Type 2 Diabetes and Cognitive Decline in Middle-Aged Men and Women

The Doetinchem Cohort Study

Astrid C.J. Nooyens, PhD  
Caroline A. Baan, PhD  
Annemieke M.W. Spijkerman, PhD  
W.M. Monique Verschuren, PhD

OBJECTIVE — To test the hypothesis that type 2 diabetes is associated with greater decline in cognitive function in middle-aged individuals.

RESEARCH DESIGN AND METHODS — In the Dutch prospective Doetinchem Cohort Study, cognitive functioning was measured twice within a 5-year time interval in 2,613 men and women. Participants were aged 43–70 years at baseline (1995–2002), and no one had a history of stroke. Change in scores on global cognitive function as well as on specific cognitive function domains (memory, speed of cognitive processes, and cognitive flexibility) were compared for respondents with and without type 2 diabetes (verified by the general practitioner or random plasma glucose levels $\geq 11.1$ mmol/l).

RESULTS — At the 5-year follow-up, the decline in global cognitive function in diabetic patients was 2.6 times greater than that in individuals without diabetes. For individuals aged $\geq 60$ years, patients with incident and prevalent diabetes showed a 2.5 and 3.6 times greater decline, respectively, in cognitive flexibility than individuals without diabetes. For most cognitive domains, the magnitude of cognitive decline in patients with incident diabetes was intermediate between that of individuals without diabetes and that of patients with diabetes at baseline.

CONCLUSIONS — Middle-aged individuals with type 2 diabetes showed a greater decline in cognitive function than middle-aged individuals without diabetes.

Diabetes Care 33:1964–1969, 2010

Type 2 diabetes has been associated with cognitive impairments (1) and higher risks of developing vascular dementia (2,3) and Alzheimer disease (1,3). Cognitive dysfunction in type 2 diabetic patients may result from the interaction among metabolic abnormalities intrinsic to diabetes (hyperglycemia and hyperinsulinemia), diabetes-specific complications (such as retinopathy, nephropathy, and neuropathy), and other diabetes-related disorders (such as ischemic heart disease, cerebrovascular disease, hypertension, low serum HDL cholesterol, central obesity, and depression) (4).

Most studies on cognitive functioning in relation to diabetes have been cross-sectional or focused on elderly individuals (5,6). We found only four longitudinal studies in which changes in cognitive functioning were evaluated in middle-aged populations (7–10). Longitudinal studies are needed to provide insight into the development of cognitive impairment and decline over time in relation to the onset and duration of diabetes. None of the four studies evaluated changes in cognitive functioning in individuals with recently diagnosed diabetes. Yet, to study the relation between onset of diabetes and cognitive decline, it is essential to include this group and measure cognitive function longitudinally, before and after the onset of diabetes. In the present study, we tested the hypothesis that individuals with prevalent diabetes at baseline and those with incident diabetes during follow-up show a greater decline in cognitive functioning than individuals without diabetes.

RESEARCH DESIGN AND METHODS — The Doetinchem Cohort Study (DCS) (11) is an ongoing prospective study, initially carried out in a random general population sample of 7,769 men and women aged 20–59 years (1987–1991). The aim of the Doetinchem Cohort Study was to study the impact of (changes in) lifestyle factors and biological risk factors on various aspects of health, such as the incidence of chronic diseases, physical and cognitive functioning, and quality of life. The cohort is reexamined every 5 years. At every reexamination lifestyle factors and biological risk factors are assessed by questionnaires and a physical examination at the research center. Three subsequent examination rounds were completed in the years 1993–1997, 1998–2002, and 2003–2007. All participants gave written informed consent. The study was approved by the external Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research according to the guidelines of the Declaration of Helsinki. Details on the DCS have been extensively described elsewhere (11).

From 1995 onward, cognitive testing for DCS participants aged $\geq 45$ years was introduced. In the years 1995–1997, a random sample of one-third of participants aged $\geq 45$ years was enrolled in the study on cognitive functioning, and a random sample of two-thirds was enrolled in an additional dietary study. Those participating in the dietary study during 1995–1997 had their baseline measurement of cognitive functioning during 2000–2002. Between 1995 and 2002, 3,350 respondents aged 43–70 years, 96% of all respondents invited, participated in cognitive testing for the first time. Five years later, between 2000 and 2007, 2,690 of them (80%) participated in cognitive testing again. At the first cognitive testing,
55% of the population were ≤55 years and 88% were ≤65 years of age. Participants who reported (at baseline or at follow-up) having experienced a stroke (n = 77) were excluded from the analyses, because stroke has direct effects on brain functions and cognition. A total of 2,613 people (1,286 men and 1,325 women) who participated in two cognitive measurements were included in this study.

Cognitive tests
The neuropsychological test battery included four tests, the 15-word Verbal Learning Test (VLT), the Stroop Color and Word Test (SCWT), a fluency test, and the Letter Digit Substitution Test (LDST), to measure global cognitive function and specific cognitive domains, namely memory, speed of cognitive processes, and cognitive flexibility (i.e., higher order information processing). In the VLT, 15 monosyllabic words printed on paper are displayed, one by one, in three subsequent trials, with a free recall procedure immediately after each presentation (immediate recall). After a delay of about 15 min, there is an additional free recall trial (delayed recall). The VLT total is calculated by summation of the words recalled correctly on the three immediate recalls. The VLT maximal represents the highest score on one of the three immediate recalls. In the SCWT, three skills are tested: 1) to read 40 written color names, 2) to name the color of 40 colored patches, and 3) to name the color of the ink in which 40 incongruously named color words are printed (so, e.g., the word “blue” is printed in red). In the fluency test, the participant is asked to name as many animals as possible within 1 min. In the LDST, nine letters are given a unique digit code (1 to 9) in a key displayed on the same sheet of paper. The participant is asked to fill in the correct digits corresponding to the letters, as fast as possible. These tests are described in more detail elsewhere (12). The tests are sensitive to age, also in the middle-age range. Cognitive tests were performed by trained investigators and took ~20 min to complete.

Distributions of scores on the SCWT were normalized (distributions were unimodal and skewed to the right). For each cognitive test, a z score was computed for each participant at baseline and at follow-up, based on the means and SDs of the test scores at baseline. In this way we were able to examine changes over time. Standardized scores on the SCWT were inverted, so that higher scores represent better cognition. All (inverted) standardized scores were then combined to form scores for specific cognitive domains, i.e., scores for memory function, speed of cognitive processes, and cognitive flexibility, and a summary score for global cognitive function, as follows:

\[
\text{Memory function} = (z_{VLT\text{total}} + z_{VLT\text{maximal}} + z_{VLT\text{delayed recall}})/3
\]

\[
\text{Speed of cognitive processes} = (-z\ln(SCWT_{color\ names}) - z\ln(SCWT_{color\ patches}) + z\text{LDST})/3
\]

\[
\text{Cognitive flexibility} = -z\ln(SCWT_{color\ link})
\]

\[
\text{Global cognitive function} = (-z\ln(SCWT_{color\ links}) + z\text{LDST} + z_{VLT\text{total}} + z_{VLT\text{delayed recall}} + z_{fluence})/5
\]

Diabetes status
At baseline and at follow-up, participants were asked whether they had diabetes by means of a self-administered questionnaire. For all patients with self-reported diabetes who had given written informed consent for it, their general practitioner was contacted for verification via mailed questionnaires. Almost all participants gave consent (98.2%). For 90% of patients with self-reported diabetes at baseline and for 88% of those with self-reported diabetes at follow-up, information regarding their diabetes status was obtained. Individuals with type 1 diabetes (n = 5) or with an unknown type of diabetes (n = 4) were excluded from the analyses. Three individuals with self-reported diabetes for whom the general practitioner did not confirm the diagnosis and women with gestational diabetes mellitus in the past but no diabetes at present were classified as not having diabetes. In addition, in the entire cohort a random (nonfasting) venous blood sample was taken to determine the plasma glucose level with the hexokinase method (13). For three individuals, plasma glucose could not be determined. In conclusion, diabetes was defined on the basis of self-report confirmed by the general practitioner, self-report alone (when no general practitioner verification was available), or a random plasma glucose of ≥11.1 mmol/l (14).

Other measures
Several measures that are potentially associated with diabetes and/or cognitive function were assessed. Each assessment round included a physical examination at the research center, involving height, weight, waist circumference, and blood pressure measurements and obtaining nonfasting blood samples. BMI was determined as weight in kilograms divided by the square of height in meters. Blood pressure was measured with the subject in the sitting position using a random zero sphygmomanometer. Total and HDL cholesterol were measured using standardized enzymatic methods (11).

In every assessment, information on demographic characteristics (e.g., age and educational level), lifestyle factors (e.g., smoking, alcohol consumption, and physical activity), and history of chronic diseases (e.g., myocardial infarction) was also collected using standardized questionnaires. Educational level was evaluated as the highest level reached and classified into five categories: 1) primary school, 2) lower vocational education, 3) intermediate secondary education, 4) intermediate vocational or higher secondary education, and 5) higher vocational education or university. Smoking status was defined as being a nonsmoker (never or former smoker) or smoker (of cigarettes) and further according to the number of pack-years smoked at baseline. One pack-year corresponds to smoking 20 cigarettes/day for 1 year (or, e.g., smoking 1 cigarette/day for 20 years). Alcohol consumption was classified into five categories: 1) abstainers, 2) 0–1 glasses/day, 3) 1–2 glasses/day, 4) 2–4 glasses/day, and 5) >4 glasses/day. Physical activity level was assessed by the use of the validated European Prospective Investigation into Cancer and Nutrition (EPIC) questionnaire on physical activity (15) and classified into four categories: inactive, moderately inactive, moderately active, and active (16).

Depressive symptoms were assessed using the Dutch version (17) of the SF-36 (18). The scales “mental health” and “vitality” evaluate symptoms of depression. Scores on both scales range from 0 to 100 in which higher scores represent better (mental) health.

Statistical analyses
Multivariate linear regression analyses and ANCOVA were used to study the association between diabetes status and changes in cognitive function over follow-
Type 2 diabetes and cognitive decline

up. Changes in cognitive domains and global cognitive function were analyzed as continuous outcome measures, with diabetes status as the main independent measure. Two models were tested. First, we tested a basic model, adjusting for age, sex, level of education, and baseline level of cognitive function. Second, to find out whether associations between diabetes and change in cognitive function could be explained by other diabetes-related factors, we tested the basic model with additional adjustment for factors of the metabolic syndrome (waist circumference, systolic blood pressure, use of blood pressure-lowering medication, and HDL cholesterol level), physical activity, alcohol consumption, smoking, and history of myocardial infarction. Because depression is quite common among people with diabetes and depression negatively affects cognitive function, we additionally adjusted this second model for depressive symptoms (mental health and vitality). For all these covariates, baseline measures were taken for inclusion in the analyses.

To test whether the association between diabetes and cognitive function was different at both ends of the middle-age range, additional analyses were performed including an interaction term of diabetes and age (<60 vs. >60 years). All analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

RESULTS — Nonparticipants and individuals lost to follow-up were slightly older and less educated than individuals who completed the follow-up assessment. Individuals lost to follow-up scored ~0.4 SDs lower at baseline on all cognitive domains. In addition, the prevalence of several cardiovascular risk factors was higher among the dropouts, and the prevalence of type 2 diabetes (self-report or plasma glucose level ≥11.1 mmol/l) among them was also higher (6.2 vs. 2.6% in the follow-up group).

At follow-up, 139 individuals were classified as having type 2 diabetes: 129 based on self-report (113 verified by the general practitioner) and 10 based on their elevated plasma glucose levels. Of those 139, 61 (2.3% of the total population; 31 men and 30 women) had prevalent diabetes at baseline, and 78 (3.0% of the total population; 42 men and 36 women) developed type 2 diabetes during follow-up (incident cases).

Patients with prevalent and incident diabetes were older and less educated and had higher systolic blood pressure and BMI at baseline than individuals without diabetes. Furthermore, baseline cognitive function in diabetic patients was worse than that of individuals without diabetes (Table 1).

**Changes in cognitive function**

We observed an interaction effect of diabetes with age (<60 vs. >60 years) on the association between diabetes and change in cognitive flexibility. Therefore, results for change in cognitive flexibility will be presented separately for individuals aged ≤60 years and those aged >60 years.

Prevalent diabetic patients showed statistically significantly greater declines in memory function, cognitive flexibility, and global cognitive function than individuals without diabetes after adjustment for age, sex, and educational level. Incident diabetic patients showed about twice the decline observed in individuals without diabetes, but this decline was statistically significant for memory, speed, and flexibility (for individuals aged ≥60 years) only (Table 2).

In the fully adjusted model, cognitive decline in memory, flexibility, and global cognitive function in prevalent diabetic patients was about 3 times greater than that in individuals without diabetes, although this decline was statistically significant only for flexibility (for individuals aged ≥60 years) and global cognitive function. Differences in cognitive decline in memory and speed between incident diabetic patients and individuals without diabetes were no longer statistically significant in the fully adjusted model (Table 2). Results of the fully adjusted model are presented in Fig. 1. Associations between diabetes status and changes in cognitive function were not statistically significantly different for men compared with women.

**CONCLUSIONS** — In the present study, diabetic patients showed a greater...
Memory function /H11002
Speed of cognitive processes
Differences in baseline characteristics be-
follow-up group, some of these observed
differences would make these associations
stronger. In addition, associations were
adjusted for these confounding charac-
teristics. Therefore, the effect of dropouts on
the results will be only marginal.

Furthermore, we may have missed
some cases of diabetes because we mea-
sured random glucose levels rather than
fasting glucose levels, and we did this only
once. To diagnose diabetes, two measure-
ments of glucose levels are recom-
mended. In addition, although most self-
reported cases of diabetes were verified
with the general practitioner, we cannot
exclude the possibility of some misclas-
sifications in the diabetic groups either.
Because of these possible misclassifications,
the observed differences may be underes-
timated. In addition, no data on A1C
were available. Therefore, we could not
relate longer-term glucose levels to
changes in cognitive function.

The relation between diabetes and
cognitive decline in middle-aged individu-
als was evaluated in three previous lon-
gitudinal studies (7–10). In the
Atherosclerosis Risk in Communities
(ARIC) Study, diabetic patients showed
greater declines over 6 and 14 years in
scores representing speed of cognitive
processes and verbal fluency but not in
scores for memory (7,8). In the Interdisci-
plinary Longitudinal Study of Aging
(ILSE) diabetic patients showed a greater
decline at 4 years of follow-up in intel-
ligence tasks but not in memory and speed
than individuals without diabetes (10).
Finally, in a study by van den Berg et al.
(9), no differences in cognitive decline on
several tests were observed between indi-
viduals with and without diabetes over a
4-year period. However, our study dif-
fers from these studies as to the tests used to
determine cognitive domain functions.
Different tests might reveal different pat-
terns of decline. In addition, the age
ranges of the subjects were different
among the studies. Studying different age-
groups can result in different conclu-
sions, as reflected by the interaction be-
tween age and diabetes in our study. With
one exception (9), the overall conclusion
of the previous studies and ours is that
diabetes is associated with greater cogni-
tive decline in middle-aged individuals,
but that it remains uncertain which cogni-
tive domain is affected most.

Associations between incident dia-
betes and cognitive decline have not been
studied before. The magnitude of cogni-
tive decline in incident diabetic patients
tended to be somewhere between the cogni-
tive decline in individuals without dia-
betes and that of patients with diabetes at
baseline, but the observed association was
not significant. Incident diabetic patients
may thus also benefit from timely and ap-
propriate treatment at the level of cogni-
tive functions (19). Improved glycemic
control reduces the damaging effects of
hyperglycemia on neuronal and micro-
vascular structures (3). In this respect, it
is remarkable that random plasma glucose
levels of incident diabetic patients were
similar to those of prevalent diabetic pa-
tients (8.5 and 8.6 mmol/l, respectively),
which might be an indication that treat-
ment was insufficient. However, random
plasma glucose is not the best indicator of
glycemic control.

Results of our study seem to indicate
that hyperglycemia affects different do-
main of cognitive functioning at different
stages of the disease process. For instance,
memory seems to be affected continu-
ously (lower score at baseline and a [bor-
derline significantly] greater decline
during follow-up for diabetic patients),
whereas speed of cognitive processes
seems to be affected during the first years
of hyperglycemia only (worse score at
baseline, but no greater decline over fol-
low-up for diabetic patients than for indi-
viduals without diabetes, whereas incident
diabetic patients show a greater decline in
speed of cognitive processes). These results
suggest that early treatment of hyperglyce-
emia could prevent some of the decline in
speed of cognitive processes, but probably
less so in the case of memory.

Table 2—Relative changes in cognitive function scores by diabetes status

|                  | Basic model* | Fully adjusted model† |
|------------------|--------------|-----------------------|
|                  | No diabetes | Incident diabetes     | Prevalent diabetes |
| Memory function  | –1.0         | –2.4§                 | –2.9§               |
| Speed of cognitive processes | –1.0         | –1.9§                 | –1.2                |
| Cognitive flexibility | –1.0         | –1.9                 | –1.2                |
| ≤60 years        | –1.0         | 0.9                  | –3.2                |
| >60 years        | –1.0         | –2.6§                | –3.7||               |
| Global cognitive function | –1.0         | –1.9                 | –2.8||               |

Relative decline in cognitive domain scores is shown with individuals with no diabetes as the reference group. In the reference group of “healthy” individuals, we set the cognitive decline to –1.0. The numbers in the columns of patients with diabetes reflect how many times stronger the cognitive decline was among diabetic patients compared with individuals without diabetes. No diabetes indicates no diabetes at baseline or at follow-up (n = 2,460). Incident diabetes indicates no diabetes at baseline and diabetes at follow-up (n = 78). Prevalent diabetes indicates diabetes at baseline and at follow-up (n = 61). Diabetes was defined as reporting to have diabetes (verified by the general practitioner) or having random plasma glucose levels ≥11.1 mmol/l.

§Change scores are adjusted for age, sex, level of education, and baseline cognitive score. ¶Change scores are adjusted for age, sex, level of education, waist circumference, HDL cholesterol level, systolic blood pressure, use of blood pressure-lowering medication, history of myocardial infarction, depressive symptoms (vitality and mental health), physical activity, alcohol consumption, smoking, and baseline cognitive score. †Different from no diabetes group at P < 0.10; §P < 0.05; ¶P < 0.01.

decline in cognitive function (cognitive
flexibility and global cognitive function)
than individuals without diabetes. The
magnitude of decline in cognitive func-
tion in individuals who developed dia-
betes during follow-up was between that of
individuals without diabetes and those
who had diabetes at baseline but was not
statistically significantly different from ei-
ther group after adjustment for other car-
diovascular risk factors.

Strengths of the present study are its
prospective design, the relatively young
population, and the long follow-up pe-
riod with repeated assessment of cognitive
function using a sensitive cognitive test bat-
tery. For most patients who reported dia-
betes, the diagnosis could be verified with
their general practitioner. Further, a large
number of covariates were assessed, which
enabled adjustment for a broad array of po-
tential confounders.

Limitations of the present study can be
found in the dropout of individuals during
follow-up. Although dropout of this order of magnitude (20%) is inherent
to cohort studies, there are reasons to be-
lieve that in our study it was selective to
some extent. Overall, cognitive function
was better in the follow-up group and es-
specially among individuals without dia-
betes. Based on associations in the
follow-up group, some of these observed
differences in baseline characteristics be-
tween the group of dropouts and the fol-
low-up group would weaken associations
between diabetes and change in cognitive
function, whereas other observed differ-
ences would make these associations
stronger. In addition, associations were
adjusted for these confounding charac-
teristics. Therefore, the effect of dropouts on
the results will be only marginal.

Furthermore, we may have missed
some cases of diabetes because we mea-
sured random glucose levels rather than
fasting glucose levels, and we did this only
once. To diagnose diabetes, two measure-
ments of glucose levels are recom-
mended. In addition, although most self-
reported cases of diabetes were verified
with the general practitioner, we cannot
exclude the possibility of some misclas-
sifications in the diabetic groups either.
Because of these possible misclassifications,
the observed differences may be underes-
timated. In addition, no data on A1C
were available. Therefore, we could not
relate longer-term glucose levels to
changes in cognitive function.

The relation between diabetes and
cognitive decline in middle-aged individu-
als was evaluated in three previous lon-
gitudinal studies (7–10). In the
Atherosclerosis Risk in Communities
(ARIC) Study, diabetic patients showed
greater declines over 6 and 14 years in
scores representing speed of cognitive
processes and verbal fluency but not in
scores for memory (7,8). In the Interdisci-
plinary Longitudinal Study of Aging
(ILSE) diabetic patients showed a greater
decline at 4 years of follow-up in intel-
ligence tasks but not in memory and speed
than individuals without diabetes (10).
Finally, in a study by van den Berg et al.
(9), no differences in cognitive decline on
several tests were observed between indi-
viduals with and without diabetes over a
4-year period. However, our study dif-
fers from these studies as to the tests used to
determine cognitive domain functions.
Different tests might reveal different pat-
terns of decline. In addition, the age
ranges of the subjects were different
among the studies. Studying different age-
groups can result in different conclu-
sions, as reflected by the interaction be-
tween age and diabetes in our study. With
one exception (9), the overall conclusion
of the previous studies and ours is that
diabetes is associated with greater cogni-
tive decline in middle-aged individuals,
but that it remains uncertain which cogni-
tive domain is affected most.

Associations between incident dia-
betes and cognitive decline have not been
studied before. The magnitude of cogni-
tive decline in incident diabetic patients
tended to be somewhere between the cogni-
tive decline in individuals without dia-
betes and that of patients with diabetes at
baseline, but the observed association was
not significant. Incident diabetic patients
may thus also benefit from timely and ap-
propriate treatment at the level of cogni-
tive functions (19). Improved glycemic
control reduces the damaging effects of
hyperglycemia on neuronal and micro-
vascular structures (3). In this respect, it
is remarkable that random plasma glucose
levels of incident diabetic patients were
similar to those of prevalent diabetic pa-
tients (8.5 and 8.6 mmol/l, respectively),
which might be an indication that treat-
ment was insufficient. However, random
plasma glucose is not the best indicator of
glycemic control.

Results of our study seem to indicate
that hyperglycemia affects different do-
main of cognitive functioning at different
stages of the disease process. For instance,
memory seems to be affected continu-
ously (lower score at baseline and a [bor-
derline significantly] greater decline
during follow-up for diabetic patients),
whereas speed of cognitive processes
seems to be affected during the first years
of hyperglycemia only (worse score at
baseline, but no greater decline over fol-
low-up for diabetic patients than for indi-
viduals without diabetes, whereas incident
diabetic patients show a greater decline in
speed of cognitive processes). These results
suggest that early treatment of hyperglyce-
emia could prevent some of the decline in
speed of cognitive processes, but probably
less so in the case of memory.
Several pathways have been hypothesized between type 2 diabetes and cognitive decline. For example, hyperglycemia causes oxidative stress and glycation of important functional and structural proteins (20), which can have a direct detrimental effect on brain cells and the microcirculation in the brain (21). In addition, higher fasting plasma glucose has been associated with functional changes in regional cerebral perfusion (22). In addition, type 2 diabetes is associated with increased central arterial stiffness (23), which has been shown to be a strong predictor of loss in cognitive function in older individuals (24). Improvement in glycemic control may improve cognitive functioning in adults with type 2 diabetes (19) and reduce the risk for cardiovascular complications.

Because we observed that cognitive decline was greater in prevalent diabetic patients than in incident diabetic patients and individuals without diabetes, duration of exposure to hyperglycemia could be the main factor that induces and maintains cognitive decline. To further explore this hypothesis, we performed ad hoc analyses on a subset of our data, relating diabetes duration to cognitive decline. A verified date of diagnosis of diabetes was available for 109 (57 incident and 52 prevalent) diabetic patients at follow-up. On average, diabetes in these patients had been diagnosed $6.5 \pm 6.8$ (mean $\pm$ SD) years before the follow-up assessment. We did not observe an association between duration of diabetes and change in cognitive functioning within this subgroup of diabetic patients. Thus, this result did not confirm our hypothesis.

Type 2 diabetes is often associated with other conditions that may influence cognitive function, such as hypertension, hypercholesterolemia, and central obesity. Therefore, we adjusted for these cardiovascular risk factors. However, trends observed in the fully adjusted model were similar to those in the basic model, indicating that comorbidities of diabetes only partly explain the associations between diabetes and cognitive decline.

In summary, middle-aged diabetic patients have greater cognitive decline than individuals without diabetes. Therefore, cognitive function should be assessed and monitored in middle-aged individuals with type 2 diabetes.

Acknowledgments—The Doetinchem Cohort Study is supported by the Dutch Ministry of Health, Welfare and Sport and the National Institute for Public Health and the Environment.

No potential conflicts of interest relevant to this article were reported.

A.C.J.N. analyzed data, interpreted results, and wrote the manuscript. C.A.B. originated the idea for analyses, interpreted results, and reviewed/edited the manuscript. A.M.W.S. interpreted results and reviewed/edited the manuscript. W.M.M.V. supervised data collection, interpreted results, and reviewed/edited the manuscript.

We thank the respondents, epidemiologists, and fieldworkers of the Municipal Health Service in Doetinchem for their contribution to the data collection for this study. Principal investigator is W.M.M.V. Logistic management was provided by J. Steenbrink and P. Vissink and administrative support by E.P. van der Wolf. Data management was provided by A. Blokstra, A.W.D. van Kessel, and P.E. Steinberger. Further, we thank Dr. M.T. Schram, Maastricht University, for her input; M.M. Ros and Dr. D.L. van der A, National Institute for Public Health and the Environment, for their work on the diabetes verification data; and L.C.M. Limburg and P.M. Engelfriet, National Institute for Public Health and the Environment, for their help with English writing.

References
1. Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. Vasc Health Risk Manag 2008;4:363–381
2. Pasquier F, Boulogne A, Leys D, Fontaine P. Diabetes mellitus and dementia. Diabetes Metab 2006;32:403–414
3. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74

4. Strachan MW, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. Diabetes Care 1997;20:438–445

5. 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

6. van den Berg E, Klopperborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. Biochim Biophys Acta 2009;1792:470–481

7. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szkelo M, McGovern P, Folsom AR. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42–48

8. Knopman DS, Mosley TH, Catellier DJ, Coker LH, Atherosclerosis Risk in Communities Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC-MRI Study. Alzheimers Dement 2009;5:202–214

9. van den Berg E, Reijmer YD, de Bresser J, Kessels RP, Kappelle LJ, Biessels GJ. Utrecht Diabetic Encephalopathy Study Group. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia 2010;53:58–65

10. Aberle I, Kliegel M, Zimprich D. Cognitive development in young-old type-2 diabetes patients: a longitudinal analysis from the ‘Interdisciplinary Longitudinal Study of Aging.’ Curr Psychol 2008;27:6–15

11. Verschuren WM, Blokstra A, Picavet HS, Smit HA. Cohort profile: the Doetinchem Cohort Study. Int J Epidemiol 2008;37:1236–1241

12. Nooyens AC, van Gelder BM, Verschuren WM. Smoking and cognitive decline among middle-aged men and women: the Doetinchem Cohort Study. Am J Public Health 2008;98:2244–2250

13. Tietz NW, Ed. Clinical Guide to Laboratory Tests. 3rd ed. Philadelphia, WB Saunders, 1995

14. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation. Geneva, World Health Organization, 2006

15. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62:275–280

16. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6:407–413

17. Van der Zee KI, Sanderman R. Het meten van de gezondheidsstoestand met de RAND-36: een handleiding. Groningen, Netherlands, Noordelijk Centrum voor Gezondheidszorgstukken, 1993

18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483

19. Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MW. Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care 2006;29:345–351

20. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813–820

21. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62:275–280

22. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6:407–413

23. Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouyer LM, Westerhof N, Stehouwer CD. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. Hypertension 2004;43:176–181

24. Scuteri A, Tesauro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. J Hypertens 2007;25:1035–1040