Vascular Cognitive Impairment: risk factors and brain MRI correlates

Yael Reijmer

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Vascular Cognitive Impairment: risk factors and brain MRI correlates

Vasculaire cognitieve beperkingen: risicofactoren en
gerelateerde hersenschade op MRI
(met een samenvatting in het Nederlands)

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Chapter 1

General introduction

Vascular cognitive impairment

Dementia affects around 7% of the general population over 65 years, and 30% of people over 80 years.[1,2] The prevalence of dementia is expected to double over the next 30 years[3], making disorders of cognition a priority for healthcare and social-care services.

Alzheimer's disease and vascular dementia are the two most common forms of dementia, accounting for over 75% of all dementia cases.[4] Although Alzheimer's disease and vascular dementia have been considered two separate entities for decades, we now know that the majority of older individuals with dementia show mixed pathology, despite the clinical diagnosis.[5] In fact, there is probably a continuum in underlying pathologies ranging from patients with pure vascular dementia to pure AD[6]. The close relation between vascular dementia and Alzheimer's disease is further supported by studies showing that risk factors for cerebrovascular disease such as hypertension, obesity, hypercholesterolemia, and hyperglycemia are also risk factors for Alzheimer's disease.[7,8] These findings have lead to the introduction of the concept 'vascular cognitive impairment' (VCI). VCI refers to all forms of mild to severe cognitive impairment associated with, and presumed to be caused by, cerebrovascular disease.[9] Given the important role of cerebrovascular disease in the development of cognitive decline, further research into progression rates, risk factors and imaging changes of VCI is needed to gain insight in possible mechanisms and to develop effective treatment strategies.

The current emphasis in the literature on VCI is on the late stages of cognitive decline, i.e. dementia. However, twice as many people suffer from more mild forms of cognitive impairment.[10,11] Examination of underlying mechanisms of these early stages of cognitive dysfunction is relevant, because treatment benefits are expected to be largest when the underlying brain damage is still relatively modest. Moreover, mild cognitive deficits are a problem by itself, leading to complaints and affecting functional abilities, also in individuals who will not progress to dementia.[12,13] Addressing mild cognitive deficits will therefore help to identify a much larger group of individuals who can benefit from treatment strategies.
The present thesis focuses on these milder forms of vascular related cognitive impairment by addressing i) their course of development (first part), ii) vascular risk factors (second part), and iii) cerebral white matter correlates (third part). The following paragraphs will give a short introduction to the different research questions addressed in each chapter.

The development of VCI over time in individuals with type 2 diabetes mellitus

Patients with type 2 diabetes mellitus (T2DM) are at risk of developing VCI. T2DM is present in 8-12% of patients of 60 years and older.[14] It is characterized by chronic hyperglycemia, caused by insulin resistance and an inadequate compensation in the secretion of insulin.[15] Long-term exposure to hyperglycemia has an adverse affect on the vasculature, which is reflected by an increased risk of macro- and microvascular complications, including nephropathy, retinopathy, cardiovascular disease and stroke.[16] In addition, diabetes is often accompanied by other vascular risk factors, such as hypertension, dyslipidemia, and obesity. Together, these vascular risk factors are suggested to play an important role in the cognitive decrements observed in older patients with diabetes.[17] Brain imaging studies have demonstrated vascular lesions on MRI in patients with T2DM, in particular a higher prevalence of lacunar infarcts[18] and increased white matter hyperintensity (WMH) volume[19,20] compared to controls. The cognitive deficits observed in individuals with T2DM are typically associated with WMHs and lacunar infarcts including subtle reductions in mental speed, mental flexibility, and verbal memory performance.[21,22] Cognitive dysfunction in the context of T2DM may thus be regarded as a form of mild VCI.

T2DM is also associated with a two-fold increased risk of dementia.[23] It is not yet clear how mild cognitive deficits observed in individuals with T2DM relate to the development of dementia later in life. The most intuitive explanation is that T2DM related pathology progresses over time leading to accelerated cognitive decline and an accelerated progression to dementia. An alternative explanation is that T2DM affects the reserve capacity of the brain. As a consequence, individuals with T2DM are less able to cope with additional brain pathology, e.g. AD pathology. In this case the combination of diabetes related pathology with a secondary pathology will accelerate the progression to dementia. *The first part* of this thesis addresses this topic by examining how the cognitive profile associated with diabetes evolves over time, also in relation to structural changes in the brain.

Vascular risk factors of VCI: time of exposure

Studies addressing the association between vascular risk factors and dementia have reported inconsistent results. While high levels of blood pressure, body weight and cholesterol at midlife are associated with an increased risk of dementia[24,25], this relation is not observed when these risk factors are assessed at late-life.[26,27] These inconsistencies can be explained by the complex interplay between age,

duration of exposure, selective survival and changes of risk factors over time. For example, blood pressure and bodyweight tend to rise in middle-age, but decrease in very old-age.[28,29] In addition, blood pressure and body weight may change during the dementia process, well before dementia becomes clinically manifest.[30-32] *The second part* of this thesis aims to further unravel the complex dynamics between vascular risk factors, age and cognition by examining how vascular risk factors evolve over time in relation to late-life cognitive functioning in non-demented individuals.

Atherosclerosis: a potential link between vascular risk factors and VCI

A potential mechanism through which vascular risk factors can affect the brain is through the accelerated development of atherosclerosis. Atherosclerosis is a condition in which fatty material, such as cholesterol, collects along the walls of arteries. This leads to plaque formation and eventually to the occlusion of arteries. Atherosclerotic vascular disease may affect the brain, by increasing the risk of thromboembolic stroke[33], but also by affecting cerebral perfusion, leading to malfunction and degeneration of neuronal cells.[34]

Individuals with the metabolic syndrome (MetS) are at increased risk of developing atherosclerotic vascular disease.[35,36] The MetS refers to the clustering of vascular risk factors, including hypertension, obesity, hypercholesterolemia and insulin resistance. Because the MetS often precedes the development of T2DM, it is also referred to as a pre-diabetic stage. Individuals with MetS show the same cognitive deficits as individuals with T2DM, with most pronounced decrements in information processing speed and attention and executive functioning.[37] Although atherosclerosis is often assumed to mediate the relation between the MetS and cognitive dysfunction, it is not yet examined in sufficient detail. This mechanism is also addressed in *the second part* of the thesis.

Microstructural white matter correlates of VCI

Cerebrovascular disease is often reflected by structural changes on brain MRI scans, such as WMHs, lacunar infarcts and global brain atrophy.[38] Although these MRI markers are a frequent finding in patients with T2DM, they are only modestly correlated with the cognitive decrements.[39] Brain autopsy studies have identified small vascular lesions in the white matter in patients with T2DM that are not visible on conventional MRI scans.[40,41] This subtle white matter pathology may play an important role in the etiology of T2DM-related cognitive dysfunction.

A more advanced brain imaging technique that is sensitive to subtle white matter pathology in the brain is diffusion tensor imaging (DTI). DTI is a non-invasive technique that allows to examine the 'microstructural organisation' of the white

matter in vivo. Microscopic vascular and non-vascular white matter abnormalities such as demyelination, axonal changes and enlargement of periventricular space, may lead to changes in the diffusion of water molecules and therefore to a change in the DTI parameter. Previous studies, not specifically targeting T2DM, indeed have demonstrated that DTI can provide information on white matter abnormalities that is clearly complementary to the classical MRI markers of small vessel disease.[42,43]

DTI can also be used to reconstruct white matter tracts in the brain, a process called tractography.[44] Unfortunately, DTI based tractography has considerable limitations in regions where multiple fiber bundles cross. Therefore, new tractography techniques are developed to deal with these shortcomings. One of these techniques is constraint spherical deconvolution (CSD) based tractography.[45,46] Although CSD based tractography has shown to markedly improve the reconstruction of fiber tracts, the feasibility of this new fiber tractography method to detect white matter abnormalities underlying cognitive performance is not known. The clinical feasibility of CSD based tractography in combination with DTI metrics was evaluated in *the third part* of this thesis on a group of patients with more pronounced cognitive deficits (patients with Alzheimer's disease). We also used this method to examine whether microstructural white matter abnormalities are related to cognitive dysfunction in older patients with T2DM, independent of conventional MRI markers of cerebrovascular disease (i.e. infarcts, white matter hyperintensities).

Outline of the thesis

The first part of the thesis evaluates the development of VCI over time in patients with type 2 diabetes (T2DM).
Chapter 2 provides a review of the literature on cognitive dysfunction in patients with T2DM. It addresses the nature and severity of cognitive changes in patients T2DM and includes a pooled analysis of previous studies from our group. Possible risk factors are discussed, as well as findings from brain imaging and autopsy studies.
In **chapter 3** we examined how the cognitive profile of T2DM evolves over time, relative to age matched older individuals without T2DM.
In **chapter 4** we examined brain imaging correlates and vascular and metabolic risk factors of accelerated cognitive decline in patients with T2DM.

The second part of the thesis investigated the relation between exposure to vascular risk factors over time and VCI and the possible mediating effect of atherosclerosis. These questions were addressed in a large community based

sample of non-demented individuals, recruited as part of the Hoorn study.
In **chapter 5** we evaluated the time-course of vascular risk factor levels between midlife and late-life in relation to late-life cognitive functioning. The risk factors examined were: blood pressure levels, waist-to-hip ratio, blood cholesterol and blood glucose.
In **chapter 6** we tested whether a previously developed risk score for dementia, based on midlife vascular risk profiles, also predicts more mild forms of late-life cognitive impairment.
In c**hapter 7** we examined the possible mediating effect of atherosclerosis and clinical manifest cardiovascular disease on the relation between the metabolic syndrome and late-life cognitive dysfunction.

The third part of the thesis focuses on the quantification and localization of microstructural white matter correlates of VCI using diffusion tensor imaging (DTI) in combination with advanced fiber tractography methods.
In **chapter 8** we tested the feasibility of a new fiber tractography method (CSD based tractography) to detect white matter abnormalities underlying cognitive performance in patients with Alzheimer's disease. Because patients with AD have more pronounced cognitive deficits than patients with VCI, this group was selected to evaluate this new method.
In **chapter 9** we applied CSD based fiber tractography to detect microstructural white matter correlates of cognitive dysfunction in older patients with T2DM.

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Chapter 2

Cognitive dysfunction in patients with type 2 diabetes

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Abstract

People with diabetes mellitus are at increased risk of cognitive dysfunction and dementia. This review explores the nature and severity of cognitive changes in patients with type 2 diabetes. Possible risk factors such as hypo- and hyperglycemia, vascular risk factors, micro- and macrovascular complications, depression and genetic factors will be examined, as well as findings from brain imaging and autopsy studies. We will show that type 2 diabetes is associated with modest cognitive decrements in non-demented patients that evolve only slowly over time, but also with an increased risk of more severe cognitive deficits and dementia. There is a dissociation between these two 'types' of cognitive dysfunction with regard to affected age groups and course of development. Therefore we hypothesize that the mild and severe cognitive deficits observed in patients with type 2 diabetes reflect separate processes, possibly with different risk factors and etiologies.

Introduction

The effects of type 2 diabetes on the brain are attracting more and more attention. Numerous studies report changes in cognitive functioning and brain structure in patients with diabetes relative to controls. The present review gives an overview of the nature and severity of cognitive changes in patients with type 2 diabetes and provides a pooled analysis of previous studies from our group. Potential risk factors are discussed, as well as findings from brain imaging and autopsy studies. We will show that type 2 diabetes is associated with subtle cognitive decrements, but also with an increased risk of more severe cognitive impairment, in particular dementia. We will conclude with the clinical implications of these findings and directions for future research.

Cognitive decrements in non-demented patients with diabetes

Cross-sectional studies

Cross-sectional case-control studies generally show worse performance for patients with type 2 diabetes compared to age-, sex- and education-matched controls on measures of verbal memory, information processing speed and attention and executive functioning (e.g.[1-5]). These cognitive decrements are observed across different age groups (50-80 years) with mild to moderate effect-sizes ranging from 0.2 to 0.8.[6] The cognitive domains perception, visuoconstruction and language, have been examined in only a minority of studies, but are generally not reported to be affected.[3,7,8]

Figure 1 shows the pooled results from three studies from our research group using the same standardised cognitive assessment battery in 366 patients with type 2 diabetes relative to controls.[3,8,9] Patients were recruited in a primary care setting and had no dementia or other neurological or psychiatric conditions that might confound the results. Details on patient selection criteria have been provided in the original publications.[3,8,9] The figure indicates which cognitive tests were most consistently affected across the different study populations. After adjustment for age, sex and estimated IQ, patients performed worse than controls on almost all measures. The standardised mean differences between the groups varied from -0.1 to -0.4 indicating that the difference between patients and controls were small. Tests measuring attention and executive functioning, verbal memory and information processing speed showed the largest and most consistent adjusted mean difference between patients and controls. Interestingly, decrements in memory performance were predominantly observed with a test for verbal memory, while visual memory was less affected. To distinguish long-term memory performance (recall after a delay of 30 minutes) from short-term memory performance (immediate recall), delayed recall was adjusted for

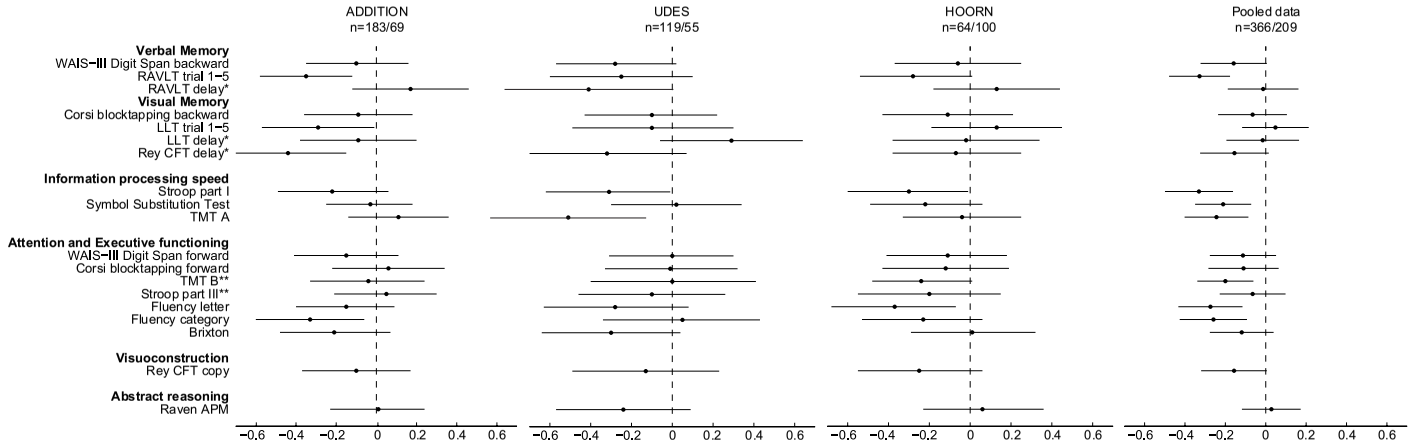

Figure 1. Cognitive functioning in patients with type 2 diabetes relative to controls: pooled results from three studies using the same standardised cognitive assessment battery. The ADDITION study involved recent screen-detected patients with type 2 diabetes.[8] The UDES was a population based case-control study involving patients with type 2 diabetes with a mean diabetes duration of ±8.7 years.[3] The Hoorn study[9] was a longitudinal population based cohort involving patients with mostly screen-detected diabetes, diagnosed up to 5 years before cognitive assessment. Mean ages of the patients were 63±5 (ADDITION), 66±6 (UDES), 74±6 (HOORN) and 66±7 (pooled data). The control group was matched on age, sex and level of education. Participants were excluded if they were known to have a history of alcohol or drug abuse, psychosis, dementia, or neurological or psychological disorder unrelated to diabetes. The figure shows age, sex, and IQ adjusted mean differences in z-scores with their 95% confidence intervals. The n represents numbers of patients/controls. Z-scores are transformed such that a negative value means worse performance for the diabetes group.

RAVLT: Rey Auditory Verbal Learning Test; LLT: Location Learning Test; Rey CFT: Rey Complex Figure Test; TMT: Trailmaking Test; Raven APM: Raven Advanced Progressive Matrices.

* The delayed memory tasks are adjusted for performance on the learning trial.

** The TMT B and Stroop card 3 are adjusted for performance on TMT A and Stroop card 1 and 2, respectively.

immediate recall performance. Following this method, short-term memory was more evidently affected than long-term memory. It is not clear whether memory deficits in patients with type 2 diabetes result from problems with the storage of information or from a limited information processing capacity. Both could lead to a diminished performance on memory tests.[10]

Cross-sectional population-based studies in large cohorts such as the Atherosclerosis Risk in Communities (ARIC) study and the Framingham study report a pattern of cognitive decrements similar to the case control studies.[11,12] Nevertheless, not all studies observed differences in cognitive performance between patients and controls despite elaborate cognitive testing.13-16 and relatively large sample sizes.[14,16]

Longitudinal studies

An increasing number of studies have examined the impact of diabetes on cognitive functioning longitudinally.[17-26] Several large studies have reported cognitive decline over an average period of 5 years that exceeded the effects of normal aging by a factor 1.5 to 2.[17,19-23] However, in most studies only a limited number of cognitive tests were affected and the absolute magnitudes of the observed differences were small, and clearly distinct from the rate of decline that is typical for pathological conditions such Alzheimer's disease.[27] Other studies did not observe accelerated cognitive decline in patients with type 2 diabetes[18,24-26], despite elaborate testing.[24,26] Taken together these studies show relatively subtle decrements in cognitive functioning, which slowly progress over time.

Cognitive impairment and dementia

Several longitudinal studies showed that patients with type 2 diabetes were overrepresented by a factor 1.5 to 2 in subgroups of older individuals (>65 years) with severe cognitive deficits.[17,21,22,25,28,29] Population-based studies observed a 1.5-fold increased risk for patients with type 2 diabetes to develop amnestic mild cognitive impairment (MCI) or non-amnestic MCI.[30-33]

Moreover, a large number of studies have identified type 2 diabetes as a risk factor for dementia.[34] Currently, 6 to 8% of all cases of late life dementia may be attributable to type 2 diabetes.[35] Type 2 diabetes is associated with a 2 to 4-fold increased risk of vascular dementia[30,36-39] and an 1.5 to 2-fold increased risk of Alzheimer's disease[36-42], although it should be noted that it is difficult to distinguish between these two subtypes of dementia based on a clinical diagnosis. Moreover, many patients may be affected by both vascular and Alzheimer type pathology.[43]

Cognition in pre-diabetic stages

Changes in insulin sensitivity and glucose metabolism may occur years before type 2 diabetes is diagnosed. Cognitive decrements may also develop in these early stages of glucose dysmetabolism. Hyperinsulinemia and impaired glucose tolerance, for example, have been linked to reduced cognitive performance in individuals without type 2 diabetes[23,44-46], although not invariably.[16,47,48] Insulin resistance often co-occurs with vascular risk factors such as hypertension, dyslipidemia and obesity, also in the years preceding diabetes. This clustering of insulin resistance and vascular risk factors is referred to as the metabolic syndrome.[49] Individuals with the metabolic syndrome, show the same profile of cognitive decrements as patients with type 2 diabetes.[9,50] Still, the magnitude of the observed decrements in cognitive functioning associated with the metabolic syndrome and other pre-diabetic stages is less pronounced than in type 2 diabetes, with effect sizes ranging from 0.1 to 0.3.

Longitudinal population based studies addressing the relation between pre-diabetic stages and more severe cognitive deficits have found that hyperinsulinemia, impaired glucose tolerance, and the metabolic syndrome are all associated with an increased risk of developing cognitive impairment [23,51,52] or dementia.[53,54]

Depression

Patients with type 2 diabetes have an increased risk of depression compared to non-diabetic persons.[55] Depressive symptoms were observed in 31% of the patients with type 2 diabetes, while the prevalence of a major depressive disorder was estimated at 11%. A study in 907 elderly patients with type 2 diabetes showed that depression was associated with a 14% increased risk of cognitive impairment, measured with MMSE, relative to patients without depression.[56]

The exact nature of the relation between type 2 diabetes and depression is not completely understood. Depression may result from difficulties in coping with chronic disease. On the other hand metabolic consequences of type 2 diabetes may disturb the levels of cerebral neurotransmitters, thus predisposing people to depression[57] In addition, depression might result from vascular damage in the brain.[58,59] Importantly, the relation between diabetes and depression may be bi-directional, as, depression may even predispose the development of type 2 diabetes.[60] Although depressive symptoms can affect cognitive performance, and may thus play a role in the aetiology of diabetes-associated cognitive decrements, only a proportion of the patients with diabetes develop clinically relevant depressive symptoms.[55] It is therefore unlikely that depression is the sole explanation for the association between diabetes and cognitive dysfunction. Moreover, the majority of studies that assessed cognition in relation to diabetes controlled for the potential confounding effects of depression.

Risk factors

Type 2 diabetes is associated with various risk factors that may influence cognitive functioning, including diabetes-specific factors (e.g. hyperglycemia, microvascular complications), risk factors that are linked to diabetes but are not specific to the disease (e.g. hypertension, obesity, depression, stroke), and genetic, demographic, and lifestyle factors. All of these risk factors may mediate or modulate cognitive functioning at different times during life span. We will discuss each of these factors separately, but it is important to emphasize that many of them are interrelated, and it therefore remains difficult to assess their individual impact on cognition.

Demographics and lifestyle

Demographic factors such as age, sex, ethnicity, and level of education are usually treated as confounders in studies on the association between type 2 diabetes and cognitive dysfunction. Nevertheless, these factors may play an important role and their impact on diabetes and cognitive performance should not be overlooked. Especially the effect of age deserves attention, since age is an important risk factor for both type 2 diabetes and cognitive decline. The pattern of mild cognitive decrements associated with type 2 diabetes, resembles the pattern seen in normal aging.[61] Moreover, the mechanisms that are assumed to mediate the toxic effects of hyperglycemia on the brain are also implicated in brain aging.[62] Therefore, the effects of age and type 2 diabetes may share a common etiology. A survey of the literature indicated that relative to controls cognitive decrements become more evident in patients with diabetes above the age of 65.[63] However, if we reanalyze the data presented in *Figure 1* separately for people below or above 65 years of age we cannot confirm this.

Studies that have focussed on potential effects of gender on cognitive functioning in type 2 diabetes showed essentially the same cognitive impairments across both sexes.[64] Nevertheless, the rate of cognitive decline may vary a little between older men and women, possibly due to confounding effects of a higher mortality at a younger age in diabetic men.[22,65]

Socio-economic status and ethnic background can affect the incidence of diabetes, vascular disease, vascular risk factors and dementia, but also availability of, and compliance with, treatment.[66-69] The contribution of these factors to the association between diabetes and dementia is not clear. Finally, lifestyle factors such as smoking, physical activity and diet, are associated with the development of type 2 diabetes[70,71] and cognitive decline and dementia.[72-74]

Hyper- and hypoglycemia

Studies in patients with type 1 diabetes suggest that chronic exposure to hyperglycemia may have a negative impact on cognitive functioning.[75] Similar

evidence exists from cross-sectional studies in patients with type 2 diabetes. Mild cognitive decrements in patients with type 2 diabetes have been associated with longer diabetes duration[20,28,99-101] and elevated HbA1c levels[4,76-80], although this has not been observed in other studies[16,81,82] (*See also Figure 2*). Longitudinal studies in patients with type 2 diabetes also showed that longer diabetes duration and higher HbA1c levels were associated with a faster rate of cognitive decline.[17,22,64,65,83] It is important to note however, that diabetes duration may reflect chronic exposure to factors other than hyperglycemia alone. Hyperglycemia may also lead to acute changes in cognitive functioning. Patients with type 1 and 2 diabetes showed acute psychomotor slowing and an increase in the amount of errors over a 4 week period as soon as blood glucose levels increased above 15 mmol/l.[84]

The relation between hyperglycemia and more severe cognitive deficits, such as dementia is less clear. Data from the Kungsholmen project showed that very old patients with uncontrolled diabetes (HbA1c ≥ 11.0 mmol/l) had the highest risk of stroke and Alzheimer's disease independent of vascular co-morbidities.[85] Another study found no association with baseline HbA1c values, but long diabetes duration was associated with an increased risk of dementia.[86]

Hypoglycemia is a well-known complication of glucose-lowering therapy and hypoglycemic episodes may have detrimental effects on the brain. Although severe hypoglycemic episodes are generally less common in type 2 than in type 1 diabetes, the incidence increases steadily the longer patients are treated with insulin.[87,88] Cognitive function becomes rapidly impaired when the blood glucose falls below 3.0 mmol/l (54mg/dl) and improves again with restoration of glucose levels.[89,90] However, the long term effects of repeated hypoglycaemic episodes on cognition are less clear.[91] Two recent longitudinal studies examined the relation between severe hypoglycaemic events and cognitive decline.[92,93] The Fremantle diabetes study found no evidence that severe hypoglycaemia contributes to cognitive decline in older patients with type 2 diabetes, but people with dementia were at increased risk of further severe hypoglycaemic episodes over the subsequent 5 years.[93] In contrast, data from a large diabetes registry from northern California showed a dose response relation between the number of severe hypoglycaemic episodes and the risk of developing dementia up to 17 years after the event.[92] The latter finding is intriguing considering the fact that a meta-analysis[75] and results from the Diabetes Control and Complications Trial[94] did not provide evidence for an association between the occurrence of hypoglycemic episodes and impaired cognition in young adult patients with type 1 diabetes. Differential vulnerability of the brain to hypoglycaemia in young and older patient populations may be the reason for the observed discrepancy.[91]

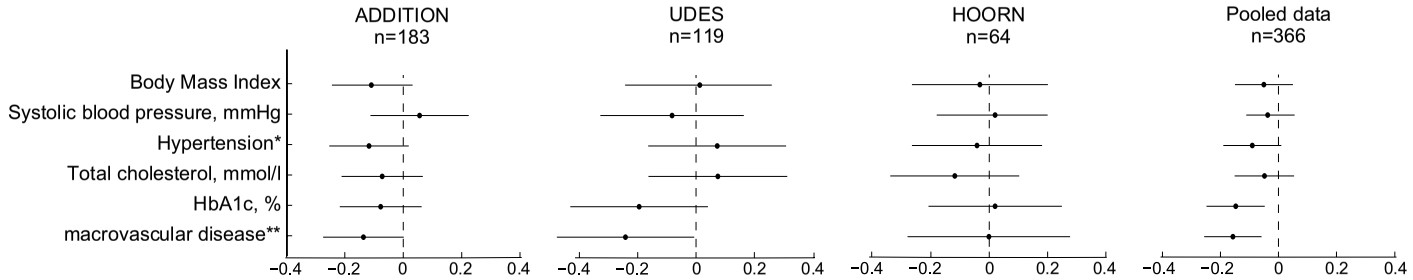

Figure 2. Risk factors for decrements on tests measuring information processing speed in patients with type 2 diabetes: pooled analysis of three studies using the same standardised cognitive assessment battery (for details see figure 1).The figure shows age and sex adjusted standardised regression coefficients with their 95% confidence intervals. In separate analyses for patients above and below the age of 65 years results were similar (data not shown).
* Hypertension was defined as an average systolic blood pressure ≥160 and/or a diastolic blood pressure ≥95 and/or use of antihypertensive medication.
** A history of macrovascular disease was defined as a history of myocardial infarction, stroke, or endovascular treatment of carotid, coronal or peripheral arteries.

Vascular risk factors

Diabetes is often accompanied by other well known vascular risk factors, such as hypertension, hypercholesterolemia and obesity, which might also affect the brain. Several studies have shown cumulative or interactive effects of hypertension and type 2 diabetes.[12,20,95] One longitudinal study found that cognitive functioning in patients with type 2 diabetes was related to long-term exposure to hypertension, even in pre-diabetic stages.[96]

Data on the relation between lipid levels, obesity and cognitive functioning in patients with type 2 diabetes are limited. In a group of middle aged patients with diabetes, dyslipidemia was associated with worse declarative memory performance.[97] In addition, a cross-sectional study showed a modest association between the use of lipid-lowering drugs and better cognitive performance.[95]

In the general population the presence of vascular risk factors has been associated with a higher risk of dementia, particularly if these risk factors are present at midlife.[35] In older age groups, the relation between vascular risk factors and cognitive decline is generally less consistent.[98,99] This may explain why longitudinal studies in older (>70 years) patients with type 2 diabetes report inconsistent results on the relation between vascular risk factors and cognitive impairment or dementia.[17,22,30,86,100] One study observed the greatest cognitive decline among patients with comorbid hypertension[100], but others failed to show such interaction effects.[17,22,30] Another longitudinal study in very old patients with diabetes, found that higher baseline total cholesterol level and higher baseline waist-to-hip ratio were associated with a *decreased* risk of cognitive impairment.[86] Such reverse associations have also been observed in the general population and might be due to weight loss immediately preceding the onset of dementia.[99] These results demonstrate the importance of addressing vascular risk factors over a long time frame, long before the development of dementia, probably because their relation with dementia is mediated by slow and gradual processes such as the development of atherosclerosis.[7] Moreover, risk factor levels may change under the influence of aging, but also under the influence of processes related to cognitive decline.[99] Unfortunately, there are no studies examining the relation between vascular risk factors and dementia in patients with type 2 diabetes over such a long time frame.

Micro- and macrovascular complications

The prevalence, progression and severity of diabetic microvascular complications, including diabetic retinopathy, neuropathy and nephropathy, are associated with longer diabetes duration and worse glycaemic control in both type 1 and type 2 diabetes.[126,127] In patients with type 1 diabetes, advanced microvascular disease is associated with cognitive decrements.[101-103] Cross-sectional studies in patients with type 2 diabetes, however, did not observe a consistent association between

relatively milder forms of microvascular disease and cognition[95,104], although microalbuminuria was related to the development of cognitive impairment in older patients with type 2 diabetes.[105] In this context, it is noteworthy that microvascular damage in the kidneys or retina is also associated with an increased risk of cognitive impairment or dementia in older individuals without diabetes.[106,107] Diabetes is an established risk factor for atherosclerotic disease.108 It is known from studies in the general population that atherosclerotic disease increases the risk of cognitive dysfunction, also in people without a history of stroke.109 In patients with type 2 diabetes, a history of atherosclerotic disease has been shown to be associated with cognitive decrements[8,95,110] (*see also Figure 2*). Moreover, a history of stroke or the presence of peripheral arterial disease substantially increased the risk of cognitive impairment in patients with diabetes.[56,86] and doubled the relative risk of dementia.[30] However, among individuals with clinically manifest vascular disease, type 2 diabetes is still associated with modest cognitive decrements[111], indicating that the effect of diabetes and vascular disease on cognition may be additive.

Figure 2 shows the pooled results from three studies on several possible risk factors of modest cognitive decrements in type 2 diabetes from our research group.[3,8,9] Across the three studies, a history of macrovascular disease and elevated HbA1c levels, were the most consistent risk factors for reduced cognitive performance. When all patients with a history of stroke, or patients with a history of any type of macrovascular disease are omitted from the pooled analyses as presented in *Figure 1*, type 2 diabetes is still associated with cognitive decrements, indicating that the cognitive decrements are not solely due to vascular co-morbidity.

Genetic factors

Genetic predisposition may play a role in the association between type 2 diabetes, cognitive decrements and dementia, but thus far only few studies have been performed in this context. The most widely examined risk factor is the *APOE* ε4 allele, an important risk factor for cardiovascular disease and late-onset Alzheimer's disease in the general population.[112] Several studies have shown interaction effects between type 2 diabetes and the *APOE* ε4 allele, further increasing the diabetes associated risk of cognitive decline.[7,113] and cognitive impairment or dementia.[38,39,114,115] Results from the Rancho Bernardo Study, however, failed to show such interaction.[22] Another gene which is suggested to mediate the relation between type 2 diabetes and Alzheimer's disease is insulin-degrading enzyme (IDE).[116] IDE degrades both insulin and amyloid-β, the main component of amyloid plaques, the pathological hallmark of Alzheimer's disease. Variations in the IDE gene were associated with an increased risk of type 2 diabetes and Alzheimer's disease.[117,118] Interestingly, these associations were only observed in individuals who do not carry the *APOE* ε4 allele.

Mechanistic studies

Mechanisms through which type 2 diabetes may affect the brain include vascular disturbances, glucose toxicity, hypoglycemic episodes, and disturbances of cerebral insulin signalling.[119-122] Other factors, such as glucocorticoids, may modulate these effects.[123,124] A detailed description of these mechanisms is beyond the scope of this paper, the reader is referred to other reviews.[119-124]

Brain correlates of cognitive dysfunction in type 2 diabetes

Imaging studies

Brain imaging studies in type 2 diabetes have examined vascular lesions and cerebral atrophy as possible structural correlates of impaired cognition. As type 2 diabetes is an important risk factor for stroke, it is not surprising that population-based studies report a 1.5 to 2-fold increased prevalence and incidence of lacunar infarcts.[125-127] (see for meta-analysis:[128]). The relationship between type 2 diabetes and white matter hyperintensities (WMHs) is less clear. Several large population-based studies did not observe a significant association between diabetes and WMHs.[129-131] However, case-control studies that applied a more refined WMH rating scale and volumetric measurements did observe a modest increase in WMH severity in patients with type 2 diabetes[76,132-134], and a recent study also indicates that diabetes is a risk factor for WMH progression.[135] Microbleeds are another emerging marker of cerebrovascular disease. Although this topic needs further exploration, the first studies suggest that microbleeds are more prevalent in patients with type 2 diabetes.[136]

Cross-sectional studies consistently report modest degrees of global atrophy in patients with type 2 diabetes (reviews:[128,137]). Given the association between type 2 diabetes and Alzheimer's disease, atrophy in specific brain regions such as the frontal or medial temporal lobe is of particular interest. There are indeed clear indications that medial temporal lobe structures, including the hippocampus and amygdala, are particularly affected in type 2 diabetes.[78,97,127,130,138,139] Two studies which specifically examined the prefrontal cortex in patients with diabetes reported a reduction in prefrontal brain volume in patients relative to controls.[97,140] However, in one study the effect was modified after adjusting for hypertension.[97]

A small number of studies have examined the relationship between brain imaging abnormalities and cognitive functioning in relatively healthy patients with type 2 diabetes. In a cross-sectional study we observed an association between modest cognitive decrements and the presence of infarcts, severity of WMHs and atrophy in patients with type 2 diabetes.[76] This relation was most evident for decrements in information processing speed and attention and executive functioning. Two other studies also observed an association between the severity of WMHs and slowing of information processing.[4,141] In addition, reduced information processing speed and

memory performance was related to subcortical atrophy.[141] In patients with type 2 diabetes and symptomatic arterial disease, global cognitive test performance was associated with the presence of large infarcts and global atrophy.[111]

Autopsy studies

An increasing number of autopsy studies have addressed the relation between type 2 diabetes, cerebrovascular disease and Alzheimer's pathology. In line with imaging studies, type 2 diabetes is related to a 2.5-fold increased risk for cortical and subcortical cerebral infarction.[38,142,143] Diabetes is also associated with changes in the cerebral microvasculature, including amyloid angiopathy.38 and capillary basement thickening.[144,145] Recent autopsy studies of population-based cohorts, not specifically directed at diabetes, indicate that microvascular lesions in the brain, such as microbleeds and cortical and subcortical microinfarcts, are important correlates of impaired cognition.[145-148] Hence, microvascular brain pathology could also explain part of the association between diabetes and dementia.

In contrast, no link has been demonstrated between type 2 diabetes and the severity of amyloid plaques and neurofibrillary tangles.[142,143,149] Some studies even reported a reverse association, with a decreased amount of Alzheimer pathology in patients with diabetes.[145,150] In the Honolulu-Asia Aging Study, no relation between type 2 diabetes per se and the amount of plaques and tangles was observed, however, there was an interaction between type 2 diabetes and the presence of the *APOE* ε4 allele, showing that patients with type 2 diabetes who carried the *APOE* ε4 allele had a higher number of plaques and tangles, than non-diabetic *APOE* ε4 carriers.[38] Thus, based on the current evidence from autopsy studies, a direct link between diabetes and Alzheimer pathology is not confirmed. However, it is possible that the diabetes associated vascular pathology may lower the threshold at which Alzheimer-type pathology becomes clinically manifest.[151]

Treatment

There is as yet no evidence based disease-modifying treatment for diabetes-related cognitive decrements. However, there are indications that modest cognitive decrements in patients with type 2 diabetes are partially reversible with improvement of glycemic control[152-157], though not invariably.[158] A randomised trial comparing the effects of rosiglitazone to glyburide therapy found statistically significant cognitive improvement in both treatment groups on measures of working memory, but not on learning and cognitive speed.156 The magnitude of the improvement was correlated with the degree to which fasting plasma glucose improved (correlation coefficient r=0.30). The DCCT trial, however, showed no differences in cognitive functioning after 6.5 years between patients with type 1 diabetes who received conventional treatment versus those who received

intensive treatment.[159] Cognitive performance also remained similar in the two groups after 18 years of follow up.[160]

It is yet uncertain whether reductions in the level of vascular risk factors will prevent cognitive decline in patients with type 2 diabetes. Studies in the general population do not consistently demonstrate that modifications of vascular risk factors can delay the development of dementia, although treatment of hypertension may be associated with a modest reduction in dementia incidence.[161] Limitations of the available studies, including timing and duration of the interventions, may be a source of this uncertainty and vascular risk factors remain a promising target for therapy. A study in a small cohort of hyperlipidemic patients with type 2 diabetes who were treated with atorvastatin showed that verbal memory improvement was associated with improvement of the diabetic dyslipidemia profile, regardless of high- or low-dose atorvastatin.[162] Results from further studies on this topic are eagerly awaited, in particular those of the ACCORD_MIND study, which should be reported later this year.

Other approaches that have been examined include physical activity, lowering of glucocorticoid levels and reducing oxidative stress. Observational studies suggest that certain types of physical activity, including light and moderate exercise, are associated with better cognitive functioning in patients with type 2 diabetes.[163] In a small randomized, placebo-controlled study administration of the 11β-Hydroxysteroid dehydrogenase inhibitor carbenoxolone improved verbal memory after 6 weeks in 12 patients with type 2 diabetes.[164] Moreover, reduction of oxidative stress by taking high dose antioxidant supplements after a high fat meal prevented an acute postprandial decline in delayed verbal memory in 16 patients with type 2 diabetes.[165]

Discussion and implications for clinical care

Studies on cognitive functioning in type 2 diabetes reviewed here reveal two important findings. Non-demented patients with type 2 diabetes show small decrements in cognitive functioning leading to mental slowing, mental inflexibility and problems with verbal memory. These subtle cognitive deficits are observed across all age groups and seem to develop slowly over time, with an onset in pre-diabetic stages and a modest progression thereafter. Second, large population based studies examining people at an older age (>70 years) demonstrate that patients with type 2 diabetes are overrepresented among individuals with dementia. Hence, there is a clear dissociation between modest and severe cognitive dysfunction with regard to affected age groups and course of development. *Figure 3* summarizes these observations. While modest cognitive decrements can be considered as a pre-dementia stage, the majority of patients with diabetes with modest cognitive decrements, particularly those below the age of 70 years, do not

progress to dementia within a couple of years. In our view the mild and severe cognitive deficits observed in patients with type 2 are likely to reflect separate processes with different risk factors and underlying etiologies that may require different treatment strategies.

Given the relatively mild nature of the cognitive decrements in the majority of patients with type 2 diabetes, particularly in those below the age of 60-70 years, there is, in our view, no indication for screening or active case finding in daily clinical care. Rather, a treating physician can act on cognitive complaints. In older patients, increased awareness for the occurrence of severe cognitive deficits in patients with diabetes is warranted. Such deficits are associated with reduced treatment adherence, an increased frequency of hospital admissions, and an increased occurrence of severe hypoglycaemic episodes.[93,166]

The question remains why patients with type 2 diabetes are more prone to develop dementia. Diabetes could interact with the dementia process, by accelerating the pathological processes underlying Alzheimer's disease, for example through disturbances of amyloid metabolism or through vascular (co)morbidity.[115,151] An alternative explanation is that diabetes affects the reserve capacity of the brain, possibly through the same mechanisms that cause the subtle cognitive decrements, and thereby reduce the threshold for the dementia process to become clinically manifest. Future etiological studies should try to distinguish between these two possibilities. Another key target for future studies is to find ways to prevent diabetes-associated cognitive dysfunction, particularly for the more severe types of cognitive dysfunction (i.e. dementia). Strategies to prevent dementia should probably be initiated in an early, possibly even presymptomatic, stage. Therefore we will need to identify people at increased risk of dementia in these very early stages, through biomarkers or risk factor profiles.

Moreover, we should gain more insight into the etiology to direct treatment at the mechanisms that drive accelerated cognitive decline. Because risk factors and mechanisms of the subtle diabetes-associated cognitive decrements may differ from those leading to dementia, studies should differentiate between these separate types of cognitive dysfunction when examining risk factor profiles. These major challenges need to be met because in the decades to come demographic and lifestyle trends will lead to a further increase in the prevalence of both diabetes and dementia around the world, with an increasing burden for affected individuals and society as a whole.

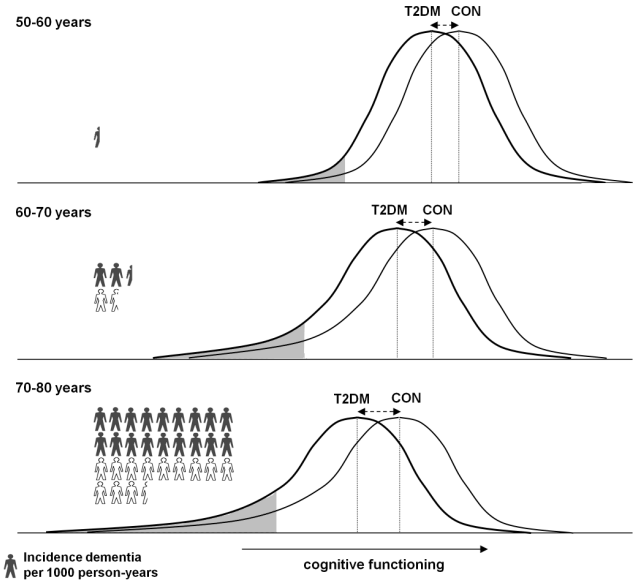

Figure 3. Different types of cognitive dysfunction in patients with type 2 diabetes.
The figure illustrates that type 2 diabetes (T2DM) is associated with modest and severe cognitive dysfunction. There is a dissociation between these two 'types' of cognitive dysfunction with regard to affected age groups and course of development, and they do not necessarily form a continuum. Modest cognitive decrements in patients with T2DM relative to controls (CON) are reflected by a small shift between the Gaussian curves (dotted arrow). The modest decrements occur across all age groups and are slowly progressive over time. Severe cognitive deficits are represented by the shaded areas under the Gaussian curve and dementia incidence, as depicted by the human icons. The closed icons reflect dementia incidence according to age in the general population[71], the open icons the added incidence attributable to T2DM.[34,166] These severe deficits affect only a subgroup of individuals, mainly at an older age, and show rapid further decline.

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Chapter 3

A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus

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Abstract

Background

Type 2 diabetes mellitus is associated with moderate decrements in cognitive functioning, mainly in verbal memory, information-processing speed and executive functions. How this cognitive profile evolves over time is uncertain. The present study aims to provide detailed information on the evolution of cognitive decrements in type 2 diabetes over time.

Methods

Sixty-eight patients with type 2 diabetes and 38 controls matched for age, sex, and estimated IQ-matched performed an elaborate neuropsychological examination in 2002-2004 and again in 2006-2008, including 11 tasks covering five cognitive domains. Vascular and metabolic determinants were recorded. Data were analyzed with repeated measures analysis of variance, including main effects for Group, Time and the Group × Time interaction.

Results

Patients with type 2 diabetes showed moderate decrements in information processing speed (mean difference in z-scores (95%CI) -0.37 (-0.69 to -0.05)) and attention and executive functions (-0.25 (-0.49 to -0.01)) compared with controls at both the baseline and the 4 year follow-up examination. After 4 years both groups showed a decline in abstract reasoning (-0.16 (-0.30 to -0.02)) and attention and executive functioning (-0.29 (-0.40 to -0.17)), but there was no evidence for accelerated cognitive decline in the patients with type 2 diabetes as compared with controls (all $p>0.05$).

Conclusions

In non-demented patients with type 2 diabetes cognitive decrements are moderate in size and cognitive decline over 4 years is largely within the range of what can be viewed in normal ageing. Apparently, diabetes-related cognitive changes develop slowly over a prolonged period of time.

Introduction

The global prevalence of diabetes is expected to rise from 171 million persons in 2000 to 366 million in 2030.[1] Prevalence estimates for dementia rise from 24 million in 2001 to 84 million in 2040.[2] There is compelling evidence for a link between diabetes and dementia, particularly in persons over 65 years of age. Longitudinal studies report a 1.5- to two-fold increased risk of dementia, both Alzheimer's disease or vascular dementia, in individuals with diabetes compared with those without.[3]

Numerous cross-sectional studies have reported on neuropsychological functioning in non-demented patients with type 2 diabetes mellitus (e.g.[4,5]). Systematic reviews of the literature report a cognitive profile of mild to moderate decrements in cognitive functioning in patients with type 2 diabetes.[6, 7] These decrements are most consistently found in information-processing speed, verbal memory and executive functioning[6,7], possibly reflecting a diminished ability to efficiently process unstructured information.[8] It is, however, less clear how these cognitive decrements evolve over time. Several longitudinal population-based studies have examined the risk of cognitive decline associated with type 2 diabetes in individuals who were not demented at baseline, but these studies have generally included only a limited number of psychometric tests or applied cognitive screening instruments, such as the Mini Mental State Examination (MMSE), that may be criticized for lack of sensitivity.[9, 10] The present study provides detailed assessment of the evolution of cognitive decrements in patients with type 2 diabetes over a 4 year period, relative to control participants, using an elaborate neuropsychological examination. We hypothesized that type 2 diabetes is associated with accelerated cognitive decline.

Methods

Participants

The baseline examination (2002-2004) included 122 patients with type 2 diabetes and 56 control participants aged between 56 and 80 years, matched on age, sex and estimated IQ.[8,11] Patients were recruited through general practitioners in the region. Control participants were recruited among the spouses or acquaintances of the patients. For inclusion the patients had to have type 2 diabetes for at least 1 year, be functionally independent and Dutch speaking. Exclusion criteria for all participants were a psychiatric or neurological disorder (unrelated to diabetes) that could influence cognitive functioning and a history of alcohol or substance abuse or dementia. Control participants with a fasting blood glucose ≥7.0 mmol/l were also excluded. At follow-up 4 years later, 7 participants had died, 4 could not be contacted and 59 were not willing or able to participate.

Reasons for not participating were: lack of interest (n=28), comorbidity (n=22; 3 reported dementia; 2 patients, 1 control), and other reasons (n=9). The remaining 108 participants were re-examined between 2006 and 2008 (mean follow-up time 4.1 ± 0.4 years). One patient with type 2 diabetes was excluded because of severe comorbid disease and one control participant fulfilled the criteria for type 2 diabetes and was therefore excluded from the control group, leaving 106 participants (68 patients and 38 control participants) in the present analysis.
The non-participants (n=70) did not differ from the participants (n=106) with regard to baseline age, sex or estimated premorbid IQ (all p>0.05). To control for possible selective loss at follow-up we examined the cognitive status of both non-participants and participants (± 1 week after their participation in the follow-up examination) with the Dutch version of the Telephone Interview for Cognitive Status (TICS)[12], a 12-item screening instrument designed to identify persons with dementia.[13] The interview was slightly modified (TICS-m) by including a delayed word-list recall which resulted in a maximum score of 50.[14] The TICS-m could be obtained from 43 of the 70 non-participants (i.e. 73% of the 59 non-participants who were still alive and could be contacted) and 99 of the 106 participants (93%). TICS-m scores were normally distributed across the whole study sample. The TICS-m performance for the nonparticipants was similar to the participants (non-participants mean score 35.4 ± 5.2, participants 36.5 ± 4.6, $F(1,140)=1.67$, $p=0.20$). Only 3 patients with type 2 diabetes (2 nonparticipants, 1 participant) and 2 control participants (1 non-participant, 1 participant) performed below the cut-off score of 28 ($\chi^2(1)=0.24$, $p=0.62$), which is indicative for cognitive impairment.[15] Hence, among the non-participants 4 patients with type 2 diabetes (3% of baseline sample) and 2 controls (4% of baseline sample) had cognitive impairment based on self-reported dementia or a low TICS-m score ($\chi^2(1)=0.10$, $p=0.76$). The study was approved by the medical ethics committee of the University Medical Center Utrecht, Utrecht, the Netherlands. Written informed consent was obtained from all participants.

Neuropsychological assessment

At follow-up all participants performed an extensive neuropsychological assessment, identical to the baseline examination.[8] Parallel versions were used for memory tests to control for possible material-specific learning effects.[16] The neuropsychological assessment consisted of 11 verbal and nonverbal tasks, administered in a fixed order that took about 90 minutes to complete. The tasks were divided into five cognitive domains to reduce the amount of neuropsychological variables in the analysis and for clinical clarity.[8] This division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak et al.[16] The domain *abstract reasoning* was assessed by Raven Advanced Progressive Matrices (12-item short

form). The domain *memory* included four subdomains: *working memory* assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Corsi Block-tapping Task (the product scores of the span length × the number of correctly recalled sequences were recorded[17]); *immediate memory and learning rate*, including verbal memory assessed by the Rey Auditory Verbal Learning Test and visual memory assessed by the Location Learning Test; *forgetting rate* assessed by the delayed task of the Rey Auditory Verbal Learning Test and of the Location Learning Test; and *incidental memory* assessed by the delayed trial of the modified Taylor Complex Figure. The domain *information processing speed* was assessed by the Trail Making Test - Part A, the Stroop Color-Word Test (Parts I and II), and the subtest Digit Symbol of the WAIS-III. The domain *attention and executive function* was assessed by the Trail Making Test - Part B (ratio score), the Stroop Color-Word Test (Part III; ratio score), the Brixton Spatial Anticipation Test, a letter fluency test using the 'N' and 'A', and category fluency (animal naming The domain *visuoconstruction* was assessed by the copy trial of the modified Taylor Complex Figure.

To compare the five different cognitive domains between the two groups the raw test scores were standardized into z-scores per cognitive domain. These z-scores were calculated by using the pooled mean of baseline scores of the whole study sample. The z-score for each domain was derived by calculating the mean of the z-scores for tests comprising that domain. Depressive symptoms were assessed with the Dutch version of the Beck Depression Inventory 2nd Edition (BDI-II[18]). The total score on this self-rated depressive symptoms inventory and the proportion of persons scoring >13 were recorded.[19]

Medical history and biometric measurements

Procedures at baseline and follow-up were identical.[8] Medical history was assessed with a standardized questionnaire addressing diabetes duration, medication use, history of cardiovascular disease (including stroke), smoking and alcohol consumption. Fasting glucose, HbA1c, and cholesterol levels were measured with standard laboratory testing. Blood pressure was measured in a seated position at three time-points during the half-day visit (Omron MX3; Omron, Mannheim, Germany). Hypertension was defined as a systolic blood pressure >160 mmHg, a diastolic blood pressure >95 mmHg or self-reported use of blood pressure lowering medication. 'Any macrovascular event' was defined as a history of myocardial infarction, stroke, or surgery or endovascular treatment for coronary, carotid or peripheral (legs, abdominal aorta) artery disease. Retinopathy was defined as a score of ≥1.5 on the Wisconsin Epidemiologic Study of Diabetic Retinopathy scale.[20] Neuropathy was defined as a score ≥6 on a modified version of the Toronto Clinical Neuropathy Scoring System.[21, 22]

Statistical analysis

Between-group differences in characteristics were analyzed with analysis of variance for continuous variables, Mann-Whitney U tests for non-parametric data and chi-square tests for proportions. The primary outcome measures were the *z*-scores of the five cognitive domains, which were analyzed with repeated-measures analysis of variance (ANOVA), including the effect of Time, Group and the Time × Group interaction. The effect of Time reflects the mean change in cognitive performance over time for the whole study sample; the effect of Group reflects the mean difference between the patients with type 2 diabetes and the control group; the Time × Group interaction reflects the additional change over time attributable to diabetes status. A p-value <0.05 was considered statistically significant. In a secondary analysis additional adjustment for BDI-II depressive symptoms was performed to examine a possible confounding effect of depression. Moreover, within the diabetes group cognitive functioning (domains information processing speed and attention and executive functioning) was compared between patients with high or low baseline HbA1c (dichotomized at the median level of 6.6 mmol/l), with or without baseline hypertension and with or without 'any macrovascular event' at baseline.

Results

Table 1 shows the characteristics of the patients with type 2 diabetes and the control group at baseline. The groups were similar in age, estimated IQ and sex distribution. As expected, between-group differences in glycemic control, vascular risk factors and vascular events were still present at the follow-up examination after 4 years (data not shown). At baseline 6 (9%) patients were treated with diet only, 42 (62%) used oral glucose-lowering medication and 20 (29%) used insulin. The baseline prevalence of retinopathy and neuropathy was 32% and 35%, respectively.

Table 2 shows the raw test scores of the neuropsychological examination for both groups at baseline and follow-up. To limit the number of comparisons, only the differences in domain scores were compared statistically (*Table 3*). As is shown in *Figure 1* the results of the repeated measures ANOVA demonstrated a significant decline in performance over 4 years for the whole sample on the domains abstract reasoning and attention and executive functions (mean change in *z*-scores -0.16, $F(1,93)=4.83$, $p=0.03$ and -0.29, $F(1,103)=25.59$, $p<0.001$, respectively). A significant main effect of Group was found in information-processing speed (mean difference in *z*-scores for patients with type 2 diabetes compared with controls: -0.37, $F(1,102)=6.68$, $p<0.05$) and attention and executive functions (-0.25, $F(1,103)=3.01$, $p<0.05$), and a trend in the same direction on memory (-0.16, $F(1,103)=3.42$, $p=0.07$). There were no significant Time × Group interactions,

Table 1. Baseline characteristics of the patients with type 2 diabetes and the control group

	Baseline			Follow-up		
	Type 2 diabetes	Control group	p-value	Type 2 diabetes	Control group	p-value
n	68	38	-	68	38	-
Age (years)	65.6 ± 5.6	64.8 ± 4.8	0.44	69.8 ±5.6	68.9 ± 4.8	0.44
Male sex (n)	32 (47%)	19 (50%)	0.77	-	-	-
Educational level (median (IQR))	4 (3-5)	4 (4-5)	0.87	-	-	-
Estimated IQ (points)	100 ± 16	103 ± 13	0.39	97 ± 15	98 ± 15	0.64
Diabetes duration (years)	9.1 ± 6.3	-	-	-	-	-
HbA1c (%)	6.9 ± 1.1	5.5 ± 0.3	<0.001	7.2 ± 1.0	5.7 ± 0.4	<0.001
Hypertension[a]	49 (72%)	11 (29%)	<0.001	53 (78%)	19 (50%)	<0.01
BMI (kg/m^2)	27.9 ± 4.0	26.7 ± 5.2	0.19	28.4 ± 4.8	26.7 ± 4.5	0.09
Total cholesterol (mmol/l)	5.0 ± 0.9	5.9 ± 1.2	<0.001	4.5 ± 1.0	5.9 ± 1.0	<0.001
History of stroke	3 (4%)	1 (3%)	0.65	3 (4%)	1 (3%)	0.65
Any macrovascular event[b]	18 (27%)	2 (5%)	0.007	20 (29%)	3 (8%)	0.01
Beck Depression Inventory	7.2 ± 5.0	4.4 ± 3.5	0.005	8.5 ± 7.0	5.5 ± 5.1	0.03
Beck Depression Inventory >13	5 (9%)	0 (0%)	0.07	9 (16%)	1 (3%)	0.04

Data are presented as mean±SD or n (%) unless otherwise specified; IQR interquartile range
[a]Defined as systolic blood pressure >160, diastolic blood pressure >95 or use of blood pressure lowering medication.
[b] Defined as a history of myocardial infarction, stroke, or surgery or endovascular treatment for coronary, carotid of peripheral (legs, abdominal aorta) artery disease.

although there was a trend towards interaction for visuoconstruction (p=0.07). Additional adjustment for BDI-II score or exclusion of persons with a BDI-II score >13 did not change the results. Visual inspection of the distribution of the individual z-scores for each domain did not reveal differences between the diabetes group and the control group. This indicated that it was the diabetes group as a whole that had a worse mean performance, rather than a subgroup of patients with type 2 diabetes performing in the lowest part of the z-score distribution.

In secondary analyses within the diabetes group no significant group differences or Time × Group interactions with regard to HbA1c level were found (information processing speed mean group difference (95% CI) = 0.07 (-0.37 to 0.51); attention and executive functions -0.08 (-0.38 to 0.23)) or the presence of hypertension (information-processing speed 0.11 (-0.38 to 0.60); attention and executive functions 0.01 (-0.33 to 0.34)). For patients with type 2 diabetes with 'any macrovascular event' there was a trend toward a worse performance on information processing speed (-0.46 (-0.95 to 0.03)), but no differences were found on attention and executive functions (-0.19 (-0.53 to 0.15)).

Table 2. Raw test scores of the patients with type 2 diabetes and the control group at the baseline and follow-up examination

	Type 2 diabetes (n=68)		Control group (n=38)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Raven APM (short form)	6.3 ± 2.9	6.3 ± 2.9	7.3 ± 2.1	6.5 ± 2.4
WAIS-III Digit Span				
Forward (product score)	45.1 ± 20.5	41.0 ± 20.0	47.6 ± 19.1	48.6 ± 20.6
Backward (product score)	23.1 ± 15.7	21.0 ± 15.0	32.5 ± 23.0	27.5 ± 22.0
Corsi Block-tapping Test				
Forward (product score)	38.0 ± 13.8	36.5 ± 11.7	37.8 ± 9.5	37.2 ± 11.3
Backward (product score)	37.1 ± 13.8	37.4 ± 13.6	41.3 ± 12.8	38.8 ± 13.2
Rey Auditory Verbal Learning Test				
Total trials 1-5	39.2 ± 9.0	38.4 ± 10.8	43.1 ± 11.4	43.4 ± 10.8
Delayed recall	7.6 ± 2.7	7.7 ± 2.8	8.7 ± 2.8	9.2 ± 3.1
Recognition	28.2 ± 1.9	28.5 ± 1.7	29.1 ± 1.4	29.0 ± 1.5
Location Learning Test				
Total trials 1-5 [a]	24.9 ± 21.0	23.7 ± 22.1	24.8 ± 19.9	20.5 ± 17.1
Learning index	0.59 ± 0.28	0.54 ± 0.31	0.66 ± 0.28	0.61 ± 0.29
Delayed trial [a]	2.0 ± 3.3	2.5 ± 3.5	1.7 ± 2.9	1.7 ± 2.8
Complex Figure Test				
Copy	32.4 ± 3.9	33.7 ± 2.7	33.0 ± 3.3	33.1 ± 3.0
Delay	17.4 ± 6.6	17.8 ± 6.1	19.9 ± 4.5	18.4 ± 5.2
Stroop Color-Word Test				
Part I [a]	50.4 ± 12.8	51.2 ± 9.6	47.0 ± 8.9	46.1 ± 7.6
Part II [a]	65.1 ± 13.6	66.6 ± 11.6	61.3 ± 14.2	62.8 ± 13.8
Part III [a]	124.6 ± 46.6	135.2 ± 46.3	113.1 ± 45.5	118.6 ± 41.5
Trail Making Test				
Part A [a]	49.5 ± 21.0	47.1 ± 22.9	38.6 ± 9.7	38.1 ± 12.1
Part B [a]	114.2 ± 44.2	138.0 ± 83.8	89.1 ± 25.1	97.1 ± 30.7
WAIS-III Digit Symbol	54.9 ± 16.8	50.4 ± 15.7	56.6 ± 12.2	56.6 ± 13.5
Verbal fluency				
Letter (mean of N+A)	10.4 ± 4.8	9.7 ± 4.2	12.0 ± 4.1	11.1 ± 4.0
Category (Animals)	33.8 ± 10.0	31.4 ± 10.1	34.1 ± 7.7	31.4 ± 10.1
Brixton Spatial Anticipation Test [a]	20.8 ± 7.3	22.1 ± 6.3	18.1 ± 6.6	22.1 ± 6.3

Data are mean raw test scores ± SD. [a] Higher test scores reflect worse performance.
Raven APM: Raven Advanced Progressive Matrices; RALVT: Rey Auditory Verbal Learning Test; LLT: Location Learning Test; TMT: Trail Making Test; WAIS-III: Wechsler Adult Intelligence Scale – Third Edition.

Table 3. Differences in cognitive domain scores for patients with type 2 diabetes and the control group at the baseline and follow-up examination

Domains	Mean change over time [a]	Mean difference between T2DM and control group [b]	Time × Group interaction p-value
Abstract reasoning	-0.16 (-0.30 to -0.02)	-0.17 (-0.57 to 0.22)	0.20
Memory	-0.06 (-0.14 to 0.02)	-0.16 (-0.34 to 0.01)	0.15
Information processing speed	-0.05 (-0.14 to 0.04)	-0.37 (-0.69 to -0.05)	0.23
Attention and Executive functions	-0.29 (-0.40 to -0.17)	-0.25 (-0.49 to -0.01)	0.37
Visuoconstruction	0.16 (-0.06 to 0.38)	-0.06 (-0.36 to 0.24)	0.07

Data are mean differences in z-scores with (95% CI). Analyzed with repeated-measures analysis of variance. [a] For the whole sample [b] Control group is reference.

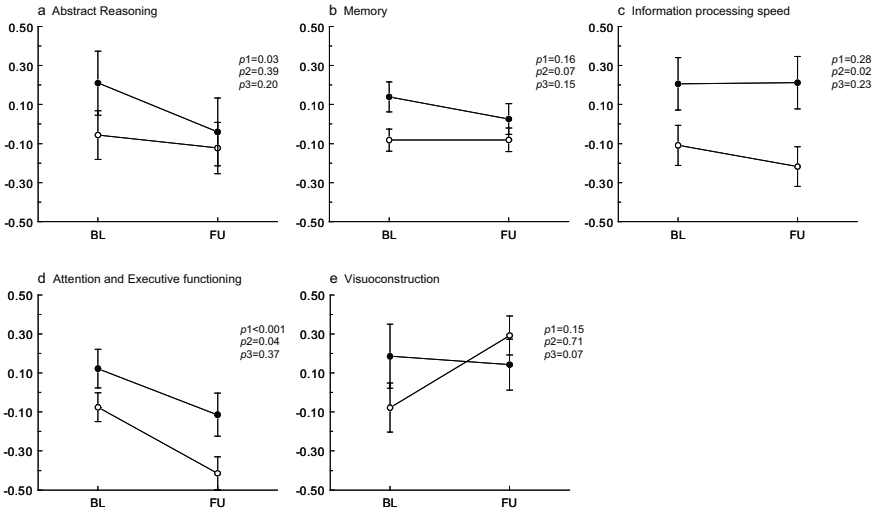

Figure 1 a-e. Cognitive functioning (mean standardized domain score ± SEM) for the patients with type 2 diabetes (open circles; n=68) and the control group (filled circles; n=38) at baseline (BL) and 4-year follow-up (FU). *P*-values indicate the results of the repeated-measures ANOVA; *p*1 = main effect of Time, *p*2 = main effect of Group, *p*3 = Time × Group interaction.

Discussion

Patients with type 2 diabetes showed moderate decrements in cognitive functioning compared with control participants matched for age-, sex- and estimated IQ, both at baseline and after 4 year follow-up in the domains information processing speed and attention and executive functioning. After 4 years a decline in abstract reasoning and attention and executive functioning was found for the whole sample, but no evidence was shown for accelerated decline in the patients with type 2 diabetes.

The profile of cognitive decrements and the size of the effects observed in the present study are comparable with the results from previous cross-sectional studies on cognition in type 2 diabetes, which show small to moderate decline (effect sizes -0.3 to -0.6) particularly in the domains information processing speed, executive functioning and memory.[6] Interestingly, the effect sizes of cross-sectional studies in patients with different stages of type 2 diabetes or even pre-diabetic stages are remarkably similar, generally ranging from -0.3 to -0.6[4, 23-25], indicating that these decrements may develop in the early stage of the disease and progress only gradually thereafter. Our findings on the domain visuoconstruction were dissimilar to the other domains, as the performance of the patients with type 2 diabetes tended to improve. We have no certain explanation for this observation, but the fact that this domain only comprised a single test, in contrast to the other domains, may have affected the reliability of this domain score and increased the potential impact of confounding factors such as motivation, ceiling effects or practice effects, particularly for those participants with an initial worse performance.

To date, longitudinal studies that examine the cognitive profile of patients with type 2 diabetes and control participants by means of a detailed neuropsychological test battery are scarce. Two previous case-control studies, with smaller samples of patients with type 2 diabetes than the present study, did not consistently observe accelerated cognitive decline in patients with type 2 diabetes after a 3 to 4 year follow-up.[26, 27] Longitudinal population-based studies, which included less detailed assessment of cognitive functioning than the present study, showed moderate differences in cognitive performance between patients with type 2 diabetes and controls at baseline and follow-up [9, 10, 28, 29], similar to the differences found in the present study. Some of these studies also observe a modest accelerated decline after a 3 to 6 year period on a subset of the cognitive measures[9, 10, 29] of approximately 1.5 times the decline of the non-diabetic participants. Apparently, no marked accelerated cognitive decline is found in the majority of patients with type 2 diabetes relative to persons without type 2 diabetes. This is in contrast with prototypic diabetic complications, such as retinopathy, nephropathy and neuropathy, for which prevalence and severity clearly increase with diabetes

duration and exposure to elevated glucose levels. Future etiological studies should answer the question why cognitive decrements can already be found in pre-diabetic stages, or at the time of diabetes diagnosis, and progress only slowly thereafter. In pre-diabetic stages exposure to vascular risk factors such as hypertension, dyslipidemia and obesity may play a role. Although acute effects of elevated blood glucose levels on cognitive functioning have been reported[30], the present findings suggest that long-term exposure to elevated blood glucose levels apparently do not have a major impact on cognition in patients with type 2 diabetes, a finding in line with recent observations in adult patients with type 1 diabetes.[31]

The question also is how these findings relate to the 1.5 to twofold increased risk of dementia that is observed in individuals with type 2 diabetes.[3] A likely explanation is that the subtle cognitive decrements that are found in non-demented populations do not necessarily evolve into frank cognitive decline in all individuals, but rather that within the population of older patients with type 2 diabetes, severe cognitive decline only occurs in a subgroup of persons, possibly in interaction with other risk factors such as the apolipoprotein E status[32], hypertension[33] or the metabolic syndrome.[34] Furthermore, particularly below the age of 70 years, incident dementia is relatively rare (annual incidence <1% per year.[35] This makes dementia a fundamentally different cognitive outcome measure than the more subtle cognitive decrements that are addressed in the present study, which show a normal distribution across the whole study sample.

The present detailed analysis of the neuropsychological profile associated with type 2 diabetes revealed a pattern of modest decrements in information-processing speed and attention and executive functioning, with a nonsignificant trend in the same direction for memory. This profile appears to reflect an overall diminished performance level rather than deficits in specific cognitive functions[36] and resembles the pattern that is found in normal ageing.[36]

The principal strength of the present study is the detailed neuropsychological examination that was performed twice over a 4 year interval in a relatively large sample of patients with type 2 diabetes. Limitations include possible selection bias due to selective attrition during the follow-up period. The results of the TICS-m showed that selection bias due to drop out of persons with severely impaired cognitive functioning was limited. Nevertheless, during follow-up of the non-participants we observed that several persons with marked cognitive decline dropped out of the study, albeit at a low rate that was similar in the two groups. Moreover, the reduction in sample size at the follow-up examination may have limited the power of the statistical analyses, particularly with regard to the time × group interactions.

In summary, the results of the present study indicate that in functionally independent patients with type 2 diabetes cognitive decrements are modest in size and decline is largely within the range of what can be viewed in normal ageing. Apparently, diabetes-related cognitive changes progress slowly over a prolonged period of time, probably much longer than the 4 years of follow-up in the present study.

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Chapter 4

Accelerated cognitive decline in patients with type 2 diabetes: MRI correlates and risk factors

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Abstract

Background

Type 2 diabetes mellitus is associated with an increased risk of cognitive decline and dementia. We examined brain imaging correlates and vascular and metabolic risk factors of accelerated cognitive decline in patients with type 2 diabetes.

Methods

Cognitive functioning, brain volume and metabolic and vascular risk factors were assessed twice in 68 non-demented patients with type 2 diabetes with a 4-year interval. 38 control participants served as a reference group. Volumetric measurements of the total brain, lateral ventricles and white-matter hyperintensities (WMH) were performed on 1.5T MRI scans. A regression based index score was calculated based on the reference group to assess changes in cognitive performance over time, adjusted for age, sex and estimated IQ. Brain volumes were compared between patients with and without accelerated cognitive decline. Logistic regression analyses were used to identify baseline risk factors for accelerated cognitive decline within the diabetes group.

Results

Accelerated cognitive decline was found in 17 (25%) patients with type 2 diabetes and was associated with a greater increase in ventricular volume (mean difference(95%CI): 0.23%(0.08 to 0.38); p=0.003) and WMH volume (0.16%(0.05 to 0.27); p=0.006) over the 4-year period. There were no specific vascular or metabolic risk factors associated with accelerated cognitive decline.

Conclusions

Accelerated cognitive decline in patients with type 2 diabetes was associated with progressive changes on brain MRI, comprising both vascular damage and global atrophy. Exploration of vascular and metabolic risk factors revealed no specific determinants of accelerated cognitive decline.

Introduction

Type 2 diabetes mellitus is associated with a twofold increased risk of dementia.[1] The underlying cause of this increased risk is not clear. Cognitive decline can be observed several years before the clinical diagnosis of dementia.[2] By addressing accelerated cognitive decline in patients with type 2 diabetes we may identify patients at increased risk of developing dementia at an early stage.

In the general population, brain imaging abnormalities such as cortical and subcortical atrophy and white matter hyperintensities (WMH) are associated with the development of dementia.[3] These brain imaging abnormalities are relatively more pronounced in patients with type 2 diabetes than in people without diabetes.[4] Cross sectional studies indicate that the degree of atrophy and WMH in patients with type 2 diabetes is associated with reduced cognitive performance[5-8], but it is unclear how progression of these imaging abnormalities over time relate to cognitive decline.

Identification of risk factors for accelerated cognitive decline may provide leads on the etiology and targets for treatment. In the general population, vascular risk factors which are common in type 2 diabetes, such as hypertension, hypercholesterolemia and obesity are independently associated with an increased risk of dementia[9] and stroke.[10] In patients with diabetes, the relationship between these vascular risk factors and cognition is less clear.[11,12] Other studies have indicated that factors intrinsic to diabetes, such as chronic hyperinsulinemia and hyperglycemia, may contribute to cognitive dysfunction, independent of vascular co-morbidity.[8,13,14]

The present study examined brain imaging correlates and vascular and metabolic risk factors of accelerated cognitive decline in patients with type 2 diabetes.

Materials and Methods

Participants

The Utrecht Diabetic Encephalopathy Study (UDES) is a longitudinal study on determinants of impaired cognition in type 2 diabetes. The baseline examination (2002-2004) included 122 patients with type 2 diabetes and 56 age, sex and IQ matched control participants aged between 56 and 80. Details of the study design are described elsewhere.[15,16] In brief, patients with type 2 diabetes were recruited through their general practitioners and controls among their spouses and acquaintances. Participants were functionally independent and Dutch speaking and patients had type 2 diabetes for at least 1 year. At follow up (mean follow-up time 4.1 ± 0.4 years), 7 participants had died, 4 could not be contacted, 2 were excluded because they no longer fulfilled the inclusion criteria and 59 were not willing or able to participate; leaving 106 participants (68 patients, 38 controls)

for the present study. Reasons for not participating were lack of interest (n=29), comorbidity (n=21), or other reasons (n=9). MRI scans were available in 83 of the 106 participants (78%).
The Utrecht Diabetic Encephalopathy Study was approved by the medical ethics committee of the University Medical Center Utrecht, Utrecht, the Netherlands. Written informed consent was obtained from all participants.

Neuropsychological assessment

At follow up all participants performed an extensive neuropsychological assessment, identical to the baseline examination.[15] Parallel versions were used for memory tests to control for possible material-specific learning effects.[17] The neuropsychological assessment consisted of 11 verbal and nonverbal tasks, administered in a fixed order that took about 90 minutes to complete. In addition, IQ was estimated with the Dutch version of the National Adult Reading Test, which is generally accepted to reflect the premorbid level of intellectual functioning.[18] The tasks were divided into five cognitive domains. This division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak.[17] Detailed description of the test battery has been reported elsewhere.[19] Depressive symptoms were assessed with the Dutch version of the Beck Depression Inventory, 2nd edition (BDI-II).[20] Possible depression was defined as a score > 13 on this inventory.[21]
For each domain, the raw test scores were standardized into z-scores, based on the pooled mean of the baseline scores of the whole study sample. The z-score for each cognitive domain was derived by calculating the mean of the z-scores for tests comprising that domain. In the present study we limited our analyses to the cognitive domains that showed differences in performance at baseline between patients with type 2 diabetes and controls: memory, information processing speed and attention and executive functioning.[15] The z-scores of these three cognitive domains were averaged to obtain a composite z-score. To control for selective loss at follow up we examined cognitive status of participants and non-participants at follow-up with the Dutch version of the Telephone Interview for Cognitive Status (TICS)[22], which was slightly modified by adding a recognition condition of 10 previously presented words (TICS-m).[19] A TICS-m score below 28 indicates cognitive impairment.[23]

Cognitive change

Change in cognitive performance over time was expressed by a regression based index (RBI) score.[24] The RBI score was obtained by calculating the predicted follow up score (FUpredict), based on the baseline cognitive z-score, age, sex, and estimated IQ by means of regression analysis. The control group was used as a

reference therefore, beta values for each factor in the model were based on data from the control group. The RBI score for each cognitive domain is calculated as follows: RBI = FUobserved – FUpredict / SDresiduals. Thus, the difference between the observed and predicted follow up score, divided by the standard deviation of the residuals, determines the amount of cognitive change. For example, the rate of decline in a patient with an RBI of 0 is exactly similar to that of an average control participant with the same baseline cognitive performance and demographic profile. A negative RBI value indicates that a patient declined faster than was expected from a similar control participant, thus more than can be attributed to normal aging. The RBI score is preferred over the change in z-score over time, because it adjusts for potential confounding factors such as learning effects and regression to the mean.[24] The RBI score was calculated for the three cognitive domains (memory, information processing speed and attention and executive functioning) separately and subsequently averaged across these domains to obtain one outcome measure for cognitive change. This study investigates early stages of accelerated cognitive decline, therefore we defined accelerated cognitive decline as a composite RBI score below 1 SD from the mean of the control group.

Brain MRI and image processing

MRI scans were acquired at baseline and follow up on a 1.5T Philips MR scanner using a standardized protocol (38 contiguous slices, voxel size: 0.9 x 0.9 x 4.0) and consisted of an axial T1 (repetition time in ms (TR): 234, echo time in ms (TE): 2), T2 (TR: 2200, TE: 100), proton density (TR: 2200, TE: 11), inversion recovery (TR: 2919, TE: 22, inversion time in ms (TI): 410) and fluid attenuated inversion recovery (TR: 6000, TE: 100, TI: 2000).

Total brain, lateral ventricular and WMH volumes were measured by k-Nearest Neighbour-based probabilistic segmentation, an automatic and validated approach to brain segmentation.[25] Detailed description of the image processing is reported elsewhere.[26] Volumes were expressed as percentage of total intracranial volume to correct for between-subject differences in brain volumes. To determine the change over time difference scores between baseline and follow-up measurements were calculated within participants. Cerebral infarcts were identified by two raters (MB, JB) who were blinded for clinical data. In case the raters disagreed, consensus was obtained with a third rater (GB).

Medical history and biometric measurements

Procedures at baseline and follow up were identical.[15] Medical history was assessed with a standardized questionnaire addressing diabetes duration, medication use, smoking and cardiovascular disease (self reported myocardial infarction or surgical or endovascular treatment of atherosclerotic arterial disease). Stroke,

defined as a cerebral infarct on MRI, was considered separately (see previous paragraph). Fasting glucose, glycated haemoglobin (HbA1c) and cholesterol levels were measured with standard laboratory testing. Blood pressure was measured automatically at home on 10 different time points during the day and averaged (Omron MX3; Omron, Mannheim, Germany). Body mass index (BMI) was calculated as weight divided by height squared.

Statistical analysis

Differences in baseline characteristics and cognitive outcome measures between patients with and without accelerated cognitive decline were analyzed with an independent sample t-test with accompanying 95% confidence intervals for continuous data and a χ^2 test for proportions. Between-group differences in brain volumes were analyzed with analysis of variance, adjusted for age and sex, and for possible depression in a secondary analysis. Baseline WMH volume was multiplied by 100 and natural log-transformed because of non-normal distribution. The relation between baseline metabolic and vascular risk factors and accelerated cognitive decline was assessed with logistic regression analysis, adjusted for age and sex. Information on determinants of changes in brain measures in this population have been analysed and reported separately.[26] In secondary analyses, additional adjustment was performed for baseline medication use, depression, and cerebral infarcts observed on MRI at follow up. Analyses were also performed with the RBI score as a continuous variable with linear regression analysis. A p-value of less than .05 was considered statistically significant. Information on determinants of changes in brain measures in this population have been analysed and reported separately.[26]

Results

Baseline age, sex and estimated IQ, as well as baseline brain volumes, were not significantly different for participants attending compared to those not attending follow up (all $p>0.05$). The TICS-m could be obtained in 43 of the 59 (73%) nonparticipants who were still alive and could be contacted and in 99 of the 106 actual participants (93%). TICS-m performance was similar for participants (mean±SD: 36.5 ± 4.6) and non-participants (35.4 ± 5.2; $p=0.20$). Among the non-participants, 4 patients with type 2 diabetes (3% of baseline sample) and 2 controls (4% of baseline sample) had cognitive impairment based on self-reported dementia or a TICS-m score <28 ($\chi^2(1)=0.22$, $p=0.64$).

Accelerated cognitive decline

Within the diabetes group, 17 (25%) patients with type 2 diabetes were defined as having accelerated cognitive decline and 51 as having no accelerated decline.

Table 1 summarizes baseline demographic and clinical variables for the control group and patients with type 2 diabetes, with and without accelerated cognitive decline. None of the baseline characteristics presented in *table 1* were statistically significant between the T2DM decline and T2DM no-decline group. Since the control group was used as reference for the RBI scores, the mean RBI scores of the control group were close to zero with a standard deviation of one (*Table 2*). The difference between baseline and follow up performance for the group of patients with no cognitive decline was small (difference mean composite z-score:-0.03), corresponding with a positive RBI score (mean composite RBI±SD: 0.23±0.48). The subgroup of patients with cognitive decline showed a much larger decrease in z-score over time (difference composite z-score:-0.35), which is reflected in a negative RBI score (mean composite RBI:-0.99±0.64).

Table 1. Baseline characteristics of controls and patients with type 2 diabetes mellitus (T2DM), with and without accelerated cognitive decline

	Controls	**T2DM**	
		no decline	decline
N	38	51	17
Age, years	64.8 ± 4.8	65.8 ± 5.4	65.2 ± 6.2
Sex, male	18 (47)	26 (52)	6 (12)
Level of education (1-7)	4 (1-7)	4 (1-7)	4 (1-6)
Estimated premorbid IQ[a]	103 ± 13	98 ± 17	101 ± 15
Beck Depression Inventory > 13	4 (10)	8 (16)	6 (35)
Vascular risk factors			
Body Mass Index	26.7 ± 5.2	28.4 ± 4.1	26.5 ± 3.6
Systolic blood pressure, mmHg	137 ± 20	147 ± 19	145 ± 22
Diastolic blood pressure, mmHg	79 ± 8	80 ± 10	83 ± 12
Total cholesterol, mmol/l	5.9 ± 1.2	5.0 ± 0.9	5.1 ± 0.9
Antihypertensive medication	12 (32)	39 (76)	12 (71)
Lipid-lowering medication	8 (21)	27 (53)	7 (41)
Cardiovascular diseaseb	1 (3)	12 (24)	3 (18)
Cerebral infarct on MRI	6 (16)	13 (26)	3 (18)
Metabolic factors			
Fasting glucose levels, mmol/l	5.5 ± 0.6	8.6 ± 2.4	8.8 ± 3.5
HbA1c, %	5.5 ± 0.3	6.9 ± 0.9	7.0 ± 1.5
Fasting insulin levels, pmol/l	10.0 ± 6.5	20.1 ± 21.3	13.8 ± 9.7
Insulin vs. oral medication/diet		18/33 (35/65)	2/15 (12/88)
Diabetes duration, years		8 (1-36)	7 (1-17)

Data are presented as mean ± SD, median (range) or n (%). None of the baseline characteristics were statistically significant between the T2DM decline and T2DM no-decline group.
a Estimated with the Dutch version of the National Adult Reading Test (NART).

Table 2. Cognitive performance at both time points per cognitive domain in the reference group and patients with type 2 diabetes mellitus (T2DM) with and without accelerated cognitive decline

	z-score baseline	z-score follow-up	RBI
Controls			
Information processing speed	0.20 ± 0.61	0.22 ± 0.65	0.02 ± 1.00
Executive functioning	0.11 ± 0.50	-0.11 ± 0.58	0.13 ± 1.00
Memory	0.14 ± 0.38	0.07 ± 0.44	0.09 ± 1.00
Composite score[a]	0.15 ± 0.36	0.06 ± 0.44	0.08 ± 0.62
T2DM no decline			
Information processing speed	-0.04 ± 0.87	-0.14 ± 0.88	-0.34 ± 1.15
Executive functioning	-0.11 ± 0.68	-0.23 ± 0.60	0.44 ± 1.41
Memory	-0.08 ± 0.54	0.05 ± 0.48	0.58 ± 1.01
Composite score[a]	-0.08 ± 0.58	-0.11 ± 0.54	0.23 ± 0.48
T2DM decline			
Information processing speed	-0.49 ± 1.18	-0.39 ± 0.95	-0.57 ± 1.58
Executive functioning	-0.01 ± 0.63	-0.90 ± 0.82	-1.96 ± 1.58
Memory	-0.08 ± 0.44	-0.30 ± 0.44	-0.39 ± 0.94
Composite score[a]	-0.19 ± 0.53	-0.54 ± 0.47	-0.99 ± 0.64

Standardized z-scores and regression based index (RBI) scores are presented as mean ± SD. A negative RBI score reflects accelerated cognitive decline relative to the control group. a The composite score is obtained by taking the average of the three cognitive domains.

In patients with accelerated cognitive decline, the domains executive functioning and memory were most evidently affected compared with patients without accelerated decline (mean difference RBI score(95%CI) executive functioning: -2.39(-3.21 to -1.58); memory: -0.97(-1.53 to -0.42); both p<0.001; information processing speed: -0.23(-0.95 to 0.50); p=0.53).

Changes in brain volume

At baseline, patients with accelerated cognitive decline had a larger WMH volume (Ln 0.06%(0.004 to 0.12); p=0.04) than patients without accelerated cognitive decline, and also a larger total brain volume (adjusted mean difference±SE: 1.87%(0.45 to 3.30); p=0.01). Ventricular volume did not differ significantly between groups (0.26%(-0.44 to 0.96); p=0.46). *Figure 1* shows the change in brain volume over the 4-year period in both groups. There was a greater increase in ventricular volume (0.23%(0.08 to 0.38); p=0.003) and WMH volume (0.16%(0.05 to 0.27); p=0.006) over time in the group with accelerated cognitive decline compared to the group without accelerated decline. Patients with accelerated cognitive decline also tended to have a greater decrease in total brain volume (-0.39%(-0.81 to 0.04); p=0.07). Secondary analyses with the RBI score as continuous outcome

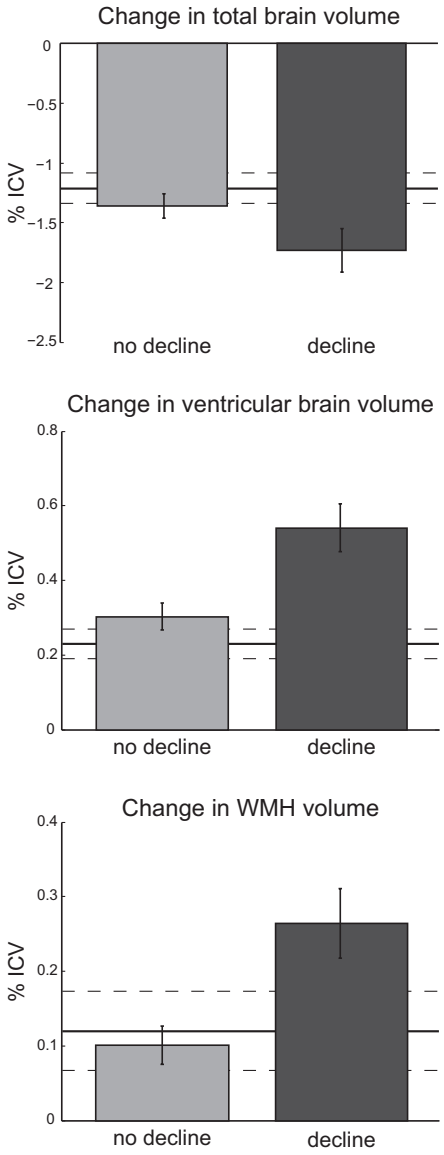

Figure 1. Bar charts of change in total brain, ventricular and white matter hyperintensity (WMH) volume expressed as % of intracranial volume (ICV) for patients with and without accelerated cognitive decline, adjusted for age and sex. The three horizontal lines indicate the mean of the control group (black line) the standard error of the mean (dashed lines). A negative value reflects a loss in volume and a positive value an increase in volume over the 4-year period.

measure showed a clear linear association between RBI and change in brain volume over time (B(95%CI) total brain: 0.28(0.02 to 0.54);p=0.04; ventricular: -1.20(-1.82 to -0.57);p<0.001; WMH:-1.58(-2.45 to -0.72);p=0.001). The relation between accelerated cognitive decline and brain volumes did not change after adjustment for possible depression (data not shown).

Predictors of accelerated cognitive decline

Baseline BMI, systolic blood pressure, total cholesterol and a history of vascular events, were not associated with an increased risk of cognitive decline (*Table 3*). Also, the metabolic factors at baseline: fasting glucose, HbA1c and diabetes duration were unrelated to the risk of cognitive decline. Additional adjustment for baseline medication use or cerebral infarcts observed on MRI at follow

Table 3. Relation between clinical determinants at baseline and the risk of accelerated cognitive decline (Y/N) in patients with type 2 diabetes

	Odds Ratio (95% CI)
Age, years	0.98 (0.88 to 1.08)
Sex, % male	2.03 (0.65 to 6.40)
Estimated IQ[a]	1.01 (0.98 to 1.05)
Body Mass Index	0.86 (0.73 to 1.01)
Systolic blood pressure, 10mmHg	0.96 (0.71 to 1.31)
Diastolic blood pressure, mmHg	0.97 (0.88 to 1.08)
Total cholesterol, mmol/l	1.08 (0.60 to 1.95)
Antihypertensive medication	0.61 (0.17 to 2.21)
Lipid-lowering medication	0.49 (0.15 to 1.61)
Cardiovascular disease[b]	0.75 (0.18 to 3.18)
Cerebral infarct on MRI	0.98 (0.89 to 1.09)
Fasting glucose levels, mmol/l	1.02 (0.83 to 1.24)
HbA1c, %	1.07 (0.65 to 1.77)
Fasting insulin levels, pmol/l	0.97 (0.92 to 1.02)
Insulin/oral medication	0.22 (0.04 to 1.11)
Diabetes duration, years	0.94 (0.84 to 1.05)

Odds Ratio's (OR) and 95% confidence intervals (CI) are given adjusted for age and sex.
An OR greater than one reflects an increased risk of cognitive decline.
a Estimated with Dutch version of the National Adult Reading Test (NART).
b Defined as self reported myocardial infarction or surgical or endovascular treatment of atherosclerotic arterial disease.

up, did not notably change the results. Secondary analyses with the RBI score as a continuous outcome variable yielded results that were largely similar, except that there now was a significant inverse association between the use of antihypertensive medication and accelerated cognitive decline (regression coefficient B(95%)=0.43(0.07 to 0.79); p=0.02).

Discussion

This study shows that patients with type 2 diabetes with accelerated cognitive decline over a 4-year period had a higher rate of ventricular expansion and of WMH progression than patients without accelerated cognitive decline. There were no specific vascular or metabolic risk factors associated with accelerated cognitive decline in the diabetes group.

The longitudinal design of the study allowed us to examine the development of imaging parameters in relation to cognition over time. We have previously reported that in this study population patients with type 2 diabetes showed reduced cognitive performance, had smaller brain volumes and larger WMH volumes than controls.[15,16] We have also observed that, on average, cognitive decline in the whole group of patients with type 2 diabetes was not accelerated relative to controls.[19] In the present study we examined the subgroup of patients with the fastest rate of cognitive decline relative to normal aging. Although the rate of decline was still lower than the rate of decline that is typical for (early) dementia[27], this subgroup consists of individuals who either represent the extremes of normal aging related cognitive decline or the earliest stages of pathological decline. Indeed, this subgroup also had greater progression of cerebral pathology, as reflected in vascular lesions and global atrophy. Cerebral atrophy and in particular ventricular expansion have been consistently linked to the development of dementia in the general population.[28-30] This suggests that the combined effects of vascular damage and degenerative processes contribute to accelerated cognitive decline in patients with type 2 diabetes.

A limited number of studies examined clinical determinants of accelerated cognitive decline in type 2 diabetes longitudinally.[12,13,31,32] Most of these studies, including the present study, have not found a consistent relationship between baseline metabolic or vascular risk factors and subsequent cognitive decline.[12,13,31,32] This is in contrast with observations from cross-sectional studies reporting an association between higher HbA1c levels and worse cognitive functioning.[6,33,34] This discrepancy may be explained by differences in the magnitude of the observed cognitive deficits. Most cross-sectional studies focussed on subtle variation in cognitive performance across populations of people with relatively intact cognition.[6,33,34] Other studies addressed determinants of more severe cognitive deficits, such as dementia.[12,13,31,32] These cognitive stages are fundamentally different, and are also likely to reflect a different underlying pathology. It is therefore important to dissociate between distinct stages of cognitive functioning when investigating determinants of cognitive performance in patients with diabetes.

Possibly, other mechanisms play a role that are additive to, or interact with, brain aging or early stages of a dementia process, such as genetic susceptibility and inflammation. Two large studies have shown that patients with diabetes who carried

the APOE 4 allele had a greater risk of developing dementia than non APOE 4 carriers.[35,36] In addition, inflammatory markers have shown to be associated with cognitive decline and dementia independent of cardiovascular risk factors[37,38], also in patients with type 2 diabetes.[39] Unfortunately, we have no information on these factors in the present cohort.

A second explanation why we did not observe an association between clinical determinants and cognitive decline might be the relative short time window in which these studies examined the relation between risk factors and cognitive functioning. Studies in the general population have shown that vascular risk factors, such as hypertension, are associated with a higher risk of dementia, particularly if the levels of these risk factors are determined in midlife.[40] In older age groups, comparable to our population, the relation between vascular risk factors and cognitive decline is less consistent. The levels of vascular risk factors are not only influenced by age, but may also alter during the years immediately preceding dementia onset.[41,42] Such effects of age on the relation between risk factors and cognition have also been noted in diabetes: cognitive decrements in patients with diabetes may be predicted by high blood pressure up to fifteen years before cognitive assessment.[43] Possibly, the duration of the present study was too short to observe similar effects.

To the best of our knowledge, this study was the first to extensively assess the relation between vascular risk factor profile, cognitive functioning and changes in brain structure in patients with type 2 diabetes at two different time points. This allowed us to explore the vascular and metabolic risk factor profile of those patients which showed subsequent accelerated cognitive decline and corresponding brain changes. A limitation of the present study is the modest sample size, which may have reduced the statistical power for detecting associations between risk factors and accelerated cognitive decline. The number of patients that developed more severe cognitive impairment was also limited and could not be examined as a separate group. Other limitations are possible selection bias at baseline and possible selective attrition during follow up. The telephone cognitive screening questionnaire (TICS-m) did not reveal differences in cognitive performance between participants who did and did not attend follow up. Nevertheless, some participants with marked cognitive decline dropped out of the study, which may have influenced our results. Finally, because the study was specifically designed to study determinants of impaired cognition in type 2 diabetes we included a relatively small reference group. Therefore our study is not suited to examine determinants of accelerated decline in that group.

In conclusion, accelerated cognitive decline in individuals with diabetes is associated with accelerated brain atrophy and WMH progression. We could not identify specific clinical risk factors for accelerated cognitive decline. Possibly,

other mechanisms play a role, that may lead to insidious damage that is additive to, or interact with, brain aging or early stages of a dementia process. Future studies should examine risk factors for cognitive decline over a longer time frame, to identify early factors that contribute to the increased risk of dementia in patients with type 2 diabetes.

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Chapter 5

Development of vascular risk factors over 15 years in relation to cognition: the Hoorn Study

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Submitted

Abstract

Introduction

Vascular risk factors are related to cognitive decline in older individuals, although there are inconsistencies between studies, possibly due to modulating effect of age. We investigated the development of vascular risk factor levels at four time points over the course of 15 years in relation to late-life cognitive functioning.

Methods

380 non-demented individuals from the Hoorn Study (mean age 57.7±5.5 years) underwent extensive four medical examinations over a period of 15 years. Cognition was assessed in detail at the 4th examination. The time course of vascular risk factors was compared between individuals in the highest tertile (good performance) versus lowest tertile (poor performance) of cognitive functioning on three cognitive domains (memory, information processing speed, and attention and executive functioning (A&EF)). Data was analyzed using linear mixed models adjusted for age, sex and estimated IQ.

Results

Individuals with poor compared to good information processing speed had higher levels of systolic blood pressure at baseline (mean difference (SE): 11.6(2.6)mmHg; $p<0.001$). Individuals with poor A&EF had a higher waist-to-hip ratio (0.03(0.01); $p<0.01$), HbA1c (0.29(0.10)%; $p<0.01$) and total cholesterol/HDL ratio (0.38(0.19); $p<0.05$) at baseline than individuals with good A&EF. However, the differences in vascular risk factor levels between the poor and good cognition group diminished with increasing age.

Conclusion

High blood pressure, adiposity, hypercholesterolemia and hyperglycemia at midlife are associated with late-life cognitive dysfunction, but for most risk factors this relation gradually attenuates with increasing age. These results suggest that timing of vascular treatment strategies in order to prevent cognitive impairment is critical.

Introduction

The relation between cardiovascular risk factors and cognitive decline in older individuals is increasingly recognized. Several longitudinal population-based studies have shown that midlife obesity and midlife hypertension are associated with an increased risk of dementia later in life.[1,2] In contrast, studies on these risk factors in older populations did not observe these associations or even found reverse associations with cognitive dysfunction[3,4], for review.[5] This may be explained by the complex interplay between age, duration of exposure, selective survival and changes in risk factor levels over time. Risk factors such as blood pressure and bodyweight tend to rise in middle-age, but decrease in very old-age.[6,7] In addition, the levels of vascular risk factors may change during the dementia process, well before dementia becomes clinically manifest.[8-10] In order to further unravel the relation between vascular risk factors, age and cognition, longitudinal studies which assess vascular risk factors over multiple time points between midlife and late life are necessary.

Obesity, hypertension, hypercholesterolemia and impaired glucose metabolism are well known risk factors for dementia, while less is known about the association with milder decrements in late life cognitive functioning.[11] More insight in risk factors for these milder cognitive decrements is needed, as treatment to prevent impaired cognitive functioning may be most effective in early stages. In this study, we investigated vascular risk factor levels at four time points over the course of 15 years in relation to cognition in non-demented older individuals. Cognitive functioning was assessed in detail, addressing cognitive domains particularly sensitive to cognitive decline in the context of cardiovascular disease.

Methods

Study population

The Hoorn study is a population-based study on glucose metabolism and cardiovascular risk in the general population. The population and study design have been described earlier.[12] The study started in 1989 and included 2,484 randomly selected Caucasian participants aged 50-75 years from the middle-sized Dutch town of Hoorn (T1) (*Figure 1*). In 1996-1998 (T2), all surviving participants (n=2086) were invited for a second examination, to which 1513 agreed.[13] In the 2000-2001 follow up examination (T3), 1074 individuals of the Hoorn Study cohort, including all those who were diagnosed as having type 2 diabetes in the year 1996 (n=176), and random samples of individuals with normal (n=705) and impaired (n=193) glucose metabolism, were invited, of whom 647 (60%) participated.[14] The fourth examination took place in 2005-2008 (T4). After excluding persons who had died (n=86) or could not be contacted (n=35) the

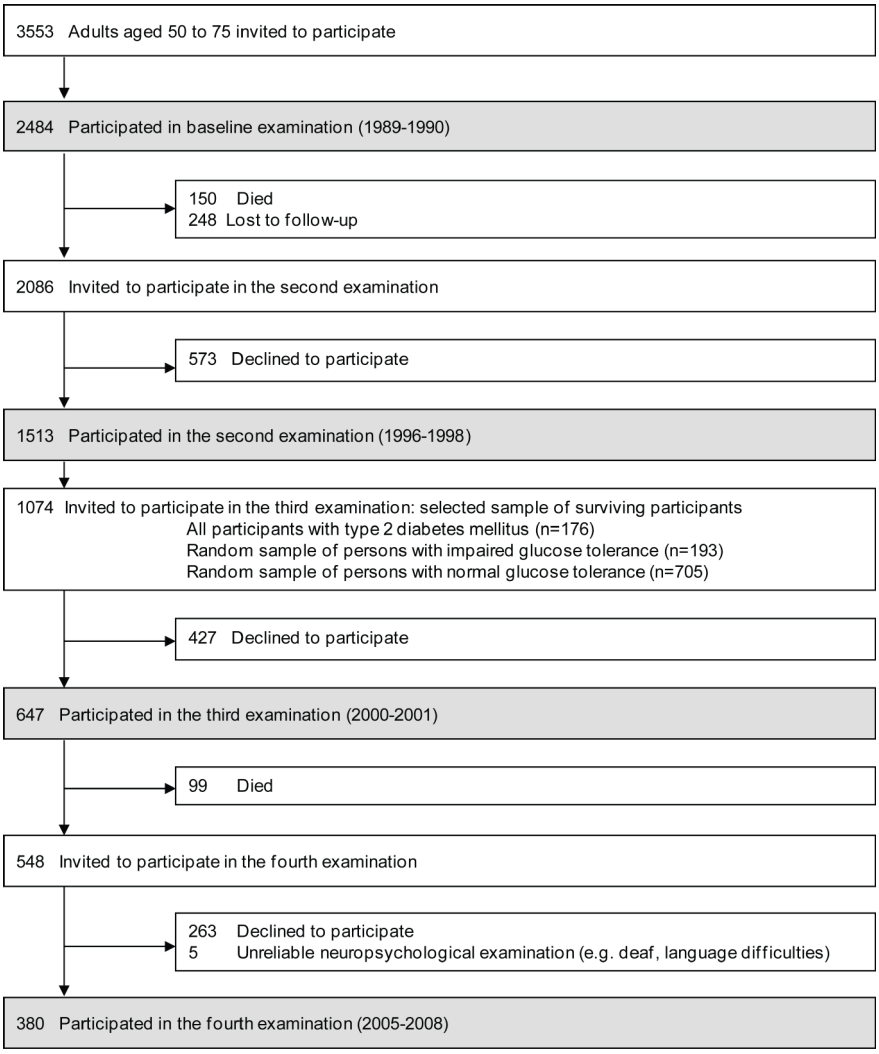

Figure 1. Hoorn study population at baseline and follow-up examinations

remaining 526 participants were invited, of which 385 (73%) agreed to participate. Reasons for not participating were lack of interest (43%), physical comorbidity (23%), high age (16%), dementia (6%), or miscellaneous reasons (12%). All 385 participants were living independently at home and none had known dementia (self-report). Cognitive functioning was first assessed in the fourth examination. For the present study we excluded participants with an unreliable assessment of cognitive functioning (e.g. deafness, language difficulties n=5). The mean follow-up time from baseline was 15.3±1.2 years.

The Hoorn study was approved by the medical ethics committee of the VU University Medical Center. All participants gave their written informed consent according to the Declaration of Helsinki.

Clinical assessment

A standardized clinical assessment was performed at all four examinations. Weight (kg) and height (cm) were measured in participants wearing light clothes. Waist-to-hip ratio was defined as waist circumference (cm), divided by hip circumference (cm). Blood pressure (mm Hg) was measured in the right arm while participants were sitting. Systolic and diastolic blood pressure was calculated as the mean of duplicate measurements. Glycated haemoglobin level (HbA1c, %), fasting glucose concentration, triglycerides, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were determined from fasting blood samples. In addition, 2-h postload glucose concentration after a 75-g oral glucose tolerance test were obtained. In participants already known with diabetes, only a fasting blood sample was taken. Diabetes was defined according to WHO criteria.[15] All blood samples were analyzed at the clinical chemistry laboratory of the VU University Medical Center.

Self-reported information on the participants' current use of medications, medical history, and smoking status was obtained by a standardized questionnaire. A history of cardiovascular disease was defined as self-reported intermittent claudication, angina pectoris or possible myocardial infarction, assessed with the Rose questionnaire[16] or a history of stroke or transient ischemic attack.

Cognitive assessment

At the last examination, all participants underwent a standardized neuropsychological examination including twelve verbal and non-verbal tasks, administered in a fixed order. The tasks were divided into six cognitive domains. For the present study we focused on the cognitive domains that are previously shown to be particularly affected in individuals with vascular risk factors, namely the domains memory, information processing speed and attention and executive functioning.[11] The domain memory included test for four subdomains: working

memory assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Corsi Block-Tapping Task; immediate memory and learning rate, including verbal memory assessed by the Rey Auditory Verbal Learning Test and visual memory assessed by the Location Learning Test; forgetting rate assessed by the delayed recall of the Rey Auditory Verbal Learning Test and of the Location Learning Test; and incidental memory assessed by the delayed trial of the modified Taylor Complex Figure. The domain information processing speed (IPS) was assessed by the Trail Making Test Part A, the Stroop Color-Word Test (Parts I and II), and the subtest Digit Symbol of the WAIS-III. The domain attention and executive function (A&EF) was assessed by the Trail Making Test Part B, the Stroop Color-Word Test (Part III), the Brixton Spatial Anticipation Test, a letter fluency test using the 'N' and 'A', and category fluency using animal names.

Raw test scores were standardized into z-scores. Test scores were averaged per domain to obtain domain scores. Because we wanted to identify people whose performance was lower than expected from their age, estimated IQ and gender, z- scores were adjusted on an individual basis for age, sex and estimated IQ based on the regression coefficients derived from the whole study population: Individual (ind) cognitive z-score = mean cognitive z-score + $(B_{age} \times (ind_{age} - mean_{age}) + B_{sex} \times (ind_{sex} - mean_{sex}) + B_{IQ} \times (ind_{IQ} - mean_{IQ})$.

Depressive symptoms were assessed with the validated Dutch version of the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D).[17] The total score (range 0-60) and the proportion of persons scoring ≥16 (indicating potentially clinically relevant depressive symptoms) were recorded.

Statistical analyses

Between-group differences in population characteristics were analyzed with an independent T-test for continuous variables and chi-square test for proportions.

For the primary analyses the study population was divided in tertiles, based on the individually age, sex and estimated IQ adjusted cognitive z-scores, representing groups with relatively 'poor' (lowest tertile), 'average' (middle tertile), and 'good' (highest tertile) performance. This was done for each individual domain. Linear mixed models were used to compare the time course of vascular risk factors over the four examinations in participants with relatively poor and good cognitive functioning in one model, consequently, the risk factors were entered as dependent variables and group (good vs. poor cognition) was entered as independent variable. To increase between-group contrast, the middle tertile was not considered in these primary analyses. The strength of linear mixed models is that it uses all available data during follow-up, it accounts for correlations between repeated measurements and allows for the use of time-dependent and time-independent

covariates [18]. A limitation of the model is that it does not allow for dichotomous variables to be entered as dependent variables (e.g. hypertension). The model estimates effects of Group, Time and Time*Group interactions. The estimate for 'Group' reflects the difference in vascular risk factors at baseline. The estimate for 'Time' reflects the average change in vascular risk factors per time interval. The 'Group x Time interaction' reflects the additional increase or decrease in vascular risk factors for participants with relatively poor and good cognitive performance. Age, sex, and in subsequent models, depression score and a history of cardiovascular disease were entered as covariates. Because patients with type 2 diabetes were oversampled during the 2000-2001 measurement[14], the analyses were repeated stratified for the presence of diabetes at T4.

For several risk factors, multiple markers were collected, e.g. waist-to-hip ratio, waist circumference and body mass index for obesity. To reduce the number of analyses only one marker for each of the following risk factors was selected for the primary analyses, based on previous literature: i.e. systolic blood pressure for hypertension[6], waist-to-hip ratio for obesity[19] total cholesterol/HDL ratio for hypercholesterolemia[20], and HbA1c for hyperglycemia.[21]

If levels for these markers were significantly different between individuals with poor and good cognitive functioning, further analyses for other markers of the risk factor concerned were performed to examine if the effects were consistent across markers. Medication use was entered as a covariate in these secondary analyses.

Results

Table 1 shows the baseline characteristics of those who did and did not participate at the fourth examination, when cognition was assessed. Those participating at T4 were relatively younger at baseline (57.7±5.5 vs. 62.4±7.4 years; $p<0.001$) and more likely to be female (55% vs. 49%; $\chi^2=0.4$) than non-participants. After adjustment for age, participants at T4 did not differ significantly from non-participants in their vascular risk factor profile at baseline. At the moment of cognitive testing, participants were on average 73.0±5.8 years old and functionally independent. Raw cognitive test scores of participants with poor and good cognitive functioning are presented in *Table 2*.

The mean between-group difference in cognitive functioning on each cognitive domain was on average 1.5 standard deviation units (*Table 3*).

Table 4 and *Figure 2* show the levels of vascular risk factors across the four examinations for participants with 'poor cognition' (lowest tertile) and 'good cognition' (highest tertile) for each cognitive domain.

An overall effect of time was observed for all risk factors ($p<0.01$). Most risk

Table 1. Baseline characteristics of participants and non-participants

	Participants at T4 N=380	Non-participants N=2104
Age, years	57.7± 5.5	62.5 ± 7.4
Sex (% male)	194 (51%)	946 (45%)
Estimated IQ[a]	97.9 ± 13.1	
Systolic blood pressure (mmHg)	130.2 ± 16.8	136.3 ± 20.5
Diastolic blood pressure (mmHg)	81.7 ± 9.8	82.2 ± 10.5
Antihyperintensive medication	40 (10.5%)	460 (22%)
BMI (kg/m2)	26.2 ± 2.9	26.6 ± 3.7
Waist-to-hip ratio	0.9 ± 0.1	0.9 ± 0.1
Total cholesterol (mmol/l)	6.6 ± 1.2	6.8 ± 1.2
HDL (mmol/l)	1.3 ± 0.4	1.3 ± 0.4
LDL (mmol/l)	4.5 ± 1.1	4.6 ± 1.1
Triglycerides (mmol/l)	1.6 ± 1.2	1.6 ± 1.0
Lipid lowering medication	7 (1.8%)	27 (1.3%)
HbA1c (%)	5.4 ± 0.8	5.5 ± 0.9
Fasting glucose (mmol/l)	5.7 ± 1.4	5.8 ± 1.6
Diabetes	31 (8.2%)	224 (10.6%)
History of cardiovascular disease	30 (7.9%)	265 (12.6%)
Current smoking	93 (24.5%)	680 (32%)

Data are presented as mean ± SD or n(%). [a]Assessed at T4 (2005-2008).

factors increased over time, except for total cholesterol/HDL ratio, which significantly decreased over time.

Systolic blood pressure was higher at baseline for participants with poor compared to good IPS (estimated mean difference (SE): 11.6(2.6); p<0.001). A Time x Group interaction effect was observed on the domains IPS (-3.1(0.8); p<0.001) and memory (-2.4(0.8); p<0.01), indicating less increase in systolic blood pressure over time in the poor cognition group.

Waist-to-hip ratio was significantly higher at baseline for participants with poor compared to good A&EF (3.03(1.15); p<0.01), but this group showed less increase in waist-to-hip over time (Group x Time: -0.44(0.22); p<0.05).

Total cholesterol /HDL ratio was higher at baseline for participants with poor compared to good A&EF (0.38 (0.19); p<0.05). A trend was observed for the Group x Time interaction effect (-0.10 (0.05); p=0.06), showing a slightly faster decrease in cholesterol/HDL ratio over time in the poor cognition group, resulting in comparable values at the follow up measurements.

Table 2. Raw cognitive test scores for individuals in the lowest and highest tertile of cognitive functioning[a]

	Range of scores	**Poor cognition** (lowest tertile)	**Good cognition** (highest tertile)
Information processing speed			
Trail Making Test part A (sec)†	20-161	65.5±25.3	38.0±9.4
Stroop Color Word Test I (sec)†	32-133	54.0±12.7	44.0±6.1
Stroop Color Word Test II (sec)†	39-137	73.2±17.0	56.7±8.0
Symbol substitution test	18-94	42.0±11.4	62.2±12.7
Attention and Executive functioning			
Trail Making Test part B (sec)†	41-407	161.1±81.7	101.6±45.2
Stroop Color Word Test III (sec)†	50-467	158.2±71.2	107.6±26.4
Brixton Spatial Anticipation test (errors)†	7-47	26.3±7.3	17.1±5.3
Letter fluency (mean N+A)	2-24	8.5±3.5	13.1±3.8
Category fluency (No. of animals)	8-63	27.4±8.0	35.1±8.1
Memory			
Working memory			
WAIS-II Digit Span forward (productscore)	12-126	40.5±17.1	50.1±21.2
WAIS-II Digit Span backward (productscore)	4-104	20.9±12.7	28.9±18.0
Corsi Block-Tapping Test forward (productscore)	9-96	34.7±10.4	42.2±13.9
Corsi Block-Tapping Test backward (productscore)	2-88	28.9±14.9	41.2±15.5
Immediate memory and learning rate			
RALVT total trials 1-5 (words)	5-61	33.2±9.7	38.8±10.3
LLT total trials 1-5 (errors)†	0-163	45.5±27.8	20.5±19.7
Forgetting rate			
RAVLT delay (words)	0-15	5.4±2.8	8.4±3.1
LLT delay (errors)†	0-33	7.2±6.9	1.4±2.9
RAVLT recognition (words)	0-30	26.9±3.0	28.4±3.1
Incidental memory			
Rey Complex Figure Test delay (points)	0-30	10.8±5.1	18.8±5.7

[a]The division in tertiles is made for each cognitive domain separately, after correcting individual scores for age, sex and estimated IQ. † Higher scores indicate worse performance.
RAVLT: Rey Auditory Verbal Learning Test; LLT: Location Learning Test.

Table 3. Mean standardised z-scores per cognitive domain for participants with 'poor' and 'good' cognitive functioning.

	Poor cognition (lowest tertile)	**Good cognition** (highest tertile)
Information processing speed	-0.78 ± 1.04	0.75 ± 0.60
Attention and Executive functioning	-0.85 ± 1.08	0.74 ± 0.51
Memory	-0.89 ± 0.68	0.99 ± 0.68

Data are presented as mean ± SD. Group division (highest vs. lowest tertile) is made after correcting individual scores for age, sex and estimated IQ.

Table 4. Vascular risk factors over time (1989-2008), for participants with 'poor' versus 'good' cognitive functioning for each cognitive domain

	Baseline group difference	**Change over time** (per 5 years)	**Group x Time interaction**
Information processing speed§			
Systolic blood pressure (mmHg)	11.60 (2.63)***	6.34 (0.54)***	-3.10 (0.76)***
Waist-to-hip ratio (x100)	0.35 (0.90)	1.52 (0.14)***	0.12 (0.20)
Cholesterol/HDL ratio	0.12 (0.19)	-0.50 (0.04)***	-0.08 (0.05)
HbA1c (%)	0.008 (0.10)	0.07 (0.02)***	0.04 (0.03)
Attention and Executive functioning§			
Systolic blood pressure (mmHg)	2.98 (2.65)	4.94 (0.53)***	-0.09 (0.76)
Waist-to-hip ratio (x100)	3.03 (1.15)**	2.00 (0.15)***	-0.44 (0.22)*
Cholesterol/HDL ratio	0.38 (0.19)*	-0.50 (0.04)***	-0.10 (0.05)†
HbA1c (%)	0.29 (0.10)**	0.08 (0.02)***	-0.008 (0.03)
Memory§			
Systolic blood pressure (mmHg)	5.04 (2.77)†	6.26 (0.56)***	-2.44 (0.79)**
Waist-to-hip ratio (x100)	-1.02 (0.90)	1.63 (0.15)***	0.13 (0.21)
Cholesterol/HDL ratio	0.03 (0.18)	-0.49 (0.03)**	-0.02 (0.05)
HbA1c (%)	-0.08 (0.09)	0.08 (0.02)***	0.02 (0.02)

Data are adjusted estimated form linear mixed models presented as estimate (± SE)
§ For each cognitive domain, vascular risk factor levels in the highest tertile of cognitive functioning ('good cognition') are compared to the lowest tertile ('poor cognition'). Group division (highest vs. lowest tertile) is made after correcting individual scores for age, sex and estimated IQ; the highest tertile ('good' cognition) is used as reference; † p<0.07 * p<0.05; **p<0.01; ***p<0.001.

HbA1c levels were higher at baseline for participants with poor compared to good A&EF (0.29(p<0.01); p<0.01), but no Group x Time interaction effect was observed, indicating that the group difference in HbA1c levels was relatively stable over time.

Additional adjustment for depression or exclusion of subjects with self-reported stroke (n=27), as well as stratification for diabetes did not modify the results.

Confounding and mediating factors

Secondary analyses were performed on the risk factors that were significantly related to cognitive performance in the primary analyses, as shown in *Table 4*.

Blood pressure: The relation between systolic blood pressure and cognitive performance on the domains IPS and memory did not notably change after adjustment of the use of anti-hypertensive medication, or after adjustment for the other three vascular risk factors (i.e. waist-to-hip ratio, cholesterol/HDL ratio and HbA1c) (data not shown). For diastolic blood pressure and pulse pressure the relation with IPS and memory was similar to that of systolic blood pressure (diastolic blood pressure: IPS: Group: 4.60(1.50)$p<0.01$; Group x Time: -1.27(0.44); $p<0.01$; Memory: Group x Time: -0.95(0.45); $p<0.05$); pulse pressure: IPS: Group: 6.79(2.17); $p<0.01$; Group x Time: -1.82(0.67); $p<0.01$; Memory: Group x Time: -1.57(0.69); $p<0.05$) .

Obesity: The relation between waist-to-hip ratio and performance on the domain A&EF was only slightly attenuated after adjustment for the other three vascular risk factors (i.e. systolic blood pressure, cholesterol/HDL ratio and HbA1c) (Group: 2.45(0.93); $p<0.01$; Time x Group: -0.40(0.22); $p=0.07$). Other measures of body weight were not significantly related to A&EF: body mass index (Group: 0.74(0.45); $p=0.10$; Time x Group: -0.04(0.08); $p=0.65$); waist circumference (Group: 2.32(1.37); $p=0.09$; Time x Group: -0.18(0.26); $p=0.49$).

Hypercholesterolemia: The relation between the total cholesterol/HDL ratio and performance on the domain A&EF became stronger after adjustment for lipid lowering medication (Group: 0.50(0.19); $p<0.01$; Group x Time: -0.13(0.05); $p<0.01$). The Group effect at baseline was attenuated after adjustment for the other three vascular risk factors (i.e. systolic blood pressure, waist-to-hip ratio, HbA1c) (Group: 0.28(0.19); $p=0.13$), but the Group x Time interaction effect remained statistically significant (-0.10(0.05); $p<0.05$). HDL levels were also significantly lower at baseline in individuals with poor A&EF (Group: -0.11(0.05); $p<0.05$), but no Group x Time interaction effect was observed. No relation was found between total cholesterol, LDL or triglyceride levels and performance on A&EF (data not shown).

Hyperglycemia: The relation between HbA1c levels and performance on the domain A&EF did not notably change after adjustment of the use of glucose lowering medication (data not shown). The relation was slightly attenuated after adjustment for the other three vascular risk factors (i.e. systolic blood pressure, waist-to-hip ratio, cholesterol/HDL ratio), but remained statistically significant (Group: 0.23(0.10); $p<0.05$). The same relation with performance on A&EF was found for fasting glucose levels (Group: 0.50(0.17); $p<0.01$), but not for post load glucose levels (0.62(0.41); $p=0.13$).

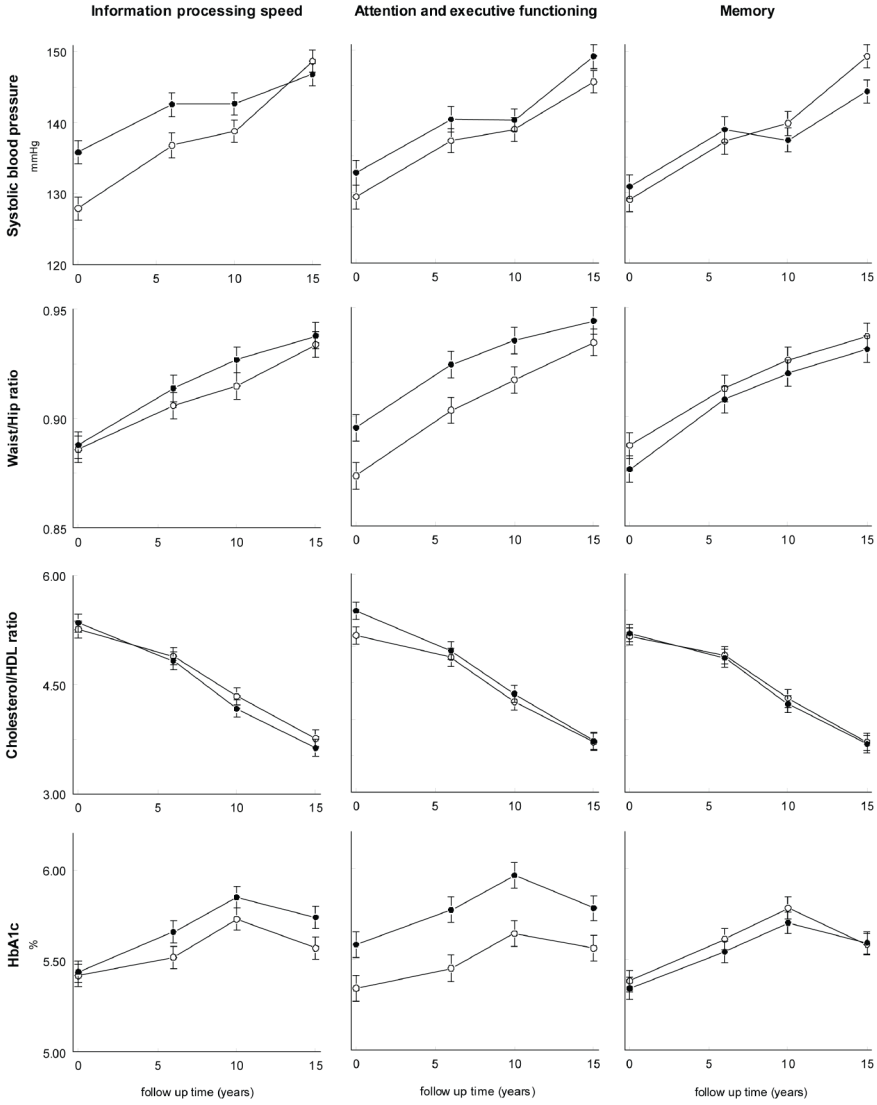

Figure 2. Time course of vascular risk factors across the four examinations in relation to late life cognitive functioning. Participants with 'poor' cognitive functioning at the final examination are represented by the closed circles and participants with 'good' cognitive functioning by the open circles. The figure shows the time course for each risk factor (rows) for each cognitive domain (column). Data are estimated means (±SE) by adjusted linear mixed models.

Discussion

In this population of non-demented individuals, the 15-year time-course of systolic blood pressure, waist-to-hip ratio, cholesterol/HDL ratio, and HbA1c levels was different for people with relatively good and poor cognitive performance. Moreover, a clear interaction with age was observed for systolic blood pressure and waist-to-hip ratio.

The present study addressed the variance in cognitive functioning in independently living older individuals. Although none of the participants had known dementia, there was a wide range in cognitive performance across the whole study population (*Table 2*). By contrasting the lowest versus the highest tertile, we compared individuals with good cognitive performance to a group that included individuals with mild to severe cognitive deficits. Including these mild stages of cognitive dysfunction as outcome measure when examining risk factors is relevant, because treatment benefits are expected to be largest when the underlying brain damage is still relatively modest. Moreover, also in individuals who do not progress to dementia, cognitive dysfunction can lead to complaints and functional consequences.[22,23]

Systolic blood pressure levels were higher at midlife for individuals with poor IPS, but became comparable to the good performance group with increasing age. This pattern was also observed for diastolic blood pressure and pulse pressure. These results extend earlier findings demonstrating a positive association between blood pressure and IPS at midlife[24-26], but not at late-life.[25,27] At the last assessment, the relation between blood pressure and cognitive performance was even reversed for the domain memory. This reverse association has previously been reported in older age groups and may be linked to processes in the years preceding the development of dementia.[3,9,10,28] The relation between systolic blood pressure and cognitive performance remained evident after adjustment of antihypertensive treatment. It should be noted, however, that the analysis strategy used in the present study does not permit to assess the effects of hypertensive treatment as such.

A similar age dependent association was observed for WHR. The relation between high midlife WHR and poor cognitive functioning was attenuated with increasing age. Only few previous longitudinal studies have examined the effects of adiposity on cognitive functioning in non-demented populations.[29-31] Two of these studies confirm the association between higher body mass index during middle age and worse cognitive functioning 5 to 8 years later, but provided no information on this association during late life.[29,30] One study showed that both weight gain and weight loss was associated with a higher risk of poor cognitive functioning, and that weight loss was more common in individuals >75 years.[31] In the present study, WHR, but not body mass index was related to cognitive functioning. Similar

results were observed in a large population based study in Sweden, which also identified midlife WHR, as the best predictor of late life dementia, among other measures of adiposity.[19] This may be explained by the finding that in particular abdominal adiposity plays an important role in the development of cardiovascular disease.[32]

Poor cognitive performance was also associated with a higher total cholesterol/HDL ratio at baseline, especially after adjustment for lipid lowering medication. The relation between total cholesterol/HDL ratio and cognitive dysfunction was modulated after adjustment for other vascular risk factors. The increase in total cholesterol/HDL ratio was explained by a reduction in HDL cholesterol rather than an increase in total cholesterol in the poor cognition group. Observational studies have demonstrated an association between the use of statins and a reduced risk of late-life cognitive decline[33,34], but this has not yet been confirmed in randomized controlled trials.

The relation between measures of hyperglycemia and cognitive performance did not change with increasing age: higher levels of HbA1c and fasting glucose were associated with worse cognitive functioning across all measurements. This is in line with cross-sectional studies showing an association between hyperglycemia and worse cognitive performance or dementia, across different age groups.[35,36] Apparently, glucose dysmetabolism is still a predictor of cognitive dysfunction, also in older individuals.

Vascular risk factors frequently co-occur. Nevertheless, the observed relation between individual risk factors and cognitive performance in the present study was largely independent of each other. Moreover, the cognitive domains involved varied across risk factors. This may imply that different vascular risk factors affect the brain, at least in part, through different mechanisms. Hyperglycemia, for example, may not only cause vascular damage, but could also have direct toxic effects on neurons.[37] Moreover, hyperglycemia is a marker of insulin resistance and abnormal insulin homeostasis may in itself adversely affect the brain.[38] Along these lines, the relation of hypertension to cognitive dysfunction could also involve disturbances of the brain renin-angiotensin system[39] and adiposity could lead to altered secretion of hormones from adipose tissue which in turn can influence synaptic activity and plasticity.[40]

Due to the long follow-up period and the intensive character of the study, substantial attrition of this elderly population has occurred. Although this is inevitable in an intensive longitudinal study in older individuals, this may have led to a relatively homogeneous sample and underestimation of the effect. Indeed, previous reports on the Hoorn study population have shown that cardiovascular mortality was associated with an unfavorable risk factor profile at baseline [41,42]. Moreover, individuals with severe cognitive impairment, such as dementia, were less likely to participate. Despite these limitations, we still observe an association

between vascular risk factors and cognition, indicating that also mild variations in vascular risk factor levels are related to worse cognitive functioning. The division in good versus poor cognitive performance was based on the variance in the whole study population and not on clinically defined cut-off points. This allowed us to examine relatively mild decrements in cognitive function. Finally, cognition was only assessed once. Therefore we were not able to determine which individuals showed cognitive decline.

Strengths of this study are the detailed recording of vascular and metabolic determinants at multiple time points over a long follow-up period in a well-defined population-based cohort, as well as the comprehensive assessment of cognitive functioning including cognitive domains sensitive to cognitive decline in the context of cardiovascular disease. This allowed us to map the time course of vascular risk factors between midlife and late-life in relation to more subtle cognitive deficits.

In conclusion, high blood pressure, adiposity, hypercholesterolemia and hyperglycemia at middle age are associated with late-life cognitive dysfunction, also in non-demented individuals. However, with exception for measures of hyperglycemia, this relation gradually attenuates with increasing age. Future studies should examine if a certain time windows exist in which treatment of these risk factors may protect the brain. Better understanding of the complex relation between risk factors, age, duration of exposure, and brain function will help to optimize such prevention and treatment regimes.

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Chapter 6

Dementia risk score predicts cognitive impairment after a period of 15 years in a non-demented population

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Abstract

Background

Cardiovascular risk factors play an important role in the development of cognitive impairment and dementia. We examined whether a dementia risk score based on midlife vascular risk profiles also predicts cognitive impairment 15 years later.

Methods

322 individuals without dementia from the population-based Hoorn study (aged 50-64 years) underwent a medical examination at baseline and a detailed cognitive assessment 15 years later. The relation between the risk score and late-life cognitive impairment in each of six domains was analysed with logistic regression analysis.

Results

The risk score was significantly related to impairment on the domains information processing speed (odds ratio with 95% confidence interval for each point increase on the score: 1.22(1.01-1.46); p=0.04), visuoconstruction (1.32(1.02-1.71); p=0.04) and abstract reasoning (1.40(1.06-1.84); p=0.02). A trend was observed for the domain attention and executive functioning (1.17(0.99-1.538); p=0.07). Participants with a risk score of 9 points or more had a three- to fourfold increased risk of late-life impairment on the domain information-processing speed (3.07(1.37-6.90); p=0.007) and abstract reasoning (3.97(1.07-14.71); p=0.04). The strength of the associations remained when only modifiable risk factors were included in the risk score.

Conclusion

A previously designed risk score for dementia also predicts late-life cognitive impairment. Because such impairment can lead to complaints and functional consequences, also in individuals who do not progress to dementia, identification of individuals at risk is important and can help to target preventive strategies.

Introduction

Cardiovascular risk factors play an important role in the development of cognitive impairment and dementia.[1,2] Several longitudinal studies have linked the presence of hypertension, obesity and hypercholesterolemia at midlife to the development of late-life dementia.[3] The clustering of these risk factors may increase the risk of dementia in an additive or synergistic manner.[4] In relation to these observations, Kivipelto and colleagues developed a risk score to predict the development of late-life dementia based on the vascular risk factor profile present in middle age.[5] Such risk scores can be used to identify people who might benefit from early prevention strategies. The present study examined whether this risk score also predicts cognitive impairment that does not meet the criteria of dementia. Cognitive impairment, across one or more cognitive domains, can precede the development of dementia by several years.[6] Although not as severe as encountered in patients with frank dementia, these cognitive impairments may lead to complaints and functional consequences, also in individuals who do not progress to dementia.[7,8] In the present study we applied the dementia risk score developed by Kivipelto to predict cognitive impairment 15 years later on several cognitive domains, in a well-defined non-demented population.

Methods

Participants took part in the Hoorn Study, a population-based study on glucose metabolism in the general population. The study started in 1989 and included 2,484 participants aged 50-75 years at baseline. Follow-up examinations of this cohort were performed in 1996-1998 (n=1,513), 2000-2001 (n=647), and 2005-2008 (n=385). Details on the design of the baseline study[9] and follow-up examinations[10,11] have been described elsewhere. Those participating at the last follow up examination were relatively younger at baseline (57.7±5.5 vs. 62.4±7.4 years; $p<0.001$) and more likely to be female (55% vs. 49%; $\pm 2=0.4$) than non-participants. After adjustment for age, participants did not differ significantly from non-participants in their vascular risk factors profile at baseline. Cognitive functioning was assessed for the first time during the 2005-2008 examination. None of the participants had cognitive disturbances interfering with functional independence at the moment of cognitive testing. For the present study we also excluded participants of 65 years or older at baseline (n=58) and with an unreliable assessment of cognitive functioning (e.g. deaf, impaired vision n=5), leaving 322 participants for the present analyses. The Hoorn study was approved by the medical ethics committee of the VU University Medical Center.

Measurements

Measures of weight (kg), height (cm), blood pressure (mmHg), and cholesterol (mmol/l), were obtained at each examination. Systolic and diastolic blood pressure was measured in the right arm with a random-zero sphygmomanometer while participants were sitting and calculated as the mean of duplicate measurements. Total cholesterol was determined from fasting blood samples by enzymatic techniques (Boehrinher-Mannheim, Mannheim, Germany). All blood samples were analyzed at the clinical chemistry laboratory of the VU University Medical Center. Self-reported information on the participants' current use of medications, medical history, smoking status, physical activities and history of cardiovascular disease was obtained by a standardized questionnaire.

We used a detailed neuropsychological test battery consisting of 12 verbal and non-verbal tasks (providing 13 measures in total). The domain memory included three measures, one for each of the following subdomains: 'working memory' (composed of the mean z-scores for forward and backward digit span of the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Corsi Block-Tapping task); 'immediate memory' (Rey Auditory Verbal Learning test and the Location Learning test) and 'delayed memory' (delayed recall of the previous two tasks and the Rey-Osterrieth Complex Figure task). The domain 'attention and executive functioning' included 4 measures, one for each of the following tasks: the Trail Making test B, the Stroop Color-Word test part III, the Brixton spatial Anticipation test and the Verbal Fluency test. The domain 'information processing speed' included 3 measures, one for each of the following tasks: the Trail Making test A, the Stroop Color-Word test part I and II, and the Digit Symbol test of the WAIS-III. The following cognitive domains included 1 measure: 'visuoconstuction' (the copy trial of the Rey-Osterrieth Complex Figure); 'language' (the short form of the Token Test) and the domain 'abstract reasoning' (Raven Progressive Matrices). Pre-morbid IQ was estimated with the Dutch version of the National Adult Reading test.[12] Detailed information on the test protocol has been published previously.[11]

Analyses

Risk scores for each individual were calculated based on the baseline measurements obtained in 1989. According to the model developed by Kivipelto et al.[5], the following scores were assigned to levels of each midlife risk factor: Age: <47y=0; 47-53y=3;.>53y=4; Education: ≥10y=0; 7-9y=2; 0-6y=3; Sex: woman=0; men=1; Systolic blood pressure: ≤140mmHg=0; >140mmHg=2; body mass index: ≤30kg/m^2=0; >30kg/m^2=2; Total cholesterol: ≤6.5mmol/l=0; >6.5mmol/l=2; Leisure time physical activity (in this study defined as regular sport activity): yes=0; no=1. The dementia risk score was the sum of these individual scores.

Cognitive test-scores were standardized into z-scores. Impairment on a particular cognitive domain was defined as a z-score of ±1.5 on at least one measure included in that domain.[6] Because we wanted to identify people whose performance was lower than expected from their age, estimated IQ and gender, z-scores were adjusted on an individual basis for age, sex and estimated IQ based on the regression coefficients derived from the whole study population: Individual (ind) z-score = mean z-score + (B_{age}×(ind_{age} - $mean_{age}$) + B_{sex}×(ind_{sex} - $mean_{sex}$) + B_{IQ}×(ind_{IQ} - $mean_{IQ}$). To examine whether the risk score predicted impairment on specific cognitive domains, we analyzed the relation between the risk score and each cognitive domain separately, with logistic regression analysis. Second, odds ratios for cognitive impairment were calculated for participants with a score above the proposed cut-off value of 9 points or more.[5] For each significant association a Receiver Operation Curve-analysis was performed. Since the aim of this study was to examine the predictive value of the earlier established dementia risk score, we did not adjust for other potential confounders. To determine the contribution of modifiable risk factors to the predictive value of the risk score, we re-analysed the data after excluding non-modifiable risk factors from the risk score (i.e. age, sex and education).

Results

Table 1 shows the characteristics of the study population at baseline and at the follow-up measurement. Most risk factor levels increased over time, except for total cholesterol levels, which decreased over the years. In our population no individuals below 47 years were present, therefore, the minimum risk score was 3. The maximum score was 14 points. Risk scores were normally distributed across the study population, with a median score of 8. All individuals who met the criteria for cognitive impairment were functionally independent and did not meet diagnostic criteria for dementia.[13] Cognitive domains which were addressed by multiple measures contained a higher proportion of individuals with cognitive impairment, indicating more sensitive testing of performance on those domains (*Table 2*).

Table 1. Population characteristics (n=322)

	Midlife examination (1989)	Late-life examination (2005-2008)
Age, years	55.9 ± 3.7	71.2 ± 4.1
Sex (male)	164 (51%)	
Years of education	7.9 ± 2.0	
Estimated IQ		97.8 ± 13.2
Systolic blood pressure (mmHg)	128.9 ± 16.2	146.3 ± 19.6
BMI (kg/m^2)	26.1 ± 3.0	27.3 ± 3.8
Total cholesterol (mmol/l)	6.6 ± 1.2	5.4 ± 1.1
Sports	142 (44%)	164 (51%)
History of cardiovascular disease	22 (6.8%)	68 (23%)

Data are presented as mean ± SD or n(%).

Table 2. Odds Ratio of cognitive impairment

Cognitive domain	Cognitive impairment[a] N (%)	OR per point increase in RF sumscore	p-value	OR RF sumscore ≥ 9	p-value
Information processing speed	31 (9,6)	1.22 (1.01 to 1.46)	0.04	3.07 (1.37 to 6.90)	0.007
Attention and Executive functioning	38 (11,8)	1.17 (0.99 to 1.38)	0.07	1.30 (0.66 to 2.56)	0.45
Visuoconstruction	15 (4,7)	1.32 (1.02 to 1.71)	0.04	1.74 (0.61 to 5.02)	0.30
Abstract reasoning	13 (4,0)	1.40 (1.06 to 1.84)	0.02	3.97 (1.07 to 14.71)	0.04
Language	13 (4,0)	1.08 (0.82 to 1.42)	0.58	1.33 (0.44 to 4.07)	0.61
Memory	42 (13,0)	0.87 (0.74 to 1.02)	0.09	0.66 (0.34 to 1.29)	0.22

[a] Impairment is defined as a score of ± 1.5 SD from the mean, adjusted for age, sex and education. RF: risk factor. Data are presented as odds ratio (OR) with 95% CI in parentheses, unless otherwise indicated.

The risk score was significantly related to impairment in the domains information processing speed (odds ratio with 95% confidence interval (OR(95%CI)) for each point increase on the score: 1.22(1.01 to 1.46); p=0.04), visuoconstruction (1.32(1.02 to 1.71) and abstract reasoning (1.40(1.06 to 1.84) (Table 2). A trend was observed for the domain attention and executive functioning (1.17(0.99 to 1.538); p=0.07). No significant relation was observed for the domain memory, nor for the subdomains of memory (working memory: 1.28(0.73 to 2.34); immediate memory: (1.03(0.71 to 1.49) and delayed memory: (0.84 (0.70 to 1.01)). Participants with a risk score of 9 points or more had a three- to fourfold increased risk of late-life impairment on the domain information-processing

speed (OR(95%CI): 3.07(1.37 to 6.90); p=0.007) and abstract reasoning (3.97 (1.07 to 14.71); p=0.04). The area under the curve (AUC) for information processing speed was 0.63(0.53 to 0.73) and for abstract reasoning 0.72(0.61 to 0.82). The cut-off score of 9 points had a sensitivity of 71% and a specificity of 44% for impairment in information processing speed. Similar values were observed for impairment in abstract reasoning (sensitivity 77% and specificity 46%).

Table 3 shows the OR's for cognitive impairment for each point increase on the risk score when only modifiable risk factors were included. Overall the strength of the associations did not differ much from those in *table 2*, except that the relation with attention and executive functioning became somewhat stronger (OR(95%CI):1.26(1.04 to 1.54)) and with abstract reasoning less strong (1.25(0.91 to 1.71).

Table 3. Odds Ratio (OR) of cognitive impairment per point increase in risk factor score when only modifiable risk factors are included

Cognitive domain	OR per point increase in sum score of modifiable RF (0-7)[a]	p-value
Information processing speed	1.22 (0.99 to 1.51)	0.07
Attention and Executive functioning	1.26 (1.04 to 1.54)	0.02
Visuoconstruction	1.26 (0.94 to 1.69)	0.12
Abstract reasoning	1.25 (0.91 to 1.71)	0.17
Language	1.09 (0.79 to 1.51)	0.58
Memory	0.84 (0.68 to 1.03)	0.10

[a] Modifiable risk factors include: systolic blood pressure, BMI, total cholesterol and leisure time physical activity. RF: risk factor

Discussion

These results show that a previously designed risk score for dementia[5] could predict cognitive impairment 15 years later on the domains information processing speed, abstract reasoning and visuoconstruction, and possibly also attention and executive functioning, in a non-demented population.

Slowing of information processing and problems with executive functioning are considered to be the main characteristics of vascular cognitive impairment[14] and are consistently associated with vascular pathology, including small vessel disease and white matter lesions.[15,16] Moreover, deficits in speed, executive functioning and visuospatial abilities are associated with ischaemic lesions on brain MRI.[17] We did not find a relation between memory impairment, a key feature of early Alzheimer's disease, and the risk score. This is remarkable, as in the original paper on the risk score the majority of dementia cases that were predicted by the score fulfilled

the diagnostic criteria for Alzheimer's disease.[5] A possible explanation is that many individuals who are diagnosed with Alzheimer's disease also have vascular brain pathology.[2] Post-mortem studies suggest that this vascular pathology lowers the threshold for Alzheimer's disease to become clinically manifest.[18,19] This may explain why in earliest stages of cognitive decline vascular risk is associated with a cognitive profile compatible with vascular cognitive impairment, while at a later stage, when neurodegenerative changes emerge and start to dominate the clinical phenotype, it is associated with a cognitive profile that is compatible with a clinical diagnosis of Alzheimer's disease.

The specificity of the risk score in the current study was lower than reported by Kivipelto and collegues.[5] This is not surprising, since cognitive impairment is a much more heterogeneous condition than dementia, both in its clinical manifestation and in its etiology. Future studies could reduce the heterogeneity of the population of individuals with cognitive impairment by specifying subgroups of patients, for example, based on brain imaging data.

Our results showed that the predictive value of the risk score remained when only modifiable risk factors were included, indicating that the relation is not solely driven by age and education. This provides opportunities for prevention of cognitive impairment through modification of those risk factors by treatment or lifestyle changes. Randomised controlled trials examining the effect of such treatment over a long follow-up period are lacking. Nevertheless, observational studies indicate that treatment of these risk factors in midlife is associated with a lower risk of late-life cognitive dysfunction and dementia.[20-22] In this context, it should be emphasized that the age at which vascular risk factors are assessed is important in their relation with cognition. For example, in older populations the association between vascular risk factors and dementia is often attenuated and sometimes even reversed.[23,24] Risk factor levels may change under the influence of aging or under the influence of processes related to cognitive decline.[22,25] Therefore caution is warranted when applying vascular risk scores such as the present score to older populations.

The strength of the present risk score is its predictive value many years before cognitive decline becomes clinically manifest, at a stage when lifestyle and treatment interventions could already be effective. However, the predictive value of the risk score is by definition limited to middle-aged individuals who survive until the late-life examination. This survival bias is inherent to such a long follow-up time and has likely affected our results. Strengths of the current study are the detailed recording of vascular determinants over a long follow-up period and the comprehensive assessment of cognitive functioning. However, some cognitive domains were addressed in less detail (e.g. language) and sensitivity to detect impairments on those domains may therefore have been lower. Another

limitation is selection bias due to the long follow up period and the intensive character of this study. Individuals who were still alive at the time of the latest assessment, but experienced serious health problems or cognitive impairment are less likely to have participated. This may also be reflected in the fact that none of the participants had dementia and may have led to an underestimation of the predictive value of the risk score.

This study demonstrates that midlife vascular risk factors not only predict the development of dementia, but also the development of milder forms of cognitive impairment. Only a proportion of the individuals with cognitive impairment will develop dementia. However, cognitive impairment is a problem by itself, leading to complaints and affecting functional abilities. Cognitive impairment should therefore also be considered as an endpoint in the development and validation of vascular risk scores, since those individuals might also benefit from early lifestyle and treatment interventions.

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Chapter 7

The metabolic syndrome, atherosclerosis and cognitive functioning in a non-demented population: the Hoorn Study

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Abstract

Background

The metabolic syndrome (MetS) is associated with cognitive deficits and atherosclerotic vascular disease. We examined whether the relation between the MetS and cognitive dysfunction is mediated by measures of atherosclerosis or the presence of clinically manifest cardiovascular disease.

Methods

In 380 individuals (153 with MetS; 60-87 years) from the population based Hoorn Study, measures of atherosclerosis including carotid intima-media thickness (c-IMT), flow mediated dilation (FMD), ankle-brachial index and the presence of clinically manifest cardiovascular disease were assessed at baseline and 7 later years at follow up. Cognitive functioning (information processing speed, memory, and attention&executive functioning) was assessed at follow-up. The relation between the MetS, atherosclerosis and cognitive functioning was assessed with linear regression analysis.

Results

Individuals with MetS showed worse performance on information processing speed (adjusted mean difference z-score±SE: -0.22±0.6; p=0.01) and attention&executive functioning (-0.32±0.07; p<0.001), but not on the domain memory. The affected cognitive domains were also associated with measures of atherosclerosis (standardised B(95%CI) c-IMT:-0.14(-0.24; -0.05); p<0.01; FMD: 0.13 (0.02; 0.24), p<0.05) and a history of clinically manifest cardiovascular disease: (-0.29 (-0.47; -0.11); p<0.01). However, the relation between the MetS and cognitive functioning did not change after adjustment for c-IMT, FMD or a history of clinically manifest cardiovascular disease (p>0.05).

Conclusion

In this population based cohort, the relation between the MetS and cognitive dysfunction was not mediated by atherosclerosis or a history of cardiovascular disease. These findings should stimulate future studies to elucidate alternative mechanisms underlying cognitive deficits in individuals with MetS.

Introduction

The clustering of cardiovascular risk factors, often referred to as the metabolic syndrome (MetS), is associated with cognitive decrements and the development of dementia.[1,2] This relation may be mediated by atherosclerotic vascular disease. Individuals with MetS are at increased risk for carotid atherosclerosis, endothelial dysfunction, ischemic heart disease and cerebrovascular disease.[3-5] Atherosclerotic vascular disease may in turn affect the brain, not only by increasing the risk of thromboembolic stroke[6], but possibly also by affecting cerebral perfusion, leading to malfunction and degeneration of neuronal cells.[7]

Large population-based studies have demonstrated a link between indices of atherosclerosis and cognitive dysfunction or dementia.[8] Affected cognitive domains include memory, information processing speed, and executive functioning[9,10], a cognitive profile which is similar to the one observed in individuals with the MetS.[11] Also in individuals without clinically manifest cardiovascular disease, carotid intima media thickness predicted subsequent cognitive decline.[12]

Although atherosclerosis has often been considered to mediate the relation between the MetS and cognitive decline, this mediating effect has not yet been studied in sufficient detail. The present study therefore examined the relation between the MetS, atherosclerosis and cognitive functioning in a population of non-demented older individuals. Presence of the MetS and several measures of atherosclerosis were related to a detailed cognitive assessment 7 years later.

Methods

Study population

The Hoorn study is a population-based study on glucose metabolism and cardiovascular risk in the general population. The population and study design have been described earlier.[13] The study started in 1989 and included 2,484 randomly selected Caucasian participants aged 50-75 years from the middle-sized Dutch town of Hoorn (T1). In 1996-1998 (T2), all surviving participants (n=2086) were invited for a second examination, to which 1513 agreed.[14] In the 2000-2001 follow up examination (T3), 1074 individuals of the Hoorn Study cohort, including all those who were diagnosed as having type 2 diabetes (n=176), and random samples of individuals with normal (n=705) and impaired (n=193) glucose metabolism, were invited, of whom 647 (60%) agreed to participate.[15] In 2005-2008 (T4) all independently living participants (n=549) were reinvited, to which 385 (70%) agreed to participate.

Cognitive functioning was only assessed at the 2005-2008 examination. None of the participants had cognitive disturbances interfering with functional independence at the moment of cognitive testing. For the present study we

excluded participants with an unreliable assessment of cognitive functioning (e.g. deafness, language difficulties; n=5), leaving 380 participants for the present analyses. In the present paper, the 2000-2001 examination will be referred to as baseline, and the 2005-2008 examination as follow-up.
Because we were interested in the possible causal relationship between the MetS, atherosclerosis and late life cognitive dysfunction, we defined the MetS and measures of atherosclerosis at baseline, 7 years prior to cognitive testing. In secondary analyses we evaluated the mediating effect of the progression of atherosclerosis over 7 years on the relation between the MetS at baseline and cognitive functioning at follow up.
The local ethics committee approved the study and written informed consent was obtained from all participants.

The metabolic syndrome

The metabolic syndrome was defined as having three or more of the following criteria at baseline: waist circumference >88 cm for women and >102 cm for men; triglycerides ≥1.7 mmol/l; HDL cholesterol <1.3 mmol/l for women and <1.0 mmol/l for men; blood pressure ≥130/85 mm Hg (or antihypertensive medication), and fasting blood glucose ≥6.1 mmol/l (ATP- III) (NCEP JAMA 2001). Since information on 2-hour postload glucose was also recorded in this population, the glucose criterion was slightly modified and was also considered fulfilled when the 2-hour glucose concentration was ≥7.8 mmol/l.[16]

Carotid intima-media thickness (c-IMT)

Ultrasound assessment of the c-IMT was performed at baseline and follow-up. Procedures and reproducibility of scanning are described in detail elsewhere.[15] In summary, an ultrasound scanner (350 Series; Pie Medical, Maastricht, the Netherlands), equipped with a 7.5-MHz linear probe, was operated by a single observer. Three measurements, 4s each, were performed in the right common carotid artery at 10mm proximal to the carotid bulb. The mean of these three measurements was calculated and included in the analysis. Images were registered and analyzed by a computer equipped with vessel wall movement detection software and an acquisition system (Wall Track System; Pie Medical).

Endothelial function

Endothelium-dependent flow-mediated dilation (FMD) of the right brachial artery was assessed at baseline. The measurement protocol has been described in detail.[3] Briefly, baseline diameter (mean of three measurements) and peak flow velocity (mean of two measurements) were determined. A pressure cuff, placed on the forearm, was then automatically inflated and kept constant at supra-systolic pressure (brachial systolic pressure +100 mmHg) in order to induce forearm

ischemia. After 5 min the cuff was released, which is followed by an increase in blood flow. This increase in blood flow increases shear stress, which serves as the stimulus for FMD. After cuff release, the diameter was measured at 45, 90, 180 and 300 s. The maximum diameter in any of these four measurements was used in the statistical analysis. In addition, non-endothelium dependent nitroglycerin-mediated dilation (NMD) was determined, which served as a control condition for FMD. NMD was calculated as the percentage change in arterial diameter from baseline to 5 minutes after administration of 400μg sublingual nitroglycerin.[3]

Clinically manifest cardiovascular disease

Peripheral vascular disease, ischemic heart disease and history of stroke were assessed at baseline and follow-up. Peripheral vascular disease was defined as intermittent claudication assessed with the Rose questionnaire, Ankle Brachial Index ≤ 0.9, history of surgery or endovascular treatment for arterial disease, or lower limb amputation. Ischemic heart disease was defined as Minnesota Code 1.1–1.3, 4.1–4.3, 5.1–5.3, or 7.1 on the electrocardiogram or self-reported history of myocardial infarction. A history of stroke was based on self-report. Any cardiovascular disease was defined as peripheral vascular disease, ischemic heart disease or history of stroke.

Cognitive assessment

An extensive standardised neuropsychological test battery was obtained at the follow up examination, including twelve verbal and non-verbal tasks, administered in a fixed order. The tasks were divided into six cognitive domains. This division was made a priori, according to standard neuropsychological practice and cognitive theory as described in detail in Lezak et al.[17] For the present study we focused on those cognitive domains which have previously been shown to be particularly affected in individuals with the MetS and individuals with atherosclerosis, namely the domains memory, information processing speed and attention and executive functioning.[9,11] The domain memory included tests for four subdomains: 'working memory' assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Corsi Block-Tapping Task; 'immediate memory and learning rate', including verbal memory assessed by the Rey Auditory Verbal Learning Test and visual memory assessed by the Location Learning Test; 'forgetting rate' assessed by the delayed recall of the Rey Auditory Verbal Learning Test and of the Location Learning Test; and 'incidental memory' assessed by the delayed trial of the modified Rey Complex Figure. The domain information processing speed was assessed by the Trail Making Test Part A, the Stroop Color-Word Test (Parts I and II), and the subtest Digit Symbol of the WAIS-III. The domain attention and executive function was assessed by the Trail Making Test

Part B, the Stroop Color-Word Test (Part III), the Brixton Spatial Anticipation Test, a letter fluency test using the 'N' and 'A', and category fluency using animal names. Raw test scores were standardized into z-scores. One z-score was derived for each domain by averaging tests comprising that domain.
Pre-morbid IQ was estimated with the Dutch version of the National Adult Reading Test. Depressive symptoms were assessed with the validated Dutch version of the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D). The proportion of persons scoring ≥16 (indicating possible depression) was recorded.

Other measurements

Systolic and diastolic blood pressure, body mass index (BMI), waist-to-hip ratio, fasting glucose concentration, 2-h postload glucose concentration, HbA1c levels, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, were determined as described elsewhere.[13] The presence of diabetes was determined based on WHO criteria (WHO 1999). Self-reported information on the participants' current use of medications, medical history and current smoking status (yes/no) was obtained by a standardized questionnaire.

Statistical analysis

Demographic variables, vascular and metabolic risk factors levels, and measures of atherosclerosis were compared between participants with and without MetS with independent T-test for continuous variables and chi-square test for proportions.
To answer the question whether the relation between the MetS and cognitive dysfunction is mediated by measures of atherosclerosis we first assessed the associations between the Mets and cognition, between the MetS and atherosclerosis, and between atherosclerosis and cognition with linear regression analyses, adjusted for age and sex, and cognition also for estimated IQ. The cognitive domains on which the MetS group performed worse than the noMetS group and the measures of atherosclerosis that were significantly related to cognitive performance were considered in the mediation analyses.
The possible mediating effect of atherosclerosis on the relation between the MetS and cognitive performance was assessed in a stepwise linear regression analysis in which we adjusted the difference in cognitive performance between the noMetS and MetS group for measures of atherosclerosis at baseline. The change in between-group difference before and after adjustment for the mediator (atherosclerosis) was assessed. In addition, we estimated the corresponding 95% confidence interval (CI) with a bootstrapping technique.[18] Bootstrapping is a computer-based method that involves repeated sampling from the data and estimation of the

mediating effect in each resampled data set. By repeating this process thousands of times, an empirical approximation of the sampling distribution is built and used to reconstruct the 95% CI. The mediating effect is said to be present if the 95% CI does not contain zero. We computed bootstrapped (bias-corrected) confidence intervals (5000 samples) for the size of the specific mediating 'effects' using SPPS macros provided by Preacher & Hayes.[18]

In secondary models, alternative mediators of the relation between MetS and cognition were addressed. To prevent multicollinearity this was done in six separate models for each individual risk factor of the MetS (hypertension, hyperglycemia, dyslipidemia, central obesity), current smoking, and possible depression. Because the study population was enriched for type 2 diabetes, which is a risk factor for cognitive decrements and atherosclerosis, we also reanalysed the data after excluding all participants with type 2 diabetes.

Finally, we evaluated whether the progression of atherosclerotic measures between baseline and follow-up mediates the relation between the MetS and cognition by repeating step 1 and 2 for measures of atherosclerosis assessed at follow-up, adjusted for the baseline measurement.

Results

Table 1 shows the baseline characteristics of the participants with and without MetS. Groups did not differ in age, sex or estimated IQ. Of the 153 participants with the MetS, 120 (78%) scored above the cut-off for waist circumference, 93 (61%) for triglyceride levels, 73 (48%) for HDL levels, 143 (94%) for blood pressure levels, and 120 (78%) for glucose levels. The raw cognitive test scores of both groups are presented in *Table 2*.

The Mets and atherosclerosis at baseline and cognitive functioning at follow-up

Individuals with the MetS had a greater c-IMT, worse endothelial function, reflected by a lower FMD and similar NMD, and a higher prevalence of ischemic heart disease at baseline than individuals without the MetS (*Table 3*). Regarding cognition, individuals with the MetS showed worse performance at follow-up on the domain information processing speed (adjusted mean z-score±SE noMetS: 0.09±0.5, MetS: -0.13±0.06; p=0.01) and attention and executive functioning (noMetS: 0.13±0.06, MetS: -0.19±0.07; p<0.001). No significant difference in memory performance was observed (*Table 4*).

Table 1. Characteristics of the study population at baseline

	No MetS (n=227)	MetS (n=153)	p-value
Age, years	67.8 ± 5.5	67.7 ± 5.4	n.s.
Sex (% male)	52 %	48 %	n.s.
Estimated IQ[a]	98 ± 12	97 ± 14	n.s.
Systolic blood pressure (mmHg)	134 ± 18	147 ± 18	<0.001
Diastolic blood pressure (mmHg)	79 ± 11	87 ± 10	<0.001
Antihypertensive medication	22%	49%	<0.001
BMI (kg/m2)	25.7 ± 2.7	29.6 ± 3.7	<0.001
Waist-hip ratio	0.90 ± 0.09	0.96 ± 0.09	<0.001
Total cholesterol (mmol/L)	5.7 ± 1.0	5.7 ± 1.1	n.s.
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.2 ± 0.4	<0.001
LDL-cholesterol (mmol/L)	3.6 ± 0.9	3.6 ± 0.9	n.s.
Triglycerides (mmol/L)	1.2 ± 0.4	2.0 ± 1.0	<0.001
Cholesterol lowering drugs	14%	22%	0.045
Fasting glucose (mmol/L)	5.7 ± 0.9	6.6 ± 1.4	<0.001
2-h post-load glucose (mmol/L)	6.3 ± 2.1	8.3 ± 2.7	<0.001
HbA1c (%)	5.8 ± 0.5	6.2 ± 0.8	<0.001
Diabetes	7 %	31%	< 0.001
Current smoking	13%	9%	n.s.

Data are presented as mean ± SD or n (%). [a]Assessed at follow up.

Table 2. Raw cognitive test scores

	Range of scores	Controls (n=227)	MetS (n=153)
Information processing speed			
Trail Making Test part A (sec)#	20-161	49.3 ± 19.9	51.5 ± 21.9
Stroop Color Word Test I (sec)#	32-133	47.9 ± 8.0	49.9 ± 11.6
Stroop Color Word Test II (sec)#	39-137	63.6 ± 11.8	66.1 ± 16.0
Symbol substitution test	18-94	52.4 ± 14.5	49.7 ± 14.4
Attention and Executive functioning			
Trail Making Test part B (sec)#	41-407	121.3 ± 62.3	139.8 ± 69.9
Stroop Color Word Test III (sec)#	50-467	125.2 ± 46.4	137.9 ± 58.3
Brixton Spatial Anticipation test (errors)#	7-47	20.7 ± 7.4	21.9 ± 6.9
Letter fluency (mean N+A)	2-24	11.0 ± 4.2	10.1 ± 4.0
Category fluency (No. of animals)	8-63	30.8 ± 8.4	30.3 ± 9.0
Memory			
Working memory			
WAIS-II Digit Span forward (productscore)	12-126	45.1 ± 17.9	44.8 ± 19.7
WAIS-II Digit Span backward (productscore)	4-104	25.0 ± 15.9	21.6 ± 13.2
Corsi Block-Tapping Test forward (productscore)	9-96	38.5 ± 12.2	36.5 ± 12.7
Corsi Block-Tapping Test backward (productscore)	2-88	34.7 ± 15.5	34.4 ± 15.9
Immediate memory and learning rate			
RALVT total trials 1-5 (words)	5-61	36.2 ± 10.4	35.4 ± 9.9
LLT total trials 1-5 (errors)#	0-163	34.2 ± 26.2	29.8 ± 23.2
Forgetting rate			
RAVLT delay (words)	0-15	6.8 ± 3.4	6.8 ± 3.0
LLT delay (errors)#	0-33	4.3 ± 5.9	3.3 ± 4.3
RAVLT recognition (words)	0-30	27.6 ± 3.0	27.8 ± 3.2
Incidental memory			
Rey Complex Figure Test delay (points)	0-30	14.2 ± 6.3	14.2 ± 6.3

RAVLT: Rey Auditory Verbal Learning Test; LLT: Location Learning Test.
Raw test scores per group are represented as mean ± SD. Higher scores indicate better performance except when indicated. # Higher scores indicate poorer performance.

Table 3. Between-group differences in measures of atherosclerosis at baseline

	No MetS (n=227)	MetS (n=153)	p-value
c-IMT, mm	0.83 ± 0.17	0.88 ± 0.15	0.01
Endothelial dependent FMD[a], %	4.7 ± 3.8	3.7 ± 3.1	0.02
Non-endothelial dependent NMD[b], %	10.7 ± 5.4	9.9 ± 5.8	0.21
Clinically manifest CVD			
Peripheral vascular disease[c]	33 (15%)	25 (17%)	0.61
Ischemic heart disease[d]	77 (34%)	65 (43%)	0.09
History of stroke	19 (8%)	10 (7%)	0.50
Any CVD[e]	111 (49%)	79 (52%)	0.60

[a] Flow mediated (endothelial dependent) dilation of the brachial artery. [b] Nitroglycerin mediated (endothelial independent) dilation of the brachial artery. [c] Rose questionnaire: intermittent claudication, ABI <0.9, arterial operation or amputation. [d] Self reported history of myocardial infarction or ischemic heart disease on ECG. [e] History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke.

Table 4. Group differences in cognitive performance at follow up

	No MetS (n=227)	MetS (n=153)	p-value
Info processing speed	0.09 ± 0.05	-0.13 ± 0.06	0.01
Attention and executive functioning	0.13 ± 0.06	-0.19 ± 0.07	<0.001
Memory	-0.06 ± 0.06	0.09 ± 0.07	n.s.

Data are presented as mean standardised z-scores±SE adjusted for age, sex and estimated IQ.

The relation between markers of atherosclerosis at baseline and cognitive functioning at follow up in the whole population is shown in *table 5*. An increased c-IMT was associated with worse information processing speed (standardised B(95%CI):-0.14(-0.24; -0.05); p=0.004) and attention and executive functioning (-0.11 (-0.21;-0.01); p=0.04). Decreased FMD was associated with worse attention and executive functioning (standardised B(95%CI): 0.13 (0.02; 0.24), p=0.02). The presence of ischemic heart disease or any CVD was associated with worse information processing speed (B(95% CI) ischemic heart disease:-0.21(-0.40;-0.02), p=0.03; any CVD: -0.29 (-0.47; -0.11), p=0.002). A trend was observed between a history of stroke at baseline and worse performance on the domain information processing speed (-0.56 (-1.15; 0.025); p=0.06) and memory (-0.63 (-1.26; 0.01); p=0.05).

Table 5. Relation between measures of atherosclerosis at baseline and cognition at follow up in the whole study sample (n=380)

	Information processing speed	Attention and executive functioning	Memory
c-IMT, mm	-0.14 (-0.24; -0.05)**	-0.11 (-0.21; -0.01)*	-0.10 (-0.21; 0.002)
Endothelial dependent FMD[a,f], %	0.05 (-0.05; 0.16)	0.13 (0.02; 0.24)*	-0.02 (-0.13; 0.09)
Non-endothelial dependent NMD[b,f], %	0.05 (-0.05; 0.16)	0.01 (-0.04; 0.18)	0.10 (-0.02; 0.21)
Clinically manifest CVD			
Peripheral vascular disease[c]	-0.21 (-0.46; 0.05)	0.03 (-0.24; 0.30)	-0.25 (-0.52; 0.02)
Ischemic heart disease[d]	-0.21 (-0.40; -0.02)*	0.07 (-0.14; 0.27)	-0.01 (-0.22; 0.19)
History of stroke	-0.56 (-1.15; 0.03)	-0.22 (-0.85; 0.41)	-0.63 (-1.26; 0.01)
Any CVD[e]	-0.32 (-0.49; -0.14)**	0.07 (-0.13; 0.26)	-0.16 (-0.35; 0.04)

Regression coefficients indicate the change in z-score per SD for continuous variables and per category (no/yes) for dichotomous variables, adjusted for age and sex.
[a] Flow mediated dilation of the brachial artery. [b] Nitroglycerin mediated dilation of the brachial artery [c] Rose questionnaire: claudicatio, ABI <0.9, arterial operation or amputation. [d] Self reported history of myocardial infarction or ischemic heart disease on ECG. [e] History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke. [f] lower values reflect worse function; *p <0.05, **p <0.01

Mediation of the association between the MetS and cognition by baseline atherosclerosis

As can be seen from *Table 6*, the mean difference in information processing speed between the MetS and noMetS group did not notably change after additional adjustment for c-IMT, FMD and any CVD at baseline (change in between-group difference final model: 0.03). The corresponding 95%CI estimated with the bootstrap method (-0.06; 0.05) indicated that these measures of atherosclerosis did not significantly mediated the association between MetS and cognition, because the 95%CIs contain zero and are relatively narrow.

Table 6. Mean difference in cognitive performance at follow up between individuals with (n=153) and without (n=227) the MetS adjusted for measures of atherosclerosis at baseline

	Information processing speed	Attention & executive functioning
Age, sex, estimated IQ	-0.22 (-0.38; -0.05)*	-0.32 (-0.49; -0.14)***
Previous + c-IMT	-0.19 (-0.36; -0.02)*	-0.33 (-0.52; -0.15)***
Previous + Endothelial dependent FMD[a]	-0.24 (-0.43; -0.06)*	-0.33 (-0.52; -0.15)***
Previous + Any CVD[b]	-0.25 (-0.43; -0.07)**	-0.33 (-0.52; -0.14)***

[a]Flow mediated dilation of the brachial artery. [b]History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke; *p<0.05; **p<0.01; ***p<0.001.

Also the mean group difference in attention and executive functioning did not change after adjustment for atherosclerosis at baseline (change in between-group difference final model (bootstrap 95%CI): 0.01 (-0.07; 0.01)). Further adjustment for current smoking, and possible depression did not alter the results (data not shown). Of the five individual risk factors of the MetS, only hyperglycemia slightly mediated the relation between the MetS and information processing speed (-0.10 (-0.22; -0.003)), but not between MetS and attention and executive functioning (-0.06 (-0.16; 0.05)).

The association between the MetS, baseline atherosclerosis and cognition in individuals without type 2 diabetes

After exclusion of all individuals with type 2 diabetes (n=64), the noMetS group included 211 individuals and the MetS group 105 (mean age 67.7±5.6 and 67.5±5.2, respectively). The between-group differences in measures of atherosclerosis, cognitive functioning and the relation between measures of atherosclerosis at baseline and cognition at follow up were similar to the values from the analyses that included the patients with type 2 diabetes, as shown in table 3-5 (supplementary material online). Only the difference in endothelial dependent FMD between the MetS and noMets group became smaller and non-significant (noMetS: 4.8±3.8, MetS: 4.2±3.4). Similar to the results shown in table 6, the group difference in information processing speed (-0.27±0.09; p=0.003) and attention and executive functioning (-0.32±0.10; p=0.002) did not change after adjustment for measures of atherosclerosis at baseline (change in between-group difference (bootstrap 95%CI): 0.03 (-0.08; 0.02) and -0.03 (-0.06; 0.02), respectively) (*table 7*).

Table 7. Mean difference in cognitive performance at follow up between individuals with (n=105) and without (n=211) the MetS and without type 2 diabetes, adjusted for measures of atherosclerosis at baseline

	Information processing speed	Attention & executive functioning
Age, sex, estimated IQ	-0.27 (-0.45; -0.09)**	-0.32 (-0.52; -0.12)**
Previous + c-IMT	-0.25 (-0.44; -0.07)**	-0.32 (-0.52; -0.12)**
Previous + Endothelial dependent FMD[a]	-0.31 (-0.51; -0.12)**	-0.29 (-0.48; -0.09)**
Previous + Any CVD[b]	-0.30 (-0.49; -0.11)**	-0.29 (-0.49; -0.09)**

[a]Flow mediated dilation of the brachial artery [b]History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke **p<0.01

Mediation of the association between the MetS and cognition by the progression of atherosclerosis between baseline and follow up

After correction for the baseline measurements of atherosclerosis, there was no association between c-IMT, peripheral vascular disease or ischemic heart disease at follow up and cognitive functioning at follow up (all p>0.05). However, incident stroke (stroke between baseline and follow up) was associated with reduced information processing speed (-0.56 (-0.97; -0.14); p=0.01), but not with attention and executive functioning or memory performance. Incident stroke did not mediate the relation between the MetS and worse performance on information processing speed or attention and executive functioning (change in between-group difference (bootstrap 95%CI): -0.02 (-0.07; 0.01) and -0.005 (-0.03; 0.004)) respectively.

Discussion

In the present population-based study both the MetS and markers of atherosclerosis were associated with reduced cognitive functioning, but the relation between the MetS and cognitive decrements was not mediated by measures of atherosclerosis or the presence of clinically manifest cardiovascular disease.

The profile and size of the cognitive decrements we observed in individuals with Mets are in line with previous findings, reflecting mild reductions in information processing speed and attention and executive functioning.[1,11] Problems with memory have also been reported.[19] However, in contrast to our study, previous studies primary assessed immediate verbal memory performance, which strongly depends on attentional capacity, and not so much on the capability to consolidate information. Differences in cognitive performance were mainly observed on tests with a high attentional demand (*Table 2*), indicating that the cognitive problems in individuals with MetS will become most evident in complex situations, e.g. when two tasks are executed simultaneously. The use of a detailed cognitive assessment allowed us to detect subtle decrements in cognitive functioning before it became clinically manifest. Examining underlying mechanisms of these early stages of cognitive dysfunction is relevant, because treatment benefits are expected to be largest when the underlying brain damage is still relatively modest.

Our results on the relation between cognitive performance and measures of carotid atherosclerosis[10,20], endothelial function[20] and clinically manifest cardiovascular disease[9,21] are also in agreement with results from previous population based studies. The important finding of our study is that despite the fact that we confirm that the MetS and atherosclerosis are both associated with impaired cognition, we now clearly demonstrate that atherosclerosis does not modulate the relation between the MetS and cognition. In addition to traditional mediation analyses, we also calculated the respective 95% CI of the mediation effect by using a

bootstrapping technique. This technique provides information on the reliability of the point estimates for possible mediation effects. The observed 95% CIs were relatively narrow, indicating that the mediation effect could be reliably estimated in this study sample. Although the modulating role of atherosclerosis on the relation between MetS and cognition had not yet been studied in sufficient detail, it has often been proposed as an important mechanism. Our results however, do not support this hypothesis, indicating that other mechanisms are likely to play a role. For example, etiological factors shared between atherosclerosis and the MetS, such as inflammation, may drive the association with cognition. Chronic inflammation is an important risk factor for atherosclerosis and is linked with the MetS and age-related cognitive decline.[11,22] In addition, each component of the MetS is individually associated with atherosclerosis and reduced cognitive functioning.[23] Previous studies have identified hyperglycemia as the main contributor to deficits in cognitive functioning in individuals with MetS.[11,24] Also in our study hyperglycemia slightly modulated the relation with information processing speed.

The other components of the MetS, including hypertension, adiposity and hypercholesterolemia, did also not mediate the relation between the MetS and cognitive functioning in this study. However, this does not rule out the association between MetS and the development of cognitive dysfunction. Indeed, exposure to vascular risk factors at midlife has shown to be more strongly related to late life cognitive function than exposure to these risk factors during late life.[25,26] The age at which the vascular risk factors are assessed should therefore be considered in interpretation of these results.

Our findings do not exclude that the relation between MetS and cognitive dysfunction is mediated by other manifestations of vascular disease, such as cerebral small vessel disease. Small vessel disease is associated with a similar cognitive profile as associated with MetS, including mental slowing and problems with executive functioning.[27] Indeed, individuals with the MetS show more white matter abnormalities[24,28] and (lacunar) infarcts[29] on brain MRI scans. Unfortunately, brain MRI data was not available from our cohort.

To our knowledge, we are the first to examine the impact of atherosclerosis on the association between the MetS and cognitive dysfunction. Strengths of this study are the detailed recording of measures of atherosclerosis over a long follow-up period in a well-defined population-based cohort, as well as the comprehensive assessment of cognitive functioning. However, some measures of cardiovascular disease, such as stroke, were based on self-report. Another limitation is attrition, which can lead to selection bias. Although this is inherent to the longitudinal design and the intensive character of this study, this may have led to an underestimation of the effects because subjects with severe vascular disease

or cognitive deficits are more likely to drop out. Indeed, previous reports on the Hoorn study population have shown that cardiovascular mortality was associated with an unfavourable risk factor profile at baseline.[30] Our results apply therefore to the variation in cognitive functioning in a relatively healthy population of older individuals, but cannot be generalised to the risk of developing dementia. Finally, cognition was only assessed once. Therefore we were not able to determine which individuals showed cognitive decline.

Despite these limitations, we still observe an association between the MetS, atherosclerosis and cognition, supporting the notion that also mild forms of atherosclerosis are related to worse cognitive functioning.

These results indicate that atherosclerosis or the presence of clinically manifest cardiovascular disease does not account for the observed reductions in cognitive functioning in individuals with the MetS. Whether shared vascular and metabolic risk factors of MetS and atherosclerosis play a role in the development of cognitive deficits remains to be elucidated. Understanding these mechanisms is essential for future intervention studies aiming to reduce the detrimental effect of MetS on the brain.

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Supplementary material

Table 8. Characteristics of the study population at baseline in individuals without type 2 diabetes

	noMetS (n=211)	MetS (n=105)	p-value
Age, years	67.7 ± 5.6	67.3 ± 5.2	n.s.
Sex (% male)	53 %	49 %	n.s.
Estimated IQ[a]	98 ± 13	97 ± 15	n.s.
Systolic blood pressure (mmHg)	133 ± 18	147 ± 18	<0.001
Diastolic blood pressure (mmHg)	79 ± 11	87 ± 10	<0.001
Antihypertensive medication	21%	47%	<0.001
BMI (kg/m^2)	25.7 ± 2.7	29.7 ± 3.5	<0.001
Waist-hip ratio	0.90 ± 0.09	0.96 ± 0.08	<0.001
Total cholesterol (mmol/L)	5.7 ± 1.0	5.8 ± 1.1	n.s.
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.3 ± 0.4	<0.001
LDL-cholesterol (mmol/L)	3.7 ± 0.9	3.7 ± 0.9	n.s.
Triglycerides (mmol/L)	1.2 ± 0.4	1.9 ± 0.9	<0.001
Cholesterol lowering drugs	13%	21%	0.045
Fasting glucose (mmol/L)	5.6 ± 0.7	6.2 ± 1.3	<0.001
2-h post-load glucose (mmol/L)	6.0 ± 1.5	7.4 ± 1.9	<0.001
HbA1[c] (%)	5.7 ± 0.5	6.0 ± 0.8	<0.001
Current smoking	13%	11%	n.s.

Data are presented as mean ± SD or n (%). [a]Assessed at follow up.

Table 9. Between-group differences in measures of atherosclerosis at baseline in individuals without type 2 diabetes

	NoMetS (n=211)	MetS (n=105)	p-value
c-IMT, mm	0.83 ± 0.17	0.87 ± 0.15	0.06
Endothelial dependent FMD[a], %	4.8 ± 3.8	4.2 ± 3.4	0.32
Non-endothelial dependent NMD[b], %	10.7 ± 5.5	10.7 ± 5.7	0.92
Clinically manifest CVD			
Peripheral vascular disease[c]	30 (15%)	15 (14%)	0.96
Ischemic heart disease[d]	72 (34%)	45 (43%)	0.13
History of stroke	19 (9%)	6 (6%)	0.30
Any CVD[e]	97 (46%)	53 (51%)	0.45

[a]Flow mediated (endothelial dependent) dilation of the brachial artery. [b]Nitroglycerin mediated (endothelial independent) dilation of the brachial artery. [c]Rose questionnaire: intermittent claudication, ABI <0.9, arterial operation or amputation. [d]Self reported history of myocardial infarction or ischemic heart disease on ECG. [e]History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke.

Table 10. Group differences in cognitive performance at follow up in individuals without type 2 diabetes (n=316)

	No MetS (n=211)	MetS (n=105)	p-value
Info processing speed	0.11 ± 0.05	-0.16 ± 0.07	0.003
Attention and executive functioning	0.15 ± 0.06	-0.17 ± 0.08	0.002
Memory	-0.04 ± 0.06	0.16 ± 0.09	n.s.

Data are presented as mean standardised z-scores±SE adjusted for age, sex and estimated IQ.

Table 11. Relation between measures of atherosclerosis at baseline and cognition at follow up in all individuals without type 2 diabetes (n=316)

	Information processing speed	Attention and executive functioning	Memory
c-IMT, mm	-0.16 (-0.26; -0.05)**	-0.11 (-0.23; -0.01)*	-0.11 (-0.22;0.01)
Endothelial dependent FMD	0.04 (-0.08; 0.15)	0.10 (-0.02; 0.21)	-0.04 (-0.16; 0.09)
Non-endothelial dependent NMD	0.05 (-0.06; 0.17)	0.04 (-0.08; 0.16)	0.11 (-0.02; 0.23)
Clinically manifest CVD			
Peripheral vascular diseasec	-0.01 (-0.29; 0.27)	0.12 (-0.19; 0.42)	-0.17 (-0.48; 0.13)
Ischemic heart diseased	-0.21 (-0.42; -0.01)*	0.002 (-0.22; 0.22)	-0.03 (-0.20; 0.25)
History of stroke	-0.55 (-1.16; 0.06)	-0.29 (-0.95; 0.38)	-0.57 (-1.24;0.10)
Any CVDe	-0.24 (-0.44; -0.05)*	0.05 (-0.16; 0.27)	-0.13 (-0.34; 0.09)

Regression coefficients indicate the change in z-score per SD for continuous variables and per category (no/yes) for dichotomous variables, adjusted for age and sex. a Flow mediated dilation of the brachial artery. b Nitroglycerin mediated dilation of the brachial artery. c Rose questionnaire: claudicatio, ABI <0.9, arterial operation or amputation. d Self reported history of myocardial infarction or ischemic heart disease on ECG. e History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke. f lower values reflect worse function; *<0.05, **<0.01.

Chapter 8

Improved sensitivity to cerebral white matter abnormalities in Alzheimer's disease with spherical deconvolution based tractography

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Submitted

Abstract

Introduction

Diffusion tensor imaging (DTI) based fiber tractography (FT) is the most popular approach for investigating white matter tracts in vivo, despite its inability to reconstruct fiber pathways in regions with "crossing fibers". Recently, constrained spherical deconvolution (CSD) has been developed to mitigate the effects of "crossing fibers" on DTI based FT. Notwithstanding the methodological benefit, the clinical relevance of CSD based FT for the assessment of white matter abnormalities remains unclear.

Methods

We evaluated the applicability of a hybrid framework, in which CSD based FT is combined with conventional DTI metrics to assess white matter abnormalities in 25 patients with early Alzheimer's disease. Both CSD and DTI based FT were used to reconstruct two white matter tracts: one with regions of "crossing fibers", i.e. the superior longitudinal fasciculus (SLF) and one which contains only one fiber orientation, i.e. the midsagittal section of the corpus callosum (CC). The DTI metrics (fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (DR), and axial diffusivity (DA)) obtained from these tracts were related to memory function.

Results

In the tract with "crossing fibers" the relation between MD, DR, DA and memory was significantly stronger with CSD than with DTI based FT. By contrast, in the CC, where one fiber direction predominates, the relation between DTI metrics and memory was comparable between both tractography methods. Importantly, these relations were most pronounced after adjustment for the planar diffusion coefficient, a measure with non-zero values typically occurring in regions of "crossing" fibers.

Conclusions

Compared to conventionally applied DTI based FT, a hybrid approach (CSD based FT combined with DTI metrics) can increase the sensitivity to detect functionally significant white matter abnormalities in tracts with complex white matter architecture.

Introduction

Diffusion tensor imaging (DTI) based fiber tractography (FT) is currently the most widely used method to reconstruct fiber pathways in the brain, despite its well known limitations in regions with complex white matter architecture.[1-3] The common second-rank diffusion tensor model, however, is based on the assumption of Gaussian diffusion, which may not be valid in white matter voxels that contain so-called "crossing fibers" [4], i.e. complex fiber bundle architecture within a single voxel including two or more crossing, interdigitating or "kissing" fiber populations, or one fiber population with a bending or splaying architecture.

In the past decade, several advanced approaches for characterizing the intra-voxel diffusion profile have been developed to overcome the limitations of the second-rank diffusion tensor model.[5-11] One of these techniques, constrained spherical deconvolution (CSD)[9], is especially promising as it can offer a reliable reconstruction of multiple fiber orientation distributions within clinically feasible MR acquisition settings.[8] Notwithstanding the promising outlook, the CSD model has not yet been applied quantitatively to clinical populations due to the lack of robust diffusion metrics that can describe the underlying microstructure unambiguously.

In this paper, we used a hybrid framework, in which CSD based FT is combined with conventional DTI metrics to assess white matter abnormalities in patients with early Alzheimer's disease (AD). This allowed us to examine the microstructural properties of specific white matter pathways in relation to memory performance, while overcoming the well-known limitations of DTI based FT in regions with "crossing fibers". We evaluated this CSD-DTI framework for two white matter tracts: one specifically selected because it contains many regions of "crossing fibers", i.e. the superior longitudinal fasciculus (SLF) and one with only one fiber orientation, i.e. the midsagittal section of the corpus callosum (CC). Diffusion measures in these tracts have been previously shown to be altered in patients with AD compared to controls using tract based analyses[12] and to the AD-associated impairments in memory function.[13]

Our hypothesis was that if CSD based FT is more accurate in reconstructing fiber bundle trajectories in regions with "crossing fibers", it should be more sensitive to microstructural abnormalities underlying cognitive dysfunction than DTI based FT in these tracts. On the other hand, in tracts without "crossing fiber" regions, both methods should perform equally. We therefore examined whether diffusion parameters of the SLF and CC obtained with CSD based FT are related to memory dysfunction in patients with early AD and compared these findings with the results obtained with DTI based FT.

Methods

Participants

Twenty five patients (mean age 80.0±5.0 years, 48% male), 19 with early stage AD and 6 with amnestic mild cognitive impairment (a-MCI) were recruited via a memory clinic at the University Medical Center Utrecht. Probable or possible AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[14] A-MCI was diagnosed according to the Petersen criteria.[15] Exclusion criteria were a history of stroke in the last 2 years, a history of stroke with subsequent cognitive deterioration, schizophrenia or other psychotic disorders, major depression, alcohol abuse, brain tumor, epilepsy or encephalitis. Patients with a severe stage of AD, indicated by a clinical dementia rating score > 1[16] or a MMSE score < 20[17], were also excluded. The study was approved by the local ethics committee and written informed consent was obtained from all participants.

Data acquisition

MRI data were collected using a Philips 3.0 Tesla scanner (Intera, Philips, Best, the Netherlands). Diffusion MRI data were obtained using a single-shot spin echo EPI sequence with the following parameters: field of view = 220x220x120 mm^3, 2.5 mm slice thickness (without gap), 48 slices, repetition time 6638 ms, echo time 73 ms, flip angle 90 degree, acquisition matrix 88x88 (in plane resolution of 2.5 mm) and reconstructed at 128x128, 45 isotropically distributed diffusion-sensitizing gradients with a b-value of 1200 s/mm^2, and one b=0 s/mm^2 image.[18] The acquisition time was 5.32 min.

Image processing

The DTI data sets were corrected for eddy current induced geometric distortions and subject motion by realigning the diffusion-weighted images (DWIs) to the b=0 s/mm^2 image with *Elastix*.[19] In this procedure, the diffusion gradients were adjusted with the proper b-matrix rotation as described by Leemans and Jones.[20] The diffusion tensor model was fitted using the RESTORE approach.[21] The DTI scans were transformed rigidly to MNI space in the motion–distortion correction procedure by using a single interpolation step (concatenation of transformation matrices) to maximize the uniformity of brain angulation across subjects.[22]

Tractography

DTI[23] and CSD[24] based tractography were performed with the *ExploreDTI* software package.[25] We reconstructed the SLF and the CC using both FT methods with a uniform seed point resolution of 2 mm^3 and a maximum deflection angle of 30

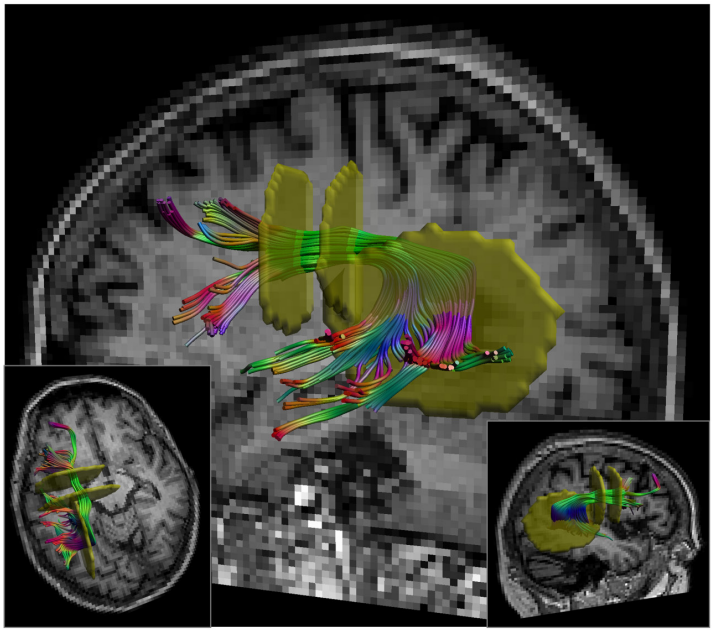

Figure 1. Selection of the superior longitudinal fasciculus in the left hemisphere using a multiple region of interest (ROI) selection approach. Two "AND" ROIs (shown in yellow) were placed on a coronal slice and one on a sagittal slice. Reconstruction was based on a standardized atlas of white matter tracts.[28]

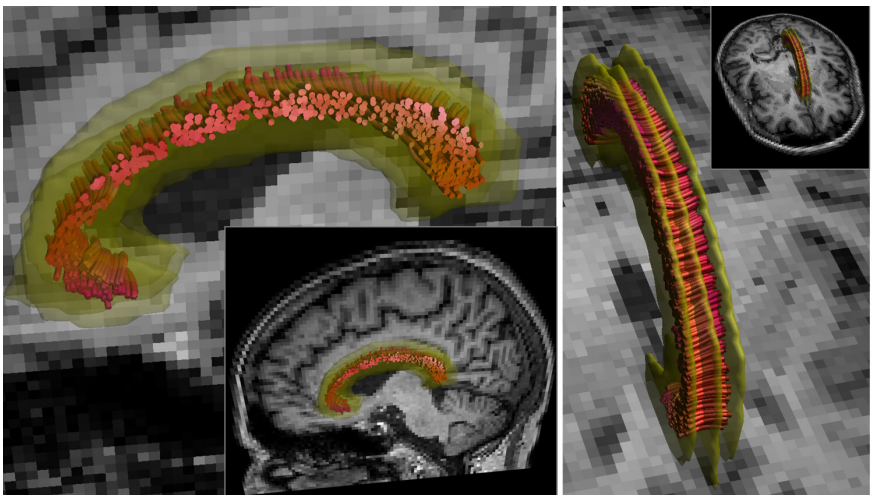

Figure 2. Selection of the medial segment of the corpus callosum using a multiple region of interest (ROI) selection approach. The median ROI was placed on the midsaggital plane in MNI space, and the two segment-selecting ROIs were drawn two voxels (4 mm) to either side of the midsagittal plane.

degrees. For the DTI based FT an FA threshold of 0.2 was applied. Analogously, the applied termination threshold for CSD based FT was a fiber orientation distribution (FOD) value of 0.1 (the harmonic degree of the estimated FOD coefficients was limited to 6).[8] We specifically examined the SLF because it contains a relatively large number of voxels with multiple fiber orientations due to the crossing of the corona radiata and/or laterally projecting fibers of the CC and is therefore particularly susceptible to tracking errors caused by the second-rank diffusion tensor model.[24] By contrast, the midsagittal section of the CC contains mainly voxels with one fiber population and is expected to be less vulnerable to tracking errors. Important to note is that microstructural changes in both the SLF and the CC have been associated previously with MCI and AD[12,26] and associated functional impairments in memory performance.[13]

The SLF, including SLF II, III and the arcuate fasciculus[27], was reconstructed from the left hemisphere (all participants were right handed) based on a standardized atlas of white matter tracts.[28] For reconstruction of the SLF, a multiple region of interest (ROI) selection approach was used. In total, three "AND" ROIs were placed, two on a coronal and one on a sagittal slice (*Figure 1*). In this ROI protocol, previously defined anatomical landmarks for slice selection and ROI placement were used to reduce subjectivity in fiber tracking.[28] High intra- and inter-rater reliability of manually segmenting fiber bundles has been demonstrated in previous studies (e.g.[29-31]).

The CC was reconstructed as described previously.[32] In summary, only the midsagittal segment of the CC was selected to exclude regions of "crossing fibers" from the more laterally projecting pathways of the CC that intersect the corticospinal fiber trajectories (*Figure 2*). Note that as all data were analyzed in MNI space, the midsagittal slice could be determined reliably in all subjects.

Diffusion parameters: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (DR), axial diffusivity (DA), and the normalized planar diffusion coefficient ($\lambda_2 - \lambda_3 / \lambda_1$)[33] were obtained for each tract. The planar diffusion coefficient ranges from zero to one and is relatively high in voxels were the tensor has a disc-like shape (i.e. the first and second eigenvalue are almost equal and larger than the third eigenvalue). This is typically the case when two fiber populations "cross" or "kiss"[34-37] (*Figures 3-5*). This planar diffusion coefficient can therefore be used to quantify the degree of fiber complexity in regions with "crossing fibers".[34] Note, however, that there is not a one-to-one correspondence: voxels with "crossing fibers" may still provide low (near zero) values of the planar diffusion coefficient (e.g., if three mutually orthogonally oriented fiber populations cross). On the other hand, if high values (near one) are encountered, these will indicate a higher degree of fiber complexity reflecting the presence of "crossing fiber" regions.[34]

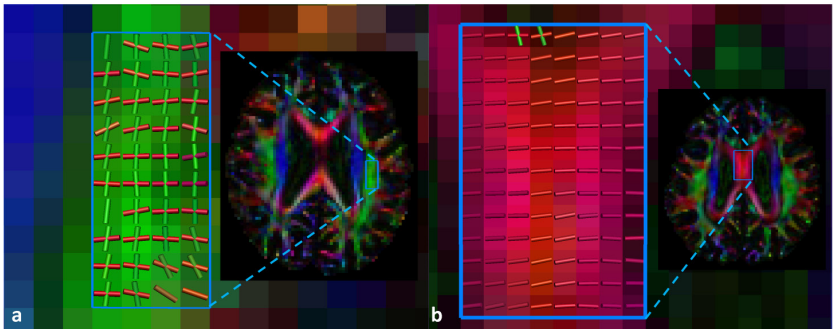

Figure 3. Fiber orientation distribution profiles estimated with the CSD method demonstrating a) two crossing fiber populations in voxels in the superior longitudinal fasciculus and b) one fiber population in the corpus callosum.

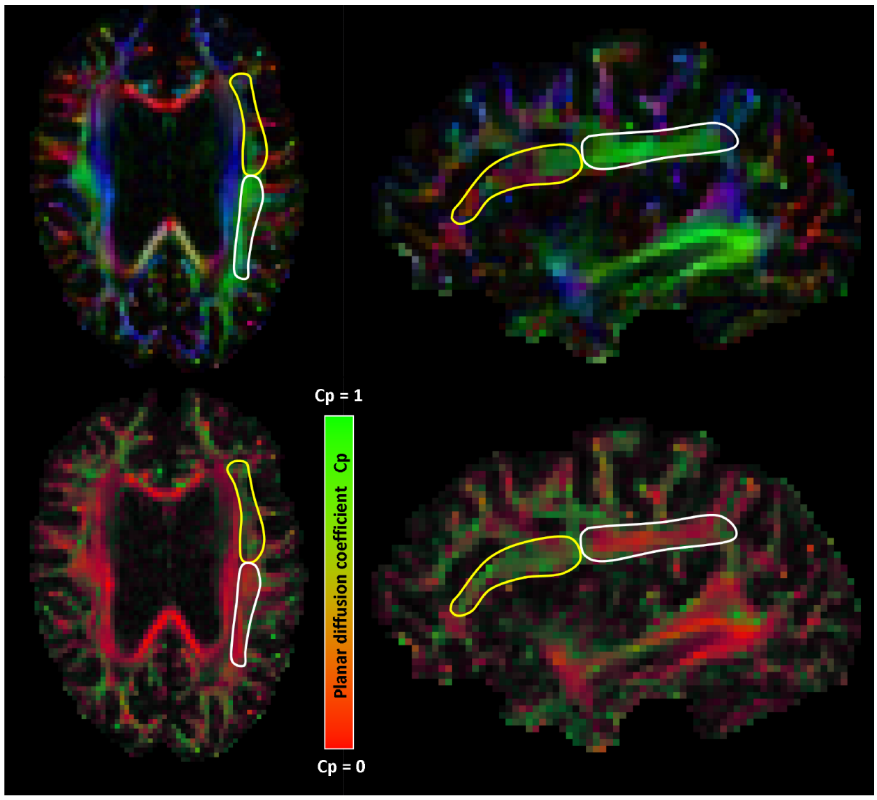

Figure 4. Sub-regions of the superior longitudinal fasciculus (SLF) marked on a directionally encoded color map (top row) and planar diffusion coefficient encoded (Cp) map (bottom row). The planar diffusion coefficient ranges from zero to one and is relatively high in voxels were the tensor has a disc-like shape, which is typically the case when two fiber populations "cross". The white line marks a sub- region of the SLF containing voxels with relatively few "crossing fibers", which is reflected by a Cp close to zero. By contrast, the more anterior sub-region of the SLF, marked in yellow, contains relatively many voxels with "crossing fibers", due to crossing with the cortico-spinal tract and/or laterally projecting fibers of the corpus callosum. This is reflected by a Cp closer to one.

Cognitive testing

All patients underwent a standardized cognitive assessment including a test assessing verbal memory: the Raven's Auditory Verbal Learning Task (RAVLT).[38] Because deficits in learning and memory are the main cognitive symptoms of (early) AD, we selected memory performance as the primary functional measure of disease severity. Immediate and delayed recall scores of the RAVLT were transformed into z-scores and averaged to obtain one composite memory score.

Statistical analyses

Differences in configurational tract characteristics (volume, length) after DTI and CSD based FT were analyzed with paired-samples T-test. The composite memory score and diffusion measures were all normally distributed. We used linear regression analyses to evaluate the relation between mean FA, MD, DA and DR values and memory performance, adjusted for age, sex, and level of education. Differences between the regression coefficients obtained with DTI- versus CSD based tractography were assessed with Steiger's Z-statistic for dependent correlations.[39]

Because DTI parameters cannot describe the underlying microstructural properties unambiguously in regions with "crossing fibers"[35,40,41], we included the planar diffusion coefficient of the diffusion tensor model as a covariate in secondary analyses[33], thereby taking the complexity of the underlying white matter structure into account. As such, we limited the adverse effect of "crossing fibers" on the relation between DTI measures (i.e. FA, MD, DR, DA) and cognition. To examine the possibility that the relation between diffusion measures and memory performance is affected by tract volume[42], we ran a separate model with age, sex, education level and estimated tract volume as covariates.

Results

CSD vs. DTI based FT

Figure 6 shows the SLF of four representative patients reconstructed with DTI and CSD based FT. In all patients, the tract volume of the SLF was larger with CSD than DTI based FT (mean tract volume ± SD (cm^3) CSD: 19.88 ± 5.25; DTI: 10.10 ± 2.78; $p<0.001$). In 75% of the patients the tract length was longer with CSD compared to DTI based FT (mean tract length ± SD (mm) CSD: 109.2 ± 10.9; DTI: 98.3 ± 13.6; $p<0.001$). The approximate tract volume of the CC segment was also larger for all patients with CSD compared to DTI based FT (mean tract volume ± SD (cm^3) CSD: 9.59 ± 0.98; DTI: 7.03 ± 0.94; $p<0.001$), whereas the mean tract length was slightly smaller (tract length ± SD (mm) CSD: 8.24 ± 0.18; DTI: 8.31 ± 0.20; $p=0.003$).

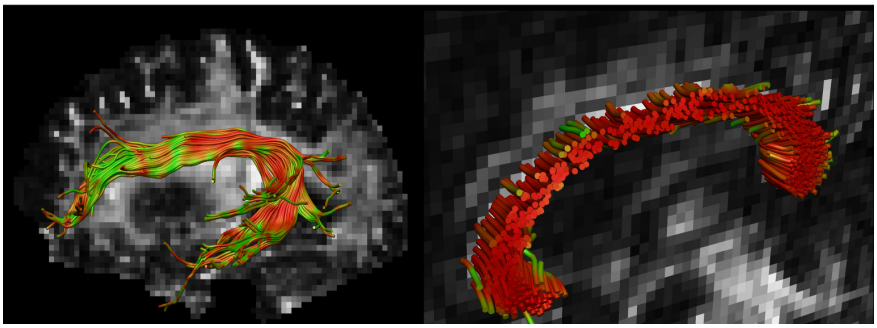

Figure 5. The superior longitudinal fasciculus (SLF) and medial segment of the corpus callosum (CC) color coded according to the value of the planar diffusion coefficient (Cp) (for interpretation of the color coding see also figure 3). The figure shows regions with "crossing fibers" reflected by a Cp close to one (green) and regions with relatively few "crossing fibers" reflected by a Cp close to zero (red). a) the SLF shows many regions with "crossing fibers" due to crossing with the cortico-spinal tract and/or laterally projecting fibers of the corpus callosum (CC) in frontal regions, and with the inferior longitudinal fasciculus in temporal regions. b) In the midsagittal segment of the CC one fiber population predominates.

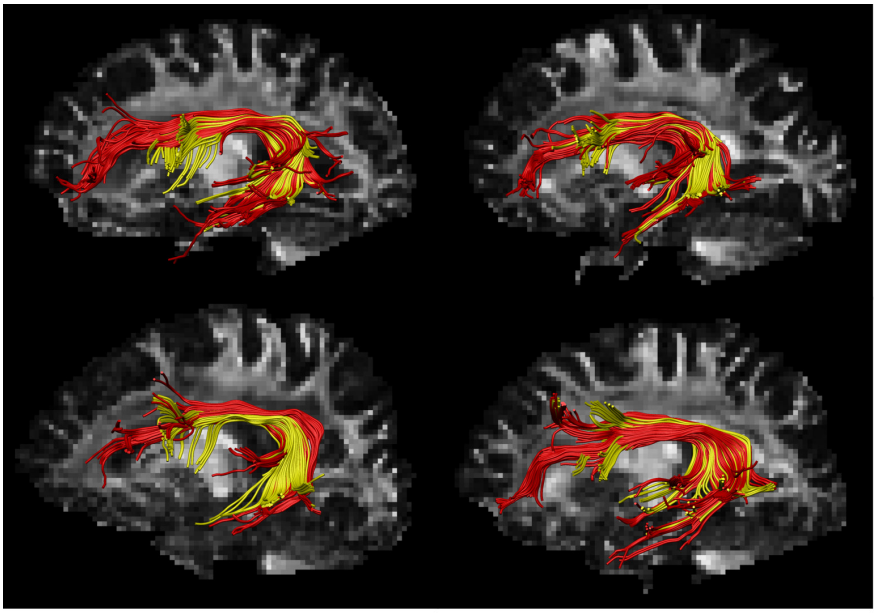

Figure 6. Segmentation of the superior longitudinal fasciculus (SLF) in four patients reconstructed with DTI (yellow) and CSD (red) based fiber tractography (FT). Delineation of the SLF resulted in larger and longer pathways with CSD compared to DTI based FT. With the DTI method, fibers of the SLF were more likely to terminate at crossings between the SLF and the cortico-spinal tract in frontal regions and between the SLF and the inferior longitudinal fasciculus in temporal regions.

Association between DTI metrics of the SLF and memory performance with CSD and DTI based FT

For the SLF, lower FA values of the SLF were associated with worse memory performance for both FT methods, but this association was only statistically significant for CSD based FT (standardized regression coefficient (95% CI) DTI: 0.39 (0.01; 0.78); p=0.054, CSD: 0.41 (0.02; 0.81); p=0.042) (*Table 2, model 1*). MD was not significantly associated with cognitive performance. Additional adjustment for the planar diffusion coefficient, reflecting the degree of fiber organization complexity, did not change the results for the DTI based method (*Table 2*, model 2). By contrast, the relation between the FA of the SLF and memory performance in combination with CSD based FT became stronger after adjustment for the planar diffusion coefficient (0.53 (0.14; 0.92); p=0.010). The modulating effect was even more pronounced for the MD: the regression coefficient became three times as large after adjustment of the planar diffusion coefficient (-0.55 (-1.07; -0.02); p=0.044). Post hoc analyses showed that memory performance was related with DR but not with DA measures (DR: -0.55 (-1.0;-0.11); p=0.018, DA: -0.22 (-0.92; 0.48); p=0.511). Adjustment for tract volume did not change these relations significantly (data not shown). Importantly, the relation between DTI parameters and memory was significantly stronger for CSD- compared to DTI based FT, for MD (Z = 4.38; p<0.0001), DR (Z = 4.18; p<0.0001), and DA (Z=2.02; p=0.02), but not FA (Z = 1.55; p = 0.06) (*Table 1, model 2*).

Tabel 1. Association diffusion parameters of the SLF and memory performance

	DTI based tractography		CSD based tractography	
	Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Model 1				
FA	0.39 (0.01; 0.78)	0.054	0.41 (0.02; 0.81)	0.042
MD	-0.18 (-0.62; 0.25)	0.383	-0.16 (-0.58; 0.27)	0.461
Axial diffusivity	0.01 (-0.45; 0.47)	0.967	0.08 (-0.39; 0.53)	0.737
Radial diffusivity	-0.27 (-0.68; 0.15)	0.195	-0.26 (-0.67; 0.15)	0.205
Model 2				
FA	0.36 (-0.04; 0.76)	0.074	0.53 (0.14; 0.92)	0.010
MD	-0.23 (-0.66; 0.20)	0.283	-0.55 (-1.07; -0.02) [a]	0.044
Axial diffusivity	-0.10 (-0.59; 0.40)	0.690	-0.22 (-0.92; 0.48) [a]	0.511
Radial diffusivity	-0.27 (-0.68; 0.14)	0.178	-0.55 (-1.0;-0.11) [a]	0.018

Data are presented as standardized regression coefficients with 95% CI.
Model 1: adjusted for age, sex, level of education
Model 2: Model 1 + adjustment for the planar diffusion coefficient, reflecting the degree of fiber organization complexity
[a] Regression coefficient is significantly larger for CSD compared to DTI based tractography, assessed with Steiger's Z-statistic.

Tabel 2. Association diffusion parameters of the CC and memory performance

	DTI based tractography		CSD based tractography	
	Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Model 1				
FA	0.31 (-0.10; 0.72)	0.134	0.27 (-0.15; 0.68)	0.197
MD	-0.39 (-0.80; 0.002)	0.051	-0.37 (-0.78; 0.04)	0.074
Axial diffusivity	-0.34 (-0.75; 0.08)	0.104	-0.35 (-0.76; 0.07)	0.097
Radial diffusivity	-0.38 (-0.79; 0.02)	0.061	-0.34 (-0.76; 0.07)	0.099
Model 2				
FA	0.54 (0.06; 1.02)	0.031	0.50 (0.01; 1.00)	0.045
MD	-0.45 (-0.86; -0.04)	0.035	-0.45 (-0.88; -0.02)	0.040
Axial diffusivity	-0.33 (-0.76; 0.10)	0.122	-0.34 (-0.77; 0.08)	0.109
Radial diffusivity	-0.51 (-0.94; -0.08)	0.022	-0.50 (-0.96; -0.05)	0.031

Data are presented as standardized regression coefficients with 95% CI.
Model 1: adjusted for age, sex, level of education.
Model 2: Model 1 + adjustment for the planar diffusion coefficient, reflecting the degree of fiber organization complexity.
Regression coefficients obtained with DTI and CSD based FT did not differ significantly, assessed with Steiger's Z-statistic.

Association between DTI metrics of the CC and memory performance with CSD and DTI based FT

We also assessed the relation between diffusion parameters and cognitive performance in a tract without "crossing fibers": the midsagittal segment of the CC. The FA of the CC was not significantly associated with memory performance with either tractography method, whereas a trend was observed for an association between memory and mean MD (DTI:-0.40 (-0.80; 0.002); p=0.051, CSD: -0.37 (-0.78; 0.04); p=0.074) (*Table 3, model 1*). After adjustment of the planar diffusion coefficient, the relation between the FA, MD and memory performance became stronger. However, the regression coefficients remained comparable between both tractography methods (all p<0.05; *Table 3, model 2*). Post hoc analyses showed that memory performance was related with DR and not with DA measures, with comparable regression coefficients with DTI and CSD based FT (-0.51 and -0.50 respectively). Again, adjustment for tract volume did not change the results significantly (data not shown).

Discussion

This is the first report on the application of CSD based FT to detect white matter abnormalities in patients with (early) AD. Our results indicate that 1) CSD based FT in combination with DTI metrics significantly increased the sensitivity to detect a relation between white matter abnormalities and memory performance in a tract with "crossing fibers" (SLF); and 2) the relation between DTI metrics and

memory was comparable between both FT methods in a tract without "crossing fibers" (midsagittal section of the CC).

In line with our expectations, fibers of the SLF were more likely to terminate in regions with "crossing fibers" with DTI-based FT. By contrast, with CSD based FT the SLF continued beyond these crossings to more temporal and dorsal frontal regions, which is in line with descriptions from autopsy studies[27,43] and with previous papers using spherical deconvolution based FT.[44] Our results extend these findings by showing that improvement of fiber tract segmentation increases the sensitivity to white matter abnormalities within the tract.

The adverse effects of "crossing fibers" on the interpretation of diffusion measures such as MD and FA have been previously demonstrated (e.g.[35,40,41]), but their impact on the detection of white matter abnormalities is not known. A number of studies have found contra-intuitive results in regions with "crossing fibers", such as the centrum semiovale, demonstrating increased FA values in patients compared to controls[45,46] and a negative correlation between FA and cognitive function.[47,48] These unexpected findings may result from degeneration of one pathway, with relatively sparing of the crossing pathway. For example in AD, late-myelinating white matter tracts such as the SLF have been shown to degenerate at an earlier stage than tracts that myelinate early in life.[49,50] This is supported by results from a recent study showing an *increased* mode of anisotropy in patients with MCI compared to controls only in areas where the SLF intersects the projection pathways.[45]

Voxels with "crossing fibers" are more likely to be included with CSD based FT. We therefore used the planar diffusion coefficient as a covariate to overcome the confounding effects of these "crossing fibers" on the diffusion metrics in relation to cognition. If two fiber populations within a voxel "cross" or "kiss", the shape of the diffusion tensor becomes more planar (disc-like). As a result, a voxel with intact crossing fibers can have a similar FA value compared to a voxel with a degenerating non-crossing fiber population. However, the planar diffusion coefficient between these voxels will be different.[51] Our results showed that co-varying for the planar diffusion coefficient effectively increased the strength of the relation between DTI metrics in the SLF and memory performance. As expected, this modulation was most pronounced in combination with CSD based FT. Adjusting for the planar diffusion coefficient also increased the association between DTI metrics and memory in the CC, despite the lack of any interdigitating fiber pathways. Possibly, this finding can be explained by the presence of residual partial volume effects between the dorsal part of the CC and the adjacent cingulum bundles. Partial volume effects also affect the tensor estimation and the measures derived from it[34,35] and may therefore confound the relation between DTI metrics and cognition in the same way.

The effects of DTI metrics on cognitive performance were more prominent for DR than for DA, suggesting that the observed association is more likely driven by myelodegeneration than by a loss of axonal integrity.[52] However, it should be noted that many more cellular characteristics, such as hydration, cell packing density and fiber diameter could cause the observed changes in diffusion measures[53-55] and that the interpretation of these diffusivity measures can be far from trivial.[40]

Our study has a number of limitations. One is the modest sample size, which may have decreased our sensitivity to detect a relation between structure and function. Still, we were able to replicate previously observed associations between diffusion measures and AD severity.[56,57] Second, FT based segmentation is laborious and time consuming. However, the advantage over automated voxel based or atlas based analyses is that it is less sensitive to individual anatomical differences, imperfect registration, and smoothing errors.[58-60] Moreover, averaging of the diffusion metrics along a fiber bundle reduces the variance in diffusion measures and thereby increases the power to detect more subtle WM changes. On the other hand, very localized changes along a fiber bundle, for instance, only in the structure's anterior part, may not be picked up when the anterior and posterior parts are combined. To limit the number of comparisons we focused in the present study on two major tracts, but future studies should demonstrate whether these findings extend to other fiber pathways containing complex and simple white matter architecture known to be affected in AD[61] or other neurological diseases.

Finally, the use of the planar diffusion coefficient as a quantitative measure to characterize "crossing fibers" may be valid in cases were two fiber bundles intersect or overlap, but may not be directly applicable in regions where three or more fiber bundles intersect. Although previous work reported that no more than two fiber populations could be observed in the SLF[62], there is still no consensus on the prevalence of multiple fiber populations.[4] In this context, future studies are needed to investigate this issue in detail and more specific measures for "crossing fibers" need to be developed to improve the sensitivity for detecting white matter abnormalities in clinical populations and to make the interpretation of structure-function relationships less ambiguous.

Since DTI based FT fails in regions with "crossing fibers", more accurate methods to characterize the microstructural properties of fiber pathways are in need. Here we showed that CSD based FT combined with standard DTI metrics increases the sensitivity to detect functionally significant white matter abnormalities in a tract with "crossing fibers" in patients with early AD compared to DTI based FT. The use of a hybrid CSD-DTI framework is therefore a promising tool to detect functionally significant white matter changes in regions with complex white matter architecture.

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Chapter 9

Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: a diffusion tensor imaging study

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Submitted

Abstract

Background

Type 2 diabetes mellitus is associated with cognitive impairment and a 2-fold increased risk of dementia. The etiology is largely unknown, but recent studies suggest that subtle microscopic abnormalities in white matter pathways play an important role.

Methods

35 non-demented older individuals with type 2 diabetes (mean age 71±5 years) and 35 age-, sex- and education-matched controls underwent a 3 Tesla diffusion weighted MRI scan and a detailed cognitive assessment. Tractography was performed to reconstruct the superior longitudinal fasciculus (SLF), uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF) and the genu and splenium of the corpus callosum (CC). DTI measures (fractional anisotropy (FA) and mean diffusivity (MD)) were compared between groups and related to cognitive performance. Analyses were adjusted for age, sex and estimated IQ.

Results

The diabetes group showed increased MD in all tracts in the left and right hemisphere ($p<0.05$), and reduced FA in the right UF. Significant Group x MD interaction effects were observed for the UF, ILF and the splenium of the CC on the domain information processing speed; and for the ILF on the domain memory (all $p<0.05$), indicating a stronger association between increased MD and worse cognitive performance in the diabetes group. These associations were independent of total white matter hyperintensity load and presence of cerebral infarcts.

Conclusions

Individuals with type 2 diabetes showed microstructural abnormalities in various white matter pathways. These abnormalities were related to cognitive functioning in patients and may contribute to the increased dementia risk.

Introduction

Type 2 diabetes is associated with a 2-fold increased risk of dementia.[1] The etiology is still largely unknown, which hampers the development of preventive treatment. Previous findings in non-demented patients with type 2 diabetes suggest that early changes in brain structure and function can contribute to the increased dementia risk.[2] The first changes in cognitive functioning include slowing of information processing speed and problems with attention, executive functioning and verbal memory.[3-5] Brain imaging studies in patients with type 2 diabetes have demonstrated a higher prevalence of lacunar infarcts.[6,7] and increased white matter hyperintensity (WMH) volume.[8,9] compared to controls, but results are not consistent.[10,11] Moreover, these lesions are only modestly associated with the cognitive decrements in type 2 diabetes[12], suggesting that other, possibly more subtle brain abnormalities play a role.

Recent brain autopsy studies report subtle microscopic vascular and non-vascular white matter abnormalities in patients with type 2 diabetes.[13,14] These subtle abnormalities cannot be detected with conventional structural MRI, but may be detected with diffusion tensor imaging (DTI).[15,16] DTI is a non-invasive technique that is sensitive to subtle white matter pathology in the brain. Damage to white matter fibers, such as demyelination and axonal changes, may lead to changes in the diffusion of water molecules and therefore to a change in the DTI parameters.[17] In addition, measurement of the directionality of the diffusion makes it possible, to obtain maps of white matter tract anatomy and to study the connectivity between brain regions.[18] Abnormalities in specific white matter tracts can lead to disruption in information transfer between brain areas resulting in deficits in cognitive functioning. Previous studies, not specifically addressing type 2 diabetes, have indeed demonstrated that DTI can provide information that is clearly complementary to the classical MRI markers of small vessel disease, such as WMH and lacunar infarcts.[19,20]

The present study examined 1) whether type 2 diabetes is associated with microstructural abnormalities in specific white matter tracts and 2) whether these microstructural abnormalities underlie decrements in cognitive functioning in non-demented older individuals with type 2 diabetes.

Methods

Participants

Thirty-five participants with type 2 diabetes and thirty-five age-, sex-, and education- matched controls were recruited through their general practitioners as part of the second Utrecht Diabetic Encephalopathy Study (UDES2). The UDES2 is a population based case control study on microvascular MRI markers

of impaired cognition in type 2 diabetes. Participants were included between april 2010 and june 2011. For inclusion, participants had to be between 65 and 80 years of age, functionally independent and Dutch speaking. Patients had to have type 2 diabetes for at least one year. Controls had to have a fasting blood glucose < 7.0 mmol/l. Exclusion criteria for both groups were TIA or non-invalidating stroke in the past 2 years or any invalidating stroke, neurological diseases (unrelated to diabetes) likely to affect cognition, known history of psychiatric disorders requiring hospitalization, indication of dementia indicated by a MMSE score ≤ 24, and alcohol abuse.
The study was approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands. Written informed consent was obtained from all participants.

Cognitive testing
All participants underwent a detailed standardized cognitive assessment, consisting of verbal and nonverbal tasks administered in a fixed order. Test selection was based on an extensive review of the literature on cognitive dysfunction in type 2 diabetes.[2] IQ was estimated with the Dutch version of the National Adult Reading Test, which is generally accepted to reflect the premorbid level of intellectual functioning. Possible dementia was assessed by the Mini-Mental State Examination (MMSE). The remaining tasks were divided into three cognitive domains to reduce the amount of neuropsychological variables in the analysis and for clinical clarity. This division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak.[21] The domain *verbal memory* was assessed by the immediate and delayed task of the Rey Auditory Verbal Learning Test. The domain *information processing speed* was assessed by the Trail Making Test - Part A, the Stroop Color-Word Test (Parts I and II), and the subtest Digit Symbol of the WAIS-III. The domain *attention and executive function* was assessed by the Trail Making Test - Part B (ratio score), the Stroop Color-Word Test (Part III; ratio score), a letter fluency test using the 'N' and 'A', and category fluency (animal naming). For each domain, the raw test scores were standardized into z-scores. The z-score for each cognitive domain was derived by calculating the mean of the z-scores for tests comprising that domain.

Medical history and biometric measurements
Systolic and diastolic blood pressure were measured on three different time points during the day and averaged. Fasting glucose, glycated hemoglobin (HbA1c) and cholesterol levels were measured with standard laboratory testing. Body mass index (BMI) was calculated as weight divided by height squared. Medication use was assessed with a standardized questionnaire.

MRI data acquisition

MRI data were acquired on a Philips 3.0 Tesla scanner (Intera, Philips, Best, the Netherlands). Diffusion MRI data were obtained using a single-shot spin echo EPI sequence with the following parameters[22] : 48 contiguous slices, reconstructed voxel size 1.72x1.72x2.50 mm^2, repetition time 6638 ms, echo time 73 ms, flip angle of 90 degrees, 45 isotropically distributed diffusion-sensitizing gradients with a b-value of 1200 s/mm^2, and one b=0 s/mm^2 (3 averages). The acquisition time was 5 min and 32 s. Data preprocessing, such as tensor estimation and correction of subject motion were performed as described previously.[23]

Fluid attenuated inversion recovery (FLAIR) scans were obtained with the following parameters: 48 continuous slices, reconstructed voxel size: 0.96x0.95x3 mm^3, repetition time 11000 ms, echo time 125 ms, inversion time 2800 ms.

Tractography

Tractography was performed with *ExploreDTI* software package (http://www.ExploreDTI.com).[24] The cognitive functions that are affected in patients with type 2 diabetes depend primary on frontal, parietal and temporal connections.[25-27] Therefore, we selected four major white matter tracts connecting those regions, namely: the superior longitudinal fasciculus (SLF), the uncinate fasciculus (UF), the inferior longitudinal fasciculus (ILF) and the genu and splenium of the corpus callosum (CC). Fiber tracts were reconstructed using constraint spherical deconvolution (CSD) based fiber tractography with a uniform seed point resolution of 2 x 2 x 2 mm^3 and a termination threshold for the fiber orientation distribution (FOD) of 0.1 (the harmonic degree of the estimated FOD coefficients was limited to 6).[28] CSD-based tractography allows fiber tracking to proceed through crossing fiber regions and is therefore one of the preferred methods for selecting white matter tracts containing voxels with multiple fiber orientations, such as the SLF, ILF and the UF.[29,30]

Tracts were reconstructed with a multiple region of interest (ROI) selection approach. Reconstruction was performed in each hemisphere and was based on a standardized atlas of white matter tracts.[31] Previously defined anatomical landmarks for ROI slice selection and placement were used to reduce subjectivity in fiber tracking. For reconstruction of the SLF three "AND" ROIs were placed, two on a coronal slice in the fronto-parietal lobe and one on a sagittal slice just after the curvature to the temporal lobe. Only those fiber trajectories that penetrated all "AND" ROIs were selected. For reconstruction of the UF, one "AND" ROI was placed on a coronal slice in the frontal lobe and one on an axial slice, after the curvature to the temporal lobe. The ILF was reconstructed by placement of two "AND" regions on a coronal slice, one in the temporal and one in the occipital lobe (*Figure 1*).

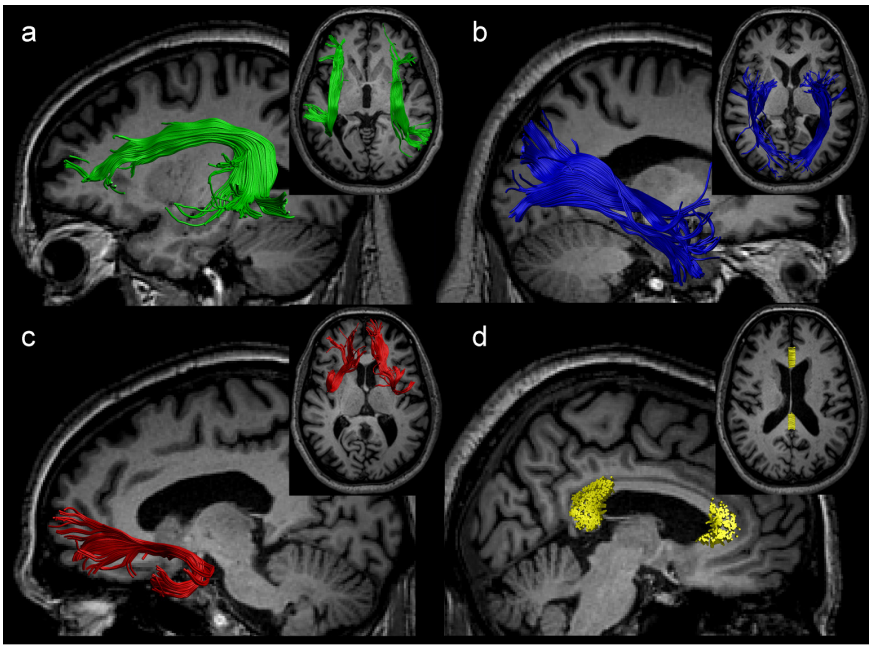

Figure 1. White matter tracts were reconstructed from each hemisphere based on a standardized atlas[31] a) the superior longitudinal fasciculus, b) the inferior longitudinal fasciculus, c) the uncinate fasciculus, and c) the genu and splenium of the medial segment of the corpus callosum.

The CC was reconstructed as described previously.[32] In summary, only the midsagittal segment of the CC was selected to exclude regions of "crossing fibers" from the more laterally projecting pathways of the CC. Subsequently, the genu and splenium of the CC were automatically segmented according to the division described by Hofer & Frahm.[33]

Diffusion parameters that were used to quantify microstructural white matter abnormalities (fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity, and axial diffusivity) were obtained for each tract. We additionally calculated the mean planar diffusion coefficient of each tract. The planar diffusion coefficient ranges from zero to one and is relatively high in voxels with a higher degree of fiber complexity such as in "crossing fiber" regions.[34]

Classical markers of small vessel disease

Quantitative assessment of WMH was performed on the FLAIR images using the Age Related White Matter Changes (ARWMC) scale.[35] by two raters (MB, YR) who were blinded for clinical data and group allocation. Five different regions were rated in the right and left hemispheres separately. In addition, cerebral large vessel infarcts and lacunar infarcts were identified. In case of disagreement consensus was obtained in a consensus meeting.

Statistical analyses

The cognitive domain scores and diffusion parameters were all normally distributed. In two participants, a cortical infarct was observed on MRI. Because tractography may not be reliably performed in areas of cortical infarction, we excluded the white matter tracts traversing through the affected regions from the analyses.

Demographic variables, cognitive performance, diffusion parameters, and classical markers of small vessel disease (WMH and lacunar infarcts) were compared between participants with and without type 2 diabetes with an independent-samples T-test for continuous variables, a Mann-Whitney U test for non-parametric data and a Chi-square test for proportions.

DTI parameters from tracts that showed significant between-group differences were selected to evaluate the relation between these parameters and cognitive performance with linear regression analyses. Because the between-group differences in DTI parameters were similar for tracts in the left and right hemisphere, we averaged diffusion measures from both hemispheres to obtain one value per tract. For significant Group x DTI parameter interactions post-hoc analyses were performed on the left and right hemisphere separately. All linear regression analyses were adjusted for age, sex, and estimated IQ. Because crossing fibers have shown to confound the relation between diffusion measures and cognition[30,36], we also adjusted for the degree of crossing fibers by entering the planar diffusion coefficient as a covariate in the model.[37]

To examine whether the relation between DTI parameters and cognition was mediated by classical markers of small vessel disease, we adjusted significant Group x DTI parameter interactions on cognition for the presence of cerebral infarcts and total WMH load.

Finally, to examine the possibility that the relation between diffusion parameters and memory performance is affected by tract volume, we ran a separate model with age, sex, estimated IQ and estimated tract volume as covariates.

Results

Between-group differences

Group characteristics are shown in *Table 1*. Groups did not differ in age, sex, or estimated IQ. Cognitive performance was not significantly different between individuals with and without type 2 diabetes on all three cognitive domains (effect sizes between 0 and -0.2; *Table 2*). Neither were there any significant differences in the presence of large vessel infarcts, lacunar infarcts or WMH load (*Table 2*). By contrast, significant between-group differences in MD values were observed in the SLF, UF and ILF in both the left and right hemisphere, and in the splenium of the CC demonstrating microstructural white matter abnormalities in patients compared to controls (*Table 3, Figure 2*). A between-group difference in FA was

Table 1. Group characteristics

	Controls (n=35)	Type 2 diabetes (n=35)	p-value
Age, years	71.0 ± 4.6	71.1 ± 4.6	0.99
Sex (% male)	60%	57%	0.81
Education level	4 (2-7)	4 (2-7)	0.90
Estimated IQ[a]	104 ± 15	101 ± 15	0.50
Systolic blood pressure (mmHg)	147 ± 23	146 ± 15	0.88
Diastolic blood pressure (mmHg)	80 ± 9	79 ± 11	0.79
Antihypertensive medication	49%	77%	0.01
BMI (kg/m^2)	26 ± 3	28 ± 3	<0.01
Total cholesterol (mmol/l)	5.6 ± 1.2	4.7 ± 0.8	0.001
HDL-cholesterol (mmol/l)	1.5 ± 0.4	1.3 ± 0.3	0.13
LDL-cholesterol (mmol/l)	3.4 ± 1.1	2.6 ± 0.8	0.001
Triglycerides (mmol/l)	1.5 ± 0.5	1.7 ± 1.0	0.37
Cholesterol lowering drugs	46%	74%	0.02
Fasting glucose (mmol/l)	5.5 ± 0.6	7.8 ± 1.8	<0.001
HbA1c (%)	5.7 ± 0.4	6.8 ± 0.8	<0.001
Diabetes duration		8.6 (1-51)	

Data are presented as mean ± SD, percentages, or median (range).
[a] Estimated by the Dutch version of the National Adult Reading Test.

Table 2. Group differences in cognitive performance and classical MRI markers of small vessel disease

	Controls	Type 2 diabetes	p-value
Cognitive performance			
MMSE	29 (25-30)	29 (25-30)	0.71
Information processing speed	0.001 ± 0.71	-0.001 ± 1.23	0.99
Attention & Executive functioning	0.07 ± 0.91	-0.07 ± 1.09	0.56
Memory	0.10 ± 1.08	-0.10 ± 0.92	0.42
MRI marker of small vessel disease			
Lacunar infarcts	7 (20%)	8 (23%)	0.77
Large vessel infarcts	0	2 (6%)	0.15
White matter hyperintensities (WMH)[a]	3 (1-13)	4 (0-10)	0.72

Data are presented as median (range), mean standardized z-scores ± SD, or number (%); estimated between-group differences are given with 95% CI.
[a] WMH were assessed in both hemispheres with the Wahlund ARWMC scale[35].

found in the right UF (p=0.046). The between-group differences in MD were driven by increased diffusivity along both the axial direction (parallel to the tract) and radial direction (perpendicular to the tract) for the left and right SLF, left and right UF, left ILF (all p<0.05); and right ILF (trend p=0.09; data not shown).

Table 3. Group differences in fractional anisotropy (FA) and mean diffusivity (MD)

	Controls	Type 2 diabetes	p-value
Superior Longitudinal Fasciculus (SLF)			
FA left	0.42 ± 0.02	0.42 ± 0.03	0.25
FA right	0.40 ± 0.03	0.39 ± 0.03	0.37
MD left	0.74 ± 0.03	0.75 ± 0.02	0.02
MD right	0.72 ± 0.03	0.75 ± 0.03	<0.01
Uncinate Fasciculus (UF)			
FA left	0.38 ± 0.04	0.38 ± 0.04	0.67
FA right	0.39 ± 0.03	0.37 ± 0.03	<0.05
MD left	0.83 ± 0.05	0.86 ± 0.05	<0.01
MD right	0.80 ± 0.05	0.84 ± 0.04	<0.001
Inferior Longitudinal Fasciculus (ILF)			
FA left	0.41 ± 0.03	0.40 ± 0.03	0.21
FA right	0.41 ± 0.03	0.40 ± 0.03	0.33
MD left	0.83 ± 0.06	0.87 ± 0.03	0.02
MD right	0.82 ± 0.05	0.84 ± 0.08	0.08
Corpus Callosum (CC)			
FA genu	0.61 ± 0.04	0.59 ± 0.05	0.15
FA splenium	0.62 ± 0.04	0.62 ± 0.04	0.83
MD genu	0.97 ± 0.09	1.00 ± 0.09	0.17
MD splenium	1.00 ± 0.07	1.04 ± 0.07	0.03

FA: dimensionless; MD: 10^{-3} mm^2/s.

Between-group difference in the splenium of the CC was explained by increased axial diffusivity (p=0.02). Important to note is that the tract volume did not differ between the diabetes and control group (p>0.05).

Association between DTI measures and cognitive performance

Significant Group x MD interaction effects were observed for the UF, ILF and the splenium of the CC on the domain information processing speed; and for the ILF on the domain memory (p<0.05), indicating a stronger negative association between MD and cognitive performance in the diabetes group. Associations between the MD of each tract and cognitive performance stratified for group are presented in *Table 4*. The Group x FA interaction effect for the UF was also significant on the domain information processing speed, indicating a stronger positive association between FA and cognitive performance in the diabetes group (standardized interaction coefficient (95% CI): 3.02 (0.57; 5.48); p<0.05). We did not observe a significant interaction effect for the SLF on any of the three cognitive domains.

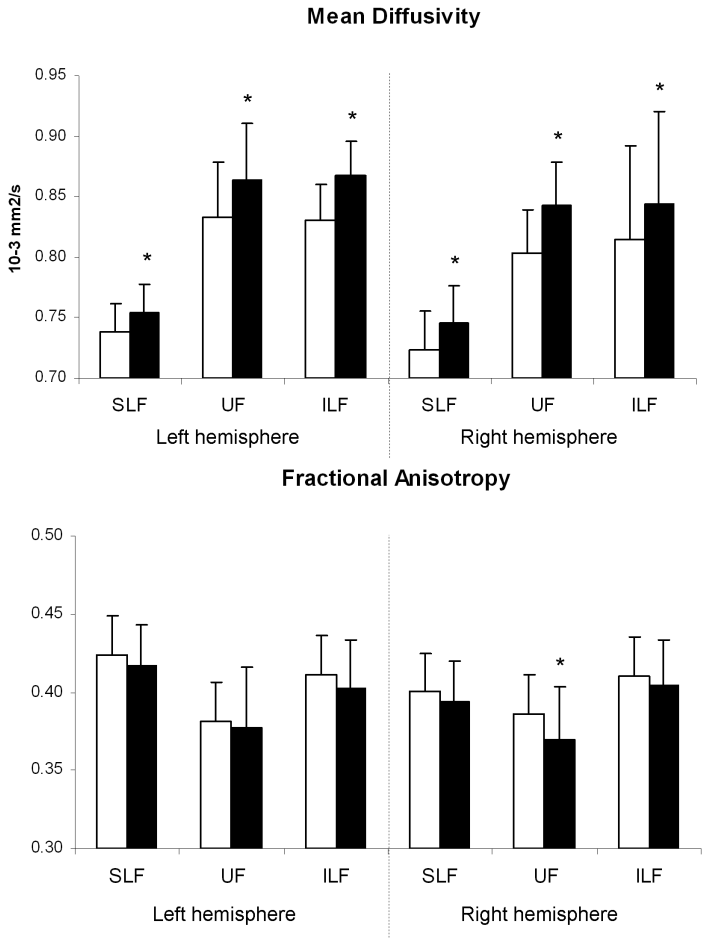

Figure 2. Differences in mean diffusivity (MD) and fractional anisotropy (FA) between the control group (white bars) and the diabetes group (black bars). High MD values and low FA values indicate reduced white matter tract integrity. SLF=superior longitudinal fasciculus; UF=uncinate fasciculus; ILF=inferior longitudinal fasciculus.

Post-hoc analyses on the significant Group x MD interaction effects showed similar interaction coefficients for the left and right hemisphere: Group x MD UF and information processing speed (left: -3.36, right: -3.40); Group x MD ILF and information processing speed (left: -2.68, right: -2.92) and Group x MD ILF and memory (left: -3.50, right: -4.30).

Adjustment for total WMH load and presence of cerebral infarcts did not modulate the significant associations (data not shown). Also, adjustment for tract volume did not change the results.

Table 4. Association between mean diffusivity (MD) and cognitive functioning stratified for group and Group x MD interaction effects

	Controls	Type 2 diabetes	P-value for Group x MD interaction effect†
Information processing speed			
MD SLF	-0.06 (-0.41; 0.30)	0.001 (-0.47; 0.47)	0.17
MD UF	-0.12 (-0.47; 0.23)	-0.37 (-0.68; -0.07)	0.01
MD ILF	0.09 (-0.24; 0.42)	-0.59 (-0.98; -0.19)	0.04
MD CC splenium	0.18 (-0.17; 0.52)	-0.49 (-0.81; -0.11)	<0.01
Attention and Executive functioning			
MD SLF	-0.28 (-0.67; 0.12)	-0.06 (-0.54; 0.42)	0.12
MD UF	-0.40 (-0.79; 0.003)	0.21 (-0.13; 0.54)	0.06
MD ILF	-0.32 (-0.70; 0.07)	-0.03 (-0.49; 0.44)	0.66
MD CC splenium	-0.11 (-0.52; 0.30)	-0.14 (-0.54; 0.27)	0.59
Memory			
MD SLF	-0.09 (-0.30; 0.47)	-0.06 (-0.52; 0.39)	0.39
MD UF	0.09 (-0.29; 0.47)	-0.07 (-0.37; 0.23)	0.25
MD ILF	0.26 (-0.08; 0.62)	-0.61 (-0.96; -0.27)	<0.01
MD CC splenium	-0.05 (-0.42; 0.33)	-0.19 (-0.56; 0.18)	0.17

Data are presented as standardized regression coefficients (95% confidence intervals), adjusted for age, sex, estimated IQ, and the planar diffusion coefficient reflecting the degree of fiber organization complexity. SLF=superior longitudinal fasciculus; UF=uncinate fasciculus; ILF=inferior longitudinal fasciculus; CC=corpus callosum. MD values of the SLF, UF and ILF are averaged across both hemispheres. † Significant interaction effects indicate a stronger association between MD and cognition in the type 2 diabetes vs. control group.

Discussion

The present study demonstrated microstructural abnormalities in several major white matter tracts in older non-demented patients with type 2 diabetes compared to controls. These microstructural abnormalities were related to worse cognitive performance independent of classical MRI markers of small vessel disease (WMH and lacunar infarcts).

Previous studies have reported modest cognitive decrements in patients with type 2 diabetes on tests measuring information processing speed, attention and executive functioning, and memory with effect sizes between 0.2 and 0.8.[38] In this study the differences in cognitive performance were less pronounced (effect sizes 0-0.2). There are several factors which may have contributed to attenuation of these effect sizes. First, vascular and metabolic risk factors were relatively well-controlled in the diabetes group, resulting in similar levels of blood pressure and even lower cholesterol values compared to controls (*Table 1*). This is a consequence of the strict diabetes treatment regime in the Netherlands and similar to other

reports from Dutch population-based cohorts.[12,39] Second, cognitive complaints were for some individuals an incentive to participate. This is reflected by low MMSE scores (<27) in both groups (*Table 2*). It is not clear how this selection bias has influenced our result, but this may have led to a relatively high number of individuals with cognitive deficits in the control group. We specifically decided not to exclude participants with mild cognitive impairment, but no dementia, because we were interested in markers of pathological brain aging. Variation in cognitive functioning was therefore important in order to detect the potential association between DTI parameters and cognitive functioning.

Despite the small differences in cognitive performance, we observed consistent group-differences in MD values in the majority of tracts, in both hemispheres, indicating microstructural white matter abnormalities in individuals with type 2 diabetes. These results are in line with recent reports from a DTI study on type 2 diabetes.[40] Based on the cognitive profile and results from previous neuroimaging studies, we expected that white matter tracts in patients with type 2 diabetes would be specifically affected in frontal, temporal, and parietal regions. Indeed, white matter abnormalities were found in the UF, SLF, and ILF. In addition, we observed group differences in the splenium of the CC, suggesting that the microstructural white matter abnormalities may also extend to occipital areas.

Importantly, increased MD was associated with worse cognitive performance in the diabetes group after adjustment for age, sex, and estimated IQ, but not in the control group, suggesting that microstructural white matter alterations underlie the cognitive decrements in older individuals with type 2 diabetes. Widespread deterioration of the brain network has previously shown to affect age-related reductions in information processing speed.[41,42] We now demonstrate that in patients with diabetes disruption of white matter tracts connecting frontal, parietal, and temporal regions are related to slowing of information processing speed independent of age. In addition, verbal memory performance was specifically related to microstructural abnormalities in the ILF, a large white matter tract crossing through the temporal lobe, a brain region well known for its role in memory processing. These region specific structure-function relationships support the hypothesis that disruption of white matter connections plays an important role in the pathogenesis of diabetes-related cognitive deficits.

The association between DTI measures, type 2 diabetes and cognition was independent of classical markers of small vessel disease (WMH and lacunar infarcts) indicating that DTI is a more sensitive marker for the subtle diabetes-related white matter abnormalities. Increases in MD and reductions in FA are previously reported in the normal-appearing white matter of patients with small vessel disease.[19] The neuropathalogical underpinnings of these DTI changes are suggested to include axonal loss, gliosis, and enlargement of perivascular space.[43-45]

However, the exact pathological basis for these DTI changes in patients with diabetes remains to be established.

How do these microstructural correlates contribute to the increased dementia risk in type 2 diabetes? Possibly, white matter alterations add or interact with grey matter pathology and thereby accelerate the progression to dementia. This would be in line with previous work showing that accelerated cognitive decline in type 2 diabetes is associated with progression of both vascular damage and global brain atrophy.[46,47] Furthermore, studies have shown local correlations between white matter and grey matter deterioration. For example, in patients with Alzheimer's disease degeneration of the posterior CC was associated with atrophy of the posterior cortices.[48] Interaction between (vascular) white matter and gray matter pathology may thus be an important mechanism of cerebral disease progression in type 2 diabetes and future longitudinal studies should examine this in more detail.

Strengths of our study are the detailed analyses of both high resolution brain imaging scans and cognitive functioning in a well defined population-based cohort. This allowed us to accurately assess the relation between these parameters. The white matter microstructure was investigated using fiber tractography. The advantage over automated voxel based analyses is that it is not sensitive to imperfect registration and smoothing errors.[49] Moreover, averaging across voxels from one tract reduces the variance in diffusion measures and thereby increases the power to detect more subtle changes in white matter structure.[50] Limitations include the relatively small study sample and possible selection bias. However, participants were recruited through their general practitioners. Bias caused by selection of hospitalized patients was thereby ruled out. Finally, to limit the number of comparisons we focused on a selection of white matter tracts, but future studies should demonstrate if these findings extend to other fiber pathways or specific segments thereof.

This study demonstrated microstructural abnormalities in specific white matter tracts in non-demented older individuals with type 2 diabetes. Microstructural changes, assessed with DTI, are a potential marker of early white matter abnormalities in type 2 diabetes and may be more sensitive than classical MRI markers of small vessel disease. Furthermore, microstructural white matter abnormalities were related to worse cognitive functioning in patients, and may also contribute to the increased dementia risk.

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Chapter 10

General Discussion

The present thesis focused on mild forms of vascular related cognitive impairment (VCI) in older individuals, addressing their course of development, risk factors, and cerebral white matter correlates. From the previous chapters it follows that the relation between vascular risk factors, structural brain changes, and cognition is complex and varies depending on the age at which these factors are assessed. Moreover, the relation between structural brain abnormalities and cognitive functioning appears to be modulated by the flexibility of the brain network and its ability to compensate for underlying pathology. In this chapter I will present my views on the dynamics of cognition, risk factors, and the underlying brain pathology in individuals with VCI.

The dynamics of cognitive decline

There is now overwhelming evidence, also from studies presented in this thesis, that vascular disease plays an important role in the development of late-life cognitive dysfunction and dementia.[1,2] Cognitive decline due to slowly developing pathological processes, such as the gradual accumulation of vascular damage, is often assumed to follow a linear progression. Results of the present thesis, however, indicate that this is not the case.

Chapter 2 and 3 show that type 2 diabetes mellitus (T2DM) is associated with modest cognitive decrements in information processing speed, verbal memory, and attention and executive functioning in non-demented patients. These subtle cognitive deficits are observed across all age groups and seem to develop slowly over time over the course of years. By contrast, a subgroup of mainly older (>70) individuals with T2DM show more severe cognitive deficits with a rapid decline. Hence, there appears to be a dissociation between modest and severe cognitive dysfunction with regard to affected age groups and course of development. Similar dissociations in cognitive trajectories were observed in a large community-based study that modeled the course of cognitive decline over 13 years prior to death: the rate of cognitive decline was gradual at first, until about 85 years of age, but accelerated in the final 4 to 5 years of life.[3] Interestingly, in this study, vascular brain pathology mainly contributed to the rate of early mild cognitive decline, while the late rapid cognitive decline seemed to be driven by pathologies other than vascular disease.[3] From this work and our findings it follows that the trajectory of cognitive decline in relation to brain disease is not linear, rather there appears to be an 'inflection point' after which the rate of cognitive decline accelerates (*Figure 1*).

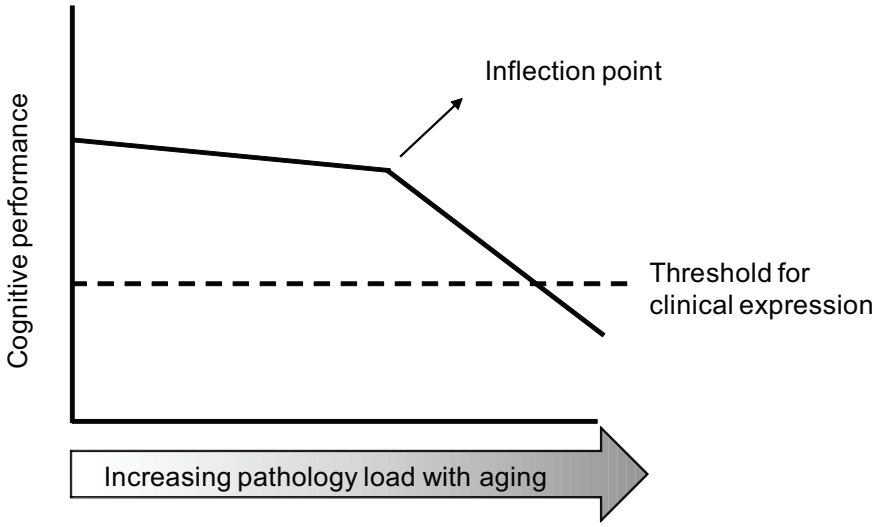

Figure 1. The non-linear trajectory of cognitive decline in relation to accumulating brain pathology. The rate of cognitive decline is gradual at first, until the total pathology load exceeds a certain threshold (inflection point). From that moment, cognitive decline accelerates and pronounced cognitive deficits emerge.

How this non-linear trajectory of cognitive decline relates to underlying brain pathology can be explained in light of the 'brain reserve model'[[4] This model assumes that individuals are able to cope with brain pathology until the reserve capacity is depleted beyond a critical threshold. Once the threshold is reached, vulnerability to further brain damage is unavoidable and clinically relevant deficits emerge. Diabetes-related (vascular) brain pathology may by itself be too subtle to deplete the cognitive reserve capacity, reflected in only modest cognitive changes. However, the development of secondary pathology on top of the diabetes-related pathology (e.g. Alzheimer-related pathology or a strategic infarct) can be eventually sufficient to exceed the threshold.

Following this view, a person with T2DM-related pathology will need less Alzheimer pathology than a person without T2DM to manifest clinically relevant cognitive deficits (*Figure 2*). This is in line with data from post-mortem studies demonstrating an equal or even decreased load of amyloid plaques and neurofibrillary tangles in patients with T2DM compared to controls, despite the same level of dementia severity.[5,6] A similar pattern was observed in brains of demented individuals with vascular lesions, but no T2DM: those with vascular lesions had fewer plaques and tangles than those without vascular lesions.[7-9] These findings suggest that there is no direct link between vascular risk factors, such as T2DM, and the development

of Alzheimer-like pathology. Instead, the development of cerebrovascular disease makes the brain more vulnerable to the effects of Alzheimer pathology developed later in life. Indeed, mixed pathologies have shown to markedly increase the odds of cognitive impairment or dementia.[7,10]

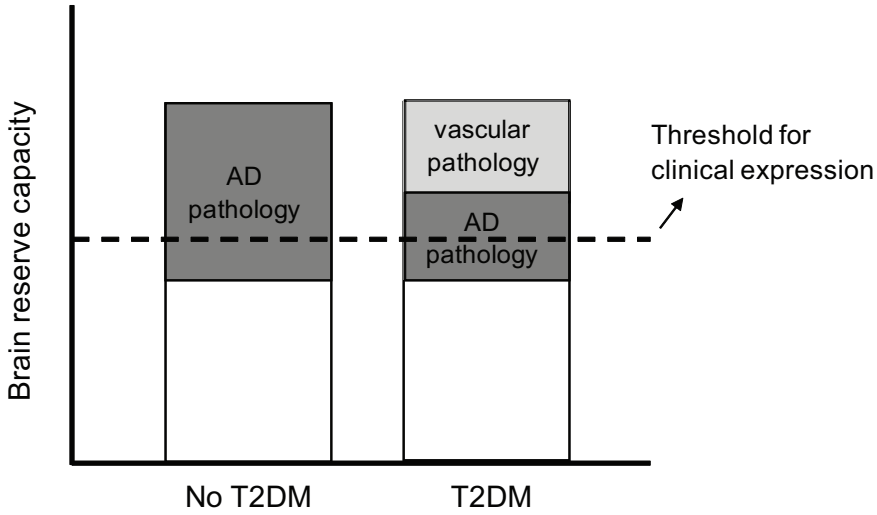

Figure 2. Two persons with initially the same amount of brain reserve capacity. Type 2 diabetes (T2DM) related pathology might be by itself too subtle to deplete the brain reserve capacity, having a modest impact on cognition. Crucially, a person with T2DM-related pathology will need less Alzheimer pathology than a person without T2DM in order to manifest clinically relevant cognitive deficits.

The dynamics of vascular risk factors

In chapter 5 we explored the time-course of vascular risk factors over 15 years in relation to late-life cognitive functioning. This association also proved to be dynamic: at midlife, high levels of blood pressure, waist-to-hip-ratio, and HbA1c were associated with poor late-life cognitive functioning, but this association gradually attenuated with increasing age. Our results are in line with those from population-based studies demonstrating that vascular risk factors are associated with an increased risk of dementia when measured at midlife.[11]], whereas these associations are not observed when risk factors are assessed at late-life.[12,13] These inconsistent findings may be explained by the complex interplay with age, duration of exposure, and modulation of risk factor levels under the influence of dementia. The results in chapter 5 showed that individuals with relatively poor late-life cognitive functioning had higher levels of blood pressure, waist-to-hip-ratio, and HbA1c over the preceding 15 years compared to individuals with good

late-life cognitive functioning. This suggests that vascular-related cognitive deficits are a consequence of long-term exposure to risk factors during life. Vascular risk factors should therefore be assessed over a long time frame, probably because their relation with cognition is mediated by slow and gradual processes, leading to accumulation of cerebral damage over the course of many years. Such processes are likely to involve the development of atherosclerosis. However, we did not find evidence for a mediating role of measures of atherosclerosis in the relation between the metabolic syndrome (MetS) and late-life cognitive dysfunction in chapter 7. An explanation for these results is that alterations in small vessels, rather than large-artery vascular disease, play an important role. Support for this hypothesis comes from brain imaging studies showing that VCI is associated with markers of small vessel disease, including WMH and lacunar infarcts, rather than large cortical infarcts.[5,14]

In very old populations, the relation between vascular risk factors and cognition is sometimes even reversed.[13,15] Chapter 5 indeed shows that in late-life poor memory performance was associated with low blood pressure levels. This inverse association may be explained by metabolic changes preceding the development of dementia.[16-18] Metabolic changes can result from neurodegenerative processes in regulatory centers such as the hypothalamus. In fact, in individuals over 85 years cognitive decline predicted subsequent decline in cholesterol and blood pressure levels.[16] Degeneration of metabolic centers may also hamper the ability to maintain adequate brain perfusion, which in turn leads to further progression of cognitive decline. Whether this vicious circle can be broken by interventions in blood pressure regulation is not clear.

Finally it should be noted that selective survival can confound the association between vascular risk factors and cognition in very old individuals. Individuals who survive until an old age may be healthier and more resistant to the development of vascular disease than those who did not survive. This could lead to an underestimation of the effect.

From these studies it follows that long-term exposure to high levels of vascular risk factors between midlife and early late-life is harmful to the brain. In late-life this association is complicated by selective survival, changes in risk factor levels under the influence of aging, and changes in risk factor levels under the influence of degenerative processes. Interventions aimed to prevent VCI by lowering vascular risk factors are expected to be most beneficial when started in midlife.

The dynamics of the brain network

The brain is a flexible system, which employs active coping strategies to maintain task performance despite a certain amount of pathology.[19] Active coping strategies involve the recruitment of alternative brain networks, and a more efficient use of intact brain networks.[19] The extent to which individuals can exploit this active coping strategy when performing a task largely depends on the integrity of the brain infrastructure: its connections.

In chapter 9 we assessed the quality of the brain network in individuals with T2DM with diffusion tensor imaging (DTI) based tractography. We showed that the microstructure of white matter pathways connecting frontal, parietal and temporal lobes is affected in patients with T2DM. Disruptions in brain connectivity may hamper the efficiency of information transfer and the recruitment of additional brain areas when performing a cognitive task. In our study, microstructural abnormalities in various white matter pathways were indeed associated with reduced information processing speed and verbal memory performance.

Evidence for altered network connectivity in individuals with VCI also comes from fMRI and EEG studies, which addressed the degree of 'functional connectivity' in relation to white matter hyperintensitiy (WMH) load. Functional connectivity refers to the correlation in activity between task-relevant brain areas, or between brain areas that are normally active at rest (the default mode network). Both fMRI and EEG studies showed reduced functional connectivity in persons with greater WMH burden during both cognitive active and passive conditions.[20-22] Impaired functional connectivity has even shown to completely mediate the relation between WMH burden and worse cognitive performance.[23] In addition, those with severe WMH showed greater activity in areas of the default-mode network compared to controls during performance of a task.[20] This suggests that the cognitive decrements in individuals with white matter lesions are driven by a failure to sufficiently activate task-related areas, and deactivate default-mode regions.

Interestingly, the association between WMH and impairment in functional connectivity was observed to be most pronounced during complex cognitive operations, when maximum efficiency in information processing and recruitment of additional brain areas become necessary.[20,23] In healthy individuals, functional connectivity becomes stronger with increasing task complexity. However, in individuals with WMH the correlation between functional connectivity and task complexity was not observed.[20,23] This is in line with our observations that individuals with vascular disease generally perform within the normal range, but

fail on tests with a high attentional demand, e.g. when two tasks are executed simultaneously or when memorizing a long list of words (chapter 2 and 7). Apparently, in those situations, the brain is not able to process at a level necessary to maintain task performance.
Overall these findings support the hypothesis that disruptions of white matter connections play an important role in the pathogenesis of vascular-related cognitive deficits.

Directions for future research

The abovementioned findings have several implications for future research on VCI. We observed that cognitive decline in the context of vascular disease generally does not become evident until the age at which additional pathology starts to develop (>70 years). At the moment that secondary pathology hits in, such as Alzheimer pathology or a strategic infarct, individuals with VCI are more likely to develop clinically manifest cognitive deficits than individuals without VCI. Before this 'second hit' not much decline is expected on a group level, because most individuals are still able to compensate for the modest amount of vascular pathology. This may explain why several case-control studies failed to quantify cognitive decline in younger populations over short follow-up periods.[24,25] It is therefore important that longitudinal epidemiological and intervention studies capture the 'moment of inflection' at which age-related cognitive decline starts to accelerate and severe cognitive deficits start to emerge (*Figure 1*).
Vascular-related cognitive impairment is probably a consequence of long-term exposure to risk factors during life. The duration of exposure cannot be captured in a single measurement. Studies addressing the association between vascular risk factors and cognition should therefore assess risk factors at multiple time points over a long time frame. However, studies with such a long follow-up period are complicated by several factors, such high attrition rates and selection bias to those who survive. Obtaining more insight in the complex interplay between exposure to vascular risk factors, age, and cognition is therefore a major challenge for future epidemiological studies.
The impact of diffuse vascular pathology on brain function seems to become clinically relevant when additional pathologies co-occur. This stresses the need for sum-scores to quantify the total amount of lesion load visible on brain scans, including different types of pathology. Total lesion load is expected to be a better predictive of cognitive outcome than individual measures of vascular lesions and brain atrophy. Moreover, such sum-scores can be used as a surrogate outcome measure in future intervention studies, particularly in the earliest asymptomatic stages. Importantly, those sum-scores should also include small cerebral changes that are not visible on conventional MRI scans, but have shown to be particularly

relevant in an early phase of the disease.[26,27] The recent development of diffusion tensor imaging, amyloid imaging, and MRI scanners with ultra-high field strengths makes it now possible to quantify these small changes in vivo.

Implications for clinical care

In clinical practice, vascular risk factors are generally treated to reduce the risk of cardiovascular events. However, it is not clear whether treatment strategies to prevent myocardial infarctions and thromboembolic stroke are also optimal to prevent VCI and dementia. It has not yet convincingly been shown that modification of risk factors for vascular disease alters the development of cognitive dysfunction or dementia.[25,28,29] However, previous intervention studies of vascular risk factor management for dementia prevention generally started treatment only a few years prior to dementia diagnosis.[30] At this moment treatment of vascular disease is probably too late. Our findings indicate that cognitive dysfunction in relation to vascular disease is a life-span process, involving accumulation of vascular damage over the course of years. Interventions aimed to reduce the risk of cognitive decline should already start in midlife. However, performing a randomized controlled trial in a large study sample over a period of 20 years is very challenging and might even be considered infeasible. A practical solution might be to perform intervention studies in high-risk groups. Risk scores, such as the one presented in chapter 6, could help to identify individuals at increased risk of VCI at a pre-symptomatic stage. In addition, follow-up time can be reduced by using imaging markers of early (vascular) brain pathology as a proxy of future cognitive decline.

It is questionable whether long-term treatment with a variety of medications will lead to a desirable outcome. Medication side effects and drug-drug interactions can have unhealthy consequences as well. Life-style interventions targeting physical activity, weight control, and smoking provide a safe alternative to reduce the risk for vascular disease, especially in midlife. Guidance and support to maintain a healthy lifestyle should be provided to those at risk for VCI, not just to prevent heart attack and stroke, but also to maintain brain health and delay dementia.

Finally, it should be noted that modest VCI is not only a risk factor for dementia, but can also be a problem by itself. Small changes in cognition can have a significant impact on day-to-day functioning, leading to cognitive complaints and affecting functional abilities. Cognitive behavioral therapy could in this regard help the patient to develop strategies for managing present-day problems in order to reduce memory failures and anxiety.[31] It is therefore important for a clinician to take the cognitive complaints in non-demented individuals seriously and provide psychoeducation for those in need.

Conclusion: Little things matter

The studies in this thesis show that small variations in brain function, as well as in brain structure, play a much larger role in the pathophysiology of VCI than previously assumed. The clinical relevance of such little changes should not be underestimated. Here I argue that these modest cognitive changes reflect subtle pathology that draws on the reserve capacity of the brain, but is still above the threshold for cognitive dysfunction to become clinically manifest. This pathology may involve microscopic vascular and non-vascular lesions in the white matter. Although not visible to the naked eye, microstructural white matter abnormalities have shown to be much stronger correlated to cognitive dysfunction than macrostructural white matter changes. This suggests that the large scale MRI markers currently used to quantify the amount of brain lesion load only reflect the tip of the iceberg. The use of new imaging techniques and neuropsychological tests sensitive to detect little structural and functional abnormalities in individuals at risk of VCI before they become large is probably the most efficient way to prevention.

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Vascular disease plays an important role in the development of dementia, including Alzheimer's disease. Individuals with vascular risk factors, such as hypertension, obesity, and type 2 diabetes, have a two-fold increased risk of developing late-life cognitive dysfunction and dementia. The development of severe vascular-related cognitive impairment (VCI) is potentially preventable if patients are recognized and treated early. The present thesis aims to gain more insight in the early stage of VCI by addressing the course of development (first part), the relation with vascular risk factors (second part), and the cerebral white matter correlates (third part).

Part 1: the development of VCI over time in individuals with type 2 diabetes mellitus

Individuals with type 2 diabetes mellitus (T2DM) are at risk of developing VCI. *Chapter 2* provides a review of the literature on cognitive dysfunction in patients with T2DM. Studies in non-demented patients show reduced cognitive performance on tests measuring attention and executive functioning, verbal memory and information processing speed. These cognitive deficits are subtle (effect sizes between -0.1 and -0.8) and observed across all age groups. In addition to the subtle cognitive deficits, T2DM is also associated with a two-fold increased risk of severe cognitive deficits and dementia, mainly at an older age (>70 years). The subtle cognitive decrements appear to occur in a much larger group of patients than the severe cognitive deficits.

In *Chapter 3* we examined how the cognitive decrements of T2DM evolves over a period of 4 years relative to controls. Sixty-nine individuals with T2DM were compared to 38 individuals without T2DM (mean age 65±5 years). At baseline, T2DM was associated with modest cognitive decrements on the domain information processing speed, memory, and attention and executive functioning (-0.2 to -0.4 decrease in adjusted z-score). These cognitive decrements were still present after 4 years. However, the rate of cognitive decline was not different between patients and controls. This indicates that modest diabetes-related cognitive deficits evolve slowly over time and are largely within the range of what can be viewed in normal aging.

From the abovementioned findings it follows that not all T2DM patients with cognitive decrements develop dementia, but only a subgroup of patients. In *Chapter 4* we aimed to identify this subgroup at increased risk of dementia by examining patients with accelerated cognitive decline over 4 years. The progression of brain abnormalities over time and the vascular risk factor profile were compared between patients with and without accelerated cognitive decline. Patients with

accelerated cognitive decline (more than 1 SD decline relative to the control group) showed a greater progression of white matter hyperintensity volume and ventricular volume over the course of 4 years than T2DM patients without accelerated cognitive decline. There were no specific differences in vascular or metabolic risk factors between the two patient groups. These results show that accelerated cognitive decline in individuals with diabetes is associated with progressive changes on brain MRI, comprising both vascular damage and global atrophy.

Part 2: exposure to vascular risk factors

High levels of blood pressure, body weight, cholesterol, and blood glucose (reflected in HbA1c) are associated with an increased risk of cognitive impairment and dementia. However, it appears that the relation between those risk factors and cognition changes depending on the age at which vascular risk factors are assessed. In *Chapter 5* the time-course of vascular risk factors over 15 years in relation to late-life cognitive functioning was evaluated. Three hundred eighty non-demented participants, aged 58±6 years at baseline, underwent 4 extensive medical examinations over a period of 15 years. Cognition was assessed at the fourth examination. The time-course of vascular risk factors was compared between individuals with relative 'poor' versus 'good' cognitive performance (defined as the lowest versus highest tertile) on three cognitive domains. Older individuals with 'poor' compared to 'good' cognitive functioning had higher levels of systolic blood pressure, waist-to-hip ratio, HbA1c, and total cholesterol/HDL ratio at midlife. However, for all risk factors except HbA1c, this relation gradually diminished with increasing age. At late-life the relation between blood pressure and memory was even reversed: high blood pressure was associated with 'good' memory performance. Overall, the 'poor' cognition group showed longer exposure to vascular risk factors across the preceding 15 years.

In *Chapter 6* we tested whether a previously developed risk score for dementia, based on midlife vascular risk profiles, also predicts more mild forms of late-life cognitive impairment. The risk score was based on the following factors: age, sex, education level, systolic blood pressure, body mass index, total cholesterol, and leisure time physical activity.
Points could be obtained for different levels of each risk factor with a maximum score of 14 points. Individuals with a risk score of 9 points or more had a 3- to 4-fold increased risk of late-life impairment on the domains information processing speed and abstract reasoning. When only modifiable risk factors were included (i.e. systolic blood pressure, body mass index, total cholesterol, and leisure time activity), the risk score predicted cognitive impairment on the domain information

processing speed and attention and executive functioning. This supports the notion that the relation with cognition is not solely driven by age and education. This study demonstrates that exposure to multiple risk factors at midlife not only predicts the development of dementia, but also the development of milder forms of late-life cognitive impairment.

A potential mechanism through which vascular risk factors can affect the brain is through the development of atherosclerosis. Individuals with multiple vascular risk factors, also referred to as the metabolic syndrome, are at increased risk of developing atherosclerotic vascular disease and cognitive impairment. In *Chapter 7* we examined whether the relation between the metabolic syndrome and late-life cognitive dysfunction could be explained by the severity of atherosclerosis. Participants were divided in 153 individuals with and 227 individuals without the metabolic syndrome. Results show that both the metabolic syndrome and markers of atherosclerosis were associated with reduced cognitive functioning 7 years later. However, the relation between the metabolic syndrome and cognitive decrements was not mediated by measures of atherosclerosis or the presence of clinical manifest cardiovascular disease. The clustering of vascular risk factors seems to affect brain function through other mechanisms than the development of atherosclerose.

Part 3: Microstructural white matter correlates of VCI

Diffusion tensor imaging (DTI) is an advanced imaging technique that is extremely sensitive to subtle white matter pathology in the brain. In addition, DTI can be used to perform tractography. Tractography is a way to visualize white matter pathways in the brain in order to study the connectivity between brain regions. Although DTI is the most widely used method to perform fibre tractography, it is known to be inadequate in regions where multiple fiber bundles cross. Recently, constrained spherical deconvolution (CSD) based tractography has been developed to overcome this limitation. The clinical relevance of CSD for the assessment of white matter abnormalities still needs to be established.
In *Chapter 8* we applied DTI- and CSD based tractography to 25 patients with early Alzheimer's disease. DTI parameters were used to assess microstructural abnormalities in each tract. In a tract with crossing fibers, the relation between microstructural abnormalities and reduced memory performance was twice as strong with CSD than with DTI based tractography. These findings indicate that, compared to conventionally applied DTI based tractography, CSD based tractography can increase the sensitivity to detect functionally significant microstructural white matter abnormalities.

CSD based tractography was then applied to patients with T2DM in *Chapter 9* to investigate whether T2DM is associated with microstructural abnormalities in specific white matter tracts, and whether these microstructural abnormalities are related to worse cognitive functioning. Participants were 35 older individuals with T2DM (mean age 71±5 years), and 35 age, sex, and education matched controls. Microstructural abnormalities were observed in white matter tracts connecting frontal, temporal, and parietal areas in patients with T2DM compared to controls. Disruption of these white matter pathways was associated with reduced information processing speed, whereas memory performance was specifically related to microstructural abnormalities in a white matter tract projecting on the temporal cortex. Importantly, these associations were stronger in the diabetes group than in the control group, after adjustment of age, sex, estimated IQ, and classical MRI markers of small vessel disease (WMH and cerebral infarcts). These results suggest that microstructural white matter alterations underlie the cognitive decrements in older individuals with T2DM.

To conclude, the studies in this thesis indicate that: 1) the acceleration of cognitive decline in individuals with VCI is triggered by the development of both vascular brain lesions and loss of brain volume; 2) prolonged exposure to vascular risk factors, such as hypertension, adiposity, and hyperglycemia can lead to the development of VCI, probably by accumulation of vascular damage over the course of years; 3) microscopic white matter lesions play an important role in the pathogenesis of VCI, by disrupting structural and functional connectivity between brain areas. Our findings contribute to a better understanding of the pathogenesis of VCI and to identify individuals at increased risk of dementia at an early stage. This may help to delay or prevent the development of dementia in the near future.

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Vaatschade in het brein speelt een veel grotere rol bij de ontwikkeling van dementie dan tot nu toe werd gedacht. Met onze westerse leefstijl komen risicofactoren voor hart- en vaatziekten, zoals diabetes type 2 (suikerziekte), hoge bloeddruk en overgewicht steeds vaker voor. Mensen met deze risicofactoren blijken op latere leeftijd een tweemaal vergrote kans te hebben op cognitieve problemen en dementie. De ontwikkeling van ernstige cognitieve problemen kan in potentie worden voorkomen als de onderliggende vaatschade op tijd wordt behandeld. Om dit te bereiken is er meer inzicht nodig in de vroege stadia van cognitieve disfunctie bij mensen met vasculaire risicofactoren. De studies in het eerste deel van dit proefschrift richten zich op de ontwikkeling van vasculaire cognitieve beperkingen over tijd. De studies in het tweede deel onderzoeken de complexe relatie tussen cognitieve disfunctie en blootstelling aan vasculaire risicofactoren. De studies in het derde deel onderzoeken welke schade in de hersenen ten grondslag ligt aan de cognitieve beperkingen bij patiënten met vasculaire schade. De bevindingen uit dit proefschrift dragen zo bij aan een vroege herkenning van mensen met een vergroot risico op vasculaire cognitieve disfunctie en het detecteren van de onderliggende hersenschade. Dit zal helpen om in de toekomst behandelstrategieën te ontwikkelen om de kans op cognitieve achteruitgang en dementie te verkleinen.

Deel 1: de ontwikkeling van vasculaire cognitieve beperkingen over tijd in mensen met diabetes type 2

Mensen met diabetes mellitus type 2 hebben een verhoogd risico op het ontwikkelen van cognitieve problemen en dementie. *Hoofdstuk 2* geeft een overzicht van studies naar cognitieve disfunctie bij patiënten met diabetes type 2. Verschillende studies laten zien dat diabetes samenhangt met verminderd cognitief functioneren, met name op het gebied van aandacht, verbaal geheugen en snelheid van informatieverwerking. Deze cognitieve beperkingen zijn relatief mild en hebben voor de meeste mensen geen grote impact op het dagelijkse leven. Aan de andere kant laten grote populatie studies zien dat mensen met diabetes op oudere leeftijd (>70 jaar) een twee keer zo groot risico hebben op het ontwikkelen ernstige cognitieve disfunctie en dementie. De milde cognitieve beperkingen lijken bij een veel grotere groep patiënten voor te komen dan de ernstige cognitieve problemen. Het is tot nu toe nog niet duidelijk hoe en bij wie de milde cognitieve beperkingen zich verder ontwikkelen tot dementie.

Om hier meer inzicht in te krijgen wordt in *Hoofdstuk 3* bestudeerd hoe de cognitieve beperkingen van mensen met diabetes zich ontwikkelen over een periode van 4 jaar. Ouderen met diabetes type 2 werden vergeleken met ouderen zonder diabetes (gemiddelde leeftijd 65±5 jaar). Tijdens de eerste meting

presteerde de diabetesgroep slechter dan de controlegroep op testen naar snelheid van informatieverwerking, geheugen en aandacht. Het verschil in cognitief functioneren tussen de groepen was echter klein, ook na een periode van 4 jaar. De diabetes groep was cognitief niet sneller achteruit gegaan dan de controle groep. Dit wijst erop dat de milde diabetes gerelateerde cognitieve beperkingen zich langzaam over de tijd ontwikkelen, vergelijkbaar met wat we zien bij 'normale' veroudering.

De bovenstaande bevindingen suggereren dat niet alle diabetespatiënten met milde cognitieve problemen later dementie ontwikkelen, maar alleen een subgroep van patiënten. In *Hoofdstuk 4* werd getracht om ouderen met een verhoogd risico op dementie te identificeren door patiënten te onderzoeken die cognitief wèl sneller achteruit gaan dan ouderen zonder diabetes. Resultaten laten zien dat diabetes patiënten met versnelde cognitieve achteruitgang zich onderscheidden van patiënten zonder versnelde cognitieve achteruitgang door een progressieve ontwikkeling van hersenschade over een periode van 4 jaar. Dit bestond uit een toename in vasculaire schade in het brein en een verlies van hersenweefsel. Het vasculaire risicofactorprofiel verschilde niet tussen de twee patiëntengroepen. Deze resultaten suggereren dat een combinatie van vasculaire en degeneratieve processen in de hersenen lijdt tot versnelde cognitieve achteruitgang in mensen met diabetes type 2.

Deel 2: de relatie cognitieve disfunctie en vasculaire risico factoren

Mensen met een hoge bloeddruk, overgewicht, hoog cholesterol, en hoog bloedglucose hebben een vergroot risico op cognitieve disfunctie en dementie. Het blijkt echter dat de relatie tussen die risicofactoren en cognitie verandert afhankelijk van de leeftijd waarop deze risicofactoren worden bepaald. In *Hoofdstuk 5* is de blootstelling aan vasculaire risico factoren over 15 jaar onderzocht in relatie tot het cognitief functioneren op latere leeftijd in 380 niet-demente deelnemers. Het cognitief functioneren werd bepaald op de laatste meting. Ouderen met een relatief 'slecht' ten opzichte van een 'goed' cognitief functioneren hadden op middelbare leeftijd een hogere bloeddruk, middel-heup-ratio, cholesterol en bloedglucose. Op latere leeftijd, het moment dat de cognitie gemeten werd, was de relatie tussen vasculaire risico factoren en cognitie niet aanwezig. Over het algemeen was de 'slechte' cognitiegroep voor een langere tijd blootgesteld aan vasculaire risicofactoren over de afgelopen 15 jaar. Deze bevindingen geven aan dat langdurige blootstelling aan hoge bloedsuiker, bloeddruk en overgewicht je cognitieve prestatie op latere leeftijd beïnvloedt. Heb je deze factoren sinds middelbare leeftijd, dan is het effect op het functioneren van de hersenen op oudere leeftijd groter.

Er bestaan risicoscores waarmee je op basis van het vasculaire risicofactor profiel op middelbare leeftijd kunt voorspellen wie op latere leeftijd een grotere kans heeft op het ontwikkelen van dementie. Milde cognitieve problemen komen op latere leeftijd 2 maal zo vaak voor als dementie. Daarom hebben we in *Hoofdstuk 6* onderzocht of een risicoscore voor dementie ook de kans op milde cognitieve disfunctie op latere leeftijd voorspelt. De risicoscore was gebaseerd op de volgende factoren: leeftijd, geslacht, opleidingsniveau, systolische bloeddruk, body mass index, cholesterol en regelmatig sporten. Punten werden toegekend voor verschillende waarden van elke factor met een maximale score van 14 punten. Mensen met een risicoscore van 9 punten of hoger, hadden 15 jaar later een 3- tot 4-maal zo grote kans op cognitieve disfunctie op de domeinen snelheid van informatieverwerking en abstract redeneren. Als leeftijd, geslacht en opleidingsniveau niet werden meegenomen voorspelde de risicoscore cognitieve disfunctie op de domeinen snelheid van informatieverwerking en aandacht. Dit bevestigt dat de relatie met cognitie niet alleen gedreven wordt door leeftijd en educatie maar ook door vasculaire risicofactoren. Deze studie laat zien dat blootstelling aan meerdere vasculaire risicofactoren op middelbare leeftijd niet alleen het risico op dementie voorspelt, maar ook het risico op mildere vormen van cognitieve disfunctie.

Vasculaire risicofactoren, zoals overgewicht, hoge bloeddruk en hoge bloedsuiker komen vaak samen voor, dit wordt ook wel 'het metabool syndroom' genoemd. Mensen met het metabool syndroom hebben later een grotere kans op cognitieve disfunctie en dementie. Tot nu toe werd er vanuit gegaan dat het metabool syndroom de hersenen beschadigt door de ontwikkeling van atherosclerose, maar dit was tot op heden nog niet goed onderzocht. Atherosclerose is een voortschrijdend proces waarbij slagaders vernauwen en verharden. Hierdoor daalt de doorbloeding van de hersenen en kunnen hersencellen niet meer goed functioneren. In *Hoofdstuk 7* hebben we 153 mensen met het metabool syndroom vergeleken met 227 'gezonde' ouderen. Resultaten laten zien dat mensen met het metabool syndroom 7 jaar later inderdaad cognitief minder goed functioneren dan 'gezonde' ouderen. Deze relatie werd echter niet verklaard door de mate van atherosclerose. Dit betekent dat het metabool syndroom de hersenen via andere mechanismen beschadigt dan via de ontwikkeling van atherosclerose. Het is belangrijk dat toekomstige studies deze mechanismen proberen te achterhalen, zodat de juiste behandeling kan worden ontwikkeld om cognitieve problemen bij mensen met het metabool syndroom te voorkomen.

Deel 3: hersenschade in de witte stof en cognitieve disfunctie

Vaatschade in de hersenen komt vaak voor in de zogenaamde 'witte stof'. De witte stof bestaat uit vezelbanen die onze hersendelen met elkaar verbinden, ook wel het 'netwerk' van het brein genoemd. Het netwerk in de hersenen zorgt voor een goede overdracht en koppeling van informatie. Als het netwerk niet goed functioneert worden hersendelen niet op de juiste manier aangestuurd. Diffusie tensor imaging (DTI) is een geavanceerde MRI techniek die extreem gevoelig is voor subtiele schade aan het netwerk van het brein.
Hoewel DTI de meest gebruikte methode is om de connectiviteit tussen hersengebieden te onderzoeken, werkt deze methode niet goed in gebieden waar verschillende vezelbanen elkaar kruisen. Het combineren van DTI met een recent ontwikkelde techniek genaamd 'constrained spherical deconvolution' (CSD), zou dit probleem kunnen oplossen. In *Hoofdstuk 8* hebben we de klinische relevantie van CSD voor het detecteren schade aan de witte stof aangetoond. De techniek werd toegepast in 25 patiënten met de ziekte van Alzheimer. In een gebied met kruisende vezelbanen, was de relatie tussen microstructurele afwijkingen en verminderde geheugenfunctie twee keer zo sterk met de gecombineerde CSD-DTI dan met de conventionele DTI methode. Deze resultaten laten zien dat het combineren van DTI met CSD de gevoeligheid voor het detecteren van klinisch relevante microstructurele schade aanzienlijk kan vergrootten.

De CSD-DTI methode werd vervolgens in *Hoofdstuk 9* toegepast op patiënten met diabetes type 2 om te onderzoeken of microstructurele schade aan het netwerk ten grondslag ligt aan de cognitieve problemen bij diabetes.
Deelnemers waren 35 ouderen met diabetes type 2 en 35 controle personen (gemiddelde leeftijd 71±5 jaar). De resultaten laten zien dat ouderen met diabetes meer schade hebben aan het netwerk dan gezonde ouderen. Daarnaast was de ernst van de schade bij diabetes gerelateerd aan een tragere snelheid van informatieverwerking en een verminderde geheugenfunctie. Dit geeft aan dat subtiele schade in de witte stof van de hersenen vaker voorkomt bij ouderen met diabetes. Deze schade zorgt mogelijk voor een verstoring van de informatie overdracht waardoor patiënten trager worden en problemen hebben met het opslaan en ophalen van informatie.

Conclusies die uit dit proefschrift kunnen worden getrokken

Mensen met vasculaire risicofactoren zoals diabetes type 2 hebben een grotere kans op dementie. Het directe effect van diabetes type 2 op de hersenen en het cognitief functioneren is echter beperkt. Het is de combinatie van subtiele vaatschade met de ontwikkeling van nieuwe hersenschade op latere leeftijd, die resulteert in versnelde cognitieve achteruitgang en uiteindelijk dementie. Vasculaire risicofactoren zoals diabetes type 2 maken het brein dus 'vatbaarder' voor het ontwikkelen van dementie.

Cognitieve beperkingen op latere leeftijd hangen niet samen met een hoge bloedsuiker, bloeddruk of overgewicht op dat moment, maar met blootstelling aan deze risicofactoren in de afgelopen 15 tot 20 jaar. Dit is waarschijnlijk het gevolg van hersenschade die sluipend over vele jaren ontstaat. Wie door middel van gezond leven de kans op dementie wil verkleinen, moet dus op tijd beginnen.

Vezelbanen in 'de witte stof' van het brein zijn van belang voor de overdracht en integratie van informatie tussen de hersengebieden. Bij ouderen met diabetes type 2 zijn de vezelbanen in de hersenen minder intact dan bij ouderen zonder diabetes. Deze schade ligt waarschijnlijk ten grondslag aan de milde cognitieve problemen van mensen met diabetes, zoals traagheid en moeite met het opslaan en ophalen van informatie.

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Chapter 2
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Chapter 3-4
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Chapter 5-7
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Yael D. Reijmer was born on the 7th of January 1982 in Jeruzalem, Israel. In 1987 she and her family returned to Holland. Between 2000 and 2005 she studied psychology at the Radboud University Nijmegen. During her study, she conducted an internship at the department of Medical Psychology in the Canisius Wilhelmina Hospital in Nijmegen. Her research project was on implicit learning in patients with Alzheimer's disease, under supervision of Prof. Dr. W. Hulstijn. In 2005 she started a Master's in Cognitive Neuroscience at the Donders Institute for Brain, Cognition and Behaviour in Nijmegen. Her main internship was carried out at the Radboud University Medical Center Nijmegen, where she examined the influence of diet on cognition and cerebral blood flow in a mouse model of Alzheimer's disease, under supervision of Dr. A.J. Kiliaan. She obtained her second Master of Science degree in 2007, after which she started a PhD project leading to this thesis at the department of Neurology of the University Medical Center Utrecht, under supervision of Prof. Dr. L.J. Kappelle, Dr. G.J. Biessels and Dr. E. van den Berg. She has presented and discussed the results obtained during this research at various national and international scientific meetings. From February 2012 she will continue her research on vascular cognitive impairment as post-doc at the department of Neurology.