Type 2 diabetes mellitus and cognitive decline in middle-aged men and women
– The Doetinchem Cohort Study

Running title: Type 2 diabetes and cognitive decline

Astrid CJ Nooyens (PhD), Caroline A Baan (PhD), Annemieke MW Spijkerman (PhD), WM Monique Verschuren (PhD).

All authors work as researcher at the Centre for Prevention and Health Services Research (PZO), National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, the Netherlands.

Address for correspondence:
Dr. Astrid CJ Nooyens
Email: astrid.nooyens@rivm.nl

Submitted 3 November 2009 and accepted 26 May 2010.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Objective To test the hypothesis that type 2 diabetes mellitus 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 five year time interval in 2613 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 GP, or random plasma glucose levels ≥11.1 mmol/l).

Results At 5-year follow-up, the decline in global cognitive function in diabetes patients was 2.6 times greater than in persons without diabetes. For persons aged 60 years or older, both incident and prevalent diabetes patients showed a 2.5 respectively 3.6 times greater decline in cognitive flexibility than persons without diabetes. For most cognitive domains, the magnitude of cognitive decline in incident diabetes patients was intermediate between that of persons without diabetes and that of patients with diabetes at baseline.

Conclusions Middle-aged persons with type 2 diabetes showed a greater decline in cognitive function than middle-aged persons without diabetes.

Type 2 diabetes mellitus has been associated with cognitive impairments (1), and higher risks of developing vascular dementia (2,3) and Alzheimer’s disease (1,3). Cognitive dysfunction in type 2 diabetes patients may result from the interaction between metabolic abnormalities intrinsic to diabetes (hyperglycaemia, 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 focussed on the elderly (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 persons with recently diagnosed diabetes. Yet, in order 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 persons with prevalent diabetes at baseline and those with incident diabetes during follow-up show a greater decline in cognitive functioning than persons without diabetes.

RESEARCH DESIGN AND METHODS
Population. The Doetinchem Cohort Study (DCS) (11) is an ongoing prospective study, initially carried out in a random general population sample of 7769 men and women aged 20-59 years (1987-1991). The aim of the
Doetinchem Cohort Study is 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 re-examined every five years. At every re-examination lifestyle factors and biological risk factors are assessed by questionnaires and a physical examination at the research centre. 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 (TNO) according to the guidelines of the Helsinki Declaration Details on the DCS have been extensively described elsewhere (11).

From 1995 onwards, cognitive testing for DCS participants aged 45 years and older was introduced. In the years 1995-1997, a random sample of one third of participants aged 45 years and older 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, 3350 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, 2690 of them (80%) participated in cognitive testing again. At the first cognitive testing, 55% of the population were younger than 55 years and 88% were younger than 65 years of age. Participants who reported (at baseline or at follow-up) to have experienced a stroke (n=77) were excluded from the analyses, since stroke has direct effects on brain functions and cognition. A total of 2613 people (1288 men and 1325 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, the Stroop Color-Word Test, a Fluency Test and the Letter Digit Substitution Test. It measures global cognitive function and specific cognitive domains, namely memory, speed of cognitive processes, and cognitive flexibility (i.e. higher order information processing). In the 15 Words Verbal Learning Test (VLT), fifteen monosyllabic words printed on paper are displayed, one by one, in three subsequent trials, with a free recall procedure immediately following each presentation (immediate recall). After a delay of about fifteen minutes, 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 Stroop Color-Word Test (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, for example, the word “blue” is printed in red). In the Fluency Test, the participant is asked to name as many animals as possible within one minute. In the Letter Digit Substitution Test (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 carried out by trained investigators and took about 20 minutes to complete.

Distributions of scores of the Stroop Color-Word Test (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 standard deviations of the test scores at baseline. In this way we were able to examine changes over time. Standardized scores of 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:

Memory function = \( \frac{z_{VLT_{total}} + z_{VLT_{maximal}} + z_{VLT_{delayed recall}}}{3} \)

Speed of cognitive processes = \( \frac{-z_{ln(SCWT_{color names})} - z_{ln(SCWT_{color patches})} + z_{LDST}}{3} \)

Cognitive flexibility = \( -z_{ln(SCWT_{color ink})} \)

Global cognitive function = \( \frac{-z_{ln(SCWT_{color ink})} + z_{LDST} + z_{VLT_{total}} + z_{VLT_{delayed recall}} + z_{Fluency}}{5} \)

Diabetes status. At baseline and at follow-up, participants were asked whether they had diabetes by means of a self-administered questionnaire. For all cases of self-reported diabetes who had given written informed consent for it, their general practitioner (GP) was contacted for verification via mailed questionnaires. Almost all participants gave consent (98.2%). For 90% of self-reported cases at baseline and for 88% of self-reported cases at follow-up, information regarding their diabetes status was obtained. Persons with type 1 (n=5) or with unknown type of diabetes (n=4) were excluded from the analyses. Three individuals with self-reported diabetes for whom the GP did not confirm the diagnosis, and women with gestational diabetes in the past, but no diabetes at present, were classified as not having diabetes. In addition, in the entire cohort a random (non-fasting) venous blood sample was taken to determine plasma glucose level with the hexokinase method (13). For three persons, plasma glucose could not be determined. In conclusion, diabetes was defined on the basis of self-report confirmed by the GP, self-report alone (when no GP verification was available), or a random plasma glucose of 11.1 mmol/l or above (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 centre, involving height, weight, waist circumference and blood pressure measurements, and obtaining non-fasting blood samples. Body mass index was determined as weight (kg) divided by height squared (m\(^2\)). Blood pressure was measured with the subject in sitting position using a random zero sphygmomanometer. Total and HDL cholesterol were measured using standardized enzymatic methods (11). In every assessment, also 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 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 non-smoker (never or ex-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 per day for one year (or e.g. smoking one cigarette per day for 20 years). Alcohol consumption was classified into five categories: 1) abstainers, 2) 0-1 glasses per day, 3) 1-2 glasses per day, 4) 2-4 glasses per day, and 5) more than 4 glasses...
per 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 0-100 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-up. Changes in cognitive domains and global cognitive function were analyzed as continuous outcome measures, with diabetes status as main independent measure. Two models were tested. First, we tested a basic model, adjusting for age, gender, 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, HDL cholesterol level), physical activity, alcohol consumption, smoking and history of myocardial infarction. As 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 (≤ vs > 60 years). All analyses were performed using SAS version 9.2 [SAS Institute Inc, Cary, NC].

RESULTS

Non-participants and persons lost to follow-up were slightly older and lower educated than persons who completed the follow-up assessment. Persons lost to follow-up scored about 0.4 SDs lower at baseline on all cognitive domains. In addition, the prevalence of several cardiovascular risk factors was higher among the drop-outs and the prevalence of type 2 diabetes (self-report or plasma glucose level ≥ 11.1 mmol/l) among them was also higher, 6.2%, versus 2.6% in the follow-up group.

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

Prevalent and incident diabetes patients were older, less educated, and had a higher systolic blood pressure and body mass index at baseline compared to persons without diabetes. Further, baseline cognitive function in diabetes patients was worse than that of persons without diabetes (Table 1).

Changes in cognitive function. We observed an interaction effect of diabetes with age (≤ 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 persons up to and those over 60 years of age. Prevalent diabetes patients showed statistically significantly greater declines in memory function, cognitive flexibility and global cognitive function than persons
without diabetes, after adjustment for age, gender and educational level. Incident diabetes patients showed about twice the decline observed in persons without diabetes, but this was statistically significant for memory, speed and flexibility (for persons aged 60 years and older) only (Table 2).

In the fully adjusted model, cognitive decline in memory, flexibility and global cognitive function in prevalent diabetes patients was about 3 times greater than in persons without diabetes, although this was statistically significant only for flexibility (for persons aged 60 years and older) and global cognitive function. Differences in cognitive decline in memory and speed between incident diabetes patients and persons without diabetes were no longer statistically significant in the fully adjusted model (Table 2). Results of the fully adjusted model are presented in Figure 1.

Associations between diabetes status and changes in cognitive function were not statistically significantly different for men compared to women.

CONCLUSIONS
In the present study, diabetes patients showed greater decline in cognitive function (cognitive flexibility and global cognitive function) than persons without diabetes. The magnitude of decline in cognitive function in persons who developed diabetes during follow-up was in between that of persons without diabetes and those who had diabetes at baseline, but was not statistically significantly different from either group after adjustment for other cardiovascular risk factors.

Strengths of the present study are its prospective design, the relatively young population, and the long follow-up period with repeated assessment of cognitive function using a sensitive cognitive test battery. For most patients who reported diabetes, the diagnosis could be verified with their GP. Further, a large number of covariates were assessed, which enabled adjustment for a broad array of potential confounders.

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

Further, we may have missed some cases of diabetes since we measured random glucose levels rather than fasting glucose levels, and we did this only once. In order to diagnose diabetes, two measurements of glucose levels are recommended. On the other hand, although most self-reported diabetes patients were verified with their GP, we cannot exclude some misclassifications in the diabetes groups either. Due to these possible misclassifications, the observed differences may be underestimations. In addition, no data on HbA1c 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 persons was evaluated in three previous longitudinal studies, (7-10). In the Atherosclerosis Risk in Communities (ARIC) Study, diabetes 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 Interdisciplinary Longitudinal
Study of Aging (ILSE) diabetes patients showed a greater decline at 4 years of follow-up in intelligence tasks, but not in memory and speed, than persons without diabetes (10). Finally, in a study by Van den Berg, no differences in cognitive decline on several tests were observed between persons with and without diabetes over a 4-year period (9). However, our study differs from these studies as to the tests used to determine cognitive domain functions. Different tests might reveal different patterns of decline. In addition, the age ranges of the subjects were different between the studies. Studying different age groups can result in different conclusions, as reflected by the interaction between 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 cognitive decline in middle-aged persons, but that it remains uncertain which cognitive domain is affected most.

Associations between incident diabetes and cognitive decline have not been studied before. The magnitude of cognitive decline in incident diabetes patients tended to be somewhere between the cognitive decline in persons without diabetes and that of patients with diabetes at baseline, but the observed association was not significant. Incident diabetes patients may thus also benefit from timely and appropriate treatment at the level of cognitive functions (19). Improved glycemic control reduces the damaging effects of hyperglycaemia on neuronal and microvascular structures (5). In this respect, it is remarkable that random plasma glucose levels of incident diabetes patients were similar to those of prevalent diabetes patients (8.5 and 8.6 mmol/l respectively), which might be an indication that treatment was insufficient. However, random plasma glucose is not the best indicator for glycemic control.

Results of our study seem to indicate that hyperglycaemia affects various domains of cognitive functioning at different stages of the disease process. For instance, memory seems to be affected continuously (lower score at baseline and a (borderline significantly) greater decline during follow up for diabetes patients), while speed of cognitive processes seems to be affected during the first years of hyperglycaemia only (worse score at baseline, but no greater decline over follow-up for diabetes patients than persons without diabetes, while incident diabetes patients show a greater decline in speed of cognitive processes). These results suggest that early treatment of hyperglycaemia 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, hyperglycaemia causing 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). Also, 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 of glycaemic control may improve cognitive functioning in adults with type 2 diabetes (19) and reduce the risk for (cardiovascular) complications.

Since we observed that cognitive decline was greater in prevalent diabetes patients compared to incident diabetes patients and persons without diabetes, duration of exposure to hyperglycaemia 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) diabetes patients.
patients at follow-up. On average, these patients had been diagnosed 6.5 (SD 6.8) 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 diabetes patients. Thus, this 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, similar trends were observed in the basic model as in the fully adjusted model, indicating that comorbidities of diabetes only partly explain the associations between diabetes and cognitive decline.

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

Author contributions: A.C.J.N. analysed 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.

ACKNOWLEDGEMENTS
The Doetinchem Cohort Study is financially supported by the Dutch Ministry of Health, Welfare and Sport and the National Institute for Public Health and the Environment. The authors thank the respondents, the epidemiologists and fieldworkers of the Municipal Health Service in Doetinchem for their contribution to the data collection for this study. Principal investigator is Dr. W.M.M. Verschuren. 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 in English writing.

The authors have no relevant conflict of interest to disclose.

REFERENCES
mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochim Biophys Acta* 1792:470-81, 2009


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


23. Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ,


**TABLE 1**: General baseline characteristics of the study population, by diabetes status.

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes (n=2460)</th>
<th>Incident Diabetes (n=78)</th>
<th>Prevalent Diabetes (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>55.0 (6.8)</td>
<td>57.4 (6.6)</td>
<td>60.6 (6.5)</td>
</tr>
<tr>
<td>Gender, % women</td>
<td>51.0</td>
<td>46.2</td>
<td>49.2</td>
</tr>
<tr>
<td>Level of education, % highly educated</td>
<td>26.8</td>
<td>12.8</td>
<td>13.1</td>
</tr>
</tbody>
</table>

*Cognitive function domain scores (z-scores)*

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes (n=2460)</th>
<th>Incident Diabetes (n=78)</th>
<th>Prevalent Diabetes (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory function, mean (SD)</td>
<td>0.01 (0.94)</td>
<td>0.00 (0.89)</td>
<td>-0.53 (0.87)</td>
</tr>
<tr>
<td>Speed of cognitive processes, mean (SD)</td>
<td>0.02 (0.83)</td>
<td>-0.18 (0.88)</td>
<td>-0.51 (0.95)</td>
</tr>
<tr>
<td>Cognitive flexibility, mean (SD)</td>
<td>0.02 (0.99)</td>
<td>-0.33 (1.00)</td>
<td>-0.30 (1.41)</td>
</tr>
<tr>
<td>Global cognitive function, mean (SD)</td>
<td>0.02 (0.72)</td>
<td>-0.19 (0.66)</td>
<td>-0.45 (0.75)</td>
</tr>
<tr>
<td>Random glucose level (mmol/l)</td>
<td>5.3 (0.9)</td>
<td>6.9 (1.6)</td>
<td>11.4 (3.9)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean (SD)</td>
<td>130 (17)</td>
<td>143 (19)</td>
<td>142 (18)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean (SD)</td>
<td>82 (10)</td>
<td>88 (11)</td>
<td>84 (12)</td>
</tr>
<tr>
<td>Use of blood pressure lowering medication, %</td>
<td>10.0</td>
<td>21.8</td>
<td>41.0</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l), mean (SD)</td>
<td>5.84 (1.00)</td>
<td>6.09 (1.19)</td>
<td>5.70 (1.02)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l) – men, mean (SD)</td>
<td>1.23 (0.32)</td>
<td>1.04 (0.26)</td>
<td>1.17 (0.36)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l) – women, mean (SD)</td>
<td>1.55 (0.38)</td>
<td>1.20 (0.33)</td>
<td>1.23 (0.23)</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>1.6</td>
<td>3.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>26.1 (3.6)</td>
<td>30.0 (4.9)</td>
<td>29.6 (4.9)</td>
</tr>
<tr>
<td>Waist circumference (cm) – men, mean (SD)</td>
<td>98.3 (8.9)</td>
<td>105.7 (7.9)</td>
<td>106.1 (14.1)</td>
</tr>
<tr>
<td>Waist circumference (cm) – women, mean (SD)</td>
<td>88.8 (10.5)</td>
<td>102.1 (12.5)</td>
<td>103.3 (10.8)</td>
</tr>
<tr>
<td>Physical activity†, % inactive</td>
<td>24.6</td>
<td>24.4</td>
<td>37.7</td>
</tr>
<tr>
<td>Alcohol consumption, % &gt; 4 glasses/day</td>
<td>4.8</td>
<td>9.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>22.2</td>
<td>23.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Mental health†, mean (SD)</td>
<td>77 (15)</td>
<td>78 (13)</td>
<td>77 (18)</td>
</tr>
<tr>
<td>Vitality†, mean (SD)</td>
<td>68 (17)</td>
<td>66 (17)</td>
<td>65 (18)</td>
</tr>
</tbody>
</table>

Diabetes, self-reported diabetes (verified by the GP) or having a random plasma glucose level at or above 11.1 mmol/l; SD, standard deviation. † Physical inactivity is defined as being classified in the lowest two of four categories (inactive and moderately inactive) according the Wareham classification for physical activity (16). Mental health and vitality scores are based on the SF-36 and represent depressive symptoms. Scores range from 0-100 in which higher scores represent better (mental) health (18).
### TABLE 2: Relative changes in cognitive function scores, by diabetes status†.

<table>
<thead>
<tr>
<th></th>
<th>Basic model‡</th>
<th>Fully adjusted model§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No diabetes</td>
<td>Incident diabetes</td>
</tr>
<tr>
<td></td>
<td>Prevalent diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No diabetes</td>
<td>Incident diabetes</td>
</tr>
<tr>
<td>Memory function</td>
<td>-1.0</td>
<td>-2.4**</td>
</tr>
<tr>
<td>Speed of cognitive processes</td>
<td>-1.0</td>
<td>-1.9**</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>-1.0</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>60-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-1.0</td>
<td>-2.6**</td>
</tr>
<tr>
<td>Global cognitive function</td>
<td>-1.0</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

† Relative decline in cognitive domain scores with persons with no diabetes as reference group: in the reference group of ‘healthy’ persons, we set the cognitive decline to -1.0. The numbers in the columns of diabetes patients reflect how many times stronger the cognitive decline was among diabetes patients in comparison to the persons without diabetes.

‡ Change scores are adjusted for age, gender, level of education and baseline cognitive score.

§ Change scores are adjusted for age, gender, level of education, waist circumference, HDL cholesterol level, systolic blood pressure, usage of blood pressure lowering medication, history of myocardial infarction, depressive symptoms (vitality and mental health), physical activity, alcohol consumption, smoking, and baseline cognitive score.

No diabetes, no diabetes at baseline or at follow-up (n=2460); Incident diabetes, no diabetes at baseline and diabetes at follow-up (n=78); Prevalent diabetes, diabetes at baseline and at follow-up (n=61).

Diabetes was defined as reporting to have diabetes (verified by the GP), or having random plasma glucose levels of or above 11.1 mmol/l.

*Different from no diabetes group at \( P < 0.10 \); ** \( P <0.05 \); *** \( P <0.01 \).

### FIGURE LEGEND

**FIGURE 1**: Average cognitive function, with 95% confidence interval, at baseline and at follow-up for persons with no diabetes (○-), incident diabetes (□-), and prevalent diabetes (■-). For change in cognitive flexibility, an interaction effect was observed for diabetes status and age. Therefore, cognitive flexibility is displayed for persons up to 60 years of age (upper lines) and persons aged 60 years and older (lower lines) separately.
Figure 1