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THESIS

The Effect of Diabetes Type 2, the Metabolic Syndrome and Co-existing Risk Factors on Cognitive Functioning within the Elderly Population

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Abstract

BACKGROUND: Type 2 diabetes mellitus is a metabolic disease with a rapidly rising prevalence. Recently, diabetes mellitus type 2 has been associated with cognitive decrement. The onset and the course of the development of the cognitive decrement within the diabetic population is still unknown. The influence of co-existing risk factors on cognition within a diabetic population has not been examined before. **METHODS:** In this study participants with diabetes mellitus type 2 (n=74), participants with the metabolic syndrome (n=99), a pre-diabetic stage, and control subjects (n=115) underwent neuropsychological and medical tests. The performance of the groups are compared on 5 cognitive domains; abstract reasoning, attention executive functioning, information processing speed, memory and visuo-construction. In the second part of the study the independent impact of vascular and metabolic risk factors associated with diabetes mellitus type 2 on cognition in a population sample (n=377) study will be examined.

RESULTS: The group with diabetics performed worse than control subjects on several cognitive domains. The metabolic syndrome group also performed worse than healthy subjects, but performed better than the diabetics. The risk factors HbA1c and blood pressure were negatively related to performance on several cognitive domains. **CONCLUSION:** The decay in cognitive functioning already commences in the pre-diabetic stage, when mainly vascular risk factors are present. Not one risk factor can be held responsible for the cognitive decrement. Both vascular and metabolic risk factors seem to have a part in this process.

Introduction

Type 2 diabetes mellitus (DM2) is a metabolic disease with a rapidly increasing number of patients (Wild *et al*., 2004). Worldwide 150 million people are estimated to suffer from DM2. Due to the demographic changes, increasing incidence of unhealthy lifestyle and the rising life expectancy, the number of people affected by diabetes is expected to be double in 2030 (Kaufman, 2002; Wild *et al*., 2004). DM2 is especially affecting people over the age of 65 (American Diabetes Association, 2002). It is caused by insulin resistance combined with an inadequate compensatory insulin secretion. Common complications due to DM2 are kidney failure, blindness, cardiovascular diseases and nerve damage (American Diabetes Association, 2002).

As we get older performance on different neuropsychological tests decline. However, the magnitude and the course of the decrease are not alike for everyone (Lyketsos, 1999; Allen *et al.,* 2004). In this study we will investigate the course of the cognitive decline within the DM2 population more thoroughly. We will do so by investigating people with DM2 and people in a pre-stadium of DM2, with the metabolic syndrome (MetS).

Several researchers have studied the relation between DM2 and cognitive functioning (Arvanitakis *et al.*, 2004; Arvanitakis *et al.*, 2006; Van Den Berg *et al.*, 2006-A; Strachan, 1997; Stewart & Liolitsa, 1999; Cosway *et al*., 2001). Stewart & Liolitsa (1999) compared in a systematic review the outcome of several studies and found that diabetic elderly perform significantly worse than healthy elderly on tasks testing attention and concentration, immediate and delayed verbal memory, psychomotor speed and mental flexibility. In the study performed by Arvanitakis and associates (2006) the relation between DM2 and the level of cognitive functioning was examined in older individuals without dementia. They found that DM2 was associated with lower performance in semantic memory and perceptual speed, but not associated with lower scores in episodic memory, working memory and visuospatial abilities. The relation between diabetes and global cognitive ability, measured by the MMSE[1], was not significant, still the effect was in the expected direction.

Cosway et al. (2001) found that individuals with uncomplicated DM2 compared to a matched group of healthy controls did not significantly perform worse on several cognitive domains. However, further analysis showed that estimated duration of DM2 was negatively correlated with several measures of cognitive functioning. This suggests that DM2 risk factors can be held accountable for at least a part of the previously observed cognitive decrement in other studies.

[1] Mini Mental State Examination

The metabolic and vascular risk factors associated with DM2 often co-occur and are clustered in the MetS. The MetS is characterized by impaired glucose metabolism, but no diabetes, accompanied by at least one of the other risk factors: hypertension, dislipidemia and obesity (ATP III, 2001). Because people with MetS are three to four times more likely to develop DM2 (Olijhoek, 2006), the MetS is often seen as a pre-diabetic stage. Moreover, several studies found a similar relation between the MetS and cognitive functioning as observed in DM2, only less pronounced.

In a 12 years follow-up population based study women aged 60 to 70 were examined (Komulainen, 2006). Participants with MetS at baseline were over four times higher at risk for poor memory at follow-up than participants without. MetS was not significantly associated with cognitive speed or the MMSE score. In another study examining the effect of MetS on cognition, 36% of the 65- to 80 year old participants was diagnosed with MetS (Dik *et al.,* 2007). Participants with MetS showed significantly lower scores for information processing speed, immediate recall, fluid intelligence and the MMSE score, but no effect was found for delayed recall.

DM2 and MetS are both associated with the same metabolic and vascular risk factors (Biessels 6; Van Den Berg et al., 2006-A). Hypertension is a condition that is not only often seen in diabetic elderly, it affects as much as 1 billion individuals worldwide (Chobanian *et al.*, 2002). Hypertension can cause stroke and cardiovascular diseases, and is also associated with cognitive decline (Morris, 2002). In a study performed by Waldstein et al. (2005) findings suggest that hypertension leads to poorer performance on tasks for nonverbal memory, working memory, executive functioning and perceptual-motor speed. In a review comparing the outcome of twenty-four studies that examined the relationship between hypertension and cognitive functioning, most studies showed a negative effect of hypertension on cognition (Van Den Berg, 2008-A). Some studies found an inverted U-shape relation of blood pressure on cognition (Waldstein, 1991; Morris, 2002). This means that both very low and high blood pressure was associated with worse cognitive functioning. The cognitive domains affected by hypertension in most studies are memory, processing speed, cognitive flexibility and attention. In another study hypertension failed to show a significant effect on either of the cognitive domains tested (Dik *et al.,* 2007).

In a study including women between 55 to 80 years of age, low HDL cholesterol was associated with lower scores on information processing speed and fluid intelligence, but not with the other cognitive domains (Dik *et al.,* 2007). Other studies examining dislipidemia found that high levels of high density lipoprotein (HDL) cholesterol were strongly associated with lower cognitive functioning (Van Den Berg, 2008). High levels of low density lipoprotein (LDL) were weakly associated with lower levels of cognitive functioning. High lipid levels administered at midlife were associated with significant lower cognitive functioning.

Obesity was associated with lower cognitive performance in several studies (Van Den Berg, 2008). However, not all studies found a significant relationship. Obesity was measured by the body mass index or the waist circumference. The cognitive profile affected by hypertension, dislipidemia and obesity, seems similar across all three risk factors (Van Den Berg, 2008).

In the studies reviewed above, the effect of type 2 diabetes on cognition has been described. However, little is known about the development of the cognitive decrements. It could well be that the cognitive decrements observed in DM2 already start to develop in a pre-diabetic stage. To examine this, the present study will compare cognitive performance in individuals with DM2, individuals with MetS and control subjects.

Given the assumption that type 2 diabetes and the metabolic syndrome have a negative influence on cognition, it is hypothesized that these groups gain lower scores compared to the controls. In the DM2 group the risk factors are expected to be apparent for a longer time and the metabolic risk factors are more severe, therefore we expect that performance of the DM2 group is more affected than in the MetS group. Moreover, performance of the DM2 and MetS group is expected to be worse than that of the control group.

Most studies reviewed earlier have not accounted for the influence of the co-existing risk factors, but these factors are often associated with cognitive decline as well. Studies examining solely the effect of these risk factors on cognitive functioning show a negative effect. Given the assumption that the risk factors that co-exist with type 2 diabetes have a negative effect on cognitive functioning, it is hypothesized that high blood pressure (systolic and diastolic), dislipidemia (LDL and HDL), obesity (waist-hip ratio) and high glucose levels (HbA1c) can at least partially account for the decrement in cognitive functioning in the elder diabetic population. The present study will also address the independent impact of vascular and metabolic risk factors associated with DM2 on cognition in a population sample derived from the Hoorn study.

Methods

Study population

All participants had previously taken part in the 'Hoorn Study' (Van Den Berg, 208-B), a longitudinal population based survey in which detailed information on glucose metabolism, cardiovascular risk factors, and vascular function has been collected from 1989 (n=1,513) to 2001 (n=647). Participants of the Hoorn Study received an invitation to participate in this study. The examination for this study is the fourth, and took place between 2005 and 2008. Cognitive functioning was only assessed during the fourth examination. All participants were inhabitants of Hoorn and the vicinity, and over the age of 65 years. All objects gave informed consent prior to participation.

In total 380 people participated in this study. Three people were excluded, based on psychosocial factors (n=2) and language barrier (n=1).

For analysis the participants were divided into three groups; diabetes type 2, metabolic syndrome and control group based on their risk factor profile at the third examination. The classification was based on the following criteria. Diabetes type 2 is determined according the ADA criteria (21): 1: body mass index of 27 for women and for men >29; 2: triglyceride level of ≥1.7 mmol/L (or medication); 3: high-density lipoprotein cholesterol level of <1.3 mmol/L for women and <1.0 mmol/L for men (or medication); 4: blood pressure of ≥ 130/85 mmHg (or medication); 5: nonfasting plasma glucose level of >7.8 mmol/L or antidiabetic medication.

Metabolic syndrome (MetS) was determined according the ATP III criteria. At least three of the following diagnostic criteria: 1: waist circumference >88 for women and >102 for men; 2: triglyceride level of ≥1.7 mmol/L; 3: high-density lipoprotein cholesterol level of <1.3 mmol/L for women and <1.0 mmol/L for men; 4: blood pressure of ≥ 130/85 mmHg (or medication); 5: fasting plasma glucose level of ≥ 6.1 mmol/L. Subjects with established Diabetes will not be included in this group.

The control group consisted of participants that did not have more than one of the criteria for metabolic syndrome and did not have DM2. In the first part of the study, the three groups (DM2, MetS, Controls) are compared. The remaining participants of the Hoorn population, who had two criteria of the metabolic syndrome, are included in the second part of the study to examine risk factors in the whole population.

Procedure

To investigate the influence of diabetes on cognitive functioning of elderly we used a medical examination, questionnaires, blood samples and neuropsychological tests.

Participants attended the Diabetic Research centre on two separate occasions. At the first visit participants were asked to fast. A medical examiner went through two questionnaires with the participants and drew blood. The questionnaires contained questions concerning their physical and mental health, lifestyle, their own and their families' medical history for diabetes and heart diseases.

For the second visit participants were asked to fast again. This visit started with a heart echo, the data the heart echo has provided is not used in this study. After the echo was made, participants received something to eat. Finally all participants received extensive neuropsychological examination. The neuropsychological battery containing 12 different tests took approximately 90 minutes to finish.

Neuropsychological assessment

The wide variety of tests in this research concentrated on five domains; abstract reasoning; attention executive functioning; information processing speed; memory and visuo-construction. The abstract reasoning domain consists of the Raven´s Advanced Matrices. The memory domain consists of the 15-Word Test, Location Learning Task, Rey Osterrich Complex Figure. The attention domain is made up out of Stroop Task, Trail Making Test, Brixton Anticipation Test, and Verbal Fluency. The information processing speed is composed by the Stroop Task (I and II), Trail Making Test (A) and Symbol Substitution. Copying the Rey Osterrich Complex Figure made up the domain visuo-construction.

The examiner started by roughly informing the participants about the sort of tests and the purpose of the neuropsychological tests. Participants were told that the focus of this study was on the relationship between the functioning of the brain, diabetes, and ageing. Then the examiner asked the participant a few questions about possibly present complaints concerning memory and/or attention. Thereafter the examiner started the neuropsychological test. The neuropsychological tests were administered in a fixed order.

Statistical Analysis

The data provided by the tests was imported in to Excel. The data was then converted and readied for SPSS. A analysis of covariance (ANCOVA) was used to investigate differences between the groups on demographic characteristics. For not continuous data the Kruskall-Wallis Chi^2 and the Wilcoxon test was used.

To compare the different cognitive domains, the sub scores of each test were standardised into Z-scores based on the pooled mean of the whole study population. Then, the Z-scores of tests

within the same domain were averaged. Hereafter, the three different groups were compared on each cognitive domain with an MANOVA, adjusted for age, sex and education.

For the second part of this study, the relation between vascular and metabolic risk factors and cognitive functioning in the whole population was analysed with a regression analyses, adjusted for age, sex and education. A p-value of $< 0,05$ was considered significant.

Results

In table 1 the demographic and vascular risk factor profile of the participants are shown per group. The groups were well balanced for sex, education and estimated IQ. The mean age of the DM2 was significant higher comparing to MetS and control subjects. In the groups DM2 and MetS a higher blood pressure and a bigger waist/hip ratio was measured than in the control group. However, the cholesterol level of DM2 was lower than that of the control subjects and MetS.

Table 1. Characteristics of the participants per group

	Controls	MetS	DM2	P value	Post Hoc
Demographic values					
n	115	99	74		
Male, %	53%	47,5%	52,7%	0.77	
Age, years	72,52 ± 5,58	72,33 ± 5,57	74,78 ± 6,10	0.01	Con + MetS vs DM2
Education, median (range) *	4 (1-7)	4(1-7)	4(2-7)	0.58	
Estimated IQ	99,35 ± 12,69	98,10 ± 13,83	96,34 ± 12,46	0.24	
Measurements					
Fasting glucose, mmol/l	5,47 ± 0,53	5,96 ± 0,59	6,96 ± 1,12	<0.001	Con vs MetS vs DM2
HbA1c, %	5,54 ± 0,27	5,80 ± 0,46	6,37 ± 0,70	<0.001	Con vs MetS vs DM2
Total cholesterol, mmol/l	5,57 ± 1,04	5,37 ± 1,21	4,79 ± 0,94	<0.001	Con + MetS vs DM2
Systolic blood pressure, mm Hg	140,15 ± 17,46	152,25 ± 20,91	151,98 ± 22,37	<0.001	Con vs MetS + DM2
Diastolic blood pressure, mm Hg	72,72 ± 10,01	76,92 ± 10,75	74,91 ± 11,06	0.015	Con vs MetS vs DM2
Body mass index	25,23 ± 2,78	29,72 ± 3,80	28,06 ± 4,26	<0.001	Con vs MetS vs DM2
Waist/hip ratio	0,91 ± 0,09	0,96 ± 0,11	0,96 ± 0,08	<0.001	Con vs MetS + DM2

Data are presented as mean ± SD or number (percentage) unless otherwise specified.

* Seven categories

Study 1

The outcome of analysis of the between-group differences is shown in figure 1 and table 2. A significant effect of group on cognition is found in three domains; attention and executive functioning [$F(2)=3,476$; $p<0.05$], information processing speed [$F(2)=3,319$; $p<0.05$] and visuo-construction [$F(2)=3,479$; $p<0.05$]. Post-hoc analyses showed that performance of the DM2 group is significantly worse than the performance of control subjects on the domains attention and executive functioning ($p<0.05$), information processing speed ($p<0.05$) and visuo-construction ($p<0.01$). The MetS group performed worse on the domain information processing speed compared to performance of the control subjects ($p<0.05$). Performance of the MetS group sits in between the performance of the control subjects and the DM2 group on the cognitive domains attention and executive functioning, information processing speed and visuo-construction. The effect sizes for the differences between controls and DM2 are between 0.2 and 0.45 for the three domains that showed significant effects. The effect sizes can be categorized as small to moderate (Cohen, 1988).

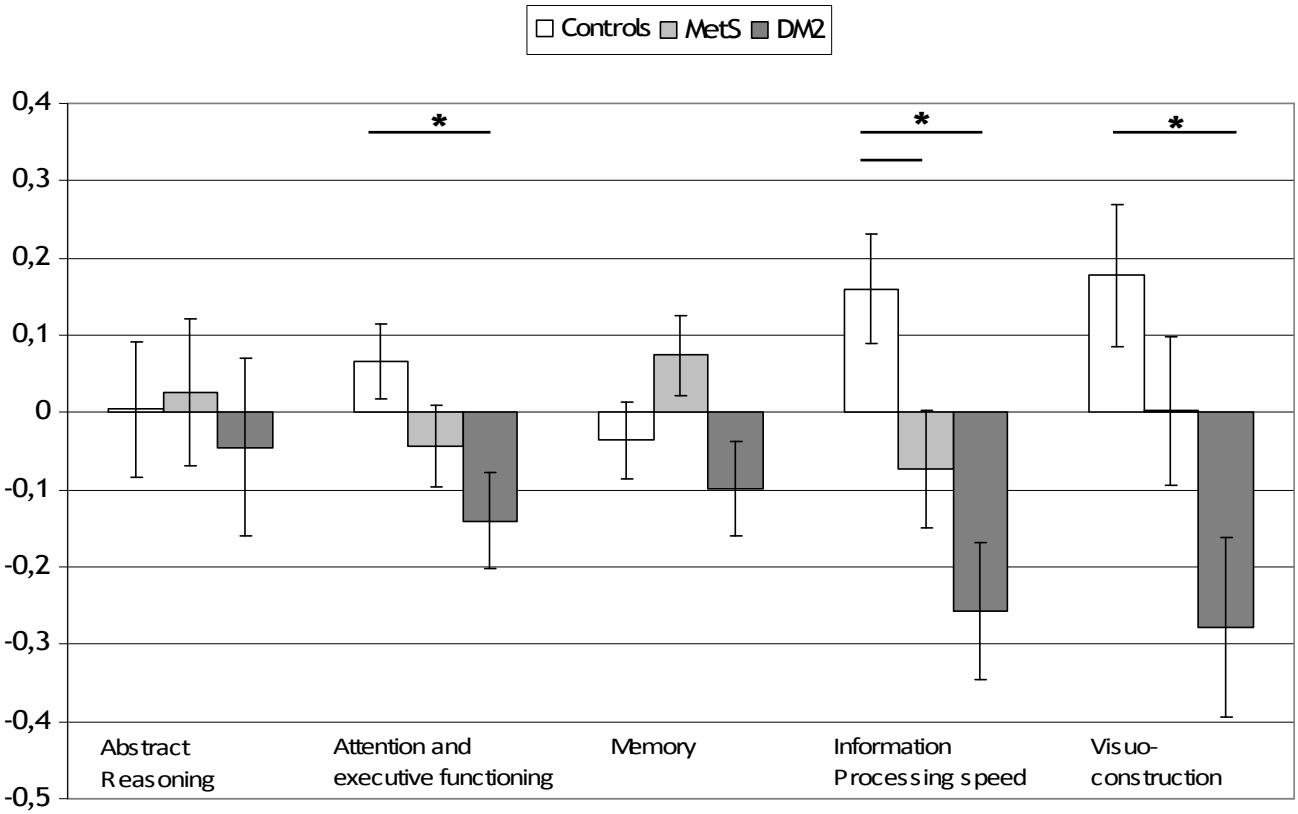

Figure 1. Between-group comparison of cognitive functioning on five cognitive domains. Raw test scores were standardized into Z-scores per cognitive domain. Data are means ± SE. * $p < 0.05$.

Study 2

The relationship between vascular and metabolic risk factors associated with DM2 and the MetS and performance on the cognitive domains, adjusted for age, sex and education, are given in table 3. In this analysis all participants (N = 377, mean age 73,7 years, ± 6,98 years) of this study are included in the analyses.

Fasting glucose, total cholesterol and waist/hip ratio did not show any statistically significant relations with one of the cognitive domains. HbA1c was related to attention and executive functioning [b= -0.114; -0.211 to -0.022; p<0.05] and information processing speed [b= -0.108; -0.290 to 0.028; p<0.05]. The direction of the relation of HbA1c was negative, which means that higher HbA1c levels predict worse cognitive performance. Both the systolic blood pressure [b= 0.134; 0.001 to 0.006; p<0.01]and the diastolic blood pressure [b= 0.188; 0.004 to 0.014; p<0.001] were positively related to performance on the domain memory. Surprisingly a higher blood pressure predicted better memory performance in this population. In contrast, diastolic blood pressure was negatively related to visuo-construction [b= -0.122; -0.021 to -0.002; p<0.05]. The systolic blood pressure did not relate to other cognitive domains.

Table 3. Relation between the risk factors of the metabolic syndrome and cognitive functioning

	Abstract reasoning	Attention and executive functioning	Memory	Information processing speed	Visuo-construction
Fasting glucose	-0.017 (-0.122 to 0.086)	-0.056 (-0.096 to 0.023)	0.050 (-0.029 to 0.087)	-0.035 (-0.115 to 0.050)	-0.001 (-0.104 to 0.101)
HbA1c	0.027 (-0.122 to 0.212)	-0.114 (-0.211 to -0.022) *	-0.017 (-0.108 to 0.077)	-0.108 (-0.290 to 0.028) *	-0.023 (-0.199 to 0.125)
Total cholesterol	0.036 (-0.060 to 0.125)	0.063 (-0.017 to -0.085)	0.037 (-0.032 to 0.068)	0.010 (-0.064 to 0.079)	0.053 (-0.045 to 0.135)
Systolic blood pressure	0.033 (-0.003 to 0.006)	-0.054 (-0.004 to 0.001)	0.134 (0.001 to 0.006) **	0.001 (-0.003 to 0.004)	-0.033 (-0.006 to 0.003)
Diastolic blood pressure	-0.028 (-0.012 to 0.007)	-0.032 (-0.007 to 0.003)	0.188 (0.004 to 0.014) ***	0.054 (-0.003 to 0.011)	-0.122 (-0.021 to -0.002) *
Waist/hip ratio	-0.002 (-1.146 to 1.115)	-0.078 (-1.137 to 0.155)	0.026 (-0.499 to 0.795)	-0.077 (-1.589 to 0.193)	-0.087 (-2.136 to 0.268)

Data are given as the stardized regression coefficient beta (95% confidence interval) adjusted for age, sex and education. * p<0.05 ** p<0.01 *** p<0.001

Discussion

In the present study we examined the effect of diabetes on cognition. More interestingly, we included participants with the metabolic syndrome, a pre-diabetes stage, to examine the course of cognitive decay. In the first part of the study the performances of participants with diabetes mellitus type 2, participants with the metabolic syndrome and control subjects on cognitive function were compared. It was expected that performance of participants in the DM2 group was significantly lower than performance of control subjects. The performance of the MetS was expected to be worse then performance of control subjects and to sit between performance of the DM2 group and control subjects. In accordance with this hypothesis performance of the DM2 group was significantly worse than that of control subject on attention and executive functioning, information processing speed and visuo-construction, but not for the domains abstract reasoning and memory (figure 1). The results found in this study corresponds to results found in other studies (Van Den Berg, 2008-A; Van Den Berg, 2008-B; Arvanitakis, 2006; Lyketsos, 2006). No significant results were found when the DM2 group was compared to the performance of the MetS group. Only for the domain information processing speed the MetS group performed significantly worse compared to control subjects. Nevertheless, the direction of the effect of the metabolic syndrome on the domains attention and executive functioning and visuo-construction was in accordance with the hypothesis. It seems that the cognitive decrements already start to develop in this

pre-diabetic stage. Only the differences are less pronounced than in subjects with DM2.

In the second part of this study the relationship between the vascular and metabolic risk factors and cognitive functioning was examined. It was expected that the risk factors were negatively related to cognitive functioning. In the results the measurements fasting glucose, total cholesterol and waist/hip ratio failed to show a significant effect on any of the cognitive domains. HbA1c was, as expected, negatively related to attention and executive functioning and information processing speed. Both the systolic and the diastolic blood pressure showed significant effects for memory. The direction however was not in the expected direction, namely it concerns a positive effect. At the same time the diastolic blood pressure was negatively related to visuo-construction. Altogether, the data partially confirms the hypothesis and partially opposes the hypothesis. We found that both vascular and metabolic risk factors were related to cognitive performance. However, for blood pressure this relationship was inconsistent. Comparing the results found in this study to population based studies examining vascular risk factors independent of DM2, the results are similar, but show smaller effect sizes and not all risk factors showed significant effects (Van Den Berg, 2008).

An important reason for the observed discrepancy could be differences in study-population. As can be seen in table 1, the DM2 group is relatively healthy. Compared to the control subjects and the MetS group, the total cholesterol of DM2 was significantly lower. For the diastolic blood pressure and the body mass index, the DM2 group showed significantly lower measurements then the Mets group. Overall, for most vascular risk factors, but not the metabolic risk factors, the DM2 group was in better health compared to the MetS group. The study population might even be in better health compared to other study populations. The relative good health of the population may be a result of the study design. It concerns a longitudinal study, participants are screen detected. The participants are well controlled for the impact of DM2 and the vascular risk factors. In addition, individuals who develop vascular risk factors or DM2 during the study are immediately detected and treated. Besides the good health of this study population, a problem of the longitudinal study design is survival bias. Due to the long duration of this study, the participants in good health survive. Furthermore, individuals in poor health are more inclined to cancel their participation then individuals in good health.

A third reason for the relatively small differences in cognitive functioning between the groups is that in this study cognitive functioning is divided into six domains. By doing so, different measures are averaged and it could be that the measures become less sensitive for detecting dysfunction. For example, the domain memory in our study contains verbal and visual memory test, while previously only verbal memory deficits have been demonstrated. Perhaps, if we look at performance per task, more specific results become visible. On the other hand, if we would not divide the neuropsychological tests in domains, the result would become task dependant. Examining a complete cognitive domain with only one task would make the results less reliable.

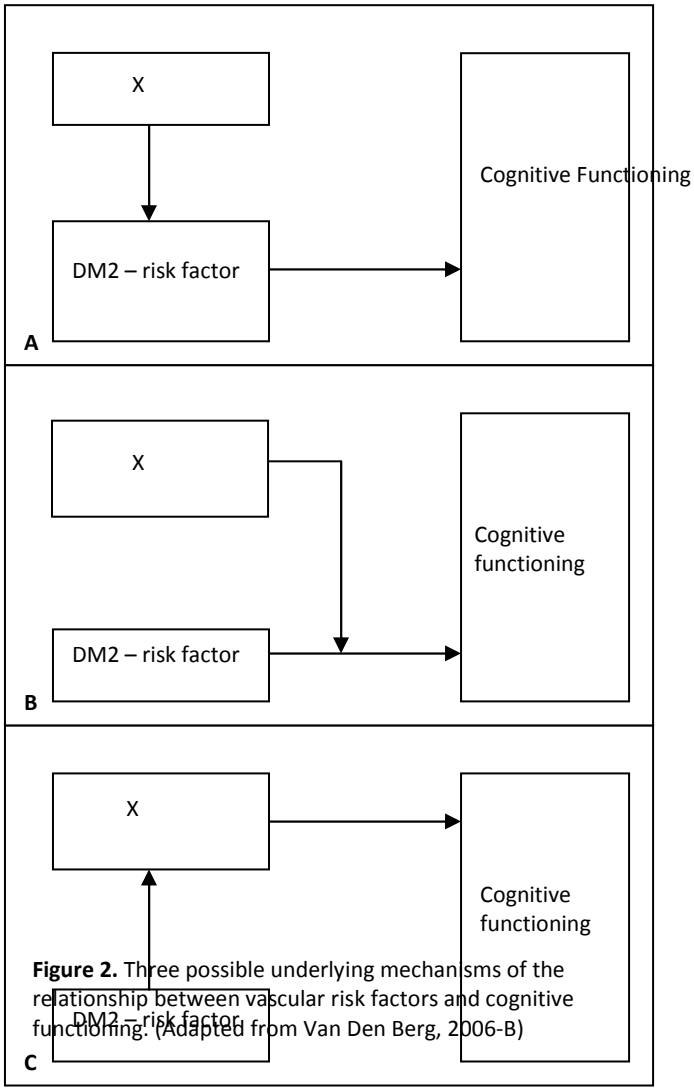

Figure 2. Three possible underlying mechanisms of the relationship between vascular risk factors and cognitive functioning. (Adapted from Van Den Berg, 2006-B)

A down side of this study is that the regression analyses performed in the second part does not necessarily represent a direct causal relationship. Because vascular and metabolic risk factors are determined at the same time as cognitive performance, we could only make inferences about associations and not about causality or underlying mechanisms. The risk factors observed in DM2 and MetS are closely related to other possible determinants of the cognitive decrement. These other possible determinants are demographic factors (socio-economic status, educational level, age sex, ethnic background), vascular disease (atherosclerosis, stroke), DM2 related factors (duration of DM2, microvascular complications, glucose lowering treatment), genetic factors (ApoE genotype) and other factors (lifestyle, depression) (Van Den Berg, 2006-B). It is still unknown how these factors affect each other and therefore how they affect cognitive functioning. In figure 2 three of many possible underlying mechanisms are described. In figure 2A the factor X is an indirect causal factor. Demographic factors could be an indirect causal factor for

developing DM2 associated risk factors, leading to cognitive dysfunction. In 2B factor X is the moderator in the relationship between DM2 and cognitive functioning. For example, the presence of a certain genetic profile could make a person more vulnerable for the damaging effects of vascular risk factors to the brain. Finally, factor X could also act as a mediator, demonstrated in 2C. A good example of a mediating factor is vascular disease. The presence of vascular risk factors could lead to the development of atherosclerosis and stroke, which in turn can influence cognitive functioning. So, there are still many uncertainties about the underlying mechanisms of the relationship.

The strengths of this research is that it is not only based on data from participants with diabetes and healthy subjects, but also consists of participants with the metabolic syndrome, so no DM2 but possess two or more diabetes associated risk factors. Furthermore, data was obtained by elaborate detailed neuropsychological testing. Likewise, this study was based on a detailed vascular profile.

In most studies only the vascular risk factors or only the metabolic risk factors and their relation to cognitive functioning was investigated. This study found for risk factors from both categories a significant effect on cognitive functioning. Probably the combination and interaction of vascular and metabolic risk factors during lifetime determines the amount of cognitive decline.

In conclusion, the results suggest that DM2 has a negative effect on cognitive functioning. The decay in cognitive functioning already commences in the pre-diabetic stage, when mainly vascular risk factors are present. Not one risk factor can be held responsible for the cognitive decrement. Both vascular and metabolic risk factors seem to have a part in this process. Interaction effects might be an explanation for the declined cognitive performance of the DM2 and MetS group.

The present study gives reason for additional research. It would be fascinating to look at the interaction effect of metabolic and vascular risk factors on cognitive functioning. Further, it would be interesting to compare the results of the present study to results of a study with an uncontrolled group of diabetics. If participants in the present DM2 group perform significantly better comparing to the uncontrolled diabetics, it could demonstrate the favorable effect of extensively monitoring the health of patients with DM2 or in pre-diabetic stages.

References

(Adult Treatment Panel III) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (2001). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). *Journal of the American Medical Association, 285,* 2486-2497

Allen, K.V., Frier, B.M. & Strachan, M.W.J. (2004). The Relationship between Type 2 Diabetes and Cognitive Dysfunction: Longitudinal Studies and their Methodological Limitations. *European Journal of Pharmacology, 49,* 169-175

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

Arvanitakis, Z., Wilson, R.S., Bienias, J.L., Evans, D.A. & Bennett, D.A. (2004). Diabetes mellitus and risk of alzheimer disease and decline in cognitive function. *Archives of Neurology, 61,* 661-666

Arvanitakis, Z., Wilson, R.S., Li, Y., Aggarwal, N.T. & Bennett, D.A. (2006) Diabetes and function in different cognitive systems in older individuals without dementia. *Diabetes Care, 29,* 560-565

Benett, D.A. (2000). Diabetes and change in cognitive function. *Archive of Internal Medicine, 160,* 141-143

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,* 1-4

Biessels, G.J., Bravenboer, B. & Gispen, W.H. (2004). Glucose, Insuline and the Brain: Modulation of Cognition and Synaptic Plasticity in Health and Disease: A Preface. *European Journal of Pharmacology, 490,* 1-4

Chobanian, A.V. *et al.,* (2003). Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension, 42,*1206-1252

Cohen, J., (1988). Statistical Power Analysis for the Behavioral Sciences. Laurence Erlbaum, New Jersey.

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

Dik, M.G., Jonker, C., Comijs, H.C., Deeg, D.J.H., Kok, A., Yaffe, K. & Penninx, B.W. (2007). Contribution of Metabolic Syndrome Components to Cognition in Older Individuals. *Diabetes care, 30,* 2655-2660

Kaufman, F.R., (2002). Type 2 Diabetes Mellitus in Children and Youth: A New Epidemic. *Journal of Pediatric Endocrinology and Metabolism. 15,* 737-744.

Komulainen, P., Lakka, T.A., Kivipelto, M., Hassinen, M., Helkala, E.L., Haapala, I., Nissinen, A. & Rauramaa, R. (2006). Metabolic Syndrome and Cognitive Function: A Population-Based Follow-Up Study in Elderly Women. *Dementia and Geriatric Cognitive Disorders, 23,* 29-34

Lyketsos, C.G., Chen, L.S. & Anthony, J.C. (1999) Cognitive Decline in Adulthood: An 11,5 Year Follow-Up in the Baltimore Epidemiologic Catchment Area Study. *American Journal of Psychiatry, 156,* 58-65

Morris, M.C., Scherr, P.A., Hebert, L.E., Bennett, D.A., Wilson, R.S., Glynn, R.J. & Evans, D.A. (2002). Association between Blood Pressure and Cognitive Function in a Biracial Population of Older Persons. *Neuroepidemiology, 21,* 123-130

Oijen, M. van, Okereke, O.I., Kang, J.H., Pollak, M.N., Hu, F.B., Hankinson, S.E. & Grodstein, F. (2008). Fasting Insuline Levels and Cognitive Decline in Older Women without Diabetes. *Neuroepidemiology, 30,* 174-179

Olijhoek, J.K. (2006). The Metabolic Syndrome and Vascular Disease. Proefschrift Universiteit Utrecht

Stewart, R. & Liolitsa, D. (1999). Type 2 Diabetes Mellitus, cognitive impairment and dementia. *Diabetic Medicine, 16,* 93-112

Strachan, M.W., Deary, I.J., Ewing, F.M. & Frier, B.M. (1997) Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care, 20,* 438-445

Strachan, M.W.J., Frier, B.M. & Deary, I.J. (2003). Type 2 Diabetes and Cognitive Impairment. *Diabetic Magazine, 20,* 1-2

Van Den Berg, E., Kessels, R.P.C., Kappelle, De Haan, E.H.F. & Biessels, G.J. (2006-A) Type 2 Diabetes, Cognitive Functioning 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., (2008-A). Type 2 Diabetes Mellitus, Hypertension, Dyslipidemia and Obesity: A Systematic Comparison of their Impact on Cognition. *Biochemica et Biophysica Acta, 1792,* 470-481

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

Waldstein, S.R., Ryan, C.M., Manuck, S.B., Parkinson, D.K. & Bromet, E.J. (1991). Learning and Memory Function in Men with Untreated Blood Pressure Elevation. *Journal of Consulting and Clinical Psychology, 59,* 513-517

Waldstein, S.R., Giggey, P.P., Thayer, J.F. & Zonderman, A.B. (2005). Nonlinear Relations of Blood Pressure to Cognitive Function: The Baltimore Longitudinal Study of Aging. *Hypertension, 45,* 374-379

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