

# Diabetes mellitus in midlife and the risk of dementia three decades later

M. Schnaider Beeri, PhD; U. Goldbourt, PhD; J.M. Silverman, PhD; S. Noy, MD; J. Schmeidler, PhD; R. Ravona-Springer, MD; A. Sverdlick, MD; and M. Davidson, MD

**Abstract—Objective:** To examine the association between diabetes in midlife (1963–1968) and dementia more than three decades later (1999–2001). **Methods:** The authors characterized dementia using standard methods for 1,892 participants among 2,606 survivors of 10,059 participants in the Israeli Ischemic Heart Disease study, a longitudinal investigation of the incidence of and risk factors for cardiovascular disease among Jewish male civil servants in Israel. Face to face interviews were conducted with the 652 subjects identified as possibly demented by the Modified Telephone Interview for Cognitive Status. Logistic regression analysis was performed to assess the association of diabetes with dementia controlling for sociodemographic and cardiovascular variables compared to those with no cognitive impairment. **Results:** Of 1,892 assessed subjects (mean age 82 at assessment), 309 (16.3%) had dementia. Diabetic subjects had significantly more dementia than non-diabetic subjects ( $\chi^2 = 7.54$ ,  $df = 1$ ,  $p = 0.006$ , OR 2.83 [95% CI = 1.40 to 5.71]). Those who survived to the time of this study were younger and healthier than those who died. **Conclusions:** Evidence for diabetes as a risk factor for dementia was found, similar to other epidemiologic studies. In contrast to the earlier studies, however, the authors linked diabetes in midlife to dementia more than three decades later in the very old survivors of a large male cohort.

NEUROLOGY 2004;63:1902–1907

Longitudinal studies have consistently but not unequivocally demonstrated an association between past or current history of diabetes and cognitive deficits<sup>1,2</sup> or dementia.<sup>3–6</sup> Diabetes almost doubled the risk of dementia in the Rotterdam study<sup>6</sup> and a positive albeit modest relationship has been observed elsewhere.<sup>7</sup> No significant association between dementia and diabetes was found in the Canadian Study of Health and Aging.<sup>8</sup>

Unlike the many studies of current risk factors, the purpose of this study was to examine the association between diabetes in midlife and dementia three decades later. We followed participants in the Israeli Ischemic Heart Disease (IIHD) project, a longitudinal investigation of the incidence of and risk factors for cardiovascular disease among about 10,000 Jewish male civil servants in Israel. This cohort was chosen by stratified sampling of six geographic regions of origin providing an extensive representation of the socioeconomic levels in the male working population of Israel at the time of inclusion.<sup>9</sup> Survivors (mean age 82 at follow-up) were examined for dementia between 1999 and 2001.

**Methods. Subjects.** The sample of the IIHD Project ( $n = 11,876$ ) were chosen by stratified sampling of civil servants and municipal employees in 1963 based on 1) men aged 40 to 65 years

at the time of inclusion, 2) place of work limited to the three largest urban areas in Israel (Tel-Aviv, Jerusalem, and Haifa), and 3) sampling fractions aimed at obtaining numbers of study subjects from six geographic areas of origin (Central Europe, Eastern Europe, the Balkan countries, the Middle East, Northern Africa, and Israeli born) approximately proportional to the Israeli male population of this age. A total of 10,232 agreed to participate. Subjects were seen upon enrollment (1963) and at two follow-up visits (1965 and 1968). Subsequent analyses excluded 173 men who were not born in the six preassigned geographic areas. The figure presents the flow chart of subjects from 1963 through 2001 (the end of the present study). According to the Israel Mortality Registry, 7,136 subjects had died by the beginning of the study in 1999; another 306 died before being approached for a phone interview and 11 subjects were lost in the matching process. The remaining 2,606 subjects qualified for a telephone interview; 2,040 had phone contact. The telephone screening identified 800 potentially demented subjects for face to face home interview. Of these, 148 could not be examined at home. Of the remaining 1,240 subjects, 51 were examined at home for a sensitivity study of the phone interview instruments of whom 50 were cognitively intact and one cognitively impaired but not demented.<sup>10</sup> Thus, the follow-up study characterized the presence or absence of dementia in 1,892 subjects, of whom 309 had dementia, 175 had cognitive impairment not sufficient for the diagnosis of dementia (cognitively impaired not demented [CIND]), and 1,408 elderly had no cognitive impairment (NCI).

Table 1 compares the 2,606 subjects who were alive by the time of the 1999 follow-up interview to the 7,453 who died. The subjects who survived were younger, and, even after adjustment for age, were taller; had lower BMI, total cholesterol, systolic, and diastolic blood pressure; had fewer cases of diabetes; and fewer smoked. More survivors were born in Eastern Europe and fewer

From the Department of Psychiatry (Drs. Schnaider Beeri and Silverman) and Biomathematical Sciences Department (Dr. Schmeidler), Mount Sinai School of Medicine, New York, NY; Division of Epidemiology and Preventive Medicine (Dr. Goldbourt), Sackler Medical Faculty, Tel Aviv University; and Neufeld Cardiac Research Institute (Dr. Goldbourt) and Department of Psychiatry (Drs. Noy, Ravona-Springer, Sverdlick, and Davidson), Sheba Medical Center, Tel Hashomer, Israel.

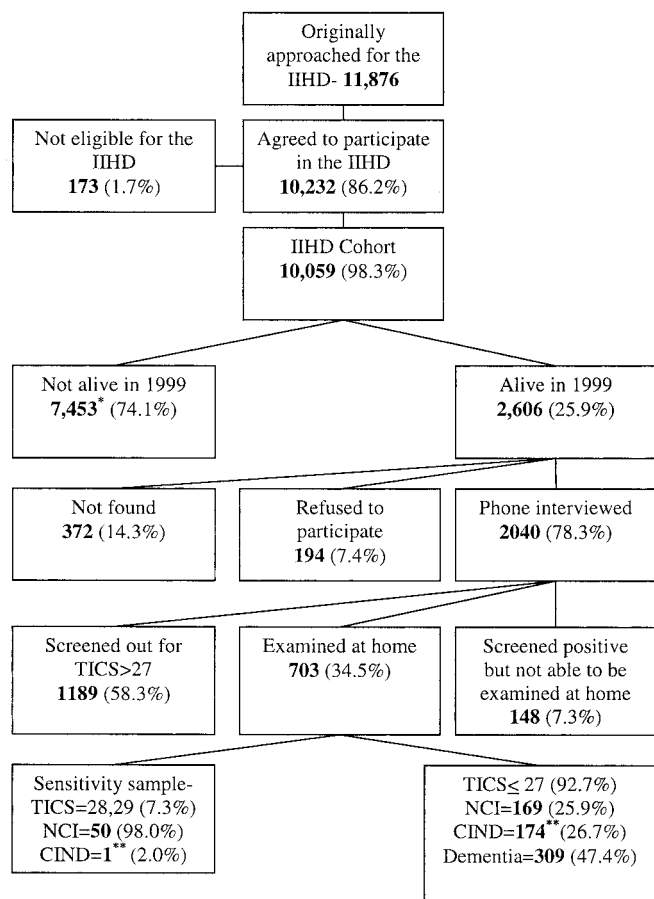
Supported in part by the Israel Science Foundation founded by the Israel Academy of Sciences and Humanities (grant no. 67/99) and by the Alzheimer Disease Research Center (grant no. AG-05138) from the National Institute on Aging (Dr. Mary Sano).

Received October 3, 2003. Accepted in final form July 16, 2004.

Address correspondence and reprint requests to Dr. Michal Schnaider Beeri, Mount Sinai School of Medicine, Department of Psychiatry, One Gustave Levy Place, Box 1230, New York, NY 10029; e-mail: michal.beeri@mssm.edu

1902 Copyright © 2004 by AAN Enterprises, Inc.

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.



**Figure.** Flow of subjects. \*This number consists of 7,136 who died before 1999, 306 who died before they could be interviewed in the 1999 follow-up, and 11 who were lost in the matching process. \*\*The CIND group was excluded from the present analysis. IIHD = Israeli Ischemic Heart Disease; TICS = Telephone Interview for Cognitive Status; NCI = no cognitive impairment; CIND = cognitively impaired not demented.

were born in the Middle East; survivors had a higher socioeconomic status (SES).

**Diagnosis of dementia.** The methods of this study have been described in detail elsewhere.<sup>10</sup> Cases of dementia were identified using a two-step procedure. The first step was a screening interview over the phone. For the purpose of the screening phone interview, subjects were located by cross-linking the database of the original study<sup>9</sup> with the population registry of the Israel Ministry of Interior, using the ID number (equivalent of US social security number) as linking identifier. All identified living participants in the original cohort were phoned, reminded of their participation in the original study, and asked for consent to participate in the new assessment. The subjects who consented to participate were administered a 20-minute phone interview, including a sociodemographic questionnaire and the Hebrew version of the Modified Telephone Interview for Cognitive Status (TICS-m<sup>10</sup>). The sociodemographic questionnaire included items that were not recorded during the original study in 1963, or might change with time, such as: marital status, retirement age, education, profession, leisure activities, degree of religiosity, smoking, and drinking habits.

The TICS-m is based on the Mini-Mental State Examination (MMSE<sup>11</sup>). It includes questions assessing long and short-term memory, orientation to time and place, attention, language, and abstraction. The scores of the TICS-m were highly correlated with the MMSE scores in clinical studies<sup>12</sup> and in the Hebrew version in this cohort.<sup>10</sup> At a level of 27/50 the sensitivity of this test was

above 99% and the specificity was 86% for dementia<sup>13</sup>; the sensitivity at this level was 100% for the Hebrew version.<sup>10</sup>

The second step was a face to face interview for all subjects with a TICS-m score of 27/50 or lower. The aim of the second phase of the study was to ascertain the diagnosis of dementia among subjects who were identified by the TICS-m as possibly cognitively impaired. The patients were assessed at their residences by a physician. All physicians involved in this study were neurologists or psychiatrists with expertise and extensive experience in the diagnosis of dementia. Physicians were blind to the TICS-m score except for knowledge that it was under 28. The clinical assessment included the Dementia Questionnaire (DQ<sup>14</sup>), MMSE,<sup>11</sup> Global Deterioration Scale (GDS<sup>15</sup>), and the Hachinski Ischemic Scale (HIS<sup>16</sup>). The entire interview lasted approximately 90 minutes.

For persons with suspected dementia, the DQ assesses, through informants, the symptoms, course, and feature of the dementia, permitting a diagnostic classification for the presence and likely type of dementia. The DQ has previously demonstrated good inter-informant and inter-rater agreement in AD probands and normal elderly control populations for detecting the presence or absence of dementia and also, among identified cases of dementia, the type of dementia.<sup>14</sup> More recently, several investigations have assessed the validity of this instrument.<sup>17</sup> Compared with a clinical assessment of dementia, the DQ was found to have excellent sensitivity (100%) and very good specificity (90%).<sup>18</sup> In addition, in a series of deceased autopsied elderly, informant-based DQ were compared with independent neuropathologic examinations; for AD, the DQ was found to be only slightly less sensitive than direct clinical assessment and its specificity was virtually at the same level.<sup>19</sup>

Dementia was diagnosed using Diagnostic and Statistical Manual of Mental Disorders-IV criteria.<sup>20</sup> Subjects were classified as CIND if a memory problem was reported by both subject and informant but they had normal activities of daily living and were not demented. Thus CIND subjects did not qualify as either demented or NCI. The present analysis compares unequivocally demented to unequivocally nondemented subjects, excluding the CIND subjects, who are heterogeneous with some subjects early in the course of cognitive decline.

A second physician, blind to the diagnosis assigned by the physician who did the face-to-face interview, examined the data gathered from each patient and assigned an independent diagnosis. In case of disagreement between the two physicians the case was presented to a third physician for a consensus diagnosis. In five cases, the patient was approached again.

**Diagnosis of diabetes and definition of covariates.** The full procedure for the diagnosis of diabetes is detailed elsewhere.<sup>21</sup> In brief, it was based on serum glucose levels (collected for all subjects in the IIHD study) with an oral glucose tolerance test when indicated, or on use of oral hypoglycemic/insulin therapy or clinical history of diabetes confirmed by the primary care physician. A subject diagnosed with diabetes at any of the three visits (1963, 1965, and 1968) was classified as having diabetes. We controlled for three sociodemographic variables: age, SES (represented by a five-point index based on education [nine levels ranging from no formal schooling to a graduate degree] and occupation [five levels ranging from "laborer" to "professional"]<sup>22</sup>), and area of birth (Israel, East Europe, Central Europe, Balkan countries, Middle East, and North Africa). We also controlled for six cardiovascular variables. Body mass index (BMI), expressed in kg/m<sup>2</sup>, was based on weight (to the nearest kilogram wearing trousers only) and height (to the nearest centimeter without shoes) at baseline (1963). Smoking habits at baseline were categorized as a dichotomy—ever and never smoked. Systolic and diastolic blood pressure (SBP and DBP) were measured in the right arm, with the subject in the recumbent position, both 30 to 45 minutes after arrival at the clinic and 15 to 30 minutes later, and also averaged over the three visits. Total cholesterol, measured by the Anderson and Keys method,<sup>23</sup> was calculated as the average of the three visits. HDL was measured for all subjects only in 1965, using the Burstein and Samaille method.<sup>24</sup>

**Data analysis.** Age, SES, BMI, SBP, DBP, and total and HDL cholesterol were treated as continuous variables; diabetes and smoking history were dichotomies, and area of birth was a categorical variable with Israel as the comparison group. For descriptive purposes, we compared the assessed to the non-assessed

**Table 1** Men alive and deceased in the 1999 follow-up\*

Variables in 1963	Deceased (n = 7,453)	Alive (n = 2,606)	p Value
Mean age, y	50.9 (n = 7,453)	44.8 (n = 2,606)	<0.0005
% Diabetic	10.3 (n = 7,254)	2.18 (n = 2,565)	<0.001
Mean height, cm	166.8 (n = 7,433)	168.1 (n = 2,601)	0.01
Mean weight, kg	71.8 (n = 7,439)	71.7 (n = 2,601)	0.064
Mean BMI, kg/m <sup>2</sup>	25.7 (n = 7,433)	25.4 (n = 2,601)	<0.001
Mean cholesterol	210.0 (n = 6,400)	202.7 (n = 2,432)	<0.001
Mean HDL cholesterol, mg/dL	40.6 (n = 6,265)	41.3 (n = 2,325)	0.08
Mean systolic blood pressure, mm Hg	138.0 (n = 6,855)	130.0 (n = 2,543)	<0.001
Mean diastolic blood pressure, mm Hg	86.4 (n = 6,846)	82.8 (n = 2,542)	<0.001
% Ever smoked (1963)	70.3 (n = 7,453)	60.4 (n = 2,606)	<0.001
Mean SES, 1 = low to 5 = high	2.7 (n = 7,397)	2.8 (n = 2,598)	<0.001
Area of birth, %	(n = 7,453)	(n = 2,606)	<0.0005
Israel	13.6	14.5	
East Europe	15.2	20.6	
Central Europe	15.0	13.2	
Balkan countries	16.5	17.5	
Middle East	26.9	22.3	
North Africa	12.8	11.9	

\* All variables (except for age) are age adjusted.

BMI = body mass index; HDL = high-density lipoprotein; SES = socioeconomic status.

subjects in the 1999 follow-up. Among the assessed subjects, the NCI group was compared to the dementia group. Student's *t*-test was used to compare the groups on the continuous variables; Pearson's  $\chi^2$  was used for comparisons of categorical variables.

Logistic regression analysis was performed to assess the association of diabetes with dementia controlling for the three sociodemographic variables and the six cardiovascular variables. A similar logistic regression analysis was performed with diabetes as a trichotomy (no diabetes, diabetes without medication [oral hypoglycemic or insulin therapy], diabetes with medication), to examine whether there was an association of dementia with diabetes medication.

**Results.** Table 2 compares the characteristics of living subjects who were or were not assessed in the 1999 follow-up. Assessed subjects were younger, had a higher SES, and were more likely to have European origin. Assessed subjects had lower SBP and DBP but the groups did not differ in diabetes, total and HDL cholesterol, BMI, and whether they smoked.

Table 3 compares the sociodemographic and cardiovascular characteristics of subjects with dementia and NCI. The mean age in 1963 of subjects with dementia (46.0) was significantly higher than NCI (44.0). Approximately half of the demented subjects were of Middle East or North African origin compared to about a third of the NCI. About 60% of the demented subjects had very low or low SES compared to about a third of the NCI. The dementia group had significantly more diabetics (4.6%) than the NCI group (2.3%).

Table 4 presents the odds ratios of diabetes for dementia. Controlling for demographic and cardiovascular characteristics in a logistic regression, diabetic subjects had significantly more dementia than nondiabetic subjects ( $\chi^2 = 7.54$ ,  $df = 1$ ,  $p = 0.006$ ). Diabetics had an OR of 2.83

(95% CI = 1.40 to 5.71). Age-adjusted rates of dementia were 34.8% for diabetic subjects and 17.4% for nondiabetic subjects. Using the trichotomy distinguishing between diabetic subjects with and without medication did not substantially improve the logistic regression ( $\chi^2 = 7.60$ ,  $df = 2$ ,  $p = 0.022$ ).

All three sociodemographic variables were associated with dementia (age: OR = 1.15 [95% CI = 1.12 to 1.19],  $p < 0.0005$ ; SES: OR = 0.62 [95% CI = 0.54 to 0.70],  $p < 0.0005$ ; area of birth: East Europe: OR = 0.83 [95% CI = 0.49 to 1.39],  $p = 0.47$ ; Central Europe: OR = 0.73 [95% CI = 0.42 to 1.26],  $p = 0.26$ ; Balkan countries: OR = 0.71 [95% CI = 0.42 to 1.20],  $p = 0.20$ ; Middle East: OR = 1.54 [95% CI = 0.98 to 2.45],  $p = 0.064$ ; North Africa: OR = 2.08 [95% CI = 1.25 to 3.47],  $p = 0.005$ ). However, cardiovascular risk factors other than diabetes, controlling for sociodemographic variables, were not (BMI: OR = 1.02 [95% CI = 0.97 to 1.06],  $p = 0.55$ ; smoking: OR = 1.02 [95% CI = 0.77 to 1.36],  $p = 0.88$ ); SBP: OR = 1.00 [95% CI = 0.99 to 1.02],  $p = 0.83$ ; DBP: OR = 1.01 [95% CI = 0.99 to 1.04],  $p = 0.64$ ; total cholesterol: OR = 1.00 [95% CI = 0.99 to 1.01],  $p = 0.82$ ; HDL: OR = 1.00 [95% CI = 0.99 to 1.02],  $p = 0.70$ ).

**Discussion.** In this large 35-year prospective historical study, diabetes in mid-life was associated with dementia—with odds of dementia almost three times as large. The small sample of diabetic subjects taking medication (oral hypoglycemic or insulin therapy) had similar rates to diabetic subjects not taking medication.

Our results regarding the relationship between

**Table 2** Living subjects who were or were not assessed in the 1999 follow-up\*

Variables	Not assessed† (n = 714)	Assessed (n = 1,892)	p Value
Mean age, y (1963)	45.6 (714)	44.5 (1,892)	<0.0005
% Diabetic (1963/5/8)	1.86 (694)	2.23 (1,871)	0.20
Mean height, cm (1963)	167.0 (714)	168.3 (1,887)	0.02
Mean weight, kg (1963)	71.4 (714)	71.7 (1,887)	0.71
Mean BMI, kg/m <sup>2</sup> (1963)	25.5 (714)	25.3 (1,887)	0.34
Mean cholesterol (1963/5/8)	204.0 (653)	201.8 (1,779)	0.98
Mean HDL cholesterol, mg/dL (1965)	41.8 (625)	41.0 (1,700)	0.58
Mean systolic blood pressure, mm Hg (1963/5/8)	130.7 (693)	129.3 (1,850)	0.02
Mean diastolic blood pressure, mm Hg (1963/5/8)	83.4 (693)	82.5 (1,849)	0.053
% Ever smoked (1963)	61.5 (714)	59.9 (1,892)	0.16
Mean SES, 1 = low to 5 = high	2.5 (711)	2.8 (1,887)	<0.0005
Area of birth, %	(714)	(1,892)	0.02
Israel	13.4	13.6	
East Europe	12.3	16.1	
Central Europe	12.9	15.8	
Balkan countries	16.7	16.5	
Middle East	30.8	25.5	
North Africa	13.9	12.5	

\* All variables (except for age) are age adjusted.

† Not assessed comprised of 372 not found, 194 who refused to participate, and 148 who screened positive but were not able to be examined at home.

BMI = body mass index; HDL = high-density lipoprotein; SES = socioeconomic status.

dementia and diabetes are in line with several cross sectional<sup>25</sup> and longitudinal studies,<sup>2,6,7,26</sup> which examined the relationship between cognitive decline and diabetes. Two reports from the Rotterdam Study<sup>3,6</sup> showed a relationship between diabetes and dementia as well as with its main subtypes (AD and vascular dementia [VaD]). In the latest report, the diabetes attributable risk for dementia was 8.8%, suggesting that diabetes contributes to the clinical syndrome in a substantial proportion of all dementia patients. The Honolulu Asia Aging study also found diabetes to be associated with dementia as well as AD and VaD. This association was particularly strong for APOE4 carriers.<sup>26</sup> To our knowledge the present study has the longest follow-up time between the recording of diabetes and the assessment of dementia, ensuring that the identified cases of diabetes were affected for a long time.

The dementia diagnoses in our study were clinical

**Table 3** Characteristics of demented and cognitively intact subjects in the 1999 follow-up\*

	Dementia (n = 309)	No cognitive impairment (n = 1,408)	p Value
Mean age, 1963	46.0	44.0	<0.005
Diabetic, 1963/5/8, %	4.6	2.3	0.02
Mean BMI, 1963	25.6	25.1	0.64
Mean cholesterol, 1963/5/8	199.1	203.9	0.11
Mean HDL cholesterol, 1965	43.2	40.8	0.47
Mean systolic blood pressure, 1963/5/8	129.8	130.2	0.87
Mean diastolic blood pressure, 1963/5/8	81.9	82.7	0.67
% Ever smoked, 1963	58.9	59.0	0.72
Mean SES, 1 = low to 5 = high	1.8	2.3	<0.005
Area of birth, %			
Israel	12.9	14.6	<0.005
Eastern Europe	13.3	16.9	
Central Europe	10.4	17.4	
Balkan countries	13.3	17.3	
Middle East	31.1	23.1	
North Africa	19.1	10.7	

\* All variables (except for age) are age adjusted.

BMI = body mass index; HDL = high-intensity lipoprotein; SES = socioeconomic status.

diagnoses. We intentionally refrained from analyzing subtypes of dementia, because a distinction based on clinical information is hard to make, especially in very elderly people, in whom dementia often is a heterogeneous disorder. There is increasing evidence that diabetes may contribute to the development of AD.<sup>6,26</sup> We found that diabetes increases the risk of dementia, of which the substantial majority of cases (82%) in our study were of the AD subtype. Thus, this relationship almost certainly pertains within the AD subtype.

The mechanisms that underlie the relationship between dementia and diabetes have not been established, but some associations have been proposed.

**Table 4** ORs\* of diabetes for dementia†

Diagnosis	Diabetes status	OR	p Value	95% CI
Dementia	All	2.83	0.006	1.40–5.71
	With medication‡	2.87	0.16	0.66–12.45
	Without medication	2.89	0.010	1.28–6.53

\* All comparisons were relative to the no cognitive impairment group.

† All logistic regression models controlled for three sociodemographic and six cardiovascular variables.

‡ Medication taken at any of the three 1960s visits.

Recent studies suggest that insulin-degrading enzyme (IDE) in neurons and microglia also degrades A-beta, the principal component of Beta-amyloid and one of the neuropathologic hallmarks of AD.<sup>27,28</sup> Thus, diabetes may reduce the availability of IDE, decreasing degradation of A-beta. There are also findings indicating an AD gene on the long arm of chromosome 10 with genetic markers that map near the IDE gene.<sup>29</sup> Another possibility is the production of glycation end products in diabetes. Advanced glycation end products (AGE), resulting from naturally occurring reactions between glucose and protein or lipid amino groups,<sup>30</sup> were found in AD patients' plaques and tangles, even in early stages of the disease.<sup>31</sup> The AGE receptor, overexpressed in AD patients' brains, is activated by Beta-amyloid.<sup>32</sup> Activation of this receptor leads to increased oxidative stress, which may result in cellular damage.

A few studies have found that diabetic patients treated with insulin have higher rates of dementia.<sup>6,7</sup> The present study sample had only 11 patients under medication to treat diabetes at midlife, limiting our ability to investigate this relationship. We lack information about changes in pharmacotherapy over the years that may have changed the risk of dementia.

The relationship between dementia and diabetes remains controversial. The differences among various studies may arise from methodologic differences (cross sectional vs longitudinal, different criteria of diagnosis and categorization of dementia, different follow-up time or sample sizes, and specific populations). This may depend on different relationships between diabetes and dementia according to characteristics of the diabetic population. For instance, diabetic patients with APOE-4 are at higher risk of AD than diabetic patients without the e4 allele<sup>33</sup>; the risk for AD may be associated with severity of diabetes as indicated by taking insulin, or having acute or recurrent hypoglycemia.<sup>34,35</sup> Future studies examining the relationship between AD and diabetes should characterize the diabetes in more detail, to identify subgroups with differing risks. This identification may facilitate the understanding of the mechanisms underlying this relationship.

The main limitation of this study is the lack of dementia characterization of the 7,453 subjects in the original IIHD study who died before the follow-up study was conducted. Those who survived to the time of this study were younger and healthier. Thus, the conclusions of this study are applicable to working men who survive to a relatively old age. Because there is differential mortality due to diabetes<sup>36</sup> and due to dementia,<sup>37</sup> it is possible that the relative mortality of demented to nondemented patients is higher in diabetics. If there is a relationship between diabetes and dementia, inclusion of nonsurvivors would have strengthened the present results.

In addition to the subjects who died before the 1999 follow-up, we could not include in the analysis subjects who were not found, refused to participate,

or screened positive but were not able to be examined at home. The rate of diabetes (1.6%) in these groups was lower (but not significantly) than that of the assessed group. However, we do not have enough information on these subjects to be able to address this result. We also did not include CIND in the analysis because of their ambiguous dementia status. Including them with the dementia group would decrease the strength of the relationship (OR = 1.8; 95% CI 0.9 to 3.5;  $p = 0.097$ ). Alternatively, including them with the NCI group would maintain the significant relationship (OR = 3.1; 95% CI 1.6 to 6.2;  $p = 0.002$ ). A repeated follow-up study of these subjects will help to refine their diagnoses.

Another limitation is that those diagnosed as diabetic at baseline (2.18%) are a minority of those expected to develop diabetes by the end of the long follow-up period (some 15%); the majority (13%) remained undiagnosed. Compared to what might have been observed if the relationship also applied to those who developed diabetes during the follow-up period, and if they had been included in the analysis as diabetics, our results may be an underestimate of the true relation between diabetes and dementia.

#### Acknowledgment

The authors thank Drs. Mary Sano and Gilberto Levy for feedback on drafts of this manuscript.

#### References

1. 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;20:1388-1395.
2. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160:174-180.
3. Ott A, Stolk RP, Hofman A, van HF, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia* 1996;39:1392-1397.
4. 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;145:301-308.
5. 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;9:175-180.
6. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999;53:1937-1942.
7. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 2001;154:635-641.
8. MacKnight C, Rockwood K, Awalt E, McDowell I. Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dement Geriatr Cogn Disord* 2002;14:77-83.
9. Groen JJ, Medalie JH, Neufeld HN, et al. An epidemiologic investigation of hypertension and ischemic heart disease within a defined segment of the adult male population of Israel. *Isr J Med Sci* 1968;4:177-194.
10. Beeri MS, Werner P, Davidson M, Schmidler J, Silverman J. Validation of the modified telephone interview for cognitive status (TICS-m) in Hebrew. *Int J Geriatr Psychiatry* 2003;18:381-386.
11. Folstein MF, Folstein SE, McHugh PR. Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
12. Brandt J, Spencer M, Folstein M. The Telephone Instrument for Cognitive Status. *Neuropsychiatry Neuropsychol Behav Neurol* 1988;1:11-17.
13. Gallo JJ, Breitner JC. Alzheimer's disease in the NAS-NRC Registry of aging twin veterans, IV. Performance characteristics of a two-stage telephone screening procedure for Alzheimer's dementia. *Psychol Med* 1995;25:1211-1219.

14. Silverman JM, Breitner JC, Mohs RC, Davis KL. Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. *Am J Psychiatry* 1986;143:1279-1282.
15. Reisberg B, Ferris SH, De Leon MJ, Crook T. Global Deterioration Scale (GDS). *Psychopharmacol Bull* 1988;24:661-663.
16. Wade JP, Mirsen TR, Hachinski VC, Fisman M, Lau C, Merskey H. The clinical diagnosis of Alzheimer's disease. *Arch Neurol* 1987;44:24-29.
17. Ellis RJ, Jan K, Kawas C, et al. Diagnostic validity of the dementia questionnaire for Alzheimer disease. *Arch Neurol* 1998;55:360-365.
18. Kawas C, Segal J, Stewart WF, Corrado M, Thal L. A validation study of the Dementia Questionnaire. *Arch Neurol* 1994;51:901-906.
19. Li G, Aryan M, Silverman JM, et al. The validity of the family history method for identifying Alzheimer disease. *Arch Neurol* 1997;54:634-640.
20. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fourth edition ed. Washington, DC: American Psychiatric Association, 1994.
21. Medalie J, Papier C, Herman J, et al. Diabetes mellitus among 10,000 adult men. *Isr J Med Sci* 1974;10:681-697.
22. Eaton CB, Medalie JH, Flocke SA, Zyzanski SJ, Yaari S, Goldbourt U. Self-reported physical activity predicts long-term coronary heart disease and all-cause mortalities. Twenty-one-year follow-up of the Israeli Ischemic Heart Disease Study. *Arch Fam Med* 1995;4:323-329.
23. Anderson J, Keys A. Cholesterol in serum and lipoprotein fractions—its measurement and stability. *Clin Chem* 1956;2:145-159.
24. Burstein M, Samaille J. Sur un dosage rapide du cholestérol lie aux alpha-lipoprotéines et aux beta-lipoprotéines du serum. *Clin Chim Acta* 1960;5:609.
25. Reaven GM, Thompson LW, Nahum D, Haskins E. Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes Care* 1990;13:16-21.
26. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes* 2002;51:1256-1262.
27. Qiu WQ, Walsh DM, Ye Z, et al. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. *J Biol Chem* 1998;273:32730-32738.
28. Perez A, Morelli L, Cresto JC, Castano EM. Degradation of soluble amyloid beta-peptides 1-40, 1-42, and the Dutch variant 1-40Q by insulin degrading enzyme from Alzheimer disease and control brains. *Neurochem Res* 2000;25:247-255.
29. Bertram L, Blacker D, Mullin K, et al. Evidence for genetic linkage of Alzheimer's disease to chromosome 10q. *Science* 2000;290(5500):2302-2303.
30. Sasaki N, Fukatsu R, Tsuzuki K, et al. Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *Am J Pathol* 1998;153:1149-1155.
31. Munch G, Schinzel R, Loske C, et al. Alzheimer's disease—synergistic effects of glucose deficit, oxidative stress and advanced glycation end-products. *J Neural Transm* 1998;105:439-461.
32. Yan SD, Chen X, Fu J, et al. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 1996;382:685-691.
33. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA* 1999;282:40-46.
34. Langan SJ, Deary IJ, Hepburn DA, Frier BM. Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. *Diabetologia* 1991;34:337-344.
35. Ryan CM, Geckle M. Why is learning and memory dysfunction in Type 2 diabetes limited to older adults? *Diabetes Metab Res Rev* 2000;16:308-315.
36. Groeneveld Y, Petri H, Hermans J, Springer MP. Relationship between blood glucose level and mortality in type 2 diabetes mellitus: a systematic review. *Diabet Med* 1999;16:2-13.
37. Noale M, Maggi S, Minicuci N, et al. Dementia and disability: impact on mortality. The Italian Longitudinal Study of Aging. *Dement Geriatr Cogn Disord* 2003;16:7-14.

## **ALERT: NEUROLOGY NOW USING ONLINE PEER REVIEW AND MANUSCRIPT SUBMISSION SYSTEM**

*Neurology* is now using an online peer review and manuscript submission system called Bench>Press.

Authors should upload all original submissions via the *Neurology* website ([www.submit.neurology.org](http://www.submit.neurology.org)). The Instructions to Authors detail the submission process and adjusted specifications.