Magnetic Resonance Imaging of the Brain in Diabetes

The Cardiovascular Determinants of Dementia (CASCADE) Study

Reinhold Schmidt,[1] Lenore J. Launer,[2,3] Lars-Göran Nilsson,[4] Andrzej Pajak,[5] Susanna Sans,[6] Klaus Berger,[7] Monique M. Breteler,[3] Maria de Ridder,[3] Carole Dufouil,[8] Rebecca Fuhrer,[9] Simona Giampaoli,[10] and Albert Hofman,[3] for the CASCADE Consortium

Diabetic patients are at increased risk for stroke, but little is known about the presence of other brain lesions. We studied the association of magnetic resonance imaging–detected brain lesions to diabetes in 1,252 individuals aged 65–75 years who were randomly selected from eight European population registries or defined working populations. All scans were centrally read for brain abnormalities, including infarcts, white matter lesions, and atrophy. We used a three-point scale to rate periventricular white matter lesions, and the volume of subcortical lesions was calculated according to their number and size. Subjective grading of cortical atrophy by lobe and summation of the lobar grades resulted in a total cortical atrophy score. The mean of three linear measurements of the ventricular diameter relative to the intracranial cavity defined the severity of subcortical atrophy. After adjustment for possible confounders, diabetes was associated with cortical brain atrophy but not with any focal brain lesions or subcortical atrophy. There was a strong interaction of diabetes and hypertension, such that the association between diabetes and cortical atrophy existed only in hypertensive but not in normotensive participants. Cognitive and pathological data are needed to determine the clinical significance of these findings as well as to understand the mechanisms underlying these associations. *Diabetes* 53:687–692, 2004

From the [1]Department of Neurology, Medical University Graz, Graz, Austria; the [2]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; the [3]Department of Epidemiology and Biometry, Erasmus Medical Center, Rotterdam, the Netherlands; the [4]Department of Psychology, Stockholm University, Stockholm, Sweden; the [5]Department of Epidemiology and Population Studies, Institute of Public Health, Jagiellonian University Medical School, Kraków, Poland; the [6]Institute of Health Studies, Department of Health and Social Security, Barcelona, Spain; the [7]Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, Germany; [8]Institut National de la Santé et de la Recherche Médicale (INSERM) Unit 360, Epidemiological Research in Neurology and Psychopathology, Hopital La Salpetriere, Paris, France; the [9]Department of Epidemiology and Public Health, University College, London, U.K.; and the [10]Istituto Superiore di Sanità, Laboratory of Epidemiology and Biostatistics, Rome, Italy.

R.F. is currently affiliated with the Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada.

Address correspondence and reprint requests to Dr. Reinhold Schmidt, Department of Neurology, Medical University Graz, Auenbruggerplatz 22, A-8036 Graz, Austria. E-mail: reinhold.schmidt@uni-graz.at.

Received for publication 24 July 2003 and accepted in revised form 4 December 2003.

CASCADE, Cardiovascular Determinants of Dementia; CVD, cardiovascular disease; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; MRI, magnetic resonance imaging; WHO, World Health Organization; WML, white matter lesion.

Diabetes is a metabolic disorder that affects many systems in the body. Nephropathy, retinopathy, peripheral neuropathy, and cardiac disease are major complications in the advanced stage of the disorder (1). Although it is known that diabetic patients are at increased risk for stroke (2), little is known about the risk for other brain pathology, such as that associated with neurodegeneration or small vessel disease. Previous radiological studies of patients with diabetes were based on highly selective groups of individuals referred to computed tomography or magnetic resonance imaging (MRI) neuroimaging (3–17). Only a few population-based studies assessed the association of diabetes—as one of many cardiovascular disease (CVD) risk factors—to only one specific type of brain lesion (18–22). The reported results are inconsistent. Only 6 (5,6,8,11,16, 20) of 19 investigations (3–22) found diabetes to be a risk factor for small vessel disease–related brain abnormalities, including white matter lesions or lacunes. Three studies found associations with cerebral atrophy (3,7,21). Interactive effects between diabetes and other major vascular risk factors, particularly arterial hypertension, have been implicated for the development of diabetes-related complications (23). The importance of such interactions for the development of brain abnormalities in diabetic patients is unclear. We hypothesized that diabetes is associated with a variety of focal and diffuse cerebral abnormalities and that there exist interactive effects between diabetes and other major vascular risk factors on the occurrence of brain lesions.

We evaluated this hypothesis in the setting of Cardiovascular Determinants of Dementia (CASCADE), a large-scale multicenter collaborative study in Europe with the objective of evaluating the long- and short-term effects of CVD risk factors on brain morphology.

RESEARCH DESIGN AND METHODS

The study design and 10 cohorts included in CASCADE have been described in detail elsewhere (24–34). Briefly, we included ongoing community-based studies with the following characteristics: *1*) data were available on cardiovascular risk factors and disease collected ≥5 years before the MRI assessment; and *2*) the cohort had been followed since inception, and data on vital status were available.

Five of the cohorts (27–31) were developed as World Health Organization–Monitoring Trends and Determinants in Cardiovascular Disease (WHO-

MONICA) projects (35) or used procedures suggested in the MONICA protocol. Furthermore, all studies originally drew their samples randomly from population registries or a defined working population. Participants for CASCADE were randomly selected from the baseline cohort within strata of those who were aged between 65 and 75 years at the CASCADE visit. All cohorts included subjects in the complete age range, except for the U.K. cohort (31), which included subjects 65–68 years of age.

Men and women were equally represented in the total sample. Excluded from the CASCADE sample before, or after, recruitment were subjects with a known clinical diagnosis of dementia or with Mini Mental Status Examination scores <15 and those with contraindications for the MRI. Data collection for CASCADE took place between 1996 and 1998 and consisted of a clinical interview, blood pressure measurement with a standard random-zero sphygmomanometer, routine laboratory assessment, MRI, and cognitive function testing. Informed consent was obtained at each center in accordance with guidelines from local institutional review boards. All of the individuals who took part in the exam were mobile and competent to understand the nature of their participation.

Study cohort. The entire CASCADE cohort comprises 1,805 individuals. The current study included the 1,252 CASCADE participants who had a physician's diagnosis of diabetes status, information on treatment for diabetes, and measured fasting or nonfasting glucose levels. This information was not available in the Augsburg WHO-MONICA (27) and the Epidemiological Prevention study of Zoetermeer (EPOZ) samples (34), comprising 194 and 267 participants, respectively. These samples were not considered for the current CASCADE analysis. The same applied for 13, 6, 52, and 21 attendees of the Rotterdam scan study (25), the Epidemiology of Vascular Aging (EVA) study (26), the POL-MONICA Krakow study (29), and the Whitehall II study (31), in which fasting or nonfasting glucose levels were not available. The diabetes cohort was not different from the entire CASCADE sample in terms of age, distribution of sex, and frequency of CVD risk factors.

Risk factor definitions. Diagnosis of prevalent diabetes was based on the 1997 recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (36). It was defined as a history of diabetes confirmed by the treating physician or as treatment for diabetes, a fasting glucose level >126 mg/dl, or a nonfasting glucose level >200 mg/dl. A total of 114 individuals had diabetes according to this definition. In 92 subjects the diagnosis relied on the presence of two or more of the diagnostic features. Diabetes diagnosis was based solely on a fasting glucose level >126 mg/dl in 21 subjects, and in one study participant, it relied solely on a nonfasting glucose level >200 mg/dl. Treatment was dichotomized into no treatment or diet only, and the use of oral antidiabetic medications or insulin. A separate analysis for insulin-dependent diabetes was precluded by the small size of this group. According to the American Diabetes Association's clinical practice recommendations (www.diabetes.org/uedocuments/overview.pdf), glycemic control at the time of glucose measurement in the treated diabetic patients of the study was in the normal range (<110 mg/dl fasting or <120 mg/dl nonfasting plasma glucose levels) in 7 (12.5%) patients, in the goal range (90–130 fasting or 110–150 nonfasting plasma glucose) in 13 (23.2%) patients, and in the range where additional action is suggested (<90 or >150 mg/dl fasting or <110 or >180 mg/dl nonfasting glucose) in 31 (55.4%) patients. In five (8.9%) subjects, the glucose values were below those requiring additional action but above the goal range.

In the current study, the group of treated diabetic patients included all patients who had been given a pharmacological treatment for diabetes, irrespective of the achieved level of glycemic control. Hypertension was defined as a history of hypertension with or without treatment or systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg. Among the 559 hypertensive study participants, diagnosis of hypertension was based on history alone in 20 (3.6%) subjects, whereas treatment or elevated blood pressure values were the sole diagnostic feature in 45 (8.1%) and 32 (5.7%) subjects, respectively. In all other cases, the diagnosis of hypertension relied on combinations of the diagnostic criteria.

Coronary heart disease was coded to be present if the study participant reported symptoms of angina pectoris, or was treated for angina or had a history of myocardial infarction, PTCA, or coronary bypass surgery before the entry into the study. Smoking status was assessed by questionnaire, and subjects were defined as never, current, or former smokers. Total cholesterol was determined by using commercially available kits. BMI was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2).

MRI

MR acquisition. All scans were made with a 1.0- or 1.5-tesla machine. The core MRI protocol included proton density and T2-weighted as well as T1-weighted sequences with 20 axial slices that were 5- or 6-mm thick with an interslice gap of 1 or 1.2 mm, respectively. The same mobile MRI machine (Siemens 1.0 tesla) was sent to five study sites (Spain, Italy, Poland, Sweden, and the U.K.) and parked centrally for 1 week. Other centers (Germany and the Netherlands) acquired the images on a 1.5-tesla machine using the core MRI protocol. Subsequent to the start of CASCADE, two other centers with already-collected scans were included (France and Austria); those scans were obtained with protocols comparable to the one used in CASCADE.

MRI reading protocol. Hard copies of the scans were evaluated at the core radiology center (Department of Radiology, Daniel Den Hoed Cancer Center, Rotterdam, the Netherlands). The evaluation protocol was based on semiquantitative scales with known inter- and intrarater reliability (25,37). All MRI scans were read for periventricular and subcortical white matter lesions, infarcts, and cortical as well as subcortical atrophy. White matter lesions were focal signal hyperintensities on proton density and T2-weighted scans, which were not seen or exhibited only faint hypointensity on T1-weighted images. Periventricular white matter lesions were abnormalities directly abutting the lateral ventricle. They were graded on a severity scale (0–3) at the frontal and occipital horns and the body of the lateral ventricle, with the total periventricular white matter lesion score being the sum of these three scores. Subcortical white matter lesions were hyperintense foci separated from the lateral ventricle. They were graded by size (small, medium, and large) and number. The total volume of subcortical white matter lesions was assessed by multiplying each lesion by a size-dependent constant (0.0042 for small lesions, 0.114 for medium lesions, and 0.95 for large lesions) and by subsequent summation of the results (25). Infarcts were focal abnormalities with clearly defined borders, and they were isointense to cerebrospinal fluid on all sequences with a diameter >3 mm. Cortical atrophy was qualitatively assessed by a semiquantitative scale (0–3) applied to each lobe and to the sylvian fissure. The sum of the lobar scores represented the total cortical atrophy score (range 0–15). Subcortical atrophy was defined as the average of ventricular indexes relative to the width of the brain measured at the level of frontal horns, occipital horns, and caudate nuclei. The extent of white matter abnormalities and atrophy was considered to be severe if it belonged to the upper quintile of the distribution.

One neuroradiologist trained three raters, who scored hard copies of the images. One rater (reading A) scored the scans from all of the studies except those from the Netherlands. The reader was blinded to center. The scans from the Netherlands were read by the two other raters (reading B). Intrarater reliability for the atrophy reading ranged from a κ value of 0.95 (frontal lobe) to a κ value of 0.67 (temporal lobe). There was no significant intrarater difference in the quantitative measure of white matter lesion load. Interrater κ values between reading A and B ranged from 0.35 for the occipital lobe to 0.72 for the frontal lobe and sylvian fissure; there were no significant differences in mean white matter lesion load between reading A and B.

Statistical analysis. We used the Statistical Package of Social Sciences (PC+, version 10.0.0; SPSS, Chicago, IL) for data analysis. Comparisons of categorical variables between nondiabetic patients and diabetic patients were performed using χ^2 test. Assumptions of a normal distribution for continuous variables were tested by nonparametric Kolmogorov-Smirnov statistics. Normally distributed continuous variables were compared by Student's t test, and the Mann-Whitney U test was used for comparison of non-normally distributed variables, including the highly skewed total periventricular white matter lesion score and the total volume of subcortical white matter lesions. Before data pooling we assessed the separate studies for heterogeneity by formal testing of the study × diabetes interaction on each outcome variable. The data were pooled because there was no evidence of heterogeneity.

To examine the independent associations of diabetes to the various types of morphologic brain changes, we performed multiple linear regression analysis. We adjusted for sociodemographics and for CVD risk factors, including hypertension, coronary heart disease, smoking status, BMI, and total cholesterol. Logistic regression analyses, with adjustment for the same covariates, were performed for dichotomized MRI variables infarcts, severe periventricular and severe subcortical white matter lesions (WMLs), and severe cortical and subcortical atrophy.

Possible interactions between diabetes and hypertension, diabetes and coronary heart disease, and diabetes and ever smoking were assessed by stratification. If stratification suggested a possible interaction, the respective interaction terms were tested in the multiple linear regression models.

RESULTS

The descriptives and frequencies of CVD risk factors of the CASCADE cohorts are shown in Table 1. Of the 114 study participants with diabetes, 58 (50.9%) subjects had no treatment or only dietary treatment, 47 (42.0%) received oral antidiabetic medications, and 9 (0.7%) received insulin. As can be seen from Table 2, diabetic patients were

TABLE 1
Description of the study cohorts

Site	*n*	Sex (% male)	Age (mean years)	Education (mean years)	Diabetes	Hypertension (%)	CHD (%)	Ever smoker (%)	BMI (mean)	Cholesterol (mean mmol/l)
Austria	169	53.8	67.9	11.1	10.7	39.6	34.3	43.8	26.8	6.0
France	186	39.2	68.4	10.7	7.0	38.2	11.8	41.9	25.9	6.3
Italy	167	44.9	69.8	4.5	9.6	46.1	13.8	37.7	28.6	6.1
The Netherlands	220	51.8	70.1	9.3	4.5	45.5	21.4	72.3	26.3	6.7
Poland	102	56.9	70.5	7.4	17.6	74.5	36.3	42.2	28.4	5.4
Spain	110	53.6	70.1	5.9	19.1	38.2	12.7	50.0	28.1	5.9
Sweden	139	47.5	68.6	9.1	7.9	60.4	15.1	48.9	26.7	6.8
U.K.	159	74.8	66.3	12.0	4.4	26.4	8.8	51.6	24.7	6.7
Total	1,252	52.3	68.9	9.0	9.1	44.6	18.8	49.7	26.8	6.3

CHD, coronary heart disease.

more commonly men, had a higher frequency of hypertension and coronary heart disease, and had a higher BMI. The univariate comparison of MRI findings demonstrated more extensive cortical atrophy and a higher ventricle-to-brain ratio in diabetic patients than in nondiabetic patients. There were no significant between-group differences for focal brain abnormalities, including periventricular, subcortical WML, and infarcts (Table 3). After adjustment for sex, age, study, education, and the CVD risk factors hypertension, coronary heart disease, smoking status, BMI, and total cholesterol, a nonsignificant trend toward more pronounced cortical atrophy in diabetic patients was seen ($\beta = 0.44$, 95% CI −0.04 to 0.92, $P = 0.07$). For severe cortical atrophy, the relative risk in diabetic patients remained significantly increased when compared with nondiabetic patients (odds ratio [OR] 1.73, 95% CI 1.06–2.81). Diabetes was not significantly associated with any other brain lesions.

Stratification of the data by hypertension, coronary heart disease, and ever smoking revealed a strong interaction between diabetes and hypertension for the extent of cortical brain atrophy. Figure 1 demonstrates the multiple linear regression results on the association between diabetes and cortical atrophy in normotensive and hypertensive subjects for each substudy and for the entire cohort. A direct relationship between diabetes and cortical atrophy was only seen in the patients who were hypertensive. There was no significant association with cortical atrophy in diabetic patients with normal blood pressure. The positive relationship between diabetes and cortical atrophy in hypertensive diabetic patients was consistently observed in all CASCADE cohorts. It reached statistical significance for the entire cohort after adjustment for all covariates ($\beta = 0.99$, 95% CI 0.37–1.62, $P = 0.002$). The OR (95% CI) for severe cortical atrophy in normotensive diabetic patients was 1.25 (0.64–2.45), whereas in hypertensive diabetic patients, it was 2.34 (1.42–3.86). Hypertension in the absence of diabetes was not significantly related to cortical atrophy ($\beta = 0.19$, 95% CI −0.11 to 0.49, $P = 0.21$). Table 4 shows the effect of the interaction between diabetes and hypertension on cortical atrophy. The first model included the interaction term total diabetes × hypertension, in addition to all sociodemographic factors and CVD risk factors. The second model included the interactions no diabetes × hypertension, untreated diabetes × hypertension, and treated diabetes × hypertension. Only the interactions total diabetes × hypertension and untreated diabetes × hypertension were significant.

DISCUSSION

These cross-sectional data from a pooled large community-based sample demonstrated a direct relationship between diabetes and cortical brain atrophy. The association between diabetes and cortical atrophy was independent of potential confounders. We observed a strong interaction between diabetes and hypertension, such that the presence of both diseases resulted in a substantially greater risk for cortical brain atrophy. Neither diabetes nor hypertension were significantly related to cortical atrophy in the absence of the other risk factor, underscoring the importance of the combination of the two risk factors for the occurrence of this MRI finding. The interaction with hypertension was seen in untreated but not in treated diabetic patients. Diabetes was not associated with any type of focal ischemic brain lesions, including abnormalities caused by small vessel disease. Possibly, these cohorts did not include individuals with the most severe stages of diabetes or with severe sequelae of brain infarcts because they are less likely to attend a health survey. Nonetheless, many previous MRI studies focusing on brain changes caused by small vessel disease presented similar results (3,4,6,9,11–15,18,19). A lack of association between diabe-

TABLE 2
Demographics and risk factors in nondiabetic and diabetic subjects

Factor	Nondiabetic subjects	Diabetic subjects	*P* value
n	1,138	114	—
Sex (% male)	51.3	62.3	0.03*
Age (years)	68.8 ± 3.2	69.3 ± 3.0	0.08†
Education (years)	9.0 ± 4.2	8.5 ± 4.7	0.34†
Hypertension (%)	43.1	60.5	<0.0001*
Coronary heart disease (%)	17.4	33.3	<0.0001*
Smoking status (%)			
Never	51.3	44.6	
Former	36.6	42.9	
Current	12.1	12.5	0.37*
BMI (kg/m^2)	26.7 ± 3.9	28.1 ± 3.8	<0.0001†
Total cholesterol (mmol/l)	6.3 ± 1.2	6.3 ± 1.4	0.59†

*χ^2 test; †Mann-Whitney *U* test.

TABLE 3
Magnetic resonance imaging findings in nondiabetic and diabetic subjects

MRI finding	Nondiabetic subjects	Diabetic subjects	*P* value
n	1,138	114	
Focal lesions			
Total periventricular WML-score	2.0 (1.0–3.0)	2.0 (1.0–4.0)	0.10*
Severe periventricular WML (%)	18.7	25.4	0.08†
Total volume of subcortical WML	0.16 (0.02–1.07)	0.31 (0.02–1.79)	0.18*
Severe subcortical WML (%)	25.7	29.8	0.35†
Presence of infarcts (%)	7.2	9.6	0.34†
Measures of brain atrophy			
Total cortical atrophy-score	7.2 ± 3.0	8.2 ± 3.2	0.001*
Severe cortical atrophy (%)	22.6	35.1	0.003†
Subcortical atrophy			
Ventricle-to-brain ratio	0.32 ± 0.04	0.33 ± 0.04	0.03*
Severe subcortical atrophy (%)	23.8	29.8	0.16†

Data are median (interquartile range) or means ± SE, unless otherwise noted. *Mann-Whitney *U* test, †χ^2 test. Severe abnormalities were considered if the extent of changes belonged to the upper quintile of the distribution.

tes and small vessel disease–related cerebral lesions has also been observed in other previous population-based MRI studies (18,19). These studies included individuals who on average were older than our cohort.

Our investigation has several strengths. With 1,252 participants, including 114 diabetic patients, it is among the largest community-based MRI investigations. It includes samples from several parts of Europe, CVD risk factor assessment was similar in all centers, and all MRI scans were read centrally to homogenize scan interpretation. Also, results were consistent across cohorts.

A weakness of the study is that fluid-attenuated inversion-recovery sequences, which are more sensitive to white matter abnormalities than standard T2-weighted spin-echo pulse sequences, were not performed because they were still in an investigational state when CASCADE was initiated. Other limitations of the study are the lack of data on diabetes-related factors that might be involved in the evolution of brain abnormalities, such as the duration and complications of diabetes or the frequency of hypo- or hyperglycemic events. Although our results suggest that diabetes treatment affects the interaction between diabetes and hypertension, additional data on the duration and quality of diabetes and hypertension therapy are needed to better interpret this finding.

This epidemiological study cannot determine the mechanism(s) by which diabetes leads to cortical atrophy. The association could be causal or could result from shared risk factors, including a common genetic susceptibility for both diabetes (38) and degenerative brain disease. Lunetta et al. (7) suggested that episodes of hypoglycemia, glycometabolic dysequilibrium, or alterations of the blood-brain barrier may be responsible for brain atrophy in young insulin-dependent diabetic patients. It is also possible that atrophy is only a consequence of a status of dehydration of the brain in patients with diabetes. Another presumed mechanism is neurodegeneration with increased production of advanced glycation end products (38–40). Epitopes of these products have been detected in very early stages of Alzheimer's disease and are thought to promote the formation of plaques and tangles (38–40). Recently, a postmortem analysis of the Honolulu-Asia Aging study demonstrated a 3-fold increased number of hippocampal neuritic plaques and a 3.5-fold higher count of cortical neurofibrillary tangles in participants with type 2 diabetes and an ε4 allele of the apolipoprotein E gene compared with those with neither risk factor (38).

Promotion of Alzheimer pathology, which has also been reported for hypertension (41), could be one pathway in the development of cortical brain atrophy in which diabetes and hypertension exert interactive effects, as seen in the current investigation. Another could be alteration of the blood-brain barrier. Both risk factors are known to cause blood-brain barrier disturbances by reduction in the density of capillaries and by thickening of the basal membrane, which can lead to cerebral hypoxia with

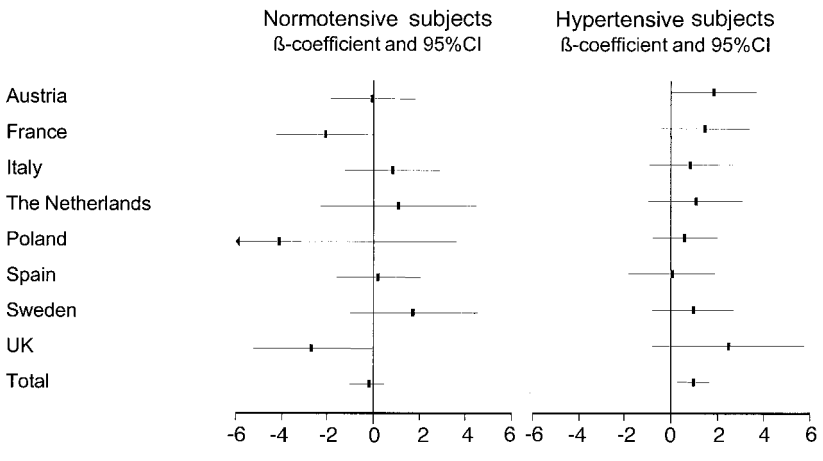

FIG. 1. Results from linear regression analysis. The figure shows diabetes and cortical atrophy in CASCADE subcohorts and in the entire CASCADE cohort stratified by the absence and presence of hypertension. The black rectangles represent β-coefficients adjusted for age, sex, years of education, smoking status, coronary heart disease, BMI, and cholesterol level. 95% CIs are denoted by lines.

TABLE 4
Results from linear regression analyses: interactions of diabetes and hypertension on cortical atrophy

Interaction term	ß	95% CI	*P**
Total diabetes × hypertension†	1.19	0.22–2.15	0.02
Untreated diabetes × hypertension†	2.20	0.88–3.51	0.001
Treated diabetes × hypertension†	0.10	−1.24 to 1.44	0.88

*Adjusted for age, sex, study, years of education, smoking status, coronary heart disease, BMI, and cholesterol level; †reference group is nondiabetic normotensive participants.

subsequent brain atrophy (42–44). Importantly, the Framingham study also described a strong interaction between non–insulin-dependent diabetes and high blood pressure as a risk factor for poor cognitive performance in the elderly (45). Although these data suggest a link between diabetes and hypertension with degenerative processes, it is important to realize that brain atrophy as seen in the current study cannot a priori be considered an equivalent of cerebral degeneration. To evaluate the causative mechanisms of this finding, studies on the clinical consequences and pathological substrates of cortical atrophy in patients with diabetes and coexisting hypertension are needed.

ACKNOWLEDGMENTS

Core funding for the collaborative work was provided by the European Union Directorate General XII. Siemens, the Netherlands, is gratefully acknowledged for making possible the use of a mobile MRI machine. Imation International provided assistance for the MRI film. Many other national and international funding agencies have provided assistance to the individual study centers, as have study center staff.

Austria: The Austrian Stroke Prevention Study was supported by the Steiermärkische Krankenanstalten and by a grant of the Austrian National Bank Jubiläumsfonds Projects 3905 and 4484 and by the Austrian Science Fund, project P13180. *Italy*: The MATISS study was partly supported by Il Progetto CUORE—Epidemiology and Prevention of Ischemic Heart Disease—of the Italian Ministry of Health. *France*: The EVA study was carried out under an agreement between INSERM, Merck, Sharp, and Dohme-Chibret Laboratories (West Point, NY) and the EISAI Company. *Germany*: The MEMO Study was supported by the German Research Society (Deutsche; Forschungs Gemeinschaft, Grant BE1996/1-1). Data collection was done within the framework of the Cooperative Health Research in the Augsburg Region (KORA). *Netherlands*: The Rotterdam Scan Study is financially supported by the Netherlands Organization for Scientific Research (NWO), the Health Research and Development Council (ZON), the National Institutes of Health (MD817876), and the Internationale Stichting Alzheimer Onderzoek (ISAO). M.M.B. is a fellow of the Royal Netherlands Academy of Arts and Sciences. *Poland*: The MONICA-Krakow study was supported by the Institute of Public Health, Jagiellonian University Medical School, Kraków, Poland; E. Kawalec, D.R. Topór-Madry; Institute of Neurology, Jagiellonian University Medical School, Kraków, Poland; and Prof. A. Szczudlik, Dr. A. Slowik, Dr. R. Motyl, and Dr. Miroslawa-Orlowiejska-Gillert. *Spain*: The MONICA-Catalonia Project was funded by the Department of Health and Social Security of Catalonia. *Sweden*: The Betula Study is funded by the Bank of Sweden Tercentenary Foundation (1988-0082:17), the Swedish Council for Planning and Coordination of Research (D1988-0092, D1989-0115, D1990-0074, D1991-0258, D1992-0143, D1997-0756, D1997-1841, D1999-0739, B1999-474), the Swedish Council for Research in the Humanities and Social Sciences (F377/1988-2000), and the Swedish Council for Social Research (1988–1990: 88-0082, and 311/1991-2000). *U.K.*: The Whitehall II study was supported by grants from the Medical Research Council; the British Heart Foundation; the Health and Safety Executive; the National Heart Lung and Blood Institute (HL36310); the National Institutes on Aging (AG13196); the Agency for Health Care Policy Research (HS06516); the New England Medical Centre, Division of Health Improvement, Institute for Work and Health, Toronto; and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socio-Economic Status and Health.

We thank B. Schra and D. Kraus (Daniel den Hoed Klinik, Rotterdam, the Netherlands) for their technical help in making and printing the MRI scans. We thank Dr. R. Motyl (Department of Neurology, University Hospital, Jagiellonian University, Kraków, Poland) for reading the MRI scans acquired outside of the Netherlands. We also thank Drs. F. de Leeuw and J.-C. de Groot for reading the scans from the Netherlands. R. Molenhoek assisted with data management.

Italy: R. Amici, L. Palmieri, F. Sciarra, and M. Fenicia Vescio are acknowledged for their contribution to data collection and management. *Spain*: L. Balañá, P. Fabré, C. Yagüe, and G. Paluzie are acknowledged for their contribution to data collection. *U.K.*: We thank all participating civil service departments and their welfare, personnel, and establishment officers; the Occupational Health and Safety Agency; the Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II study team.

REFERENCES

1. Jarrett RJ: Epidemiology and public health aspects of non-insulin-dependent diabetes mellitus. *Epidemiol Rev* 11:151–171, 1989
2. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 241:2035–2038, 1979
3. Araki Y, Nomura M, Tanaka H, Yamamoto H, Tsukaguchi I, Nakamura H: MRI of the brain in diabetes mellitus. *Neuroradiology* 36:101–103, 1994
4. Inoue T, Fushimi H, Yamada Y, Udaka F, Kameyama M: Asymptomatic multiple lacunae in diabetics and non-diabetics detected by brain magnetic resonance imaging. *Diabetes Res Clin Pract* 31:81–86, 1996
5. Kameyama M, Fushimi H, Udaka F: Diabetes mellitus and cerebral vascular disease. *Diabetes Res Clin Pract* 24 (Suppl.):S205–S208, 1994
6. Shintani S, Shiigai T, Arinami T: Subclinical cerebral lesion accumulation on serial magnetic resonance imaging (MRI) in patients with hypertension: risk factors. *Acta Neurol Scand* 97:251–256, 1998
7. Lunetta M, Damanti AR, Fabbri G, Lombardo M, DiMauro M, Mughini L: Evidence by magnetic resonance imaging of cerebral alterations of atrophy type in young insulin-dependent diabetic patients. *J Endocrinol Inves* 17:241–245, 1994
8. Fushimi H, Inoue T, Yamada Y, Udaka F, Kameyama M: Asymptomatic cerebral infarcts (lacunae), their risk factors and intellectual disturbances. *Diabetes* 45 (Suppl. 3):S98–S100, 1996
9. Fukuda H, Kitani M: Differences between treated and untreated hypertensive subjects in the extent of periventricular hyperintensities observed on brain MRI. *Stroke* 26:1593–1597, 1995
10. Perros P, Deary IJ, Sellar RJ, Best JJ, Frier BM: Brain abnormalities demonstrated by magnetic resonance imaging in adult patients with and

without a history of severe hypoglycemia. *Diabetes Care* 20:1013–1018, 1997
11. Moulin T, Tatu L, Vuillier F, Berger E, Chavot D, Rumbach L: Role of a stroke data bank in evaluating cerebral infarction subtypes: patterns and outcome of 1,776 consecutive patients from the Besancon stroke registry. *Cerebrovasc Dis* 10:261–271, 2000
12. Bradley WG Jr, Waluch V, Brant-Zawadzki M, Yadley RA, Wycoff RR: Patchy periventricular white matter lesions in the elderly: a common observation during NMR imaging. *Noninvasive Med Imaging* 1:35–41, 1984
13. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R: Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. I. Correlation with age and cerebrovascular risk factors. *Stroke* 17:1084–1089, 1986
14. Sarpel G, Chaudry F, Hindo W: Magnetic resonance imaging periventricular hyperintensity in a veterans administration hospital population. *Arch Neurol* 44:725–728, 1987
15. Kertesz A, Black SE, Tokar G, Benke T, Carr T, Nicholson L: Periventricular and subcortical hyperintensities on magnetic resonance imaging: rims, caps and unidentified bright objects. *Arch Neurol* 45:404–408, 1988;
16. Schmidt R, Fazekas F, Kleinert G, Offenbacher H, Gindl K, Payer F, Freidl W, Niederkorn K, Lechner H: Magnetic resonance imaging signal hyperintensities in the deep and subcortical white matter: a comparative study between stroke patients and normal volunteers. *Arch Neurol* 49:825–827, 1992
17. Hendrie HC, Farlow MR, Austrom MG, Edwards MK, Williams MA: Foci of increased T2 signal intensity on brain MRI scans of healthy elderly subjects. *AJNR* 10:703–707, 1989
18. Bots ML, vanSwieten JC, Breteler MMB, de Jong PT, van Gijn J, Hofman A, Grobbee DE: Cerebral white matter lesions and atherosclerosis in the Rotterdam study. *Lancet* 341:1232–1237, 1993
19. Longstreth WT, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR: Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch Neurol* 55:1217–1225, 1998
20. Longstreth WT, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L: Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: the Cardiovascular Health Study. *Stroke* 23:1274–1282, 1996
21. Longstreth WT, Arnold A, Manolio TA, Burke GL, Bryan N, Jungreis CA, O'Leary D, Enright PL, Fried L: Clinical correlates of ventricular and sulcal size on cranial magnetic resonance imaging of 3, 301 elderly people: the Cardiovascular Health Study Collaborative Research Group. *Neuroepidemiology* 19:30–42, 2000
22. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung H-P: MRI white matter hyperintensities-three-year follow-up of the Austrian Stroke Prevention Study. *Neurology* 53:132–139, 1999
23. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKDPS 38. *Br Med J* 317: 703–713, 1998
24. Launer LJ, Oudkerk M, Nilsson LG, Alperovitch A, Berger K, Breteler MM, Fuhrer R, Giampaoli S, Nissinen A, Pajak A, Sans S, Schmidt R, Hofman A: CASCADE: a European collaborative study on vascular determinants of brain lesions: study design and objectives. *Neuroepidemiology* 19:113–120, 2000;
25. de Leeuw F-E, de Groot JC, Achten E, Oudkerk M, Ramos LMP, Heijboer R, Hofman A, Jolles J, van Gijn J, Breteler MMB: Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study: the Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry* 70:9–14, 2001
26. Dufouil C, de Kersaint-Gilly A, Besançon V, Kevy C, Auffray E, Brunnereau L, Alpérovitch A, Tzourio C: Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI cohort. *Neurology* 56:921–926, 2001
27. Hense HW, Stieber J, Filipiak B, Keil U: Five-year changes in population blood pressure and hypertension prevalence: results from the Monica Augsburg Germany 1984/85 and 1989/90. *Ann Epidemiol* 3:410–416, 1993
28. Giampaoli S, Poce A, Sciarra F, Lo Noce Dima C, Minoprio A, Santaquilani P, Caiola De P, Sanctis Volpe A, Menditto A, Menotti A, Urbinati GC: Change in cardiovascular risk factors during a 10-year community intervention program. *Acta Cardiol* 5:411–422, 1997
29. Pajak A: Job and blood lipids: findings of POL-MONICA Krakow Study. *Acta Cardiol* 4:343–345, 1994
30. Rodes A, Sans S, Balana LL, Paluzie G, Aguilera R, Balaguer-Vintro I: Recruitment methods and differences in early, late and non-respondents in the first MONICA-CATALONIA population survey. *Rev Epidemiol Sante Pub* 38:447–454, 1990
31. Marmot MG, Davey Smith G, Stansfeld SA, Patel C, North F, Head J, White I, Brunner EJ, Feeney A: Health inequalities among British Civil Servants: the Whitehall II study. *Lancet* 337:1387–1393, 1991
32. Schmidt R, Lechner H, Fazekas F, Niederkorn K, Reinhart B, Grieshofer P, Horner S, Offenbacher H, Koch M, Eber B, Schumacher M, Kapeller P, Freidl W, Dusek T: Assessment of cerebrovascular risk profiles in healthy persons: definition of research goals and the Austrian Stroke Prevention Study. *Neuroepidemiol* 13:308–313, 1994
33. Nilsson L-G, Bachman L, Erngrund K, Nyberg L, Adolfsson R, Bucht G, Karlsson S, Widing M, Winblad B: The Betula prospective cohort study: memory, health, and aging. *Aging Neuropsych Cogn* 4:1–32, 1997
34. Valkenburg HA, Hofman A, Klein F, Groustra FN: An epidemiological study of risk indicators for cardiovascular diseases (EPOZ). I. Blood pressure, serum cholesterol level, Quetelet-index and smoking habits in an open population aged 5 years and older. *Ned Tijdschr Geneeskd* 124:183–189, 1980
35. Tunstall-Pedoe H, for the WHO-MONICA Project Principal Investigators: The World Health Organization Monica Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. *J Clin Epidemiol* 41:105–114, 1988
36. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
37. Scheltens P, Pasquier F, Weerts JG, Barkhof F, Leys D: Qualitative assessment of cerebral atrophy on MRI: inter- and intra-observer reproducibility in dementia and normal aging. *Eur Neurol* 37:95–99, 1997
38. 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* 51:1256–1262, 2002
39. Smith MA, Sayre LM, Vitek MP, Monnier VM, Perry G: Early Aging and Alzheimer's (Letter). *Nature* 374: 316, 1995
40. Smith MA, Sayre LM, Perry G: Diabetes mellitus and Alzheimer's disease: glycation as a biochemical link. *Diabetologia* 39: 247, 1996
41. Petrovitch H, White LR, Izmirilian G, Ross, Davis DG, Hardman J, Foley DJ, Launer LJ: Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS: Honululu-Asia Aging Study. *Neurobiol Aging* 21:57–62, 2000
42. Jakobsen J, Sidenius P, Gundersen HJ, Osterby R: Quantitative changes of cerebral neocortical structure in insulin-treated long-term diabetic rats. *Diabetes* 36:597–601, 1987
43. Knudsen GM, Jakobsen J, Juhler M, Paulson OB: Decreased blood-brain barrier permeability to sodium in early experimental diabetes. *Diabetes* 35:1371–1373, 1986
44. Skoog I, Wallin A, Fredman P, Hesse C, Aevarsson O, Karlsson I, Gottfries CG, Blennow K: A population study on blood brain barrier function in 85-year-olds: relation to Alzheimer's disease and vascular dementia. *Neurology* 50:966–971, 1998
45. Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, Wolf PA: NIDDM and blood pressure as risk factors for poor cognitive performance: the Framingham Study. *Diabetes Care* 20:1388–1395, 1997