14 percent vs. 20 percent). The final sample comprised 1,262 subjects.

Diagnosis of dementia and cognitive impairment

The diagnosis of dementia and assignment of its specific cause was made by a group of neurologists, psychiatrists, and neuropsychologists by consensus, on the basis of information gathered at the initial visit and follow-up visits. Dementia diagnosis was based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (30), and it required evidence of cognitive deficits on the neuropsychological test battery as well as evidence of impairment in social or occupational functioning (Clinical Dementia Rating >0.5) (31). Diagnosis of Alzheimer's disease was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (32). Diagnosis of dementia associated with stroke (hereafter called stroke-associated dementia) was made in all subjects with dementia in whom stroke was judged to be the main cause of the dementia based on evidence of the focal effects of the stroke, its temporal relation with dementia, or both. Brain imaging was available in 85 percent of cases of stroke; in the remainder, World Health Organization criteria were used to define stroke (33). Subjects without dementia but with a history of stroke at the baseline examination were included in the analyses. A diagnosis of cognitive impairment without dementia (hereafter called nondementia cognitive impairment) was made if neuropsychological testing detected memory impairment that was more than one standard deviation lower than normal for the subject's age but the individual reported no impairment or only mild impairment in social or occupational activities (Clinical Dementia Rating ≤ 0.5) (30).

Diagnosis of diabetes and other covariates

The presence of diabetes was based on reported use of insulin or oral hypoglycemic agents or a clinical history of diabetes. Hypertension, heart disease, and smoking were based on self-report or clinical history. Ethnic group was based on self-report using the format of the 1990 US Census (34). Individuals were asked whether they were of Hispanic origin. Subjects were then assigned to one of three ethnic groups: non-Hispanic Black, Hispanic, and non-Hispanic White. Years of education were obtained by self-report. Apolipoprotein E genotyping was obtained by amplification of genomic DNA with polymerase chain reaction subjected to *CfoI* restriction analysis using apolipoprotein E primers and conditions similar to those described by Hixson and Vernier (35). Fasting plasma total cholesterol and triglyceride levels were determined at the initial assessment using standard enzymatic techniques. High density lipoprotein cholesterol was determined after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid (36). Low density lipoprotein cholesterol levels were calculated using the formula of Friedewald et al. (37).

Data analysis

Prevalences of diabetes and other covariates were compared between subjects with and without Alzheimer's disease and between subjects with and without stroke-associated dementia. Continuous variables were compared by analysis of variance, and categorical variables were compared by χ^2 test. Cox proportional hazards modeling was used for multivariate analyses. The time-to-event variable was age at onset of dementia; the models were stratified by year of entry into the cohort in order to control for period effects, as recommended for longitudinal studies (38). There was one model for each outcome mentioned above. All covariates were treated as time-constant covariates using the baseline values. In 26 of the 255 subjects with diabetes, the diagnosis was made after baseline, but these persons were treated as having had diabetes at baseline. An additional analysis was carried out treating diabetes as a time-dependent covariate taking into account the date of reporting of the diabetes diagnosis; this analysis was conducted to examine how the definition of diabetes (baseline vs. follow-up) affected the analysis. A similar analysis was carried out treating all variables as time-dependent covariates with the beginning of exposure used as the beginning of observation (or later for the 26 subjects diagnosed with diabetes after baseline), to compare the results with the time-constant covariate model. Subjects without the outcome were censored at the time of the last follow-up visit. Subjects with a type of dementia different than the one considered in the specific model were censored at the time of onset of dementia. For example, when Alzheimer's disease was examined as the outcome, persons with stroke-associated dementia were censored at the time of dementia onset. Additional analyses were performed using nondementia cognitive impairment without stroke and nondementia cognitive impairment with stroke as the outcomes; persons with nondementia cognitive impairment at baseline were excluded.

The population attributable risk (PAR) for diabetes in relation to dementia was calculated for each ethnic group using the formula $PAR = \frac{Pr(HR - 1)}{1 + Pr(HR - 1)}$, where HR is the adjusted hazard ratio obtained from the multivariate models and Pr is the prevalence of diabetes in each ethnic group in the cohort; 95 percent confidence intervals were calculated for the population attributable risk using methods described for prospective studies (39). SAS for Windows, version 7 (SAS Institute, Inc., Cary, North Carolina), was used for all analyses.

RESULTS

The mean age of the cohort was 75.6 years (standard deviation 5.9); 68.9 percent of the subjects were women. Forty-five percent of the subjects were Hispanic, and 32 percent were Black. The prevalence of diabetes was 9.6 percent in Whites, 21.2 percent in Blacks, and 24.1 percent in Hispanics. There were 213 incident cases of dementia in the cohort. Of these, 157 cases (74 percent) were due to Alzheimer's disease, 36 cases (17 percent) were due to stroke, and 20 cases (9 percent) were due to other causes. The incidence of dementia was 1.4 per 1,000 person-years

in Whites (33 cases: 23 Alzheimer's disease, four stroke-associated dementia, and six other), 2.4 per 1,000 person-years in Blacks (80 cases: 62 Alzheimer's disease, 14 stroke-associated dementia, and four other), and 2.3 per 1,000 person-years in Hispanics (100 cases: 72 Alzheimer's disease, 18 stroke-associated dementia, and 10 other).

Table 1 shows a comparison of characteristics between all subjects in the sample and subjects with Alzheimer's disease, stroke-associated dementia, nondementia cognitive impairment without stroke, and nondementia cognitive impairment with stroke. Persons with Alzheimer's disease were older, had fewer years of education, had a higher proportion of Blacks, and had a higher prevalence of heart disease than persons without Alzheimer's disease. Persons with stroke-associated dementia were older and had a higher prevalence of diabetes, a higher level of low density lipoprotein cholesterol, a higher prevalence of hypertension, and a higher prevalence of heart disease than persons without stroke-associated dementia. After the exclusion of 174 cases of nondementia cognitive impairment at baseline, there were 1,088 persons left for the analysis of nondementia cognitive impairment. Persons with nondementia cognitive impairment without stroke were older and had fewer years of education, a higher proportion of ever smokers, and a higher proportion of Hispanics than persons without it. Persons with nondementia cognitive impairment with stroke had a higher prevalence of hypertension and heart disease than persons without it.

The multivariate adjusted hazard ratio for Alzheimer's disease in relation to diabetes, as compared with the absence of diabetes, was 1.3 (95 percent CI: 0.8, 1.9), while the hazard ratio for stroke-associated dementia in relation to diabetes was 3.4 (95 percent CI: 1.7, 6.9) (table 2). The population attributable risk for diabetes in relation to stroke-associated dementia was 36 percent (95 percent CI: 33, 37) among Hispanics, 33 percent (95 percent CI: 31, 36) among non-Hispanic Blacks, and 17 percent (95 percent CI: 13, 22) among non-Hispanic Whites.

The hazard ratio for nondementia cognitive impairment without stroke in persons with diabetes, as compared with persons without diabetes, was 1.3 (95 percent CI: 0.8, 1.9). The hazard ratio for nondementia cognitive impairment with stroke in relation to diabetes was 1.6 (95 percent CI: 0.6, 4.4) (table 2). Persons with nondementia cognitive impairment have an increased risk of developing Alzheimer's disease compared with persons without nondementia cognitive impairment (40); therefore, we conducted an analysis examining the relation between diabetes and a composite outcome of Alzheimer's disease and nondementia cognitive impairment (without stroke). The hazard ratio for this composite outcome in relation to diabetes, as compared with the absence of diabetes, was 1.6 (95 percent CI: 1.2, 2.1).

We performed a subgroup analysis examining the relation between diabetes and stroke-associated dementia in the 184 persons with stroke, to estimate the effect of diabetes independent of that of stroke. The adjusted hazard ratio for stroke-associated dementia in relation to diabetes as compared with the absence of diabetes was 1.8 (95 percent CI: 0.8, 4.1).

TABLE 1. Characteristics of subjects at baseline, Washington Heights-Inwood Columbia Aging Project, New York City, 1991–1996

	Alzheimer's disease (<i>n</i> = 157)	Stroke-associated dementia (<i>n</i> = 36)	Nondementia cognitive impairment without stroke (<i>n</i> = 133)	Nondementia cognitive impairment with stroke (<i>n</i> = 21)	Whole sample (<i>n</i> = 1,262)
Mean age (years)	79.4*** (6.6)†	77.9* (6.2)	77.1*** (5.4)	76.9 (4.9)	75.6 (5.9)
Female sex (%)	68.7	77.7	70.6	66.6	68.9
History of diabetes mellitus (%)	22.2	47.2***	23.3	28.5	20.2
Median level of education (years)	8*** (0–20)‡	7.5 (0–14)	8*** (0–18)	8 (0–18)	8 (0–20)
History of ever smoking (%)	43.3	44.8	35.9**	55.5	49.2
Mean low density lipoprotein cholesterol level (mg/dl)	118.7 (34.3)	141.9*** (37.0)	117.8 (36.6)	135.7 (36.4)	121.4 (35.3)
Presence of apolipoprotein ε4 allele (%)	32.4	40.6	33.5	28.5	27.9
History of hypertension (%)	63.0	80.5*	63.9	85.7*	60.6
Ethnic group (%)					
Black	39.4*	38.9	30.0	28.5	32
Hispanic	45.8	50.0	52.6*	47.6	44.5
History of heart disease (%)	38.8*	55.5**	38.8	55.5*	30.9

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (p value for the comparison of the subjects in the column subgroup with all other subjects).

† Numbers in parentheses, standard deviation.

‡ Numbers in parentheses, range.

We performed another analysis after reclassifying 19 cases of Alzheimer's disease with stroke as cases of stroke-associated dementia, but the hazard ratio for Alzheimer's disease in relation to diabetes (as compared with the absence of diabetes) was unchanged (relative risk = 1.3, 95 percent CI: 0.83, 1.94). The hazard ratio for Alzheimer's disease in relation to diabetes also remained unchanged after we excluded cases of stroke from the analysis.

We performed an additional analysis examining the effect of diabetes treatment on the relation between diabetes and Alzheimer's disease. Previous studies have reported an increased risk of Alzheimer's disease among subjects treated with insulin and a smaller increase or no increase in

risk among subjects using oral hypoglycemic agents, in comparison with subjects without diabetes (23, 26). Models were built including dummy variables for insulin and oral hypoglycemic agents, with subjects without diabetes used as a reference group. The hazard ratio for Alzheimer's disease in relation to diabetes, compared with the absence of diabetes, was 1.4 (95 percent CI: 0.61, 3.24) in persons reporting insulin use and 1.2 (95 percent CI: 0.66, 2.0) in persons reporting use of oral hypoglycemic agents. The hazard ratio for stroke-associated dementia among insulin-using subjects with diabetes was 3.9 (95 percent CI: 1.29, 11.56), and the hazard ratio among diabetic subjects using oral hypoglycemic agents was 2.6 (95 percent CI: 1.00, 6.53). Hazard

TABLE 2. Hazard ratios for dementia and cognitive impairment in persons with diabetes mellitus as compared with persons without diabetes, Washington Heights-Inwood Columbia Aging Project, New York City, 1992–1997

Form of impairment	No. of cases	No. at risk	Gender-adjusted hazard ratio	95% confidence interval	Hazard ratio in full model	95% confidence interval
Alzheimer's disease*	157	1,262	1.4	0.97, 2.10	1.3	0.84, 1.88
Stroke-associated dementia†	36	1,262	4.2	2.18, 8.25	3.4	1.70, 6.91
Nondementia cognitive impairment without stroke*	133	1,088	1.5	1.00, 2.27	1.3	0.82, 1.92
Nondementia cognitive impairment with stroke†	21	1,088	2.3	0.88, 5.91	1.6	0.61, 4.41

* The hazard ratios in the full models were adjusted for gender, ethnic group, education, and presence of the apolipoprotein ε4 allele.

† The hazard ratios in the full model were adjusted for gender, history of hypertension, history of heart disease, low density lipoprotein cholesterol level, ethnic group, education, and smoking.

ratios for the composite outcome of Alzheimer's disease and nondementia cognitive impairment without stroke among subjects using insulin and subjects using oral hypoglycemic agents, as compared with subjects without diabetes, were not materially different from the hazard ratio for all subjects with diabetes.

In our models, covariates such as hypertension and diabetes were treated as time-constant covariates, which assume lifetime exposure and which may have thereby overestimated exposure. Therefore, we also fitted models specifying the covariates as time-dependent covariates, with the beginning of exposure set to the beginning of observation. Of the 255 subjects with diabetes in the cohort, 26 had a diagnosis of diabetes made after the baseline examination; thus, we fitted another model with time-dependent covariates taking into account the time of diabetes diagnosis in those 26 subjects. The hazard ratios from these two models using time-dependent covariates were very close to those of the main models.

DISCUSSION

In longitudinal data on 1,262 subjects from a multiethnic community cohort with 4.3 years of follow-up, diabetes was related to stroke-associated dementia (hazard ratio = 3.4, 95 percent CI: 1.70, 6.91) and to a composite outcome of Alzheimer's disease and cognitive deficit without dementia (without stroke) (hazard ratio = 1.6, 95 percent CI: 1.21, 2.10). The association between diabetes and incident Alzheimer's disease was not statistically significant (hazard ratio = 1.3, 95 percent CI: 0.84, 1.88). The relations between diabetes and nondementia cognitive impairment with and without stroke paralleled the relations of diabetes to stroke-associated dementia and Alzheimer's disease, respectively. The population attributable risk for diabetes in relation to stroke-associated dementia varied by ethnic group; it was approximately twice as great in Hispanics and Blacks as in Whites.

The risk of vascular dementia increases greatly with stroke (13, 14), and this may be caused by large and small vessel disease (18, 41), both of which are associated with diabetes. It is likely that diabetes affects the risk of vascular dementia partly by contributing to dyslipidemia and hypertension. Hyperlipidemia and hypertension have been reported by other investigators to be associated with vascular dementia (17, 41–43), and these associations were also present in our data. The strong though statistically non-significant hazard ratio for stroke-associated dementia in diabetic persons (as compared with nondiabetic persons) among subjects with stroke (hazard ratio = 1.8, 95 percent CI: 0.8, 4.1) suggests that diabetes contributes to risk of stroke-associated dementia through additional mechanisms. One such mechanism that has been proposed is diabetes-related impairment in cerebral vasoreactivity, with accompanying changes in blood flow (44, 45).

The mechanisms underlying the possible association between diabetes and Alzheimer's disease remain unclear. One possibility is the production of glycation end products (19, 20). However, reductions in plasma amyloid precursor

protein have been reported with elevation of plasma levels of glucose and insulin (46), and insulin has been reported to decrease β -amyloid neurotoxicity in vitro (47). These findings raise the possibility that hyperinsulinemia, one of the characteristics of type II diabetes, may decrease the deposition of amyloid protein in the brain, which is a key step in the pathogenesis of Alzheimer's disease (48–53). The mechanisms underlying the weak relation between diabetes and Alzheimer's disease remain to be clarified.

Three longitudinal studies have reported an increased risk of dementia, including Alzheimer's disease, among persons with diabetes (23–26). Two of these studies used NINCDS-ADRDA criteria for the diagnosis of Alzheimer's disease (23, 25, 26); one showed that risk of Alzheimer's disease was lower than risk of overall dementia in persons with diabetes (25), and the other showed that risk of Alzheimer's disease in such subjects was decreased by excluding subjects with stroke, although the risk remained significant (26). The third study used the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised, for the diagnosis of dementia, based on medical record review and autopsy data (24). These studies had a limited ability to detect vascular dementia. The definition of vascular dementia is controversial; depending on the criteria used, the incidence of vascular dementia can vary severalfold (27). If cases of stroke-associated dementia are misclassified as cases of Alzheimer's disease, risk factors for stroke-associated dementia can appear to predict Alzheimer's disease. One study that used NINCDS-ADRDA criteria for the diagnosis of Alzheimer's disease and the criteria of the California state Alzheimer's disease diagnostic and treatment centers for the diagnosis of vascular dementia found a relation of diabetes with vascular dementia but not with Alzheimer's disease (28).

The criteria of the California Alzheimer's disease diagnostic and treatment centers are the most sensitive for the diagnosis of vascular dementia (27) and would therefore classify fewer cases of stroke-associated dementia as cases of Alzheimer's disease. Thus, it appears that the relation between diabetes and Alzheimer's disease is sensitive to the criteria used to define vascular dementia. We addressed this issue by reclassifying all subjects with Alzheimer's disease who had also had a stroke as subjects with stroke-associated dementia (including cases in which the temporal relation between dementia and stroke was unclear), but the hazard ratios in this analysis remained essentially unchanged. The criteria for the diagnosis of stroke-associated dementia used in the last analysis are consistent with those of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (54). The NINDS-AIREN criteria are not as sensitive in the detection of vascular dementia as the California criteria used in the study that found no relation between diabetes and Alzheimer's disease (27). However, misclassification of cases of stroke-associated dementia as cases of Alzheimer's disease is an unlikely explanation for our finding of a relation between diabetes and Alzheimer's disease: The results were unchanged both with exclusion of stroke cases from the analyses and with the reclassification of dementia subtypes described above. The finding of a slightly greater

risk of Alzheimer's disease among subjects using insulin than among those using oral hypoglycemic agents is consistent with findings from the Rotterdam Study (23, 26) and may reflect the possibility that diabetic subjects who used insulin had more severe or prolonged diabetes.

We performed additional analyses using nondementia cognitive impairment as an outcome; these analyses yielded results similar to those for dementia. There are inconsistent reports of an association between diabetes and cognitive impairment (21, 22, 55). Subjects with cognitive deficits and no functional disability have been determined to be at higher risk of dementia (40). Thus, the association between diabetes and cognitive impairment would be expected to be similar to that between diabetes and dementia. The findings for nondementia cognitive impairment support the results of the main analyses.

One explanation for our finding of a nonsignificant weak association between diabetes and Alzheimer's disease may be that a relation truly exists but this study lacked statistical power to detect it. Our analysis using the composite outcome of Alzheimer's disease and nondementia cognitive impairment without stroke, showing a statistically significant association with diabetes as compared with the absence of diabetes (hazard ratio = 1.6, 95 percent CI: 1.21, 2.10), is consistent with this interpretation. Another possible explanation for this nonsignificant finding is that misclassification error for diabetes or Alzheimer's disease or both may have diluted the relation between diabetes and Alzheimer's disease. Self-reported diabetes as used in this study almost certainly underestimated the true prevalence of diabetes; true prevalence has been reported to be twice the prevalence of self-reported disease when subjects with undiagnosed diabetes are considered (3).

This study had important strengths. It was a longitudinal study of nondemented elderly subjects in three ethnic groups that used standardized procedures for the diagnosis of dementia and its subtypes in a prospective fashion. The main limitations of the study were a lack of data on duration of diabetes, severity of diabetes, and the presence of undiagnosed diabetes. The multivariate models assumed a lifetime duration of exposure, which could have resulted in error in the measurement of exposures such as diabetes, lipid levels, and hypertension. However, as we noted above, this did not appreciably affect the hazard ratios for diabetes in relation to Alzheimer's disease and stroke-associated dementia.

The findings of this study support those of previous longitudinal studies that reported a weak association between diabetes and Alzheimer's disease and a strong association between diabetes and stroke-associated dementia, and they extend these observations to minority population groups. The population attributable risk for diabetes in relation to stroke-associated dementia was significantly greater in Blacks and Hispanics than in Whites.

ACKNOWLEDGMENTS

Support for this work was provided by grants from the National Institute on Aging (AG07232 and AG08702), from

the Charles S. Robertson Memorial Gift fund for research on Alzheimer's disease, and from the Blanchette Hooker Rockefeller Foundation.

REFERENCES

1. Evans DA, Funkenstien HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. *JAMA* 1989;262:2551-6.
2. Geldmacher DS, Whitehouse PJ. Evaluation of dementia. *N Engl J Med* 1996;335:330-6.
3. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care* 1998;21:518-24.
4. Harris MI. Diabetes in America: epidemiology and scope of the problem. *Diabetes Care* 1998;21(suppl 3):C11-14.
5. Tang M, Stern Y, Marder K, et al. The ApoE-ε4 allele and the risk of Alzheimer's disease among African Americans, whites, and Hispanics. *JAMA* 1998;279:751-5.
6. Gurland B, Wilder D, Lantigua R, et al. Relative rates of dementia by multiple case definitions, over 2 prevalence periods, in 3 cultural groups. *Am J Geriatr Psychiatry* 1995;3:6-12.
7. Gurland BJ, Wilder DE, Lantigua R, et al. Differences in rates of dementia between ethnic groups. In: Martin LG, Soldo BJ, eds. *Racial and ethnic difference in the health of older Americans*. Washington, DC: National Academy Press, 1997: 232-68.
8. Mayeux R, Stern Y, Ottman R, et al. The apolipoprotein ε4 allele in patients with Alzheimer's disease. *Ann Neurol* 1993; 34:752-4.
9. Maestre G, Ottman R, Stern Y, et al. Apolipoprotein-E and Alzheimer's disease: ethnic variation in genotypic risks. *Ann Neurol* 1995;37:254-9.
10. Tang M-X, Maestre G, Tsai W-Y, et al. Relative risk of Alzheimer's disease and age-at-onset base of APOE genotypes among elderly African Americans, Caucasians and Hispanics in New York City. *Am J Hum Genet* 1996;58:554-74.
11. Sahota A, Yang M, Gao S, et al. Apolipoprotein E-associated risk for Alzheimer's disease in the African-American population is genotype dependent. *Ann Neurol* 1997;42:659-61.
12. Osuntokun BO, Sahota A, Ogunniyi AO, et al. Lack of an association between apolipoprotein E ε4 and Alzheimer's disease in elderly Nigerians. *Ann Neurol* 1995;38:463-5.
13. Tatemichi TK, Desmond DW, Mayeux R, et al. Dementia after stroke: baseline frequency, risks, and clinical features in a hospitalized cohort. *Neurology* 1992;42:1185-93.
14. Tatemichi TK, Paik M, Bagiella E, et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. *Neurology* 1994;44:1885-91.
15. Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. *J Neurol Neurosurg Psychiatry* 1997;63:749-53.
16. Moroney JT, Tang M, Berglund L, et al. Low-density lipoprotein cholesterol and the risk of dementia with stroke. *JAMA* 1999;282:254-60.
17. Gorelick PB. Status of risk factors for dementia associated with stroke. *Stroke* 1997;28:459-63.
18. O'Leary DH, Polak JF, Kronmal R, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Group. *Stroke* 1992;23:1752-60.
19. Sasaki N, Fukatsu R, Tsusuki K, et al. Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *Am J Pathol* 1998;153:1149-55.
20. Smith MA, Sayre LM, Perry G. Diabetes and Alzheimer's disease: glycation as a biochemical link. (Letter). *Diabetologia* 1996;39:247.

21. Elias PK, Elias MF, D'Agostino RB, et al. NIDDM and blood pressure as risk factors for poor cognitive performance: The Framingham Study. *Diabetes Care* 1997;20:1388-95.
22. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? *Arch Intern Med* 2000;160:174-80.
23. Ott A, Stolk RP, Hoffman A, et al. Association of diabetes mellitus and dementia: The Rotterdam Study. *Diabetologia* 1996;39:1392-7.
24. Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Am J Epidemiol* 1997;145:301-8.
25. Brayne C, Gill C, Huppert FA, et al. Vascular risks and incident dementia: results from a cohort study of the very old. *Dement Geriatr Cogn Disord* 1998;9:175-80.
26. Ott A, Stolk RP, Van Harskamp F, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999;53:1937-42.
27. Chui HC, Mack W, Jackson E, et al. Clinical criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. *Arch Neurol* 2000;57:191-6.
28. Curb JD, Rodriguez BL, Abbott RD, et al. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. *Neurology* 1999;52:971-5.
29. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population. I: development of a neuropsychological paradigm and quantified correction for education. *Arch Neurol* 1992;49:453-60.
30. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV). Washington, DC: American Psychiatric Association, 1994: 143-7.
31. Hughes CP, Berg L, Danzinger W, et al. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566-72.
32. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-44.
33. World Health Organization. The ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research. Geneva, Switzerland: World Health Organization, 1993:36-40.
34. Bureau of the Census. 1990 census of population and housing: summary tape file 1, technical documentation. STF 1A database. (Computer diskette). Washington, DC: Bureau of the Census, US Department of Commerce, 1991.
35. Hixson J, Vernier D. Restriction isotyping of human lipoprotein E by gene amplification and cleavage of HhAI. *J Lipid Res* 1991;31:545-8.
36. Lopes-Virella MF, Stone P, Ellis S, et al. Cholesterol determination in high-density lipoproteins separated by three different methods. *Clin Chem* 1977;23:882-4.
37. Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
38. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997;145:72-80.
39. Kahn HA, Sempos CT. Statistical methods in epidemiology. New York, NY: Oxford University Press, 1989:72-84.
40. Ritchie K, Touchon J. Mild cognitive impairment: conceptual basis and current nosological status. *Lancet* 2000;355:225-8.
41. Mast H, Thompson JL, Lee SH, et al. Hypertension and diabetes mellitus as determinants of multiple lacunar infarcts. *Stroke* 1995;26:30-3.
42. Tatemichi TK, Desmond DW, Paik M, et al. Clinical determinants of dementia related to stroke. *Ann Neurol* 1993;33:568-75.
43. Desmond DW, Tatemichi TK, Paik M, et al. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neurol* 1993;50:162-6.
44. Albert SG, Gomez CR, Russell S, et al. Cerebral and ophthalmic artery hemodynamic responses in diabetes mellitus. *Diabetes Care* 1993;16:476-82.
45. Fülesdi B, Limburg M, Bereczki D, et al. Impairment of cerebrovascular reactivity in long term type 1 diabetes. *Diabetes* 1997;46:1840-5.
46. Boyt AA, Taddei K, Hallmayer J, et al. The effect of insulin and glucose on the plasma concentration of Alzheimer's amyloid precursor protein. *Neuroscience* 2000;95:727-34.
47. Takadera T, Sakura N, Mohri T, et al. Toxic effects of a beta-amyloid peptide (beta 22-35) on the hippocampal neuron and its prevention. *Neuroscience* 1993;161:41-4.
48. Ko L, Sheu KR, Blass JP. Immunohistochemical colocalization of amyloid precursor protein with cerebrovascular amyloid of Alzheimer's disease. *Am J Pathol* 1991;139:523-33.
49. Martins RN, Robinson PJ, Chleboun JP, et al. The molecular pathology of amyloid deposition in Alzheimer's disease. *Mol Neurobiol* 1991;5:389-98.
50. Masters CL, Multhaup G, Simms G, et al. Neuronal origin of cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. *Eur Mol Biol Org* 1985;4:2757-63.
51. Masters CL, Simms G, Weinman NA, et al. Amyloid plaque core protein in Alzheimer's disease and Down's syndrome. *Proc Natl Acad Sci U S A* 1985;82:4245-9.
52. Murphy M. The molecular pathogenesis of Alzheimer's disease: clinical prospects. *Lancet* 1992;340:1512-15.
53. Näslund J, Haroutunian V, Mohs R, et al. Correlation between elevated levels of amyloid β -peptide in the brain and cognitive decline. *JAMA* 2000;283:1571-7.
54. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. *Neurology* 1993;43: 250-60.
55. Vanhanen M, Kuusisto J, Koivisto K, et al. Type-2 diabetes and cognitive function in a non-demented population. *Acta Neurol Scand* 1999;100:97-101.