Cognitive Decline in Type 2 Diabetes Mellitus and the Relation with Vascular Risk Factors: A Longitudinal Population-Based Study

Hannah W. Post

On behalf of the Utrecht Diabetic Encephalopathy Study Group
Department of Neurology, University Medical Center Utrecht

Thesis Master Neuropsychology, Utrecht University

Utrecht University

Universitair Medisch Centrum
Utrecht

Cognitive Decline in Type 2 Diabetes Mellitus and the Relation with Vascular Risk Factors: A Longitudinal Population-Based Study

Hannah W. Post

On behalf of the Utrecht Diabetic Encephalopathy Study Group

Department of Neurology, University Medical Center Utrecht

Thesis Master Neuropsychology

University Utrecht

June 19, 2009

Drs. Y.D. Reijmer, University Medical Center Utrecht, Department of Neurology

Drs. E. van den Berg, University Medical Center Utrecht, Department of Neurology

Dr. H.C. Dijkerman, Experimental Psychology, Helmholtz Institute, Utrecht University

CONTENTS

ABSTRACT

Background/Aims Type 2 diabetes mellitus (T2DM) and co-morbid vascular risk factors (e.g. HbA_{1c}, hypertension, obesity) are associated with decrements in cognitive functioning, especially in the elderly. We hypothesized that these cognitive decrements increase over time with advancing age. The current longitudinal study examined the development in cognitive functioning in T2DM over a 4-year interval.

Methods An extensive neuropsychological assessment and vascular and metabolic risk factor profiles were obtained from 47 T2DM patients (mean age: 66.9 ± 5.6) and 26 matched-control participants (mean age: 63.4 ± 5.4). Cognitive test scores divided into five cognitive domains (Abstract Reasoning, Memory, Information Processing Speed, Attention and Executive Functioning and Visuoconstruction) and expressed as standardised z-scores, adjusted for age.

Results T2DM patients performed worse than controls on the domains Abstract Reasoning (effect size (ES): -.07 to -.07), Memory (ES: -.21 to -.16), Information Processing Speed (ES: -.33 to -.54) and Attention and Executive Functioning (ES: -.16 to -.26), but this difference was only significant for the domain Information Processing Speed. No Time and GroupxTime interaction effects were observed in cognitive functioning. However, a trend for interaction was observed on the domain Information Processing Speed (p=.066). Body Mass Index was a predictor for cognitive decline on the domain Visuoconstruction (>BMI predicts better performance on Visuoconstruction) (p<.05).

Conclusion Even though we did find changes in cognitive performance, contrary to our hypothesis accelerated cognitive decline was not observed in T2DM patients. Co-morbid vascular risk factors associated with T2DM, did not consistently predict worse cognitive performance. In this study sample BMI was related to performance on the domain Visuoconstruction.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disease and is most common in older people. It is a serious problem worldwide. In the Netherlands, the prevalence in the age group 30-74 years is 2.7-3.2%. With advancing age this prevalence increases, namely for men by 7% per year of age and for women by almost 8% per year of age. In the period 1993-2010 this age related increase will give rise to a 36% increase in the prevalence (Baan & Feskens, 2001). Estimated for the year 2025 is that over 1.3 million people in the Netherlands will have T2DM, that is 8% of the Dutch population (Baan et al., 2009). Furthermore, other demographic factors, such as western lifestyle, obesity and physical inactivity, contribute to the increase in the number of people with type 2 diabetes (Wild, Roglic, Green, Sicree & King, 2004).

Type 2 diabetes mellitus is a more prevalent form of diabetes and has a later and slower onset than type 1 diabetes mellitus (T1DM). T1DM is caused by an absolute deficiency of insulin secretion (Gavin et al., 1997). T2DM is characterized by hyperglycemia caused by resistance to insulin action combined with an inadequate compensation in the response of insulin secretion (Gavin et al., 1997; American Diabetes Association, 2002). Microvascular complications may occur such as kidney failure, foot ulcers, peripheral neuropathy and retinopathy (Laakso, 1999). Not only on microvascular level diabetes has its effect, it also manifests on macrovascular level. The complications may include atherosclerosis of the coronary arteries, peripheral arteries and carotid vessels (Beckman, Creager & Libby, 2002; Creager, Lüscher, Cosentino & Beckman, 2003). Among patients with type 2 diabetes cardiovascular disease is the most important cause of morbidity and mortality (Laakso, 1999). Diabetes mellitus may also lead to damage to the central nervous system which is known as diabetic encephalopathy (Gispen & Biessels, 2000). Diabetic encephalopathy is reflected in impaired cognitive functioning and is also associated with an increased risk of dementia (Biessels, Staekenborg, Brunner, Brayne, Scheltens, 2006; Ebady, Arami & Shafigh, 2008; Strachan, Reynolds, Frier, Mitchell & Price, 2008; Van den Berg et al., 2008; Brands et al., 2007; Allen, Frier & Strachan, 2004; Awad, Gagnon & Messier, 2004; Gispen & Biessels, 2000; Croxson & Jagger, 1995). Despite the differences in methodological designs (e.g. cross-sectional or longitudinal) of several studies, there have been several attempts to compare the findings on impairment of cognitive functioning in T2DM (Awad et al., 2004; Stewart & Liolitsa, 1999). Even though results between studies varied, the cognitive domains most consistently affected by T2DM were Memory, Processing Speed and Cognitive

Flexibility (Awad et al., 2004; Stewart & Liolitsa, 1999; Van den Berg, Kloppenborg, Kessels, Kapelle & Biessels, 2009; Messier, 2005). Yeung, Fischer and Dixon (2009) assembled cross-sectional data of 570 participants (diabetes group vs. healthy controls) and used a multidimensional spectrum of neuropsychological tests of various domains (Memory, Speed, Executive Function). The results of the study show that T2DM patients performed significantly worse only on Executive Functioning and Speed in comparison to controls. Furthermore, few significant differences were found on visuospatial processing, auditory or visual attention and language abilities (Awad et al., 2004). The cognitive profile of decrements found in T2DM is best described as a non-specific pattern of an overall modest deficit in cognitive performance (Brands et al., 2007).

Changes in brain structure may underlie the cognitive deficits observed in T2DM. In a systematic review, Van Harten, De Leeuw, Weinstein, Scheltens and Biessels (2006) attempted to integrate findings about brain imaging studies in patients with diabetes. Diabetes mellitus was found to be associated with brain abnormalities, such as cerebral atrophy and lacunar infarcts. Moreover, on brain MRI, it was found that patients with diabetes mellitus (DM) had more cortical and subcortical atrophy and more (deep)white matter lesions than controls (Manschot et al, 2006; Van Harten, Oosterman, van Loon, Scheltens & Weinstein, 2007; Asimakopoulou, Hampson & Morrish, 2001). These structural changes are related to the cognitive impairment seen in T2DM patients (Manschot et al., 2006; Brands et al., 2007; Akisaki et al., 2006) as well as an increased risk for developing dementia (Roriz-Filho et al., 2009). This leads to the suggestion that the diabetic brain shows "accelerated brain ageing" (Biessels, van der Heide, Kamal, Bleys & Gispen, 2002).

T2DM may develop in the context of a cluster of vascular risk factors, such as hypertension, obesity and dyslipidemia (Biessels, Kerssen, De Haan & Kappelle, 2007). This interrelation gives the suggestion that vascular co-morbidity is the predominant factor in the relation between T2DM and associated cognitive impairments (Manschot et al., 2006; Brands et al., 2007; Akisaki et al., 2006). Cosway and colleagues (2001) found no significant differences in several domains of cognitive functioning or Information Processing Speed between T2DM group and non diabetic control group. However, poorer performance on verbal memory was significantly correlated with duration of diabetes. In this study cognitive functioning of a group of uncomplicated type 2 diabetes patients was examined and it therefore suggests that common

vascular complications in T2DM such as macrovascular disease, hypertension and depression are associated with previously observed cognitive decrements (Cosway, Strachan, Dougall, Frier, & Deary, 2001).

Van den Berg, Kloppenborg, Kessels, Kappelle and Biessels (2009) reviewed several studies to conclude that vascular risk factors associated with diabetes all have a similar effect on cognitive functioning. Hypertension (and T2DM) was most consistently associated with cognitive decrements. For dyslipidemia and obesity a proportion of studies did not show an association with decline in cognitive performance. Similar across risk factors was the magnitude of decrements affecting Memory, Processing Speed and Cognitive Flexibility. Regarding HbA_{1c} the effects are controversial, in another study of Van den Berg and colleagues (2006) no associations were found between the level of HbA_{1c} and cognitive dysfunction. On the contrary, another study found that HbA_{1c} was associated with risk of cognitive decline, particularly in Memory (Maggi et al., 2009). Total cholesterol and Body Mass Index are also associated with cognitive decline (Van den Berg et al., 2009; Whitmer, Gunderson, Barrett-Conner, Quesenberry & Yaffe, 2005; Yaffe, Barret-Connor, Lin & Grady, 2002).

Although several studies investigated cognitive functioning in T2DM, most studies are cross-sectional and thus little is known about the development of these cognitive decrements. The present study uses a longitudinal design to investigate cognitive status and cognitive development in T2DM subjects compared to healthy controls. In a previous study, we showed that T2DM patients performed worse than controls on the domains Memory, Processing Speed and Attention and Executive Functioning (Brands et al., 2007). Patients and controls were re-examined after 4 years. Cognitive function declines with age (Allen et al., 2004) and although it is assumed that over time the control group will show decline in cognitive functioning in conformity with age, we hypothesize that the type 2 diabetes mellitus group will show a greater abatement in cognitive functioning, thus accelerated cognitive decline. In line with the baseline measurements, this decline will be seen in the domains Memory, Information Processing Speed and Attention and Executive Functioning. A second aim is to examine if vascular risk factors ($HbA_{1c,}$ total cholesterol, blood pressure and Body Mass Index (BMI)) can predict worse outcome on cognitive functioning for T2DM patients.

METHODS

Study Population

This study is part of a larger study, the Utrecht Diabetic Encephalopathy Study (UDES). This is a longitudinal study on determinants of impaired cognition in type 2 diabetes mellitus in older people over time. The study occurred between September 2002 and November 2004. In the period of September 2006 and December 2008 follow-up measurements were obtained.

From 2002 and 2004 a sample of 122 participants, diagnosed with type 2 diabetes mellitus, was recruited. Included were 61 controls. T2DM patients were between the age of 56 and 80 years and were recruited through their general practitioner. Controls (53–78 yrs) were recruited among spouses and acquaintances of the patients. The present interim-analysis study contained a sample of 73 participants, 47 T2DM patients and 26 controls that attainted follow-up.

Participants Selection

For inclusion in this study all participants had to be functionally independent and Dutch speaking. Diabetes-related co-morbid conditions, such as hypertension are considered an integral part of the diabetic condition and therefore patients with these conditions were included. Psychiatric or neurological disorders unrelated to diabetes and a history of alcohol or substance abuse were exclusion criteria. All participants signed an informed consent form.

At the University Medical Center Utrecht participants were examined neurologically and physically, participated in a MRI scan of the brain, fundus photograph, electrocardiogram and blood pressure and blood glucose levels were recorded for obtaining the baseline information. Furthermore detailed neuropsychological assessment was obtained. This was repeated for the follow-up study.

Measurements

Participants were asked about diabetes duration, hypoglycemic events, history of hypertension, head trauma, stroke or cardiovascular disease, medication use and smoking and alcohol consumption habits. Blood pressure was measured three times when participants were sitting and while they were in the medical center. At baseline participants measured blood pressure at

home, nine different time points during the day. Furthermore, glycosylated hemoglobin (HbA_{1c}) was determined, which reflects the average blood glucose level in the preceding six to eight weeks. Total cholesterol was determined from fasting blood samples. BMI was calculated as weight divided by squared height.

Neuropsychological assessment

All participants participated in a comprehensive neuropsychological examination that consisted twelve verbal and nonverbal tasks in a fixed order that took about 90 minutes to complete. The tests covered five major cognitive domains in order to reduce the amount of neuropsychological variables and for clinical clarity. This division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak and colleagues (2004).

"Abstract Reasoning" was assessed by the Raven Advanced Progressive Matrices (12-item short form).

The domain "Memory" consist of the subtests forward and backward Digit Span of the Wechsler Adult Intelligence Scale – 3rd edition (DS-WAIS-III) and the Corsi Block Tapping Task (Working Memory). The product scores of the maximum number of digit (actual span score) times the number of correctly recalled sequences were recorded (Kessels et al., 2000). The Dutch version of the Rey Auditory Verbal Learning Test (for baseline measurements and for follow-up a parallel version was used) and Location Learning Test (for baseline measurements and for follow-up a parallel version was used) (Immediate Memory and Learning Rate), the Rey Complex Figure delayed (for baseline measurements) and the Taylor Complex Figure delayed (for follow-up measurements) (Incidental Memory) and the Paired Association Test.

"Information Processing Speed" was assessed with the Stroop Colour Word Test part I and II, the Trail Making Task A and the Symbol Digit Substitution test (SS-WAIS-III).

"Attention and Executive Functioning" was assessed by the Stroop Colour Word Test part III (Response Inhibition), the Trail Making Test (task B compared to A) (Divided Attention), the Brixton Spatial Anticipation Test (Concept Shifting) and Verbal Fluency test (letters 'A' and 'N' and animal naming) (Verbal Fluency).

"Visuoconstruction" was assessed by the copy trial of the Rey Complex Figure and the Taylor Complex Figure Copy.

The Dutch version of the Telephone Interview for Cognitive Status (TICS) (Kempen, Meier, Bouwens, Van Deursen & Verhey, 2007) was included as an additional measurement (Language and Attention, Orientation and Memory (Lines, McCaroll, Lipton & Block, 2006)) for all who participated at the baseline. This was measured for both attending participants as well as participants that not attended on the follow-up study.

Psychological Assessment

After the neuropsychological test battery, the participants filled in three questionnaires.
The CFQ, which measures subjective cognitive functioning i.e. the frequency of daily cognitive complaints. The Dutch version of the BDI and the SCL-90 are filled in to control for possible depression and physical complaints which could influence the performance on the neuropsychological examination.

Analyses

Group differences in demographic data and risk factors were analysed with an independent T-test or an χ^2-test for nonparametric proportions.

Cognitive test scores were standardised into z-scores and averaged over each cognitive domain to obtain five composite z-scores. An ANOVA for repeated measures was used to examine the effect of Group (T2DM vs. control), Time (baseline vs follow-up) and GroupxTime interaction, adjusted for age ($p<.05$). Effect sizes (ES) (Cohen *d*) (Cohen, 1988) were calculated in order to determine the magnitude of cognitive deficits on the cognitive domains. Negative ES reflect worse performance of the T2DM group. Raw test scores at baseline and follow-up were separately analysed with a univariate ANOVA, adjusted for age.

Within the group of diabetic patients, linear regression analyses, adjusted for age and sex, were performed to assess the predictive value of vascular risk factors (fasting glucose, HbA_{1c}, total cholesterol, blood pressure, body mass index (BMI)) on cognitive decline, defined as the difference in z-score between baseline and follow-up. For determining predictive risk factors baseline measurements were used.

RESULTS

Participant characteristics

Table 1 shows the characteristics of the participants. No significant differences were found between the diabetes and non-diabetes groups on sex distribution or estimated premorbid IQ. The T2DM patients were significantly older compared to the control group. Therefore analyses comparing performance of T2DM patients and control patients on the cognitive tests were adjusted for age.

Table 1. Participant characteristics and vascular risk factor profile

Characteristic	T2DM group	Control group
n	47	26
Male, %	40	46
Age, years	66.9 ± 5.6*	63.4 ± 5.4
Level of education (1-7)[1]	4 ± 1.4	4.5 ± 1.3
Estimated premorbid IQ	100 ± 17	103 ± 15
Fasting glucose, mmol/l	8.8 ± 3**	5.5 ± .6
HbA_{1c} (%)	7 ± 1.2**	5.6 ± .4
Total cholesterol, mmol/l	5 ± .9**	6 ± 1.3
Systolic blood pressure, mm Hg	148 ± 20.5	141.4 ± 20.1
Diastolic blood pressure, mm Hg	81 ± 10.9	80.8 ± 7.7
BMI (kg/m²)	27.7 ± 4.1	27.3 ± 5.1

Data are presented as number or percentage (as indicated) or mean ± *SD*
*$P < 0.05$; **$P < 0.01$.
[1] Seven categories

Cognitive performances of groups over time

Table 2 shows the standardized performance (z-scores) and effect sizes on the five cognitive domains for the baseline and follow-up measurements. The performance of type 2 diabetic patients on four cognitive domains (Abstract reasoning, Memory, Information Processing Speed and Attention & Executive Functioning) on baseline as well as follow-up measurements was worse compared with that of control subjects (fig. 1-5). Repeated measure analysis showed significant between-group differences for Information Processing Speed ($F=4.551$; $p<.05$). For the domain Memory a non-significant trend was found ($p=.09$). Time and GroupxTime

interaction showed no significantly differences on the five cognitive domains (p>.05). However, for the cognitive domain Information Processing Speed a trend (p=.066) was found. The effect sizes between the groups increased over time for the domains Information Processing Speed (ES: -.33 to -.54) and Attention and Executive Functioning (ES: -.16 to -.26).

Table 2. Standardized z-scores (and SE) and Effect Sizes (ES) on the five cognitive domains over time

	Baseline			Follow-up		
Cognitive domains	T2DM group	Control group	ES	T2DM group	Control group	ES
Abstract Reasoning	.05 ± .15	.12 ± .20	-.07	-.03 ± .17	.04 ± .22	-.07
Memory	-.08 ± .07	.13 ± .09	-.21	-.12 ± .07	.04 ± .10	-.16
Information Processing Speed *†	-.11 ± .12	.22 ± .17	-.33	-.20 ± .12	.34 ± .17	-.54
Attention & Executive Functioning	-.06 ± .10	.10 ± .13	-.16	-.40 ± .11	-.14 ± .15	-.26
Visuoconstruction	-.13 ± .16	.17 ± .20	-.30	.33 ± .11	.10 ± .13	.23

Domain scores are presented as mean z-scores ± SE. Negative z-scores indicate worse performance.
*Main effect of Group p<.05
†trend for GroupxTime interaction p=.066

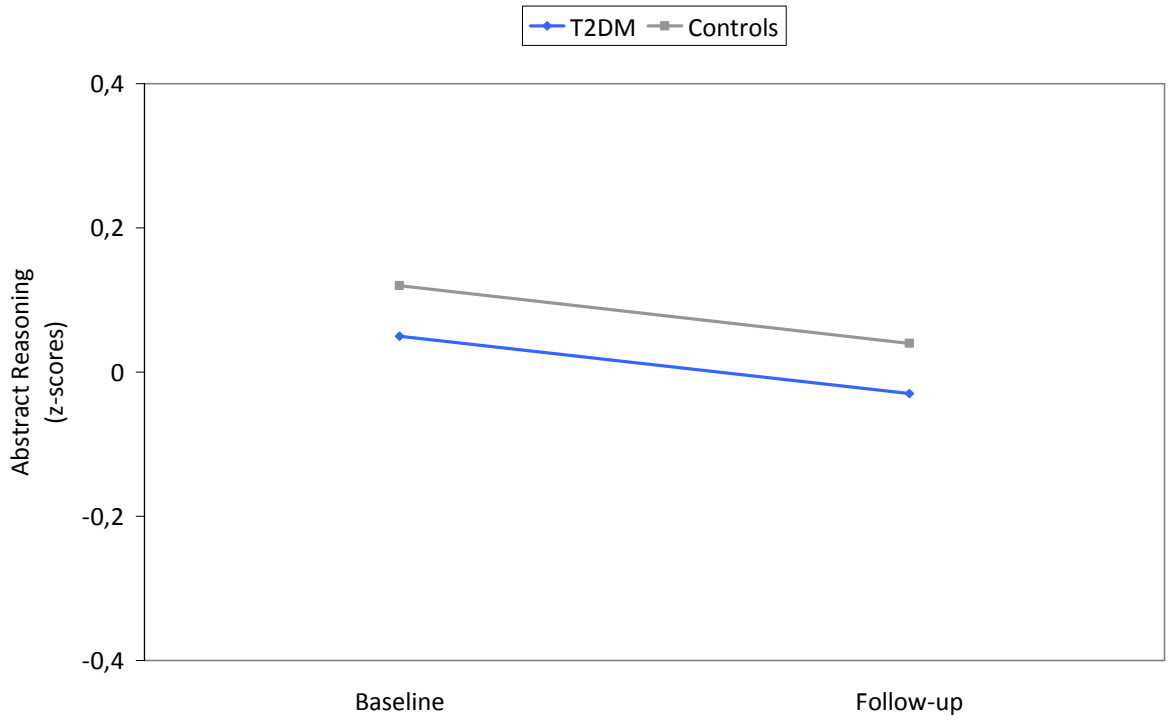

Fig. 1. Standardized z-scores at baseline and follow-up for the T2DM and control group on the domain Abstract Reasoning, adjusted for age.

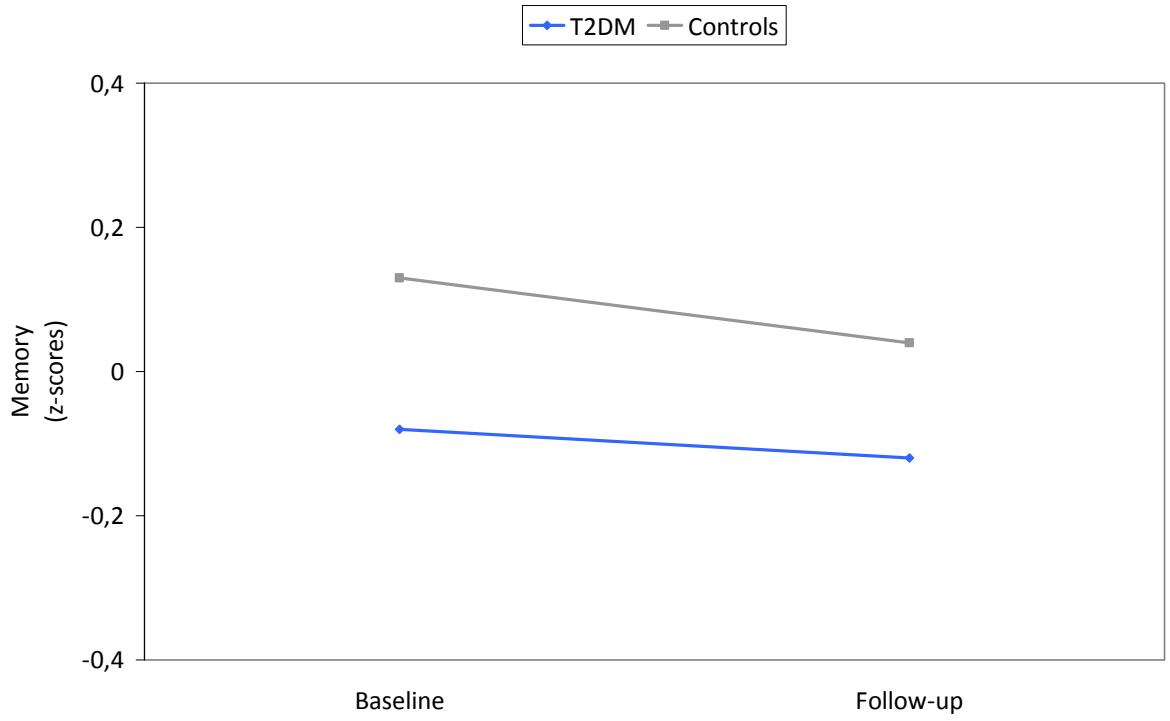

Fig. 2. Standardized z-scores at baseline and follow-up for the T2DM and control group on the domain Memory, adjusted for age.

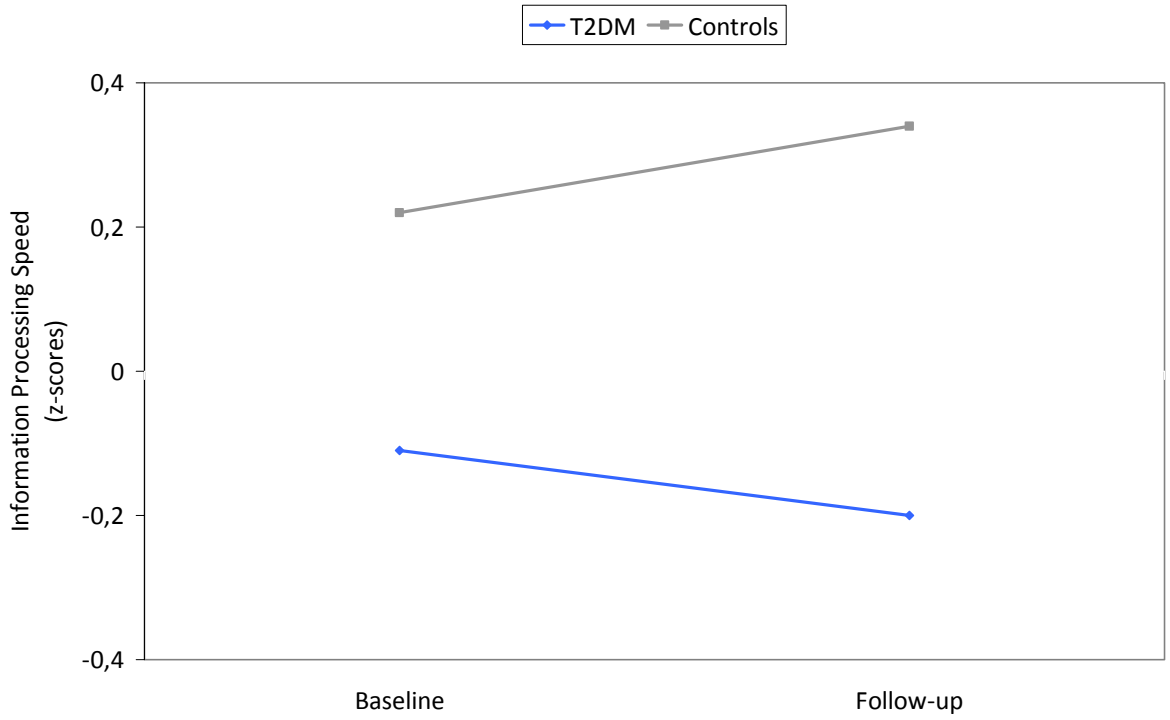

Fig. 3. Standardized z-scores at baseline and follow-up for the T2DM and control group on the domain Information Processing Speed, adjusted for age.

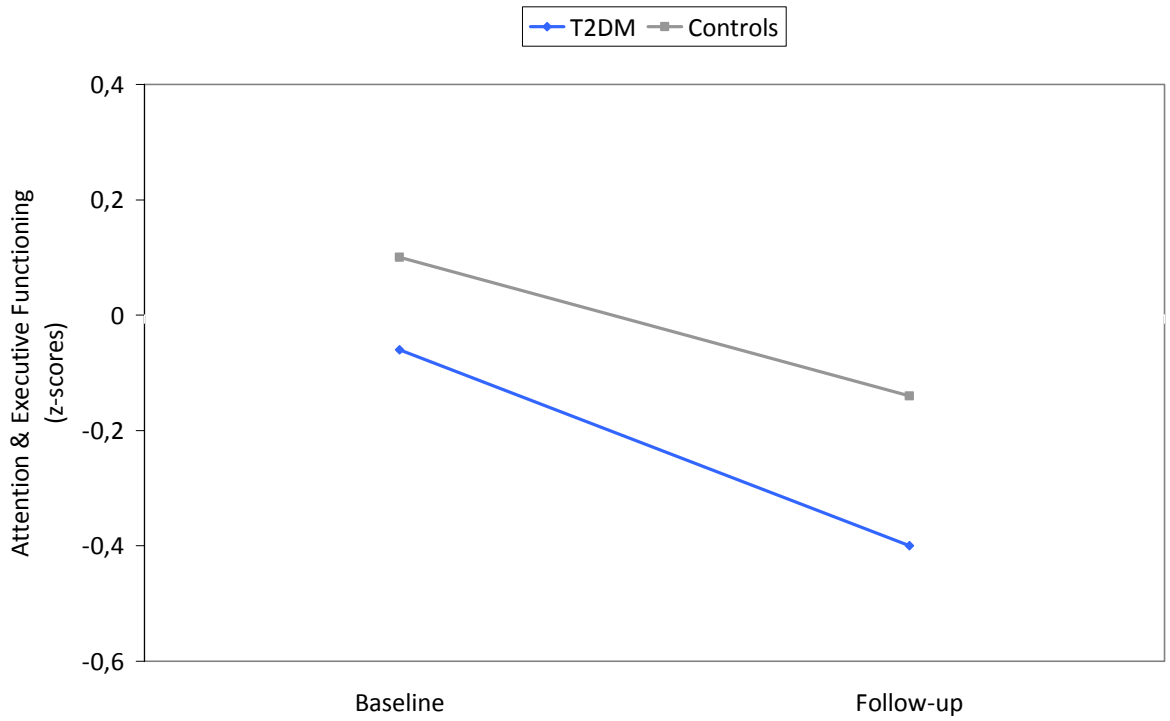

Fig. 4. Standardized z-scores at baseline and follow-up for the T2DM and control group on the domain Attention & Executive Functioning, adjusted for age.

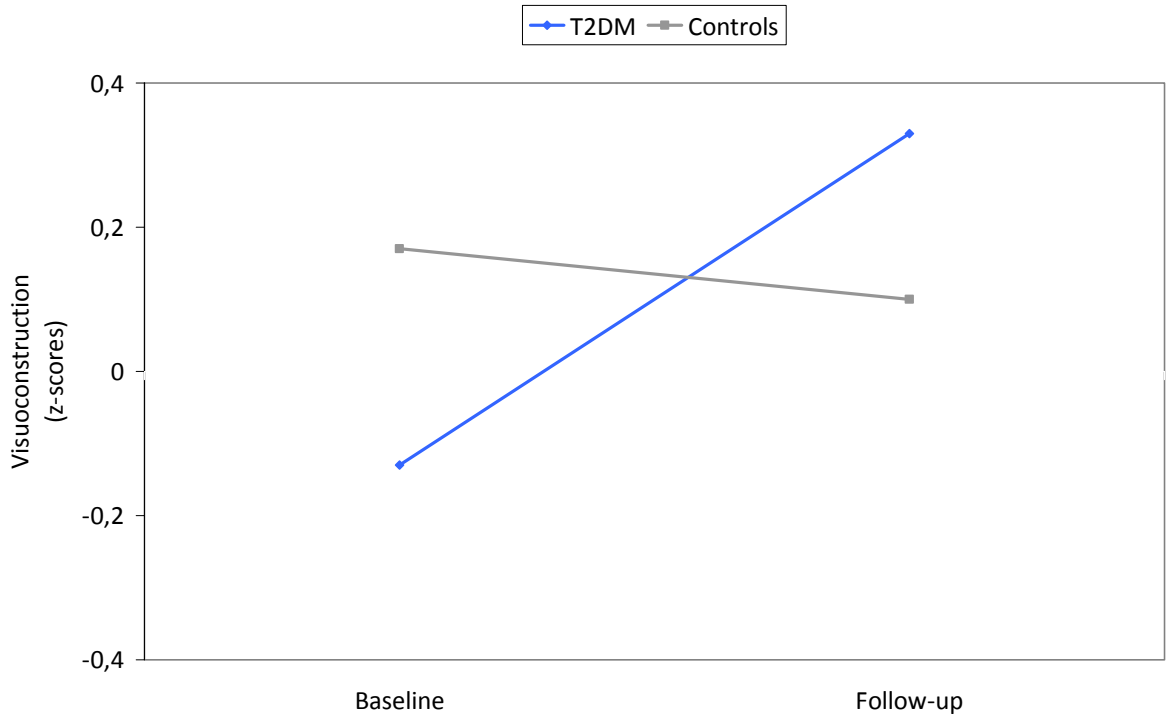

Fig. 5. Standardized z-scores at baseline and follow-up for the T2DM and control group on the domain Visuoconstruction, adjusted for age.

A univariate ANOVA with age as covariate revealed lower scores in T2DM patients on nearly all neuropsychological tests (except on the Rey Complex Figure Test copy trial). Table 3 shows the raw scores for the individual tests. In the current study sample we found significant differences ($p<.05$) in performance on the Trail Making Test A and B at baseline and several trends (RAVLT recognition ($p=.06$), Rey Complex Figure Test delayed trial ($p=.072$), Letter Fluency ($p=.058$) and Brixton Spatial Anticipation Test ($p=.08$)). At follow-up measurements, significance was reached on RAVLT total trials and the delayed trial, the Stroop Color Test I and II, the Trail Making Test A and WAIS-III Symbol Substitution ($p<.05$). We found a non-significant but noteworthy trend for Letter Fluency (A, N) ($p=.052$) and moreover we found a trend for the Brixton Spatial Anticipation Test ($p=.086$).

Table 3. Baseline and follow-up raw test scores (mean ± *SE*)

	Baseline		Follow-up	
Cognitive tests	T2DM group	Control group	T2DM group	Control group
Raven Advanced Progressive Matrices (short form)	6.3 (.4)	6.7 (.5)	6.4 (.5)	6.6 (.6)
WAIS-III Digit Span forward (product)	48.3 (3.1)	49.6 (4.3)	40.9 (2.9)	47.5 (3.9)
WAIS-III Digit Span backward (product)	24.5 (3.0)	29.2 (4.0)	21.6 (2.7)	25.3 (3.6)
Corsi Block-Tapping Test forward (product)	34.9 (1.6)	35.6 (2.2)	35.0 (1.8)	37.0 (2.4)
Corsi Block-Tapping Test backward (product)	35.4 (1.8)	40.2 (2.4)	36.7 (2.0)	38.9 (2.7)
RAVLT total trials 1-5[&]	38.0 (1.6)	42.0 (2.1)	37.5 (1.6)*	43.5 (2.2)
RAVLT delayed trial[&]	7.2 (.4)	8.1 (.6)	7.4 (.4)*	9.0 (.6)
RAVLT recognition[&]	27.9 (.3)[†]	28.8 (.4)	28.3 (.3)	28.8 (.3)
LLT total trials 1-5[#&]	29.1 (3.2)	22.2 (4.2)	28.1 (3.4)	20.1 (4.5)
LLT learning index	.6 (.04)	.7 (.05)	.5 (.05)	.5 (.06)
LLT delayed trial[#&]	2.5 (.5)	1.7 (.7)	3.1 (.5)	2.1 (.7)
Rey Complex Figure Test copy trial[&]	32.9 (.6)	33.9 (.7)	33.8 (.4)	32.8 (.5)
Rey Complex Figure Test delayed trial[&]	17.3 (.9)[†]	20.1 (1.2)	17.0 (.8)	17.7 (1.1)
Stroop Color Word Test I[#]	51.6 (1.9)	47.5 (2.7)	51.2 (1.4)*	45.3 (1.8)
Stroop Color Word Test II[#]	65.3 (2.0)	61.5 (2.8)	66.6 (1.7)*	61.0 (2.2)
Stroop Color Word Test III[#]	122.9 (6.0)	112.5 (8.2)	133.0 (5.7)	117.7 (7.5)
Stroop Color Word Test III/II	1.1 (.07)	1.1 (.10)	1.2 (.08)	1.2 (.10)

RAVLT: Rey Auditory Verbal Learning Test; LLT: Location Learning Test; WAIS-III: Wechsler Adult Intelligence Scale – Third Revision.
Adjusted for age, IQ and sex. *P < .05; ** P < .01; †trends baseline: P = .06, P = .072, P =.058, P =.08; †trends follow-up: P = .065, P = .056, P = .086
Higher test scores reflect worse performance; & parallel version for follow-up measurements

Table 3. (continued) Baseline and follow-up raw test scores (mean ± *SE*)

	Baseline		Follow-up	
Cognitive tests	T2DM group	Control group	T2DM group	Control group
Trail Making Test A[#]	52.8 (2.8)**	38.3 (3.8)	49.4 (3.1)*	37.8 (4.2)
Trail Making Test B[#]	117.5 (6.0)*	90.8 (8.2)	147.3 (12.5)[†]	107.1 (16.9)
Trail Making Test B division score (B time/A time)	1.3 (.10)	1.4 (.10)	2.0 (.2)	1.8 (.3)
WAIS-III Symbol Substitution	55.6 (2.5)	56.1 (3.3)	49.5 (2.2)*	57.6 (3.0)
Letter Fluency (A,N)	10.3 (.7)[†]	12.6 (.9)	9.5 (.6)[†]	11.7 (.9)
Category Fluency (Animal naming)	32.8 (1.5)	34.7 (2.0)	30.6 (1.6)	32.9 (2.1)
Brixton Spatial Anticipation Test[#]	20.6 (1.2)[†]	17.0 (1.6)	22.8 (.9)[†]	20.2 (1.2)

RAVLT: Rey Auditory Verbal Learning Test; LLT: Location Learning Test; WAIS-III: Wechsler Adult Intelligence Scale – Third Revision.
Adjusted for age, IQ and sex. *P < .05; ** P < .01; †trends baseline: P = .06, P = .072, P =.058, P =.08; †trends follow-up: P = .065, P = .056, P = .086
Higher test scores reflect worse performance; & parallel version for follow-up measurements

Predictive baseline vascular risk factors on cognitive performance

HbA_{1c}, fasting glucose and insulin levels were higher ($p<.01$) in patients with T2DM than in the control group. Blood pressure and BMI values were similar between both groups. In the regression analyses within the T2DM group (table 4), a predictive value for cognitive decline on Visuoconstruction was Body Mass Index ($b = .12$ (.03 to .21), $p<.05$). The remaining vascular risk factors (fasting glucose, HbA_{1c}, cholesterol and blood pressure) could not be identified as having a predictive value for cognitive decline in T2DM patients.

Table 4. Predictive value of vascular risk factors on cognitive function in type 2 diabetic patients expressed as regression ß coefficients (CI)

	Abstract Reasoning	Memory	Information Processing Speed	Executive Function	Visuoconstruction
n	41	47	46	47	40
Sex	-.15 (-.77 to .29)	-.13 (-.4 to .15)	-.08 (-.38 to .23)	-.06 (-.34 to .52)	-.05 (-.9 to .64)
Age, years	-.13 (-.07 to .03)	.28 (-.00 to .05)†	-.16 (-.04 to .01)	-.10 (-.10 to .03)	-.12 (-.09 to .04)
Fasting glucose, mmol/l	-.16 (-.19 to .07)	-.05 (-.06 to .04)	.15 (-.04 to .10)	-.10 (-.10 to .05)	-.09 (-.16 to .09)
HbA_{1c}(%)	-.21 (-.59 to .13)	.10 (-.08 to .15)	.17 (-.08 to .27)	-.08 (-.23 to .14)	-.07 (-.39 to .25)
Total cholesterol, mmol/l	-.05 (-.37 to .27)	-.07 (-.19 to .12)	-.17 (-.29 to .09)	-.04 (-.28 to .22)	-.06 (-.53 to .37)
Systolic blood pressure, mm Hg	-.10 (-.02 to .01)	-.13 (-.01 to .00)	-.07 (-.01 to .01)	.05 (-.01 to .01)	-.15 (-.03 to .01)
Diastolic blood pressure, mm Hg	-.03 (-.03 to .02)	-.04 (-.01 to .01)	.01 (-.01 to .01)	-.09 (-.03 to .01)	.13 (-.03 to .06)
BMI (kg/m^2)	.04 (-.06 to .07)	-.03 (-.04 to .03)	.09 (-.03 to .10)	.22 (-.02 to .09)	.43 (.03 to .21)*

Adjusted for age and sex. *P < 0.05; †trend P = .057

DISCUSSION

We were interested in determining if the type 2 diabetes mellitus group showed accelerated cognitive decline over time on the domains Memory, Information Processing Speed and Attention and Executive Functioning. Although the data showed that patients with T2DM perform worse on the postulated cognitive domains, statistical analyses revealed no significant differences between T2DM group and the control group and showed no accelerated cognitive decline. The T2DM group tended towards greater decline over time on Information Processing Speed, but this was not statistically significant. Between-group differences showed that T2DM patients significantly perform worse on Information Processing Speed, but only during follow-up measurements. A second aim was to examine if vascular risk factors could predict worse outcome on cognitive functioning for T2DM patients. Of the risk factors, only Body Mass Index could be identified as being a predictor in T2DM patients on the domain Visuoconstruction, the direction being positive, thus higher BMI predicts better performance on Visuoconstruction.

A number of studies address the association between cognitive functioning and T2DM (e.g. Awad et al., 2004). Generally deficits have been reported in Memory, Information Processing Speed and Executive Functioning. Our baseline as well as follow-up findings are in line with these results. Analysis of the performances on all neuropsychological tests revealed that T2DM patients show cognitive impairment not on a specific cognitive domain but a more overall modest performance decrement on test covering several domains. T2DM patients performed significantly slower on tasks that required a response within a fixed time limit. This was reflected in worse performance on the Trial Making Test and the Stroop Color Word Test and Symbol Substitution, all tests within the domain Information Processing Speed and could have influenced performance on other cognitive domains (Salthouse, 1996).

A discrepancy was found in the T2DM group on the performance on Letter and Category Fluency, namely a worse performance on Letter Fluency, indicating that more cognitive processing is required for tasks lacking intrinsic structure (Brands et al., 2007) since the Letter Fluency has less structure and the Category Fluency relies more on semantics.

Although the effect size is relatively larger on the domain Attention and Executive Functioning than on Abstract Reasoning, Memory and Visuoconstruction (ES=-.26), performances on individual tests measuring Attention and Executive Functioning showed contrasting results. This indicates that the T2DM group does not show problems on every aspect of this cognitive

domain. This immediately points out the conceivable question if putting separate tasks into five cognitive domains can make detecting cognitive changes less sensitive. However, if the tasks would not be grouped into cognitive domains, the results would depend on one single task, which can lead to a possible influence of the results due to possible problems in construct validity. Furthermore, considering the large number of tests, grouping tests into domains limits the statistical problem of multiple comparisons.

Prior to the present study, a limited number of studies have investigated the effects of T2DM on cognitive functioning longitudinally by means of a cognitive test battery (for review, see Allen et al., 2004). Two longitudinal studies demonstrated a significantly greater decline in diabetes mellitus patients on the domains Memory, Speed and Attention (Fontbonne, Berr, Ducimetiere & Alperovitch, 2001; Hassing et al., 2004). At baseline these studies revealed no significant difference between T2DM patients and controls, but showed accelerated decline on follow-up for the T2DM group. Two other longitudinal studies did find significant difference between T2DM patients and controls on baseline cognitive performance as well as cognitive decline (Kumari & Marmot, 2005; Gregg et al., 2000). Associations between diabetes and dementia are discussed in various studies and propose almost a 2-fold greater risk of future dementia (vascular dementia and Alzheimer's disease) in T2DM patients (for review, see Biessels, Deary & Ryan, 2008). A possible explanation is that T2DM patients initially have less cognitive capacity in comparison to healthy controls, due to a probable interaction between the pathogenic process of ageing and diabetes (Gispen & Biessels, 2000). Reserve cognitive capacity may hide changes in the brain. Only when this capacity is not sufficient to compensate for these changes, worse cognitive performance can be objectified (Dwyer, 2002). Furthermore, it has been observed that T2DM is cognitively equivalent to aging by three years (Okereke et al., 2008). Hence the prospect that T2DM patients develop a dementia earlier in life or more easily. Maybe the four years in this study was not enough to detect significant changes in cognitive decline.

Remarkable is the better follow-up performance of the T2DM patients in comparison to the controls on the domain Visuoconstruction. This is in contrast to the baseline measurements, although not significantly. Plausible explanations are difficult to surmise since the effect of retesting would have to be similar for the T2DM group as for the control group. Furthermore, the possible effect of different assessors would have to be equal for both groups. Thus, the outcome would have to be negatively affected for both groups. Moreover, the linear regression

analysis revealed that higher BMI is a predictive value enhanced performance on Visuoconstruction. The performance on this domain is certainly not stable over time for both groups and keeping in mind that the cognitive domain Visuoconstruction contains one task (Rey Complex Figure Test copy trial and parallel version, which are comparable (Hubley & Tremblay, 2002)), the reliability of the domain is weak. For the other domains, BMI was not a predictive risk factor.

For determining if fasting glucose, $HbA_{1c,}$ total cholesterol and blood pressure were predictive risk factors, the analysis showed no significant effect on the cognitive domains. Studies concerning poor glycemic control show controversial data. It has been reported that higher levels of HbA_{1c} in T2DM patients negatively affect performance on neuropsychological tests (Maggi et al., 2009). Others found no effect (Hewer, Mussell, Rist, Kulzer & Bergis, 2003). Mean HbA_{1c} in our T2DM population was 7 percent, which is the current target that indicates moderately good controlled diabetes (Goudswaard, Stolk, Zuithoff & Rutten, 2004). Albeit associations between cholesterol and cognitive decrements and decline are found (for review, see Van den Berg, 2009), others do not find this association (Teunissen et al., 2003; Reitz, Luchsinger, Tang, Manly & Mayeux, 2005), in accordance with the finding of the present study that cholesterol can not be determined as a predictive risk factor on any of the cognitive domains. For blood pressure contradicted results are shown as well (see review, Van den Berg et al., 2009). We did not find evidence that blood pressure is a predictive risk factor for the cognitive domains. We failed to do so possibly because the T2DM cohort participated in late life, which can alter the relation between hypertension and cognition (Van den Berg et al., 2009), and the sample size was small.

Strengths and limitations of the study need to be considered. The strength of our study is the longitudinal population-based design. The population-based sample in contrast to a clinical sample increases generalizability. From direct environment of the T2DM patients, family members or partners were recruited as controls. This was to minimise the effects of lifestyle. The strength that we recruited controls from the direct environment of the T2DM patients is at the same time a limitation because as a consequent the prevalence of risk factors such as higher BMI and hypertension could be higher than would be expected in the Dutch general population (Engberink et al., 2009). Further, a strength is that in contrast to many studies, that are based on only brief cognitive measures or a small selection of tasks, we used an extensive

neuropsychological test battery to obtain data. Another strength is related to the data which contains relatively little missing neuropsychological test scores. In this study, we included participants with almost complete datasets. Despite a selection bias could have occurred, probably the follow-up sample is a healthier sample since subjects with relatively worse health records are more likely to not attend for follow-up.

We did not include diabetes duration in these analyses, although an association has been reported between duration and cognitive decline (Okereke et al., 2008). Due to lack of power, small, non-significant differences in cognitive performance over time were revealed between the diabetes patients and the controls. To overcome this, a much larger sample size would be needed to more adequately examine subtle differences between these groups. In addition, we do find that T2DM patients and controls show cognitive decline over time but the period of four years between the baseline and follow-up measurements could also be too small to detect differences in rate of decline between the two groups.

In conclusion, this study did not find cognitive decline in type 2 diabetes mellitus, but we did find changes in cognitive performance. Mainly the domain Information Processing Speed shows decrements in T2DM patients, which could influence performance on remaining cognitive domains and lead to a diffuse affected cognitive profile. Although T2DM patients show co-morbid vascular risk factors, these factors did not have predictable value on worse cognitive performance, most plausibly due to a small sample size. Further investigation into vascular risk factors and type 2 diabetes mellitus needs to be undertaken to fully understand the mechanisms involved with cognitive functioning.

Given the increasing prevalence of patients with type 2 diabetes mellitus future treatment protocols should be developed with the cognitive status of patients with T2DM in mind. Suggested is to commence treatment of the co-morbid vascular risk factors before people are diagnosed with type 2 diabetes mellitus and directly after T2DM diagnoses to prevent possible influences on cognition and the development of dementia.

ACKNOWLEDGEMENTS

The Utrecht Diabetic Encephalopathy Study Group consists of (departments of the University Medical Center, Utrecht, the Netherlands, in alphabetical order): Department of Clinical Neurophysiology: A.C. van Huffelen; Department of Internal Medicine: H.W. de Valk;

Julius Center for Health Sciences and Primary Care: A. Algra, G.E.H.M. Rutten; Department of Medical Pharmacology: W.H. Gispen; Department of Neurology: A. Algra, G.J. Biessels, L.J. Kappelle, S.M. Manschot, J. van Gijn; Department of Experimental Psychology and Helmholtz Instituut: A.M.A. Brands (currently: Zuwe Hofpoort; Regionaal Psychiatrisch Centrum, Woerden, The Netherlands), E.H.F. de Haan, R.P.C. Kessels (currently: Departments of Medical Psychology and Geriatrics, Radboud University Nijmegen Medical Centre and NICI, Radboud University Nijmegen), E. van den Berg; Department of Radiology: J. van der Grond (currently: Leiden University Medical Center, The Netherlands).

Patients were recruited through the community based "Utrecht Diabetes Programma (UDP)" and the "IJsselstein Diabetes Project" (mentor: Ph.L. Salomé). The UDP is a long-running collaborative project between general practitioners and a hospital-based endocrinologist, with the aim to improve the level of care for patients with type 2 diabetes mellitus in the community without referral to the hospital.

Furthermore, acknowledgements go out to Yael Reijmer (PhD student, Utrecht Medical Center) for her guidance and useful and instructive suggestions in the process of conducting this thesis and the pleasant and inspiring collaboration. Also, I would like to thank the UDES group for giving me the opportunity to work with their data.

REFERENCES

Akisaki, T., Sakurai, T., Takata, T., Umegaki, H., Araki, A., Mizun, S., Tanaka, S., Ohashi, Y., Iguchi, A., Yokono, K., & Ito, H. (2006). Cognitive Dysfunction Associates With White Matter Hyperintensities and Subcortical Atrophy on Magnetic Resonance Imaging of the Elderly Diabetes Mellitus Japanese Elderly Diabetes Intervention Trial (J-EDIT). *Diabetes/Metabolism Research and Reviews, 22,* 376-384.

Allen, K.V., Frier, B.M., & Strachan, M.W.J. (2004). The Relation between Type 2 Diabetes and Cognitive Dysfunction: Longitudinal Studies and their Methodological Limitations. *European Journal of Pharmacology, 490,* 169-175.

American Diabetes Association. (2002). Standards of Medical Care for Patients with Diabetes Mellitus. *Diabetes Care, 25,* 213-229.

Asimakopoulou, K.G., Hampson, S.E., & Morrish, N.J. (2001). Neuropsychological Functioning in Older People With Type 2 Diabetes: The Effect of Controlling for Confounding Factors. *Diabetic Medicine, 19,* 311-316.

Awad, N., Gagnon, M., & Messier, C. (2004). The Relationship between Impaired Glucose Tolerance, Type 2 Diabetes, and Cognitive Function. *Journal of Clinical and Experimental Neuropsychology, 26,* 1044-1080.

Baan, C.A., & Feskens, E.J.M. (2001). Preventie van diabetes mellitus type 2. *Nederlands Tijdschrift voor Geneeskunde, 145,* 1677-1680.

Baan, C.A., Van Baal, P.H.M., Jacobs-van der Bruggen, M.A.M., Verkley, H., Poos, M.J.J.C., Hoogenveen, R.T., & Schoemaker, C.G. (2009). Diabetes mellitus in Nederland: schatting van de huidige ziektelast en prognose voor 2025. *Nederlands Tijdschrift voor Geneeskunde, 153,* A580.

Beckman, J.A., Creager, M.A., & Libby, P. (2002). Diabetes and Atherosclerosis: Epidemiology, Pathophysiology, and Management. *Journal of the American Medical Association*, *287*, 2570-2581.

Biessels, G.J., Deary, I.J., & Ryan, C.M. (2008). Cognition and Diabetes: A Lifespan Perspective. *Lancet Neurology, 7,* 184-190.

Biessels, G.J., Kerssen, A., De Haan, E.H.F., & Kappelle, L.J. (2007). Cognitive Dysfunction and Diabetes: Implications for Primary Care. *Primary Care Diabetes, 1,* 187-193.

Biessels, G.J., Staekenborg, S., Brunner, E., Brayne, C., & Scheltens, P. (2006). Risk of Dementia in Diabetes Mellitus: A Systematic Review. *Lancet Neurology, 5,* 64-74.

Biessels, G.J., Van der Heide, L.P., Kamal, A., Bleys, R.L.A.W., & Gispen, W.H. (2002). Ageing and Diabetes: Implications for Brain Function. *European Journal of Pharmacology, 441,* 1-14.

Brands, A.M.A., Biessels, G.J., Kapelle, L.J., De Haan, E.H.F., De Valk, H.W., Algra, A., & Kessels, R.P.C. (2007). Cognitive Functioning and Brain MRI in Patients with Type 1 and Type 2 Diabetes Mellitus: A Comparative Study. *Dementia and Geriatric Cognitive Disorders, 23,* 343-350.

Brands, A.M.A., Van den Berg, E., Manschot, S.M., Biessels, G.J., Kapelle, L.J., De Haan, E.H.F., & Kessels, R.P.C. (2007). A Detailed Profile of Cognitive Dysfunction and its Relation to Psychological Distress in Patients with Type 2 Diabetes Mellitus. *Journal of the International Neuropsychological Society*, *13*, 288–297.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences.* (2nd ed.). Hillsdale, New Jersey: Laurence Erlbaum.

Cosway, R., Strachan, M.W.J., Dougall, A., Frier, B.M., & Deary, I.J. (2001). Cognitive Function and Information Processing in Type 2 Diabetes. *Diabetic Medicine, 18,* 803-810.

Creager, M.A., Lüscher, T.F., Cosentino, F., & Beckman, J.A. (2003). Diabetes and Vascular Disease: Pathophysiology, Clinical Consequences, and Medical Therapy: Part I. *Circulation*, *108*, 1527-1532.

Croxson, S.C.M., & Jagger, C. (1995). Diabetes and Cognitive Impairment: A Community-Based Study of Elderly Subjects. *Age and Ageing, 24*, 421– 424.

Dwyer, D. (2002). *Glucose Metabolism in the Brain*. Amsterdam, Boston: Academic Press.

Ebady, S.A., Arami, M.A., & Shafigh, M.H. (2008). Investigation on the relationship between diabetes mellitus type 2 and cognitive impairment. *Diabetes Research and Clinical Practice, 82,* 305-309.

Engberink, M.F., Geleijnse, J.M., De Jong, N., Smit, H.A., Kok, F.J., & Verschuren, W.M.M. (2009). Dairy Intake, Blood Pressure, and Incident Hypertension in a General Dutch Population. *The Journal of Nutrition, 139,* 582-587.

Fontbonne, A., Berr, C., Ducimetiere, P., & Alperovitch, A. (2001). Changes in Cognitive Abilities over a 4-year Period are Unfavorably Affected in Elderly Diabetic Subjects: Results of the Epidemiology of Vascular Aging Study. *Diabetes Care, 24,* 366-370.

Gavin, J.R., III et al. (1997). Report of the Expert Committee on the Diagnosis and Classification of Diabetes mellitus. *Diabetes Care, 20,* 1183-1197.

Gispen, W.H., & Biessels, G.J. (2000). Cognition and synaptic plasticity in diabetes mellitus. *Trends in Neurosciences*, *23*, 542–549.

Goudswaard, A.N., Stolk, R.P., Zuithoff, P., & Rutten, G.E. (2004). Patient Characteristics Do Not Predict Poor Glycaemic Control in Type 2 Diabetes Patients Treated in Primary Care. *European Journal of Epidemiology, 19,* 541-545.

Gregg, E.W., Yaffe, K., Cauley, J.A., Rolka, D.B., Blackwell, T.L., Narayan, K.M., & Cummings, S.R. (2000). Is Diabetes Associated with Cognitive Impairment and Cognitive Decline Among Older Women? Study of Osteoporotic Fractures Research Group. *Archives Internal Medicine, 160,* 174-180.

Hassing, L.B., Grant, M.D., Hofer, S.M., Pedersen, N.L., Nilsson, S.E., Berg, S., McClearn, G., & Johansson, B. (2004). Type 2 Diabetes Mellitus Contributes to Cognitive Decline in Old Age: A Longitudinal Population-Based Study. *Journal of the International Neuropsychological Society, 10,* 599-607.

Hewer, W., Mussell, M., Rist, F., Kulzer, B., & Bergis, K. (2003). Short-Term Effects of Improved Glycemic Control on Cognitive Function in Patients with Type 2 Diabetes. *Gerontology, 49,* 86-92.

Hubley, A.M., & Tremblay, D. (2002). Comparability of Total Score Performance on the Rey-Osterrieth Complex Figure and a Modified Taylor Complex Figure. *Journal of Clinical and Experimental Neuropsychology, 24,* 370-382.

Kempen, G.I.J.M., Meier, A.J.L., Bouwens, F.S.M., Van Deursen, J., & Verhey, F.R.J. (2007). The Psychometric Properties of the Dutch Version of the Telephone Interview Cognitive Status (TICS). *Tijdschrift voor Gerontologie en Geriatrie, 38,* 38-45.

Kessels, R.P.C., Van Zandvoort, M.J.E., Postma, A., Kappelle, L.J., & De Haan, E.H.F. (2000). The Corsi Block-Tapping Task: Standardization and Normatice Data, *Applied Neuropsychology, 7,* 252 -258.

Kumari, M., & Marmot, M. (2005). Diabetes and Cognitive Function in a Middle-Aged Cohort: Findings from the Whitehall II Study. *Neurology, 65,* 1597-1603.

Laakso, M. (1999). Hyperglycemia and Cardiovascular Disease in Type 2 Diabetes. *Diabetes, 48,* 937-942.

Lezak, M.D. (2004). *Neuropsychological Assessment*. Oxford: University Press.

Lines, C.R., McCaroll, K.A., Lipton, R.B., & Block, G.A. (2006). Telephone Screening for Amnestic Mild Cognitive Impairment. *Neurology, 60,* 261-266.

Maggi, S., Limongi, F., Noale, M., Romanato, G., Tonin, P., Rozzini, R., Scafato, E., & Crepaldi, G. (2009). Diabetes as a Risk Factor for Cognitive Decline in Older Patients. *Dementia and Geriatric Cognitive Disorders, 27,* 24–33.

Manschot, S.M., Brands, A.M.A., Van der Grond, J., Kessels, R.P.C., Algra, A., Kapelle, L.J., & Biessels, G.J. (2006). Brain Magnetic Resonance Imaging Correlates of Impaired Cognition in Patients With Type 2 Diabetes. *Diabetes, 55,* 1106-1113.

Okereke, O.I., Kang, J.H., Cook, N.R., Gaziano, J.M., Manson, J.E., Buring, J.E., & Grodstein, F. (2008). Type 2 Diabetes Mellitus and Cognitive Decline in Two Large Cohorts of Community-Dwelling Older Adults. *Journal of the American Geriatrics Society, 56,* 1028-1036.

Reitz, C., Luchsinger, J., Tang, M.X., Manly, J., & Mayeux, R. (2005). Impact of Plasma Lipids and Time on Memory performance in Healthy Elderly Without Dementia, *Neurology, 64,* 1378-1383.

Roriz-Filho, J.S., Sá-Roriz, T.M., Rosset, I., Camozzato, A.L., Santos, A.C., Chaves, M.L.F, Moriguti, J.C., & Roriz-Cruz, M. (2009). (Pre)diabetes, brain aging, and cognition. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1792,* 432-443.

Salthouse, T.A. (1996). The Processing-Speed Theory of Adult Age Differences in Cognition. *Psychological Review, 103,* 403-428.

Stewart, R., & Liolitsa, D. (1999). Type 2 Diabetes Mellitus, Cognitive Impairment and Dementia. *Diabetic Medecine, 16*, 93–112.

Strachan, M.W.J., Reynolds, R.M., Frier, B.M., Mitchell, R.J., & Price, J.F. (2008). The Relationship between Type 2 Diabetes and Dementia. *British Medical Bulletin, 88,* 131-146.

Teunissen, C.E., De Vente, J., Von Bergmann, K., Bosma, H., Van Boxtel, M.P., De Bruijn, C., Jolles, J., Steinbusch, H.W., & Lutjohann, D. (2003). Serum Cholesterol, Precursors and Metabolites and Cognitive Performance in an Aging Population. *Neurobiology of Aging, 24,* 147-155.

Van den Berg, E., De Craen, A.J.M., Biessels, G.J., Gussekloo, J., & Westendorp, R.G.J. (2006). The Impact of Diabetes Mellitus on Cognitive Decline in the Oldest of the Old: A Prospective Population-Based Study. *Diabetologia, 49,* 2015-2023.

Van den Berg, E., Dekker, J.M., Nijpels, G., Kessels, R.P.C., Kapelle, L.J., De Haan, E.H.F., Heine, R.J., Stehouwer, C.D.A., & Biessels, G.J. (2008). Cognitive Functioning in Elderly Persons with Type 2 Diabetes and Metabolic Syndrome: The Hoorn Study. *Dementia and Geriatric Cognitive Disorders, 26,* 261-269.

Van den Berg, E., Kessels, R.P.C., Kapelle, L.J., de Haan E.H.F., & Biessels, G.J. (2006). Type 2 Diabetes, Cognitive Function and Dementia: Vascular and Metabolic Determinants. *Drugs of Today, 42,* 741-754.

Van den Berg, E., Kloppenborg, R.P., Kessels, R.P.C., Kappelle, L.J., & Biessels, G.J. (2009). Type 2 Diabetes Mellitus, Hypertension, Dyslipidemia and Obesity: A Systematic Comparison of their Impact on Cognition. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1792,* 470-481.

Van Harten, B., De Leeuw, F.E., Weinstein, H.C., Scheltens, P., & Biessels, G.J. (2006). Brain Imaging in Patients With Diabetes: A Systematic Review. *Diabetes Care, 29,* 2539-2548.

Van Harten, B., Oosterman, J.M., Potter van Loon, B.J., Scheltens, P., & Weinstein, H.C. (2007). Brain Lesions on MRI in Elderly Patients With Type 2 Diaetes Mellitus. *European Neurology, 57*, 70-74.

Whitmer, R.A., Gunderson, E.P., Barrett-Connor, E., Quesenberry Jr, C.P., & Yaffe, K. (2005). Obesity in Middle Age and Future Risk of Dementia: A 27 Year Longitudinal Population Based Study. *British Medical Journal, 330*,1360-1362.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global Prevalence of Diabetes: Estimates for the Year 2000 and Projections for 2030. *Diabetes Care, 27,* 1047-1053.

Yaffe, K., Barret-Connor, E., Lin, F., & Grady, D. (2002). Serum Lipoprotein Levels, Statin Use, and Cognitive Function in Older Women. *Archives of Neurology, 59,* 378-384.

Yeung, S.E., Fischer, A.L., & Dixon, R.A. (2009). Exploring Effects of Type 2 Diabetes on Cognitive Functioning in Older Adults. *Neuropsychology, 23,* 1-9.