COGNITIVE DYSFUNCTION IN TYPE 2 DIABETES

DETECTION AND TREATMENT IN PRIMARY CARE

Paula Sophia Koekkoek

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COGNITIEVE DISFUNCTIE IN TYPE 2 DIABETES -

DETECTIE EN BEHANDELING IN DE HUISARTSENPRAKTIJK

(met een samenvatting in het Nederlands)

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Type 2 diabetes is typically a disease of older age, although the incidence is also increasing among young adults and even adolescents.[1] The worldwide prevalence of diabetes has raised over the past decades, with 382 million people having diabetes in 2013, and is likely to increase further. This makes diabetes and its complications an important health issue.[2] Type 2 diabetes is caused by insulin resistance, often related to obesity, but also involves progressive ß-cell dysfunction.[3] Type 2 diabetes can lead to chronic complications such as cardiovascular disease, nephropathy, retinopathy and peripheral neuropathy. In recent years there has been increasing attention for another 'complication' of type 2 diabetes, namely cognitive impairment. Patients with type 2 diabetes have a two-fold increased risk of developing dementia, both vascular dementia and Alzheimer's disease.[4] Cognitive impairment in type 2 diabetes is associated with impaired self-management and an increased incidence of diabetes-related complications.[5;6] Moreover, people with type 2 diabetes with mild to moderate cognitive impairment are at increased risk of major cardiovascular events and even death.[7]

Against the background of the increasing number of patients with both type 2 diabetes and cognitive impairment and the great impact of having both diseases combined we formulated the following aims for this thesis:

1. to evaluate cognitive dysfunction in type 2 diabetes and its relation with depression and health status and the effect of intensive multifactorial treatment;
2. to evaluate tests that can be used in patients with and without cognitive signs and symptoms to detect cognitive impairment in primary care.

COGNITIVE DYSFUNCTION IN TYPE 2 DIABETES AND ITS DETERMINANTS

Cognitive dysfunction in type 2 diabetes is often mild, but can already be present in screen-detected type 2 diabetes patients.[8] Several risk factors that often co-occur with type 2 diabetes, like hypertension, obesity and hyperlipidemia, are associated with cognitive decrements.[9] **Chapter 2** of this thesis provides an overview of the different stages of cognitive dysfunction in type 2 diabetes and its relation with brain imaging abnormalities, risk factors and treatment options.

Depressive symptoms

Depression is related to both type 2 diabetes and cognitive decline and dementia.[10,11] In patients with type 2 diabetes the domains memory and information-processing speed are affected, comparable to depressed patients.[12] Depression might therefore be a mediator of the relation between type 2 diabetes and cognitive dysfunction. **Chapter 3** examines the role of depressive symptoms in the relation between type 2 diabetes and cognitive functioning.

Health status

Patient-reported outcomes are of importance for clinical care and research, because they provide information on the experiences of patients with a disease or treatment.[13] This information can be used, among others, for tailoring of treatment.[13] Health status is a patient-reported outcome and represents the level of health that an individual experiences. Physicians often assume that the diagnosis of cognitive impairment will influence health status and depressive symptoms negatively.[14] However, one might also argue that cognitive impairment for which the patient or a caregiver has not asked professional help yet, i.e. undiagnosed cognitive impairment, might be associated with a reduced health status and more depressive symptoms, because it is likely to bother patients before it is officially diagnosed. In **chapter 4** we describe whether undiagnosed cognitive impairment is associated with a reduced health status in patients with type 2 diabetes.

Intensive multifactorial treatment

A fundamental question is if cognitive functioning in patients with diabetes can be improved by treatment of metabolic and vascular risk factors. Improved glycemic control for several months in patients with high HbA1c levels has been reported to improve cognitive functioning[15] and observational studies in the general population indicate that cardiovascular risk management may reduce the risk of cognitive impairment.[10] These findings lead to the hypothesis that early and intensive multifactorial treatment of type 2 diabetes and its associated risk factors might reduce or prevent progression of cognitive decline. The ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care) study was a cluster-randomised trial in patients with screen-detected type 2 diabetes mellitus that compared the effectiveness of an intensive multifactorial treatment with routine care on cardiovascular outcome.[16] In a subset of patients from the Netherlands cognition was assessed in the ADDITION-Cognition study. This gave us the unique opportunity to examine the course of cognitive decline and the effect of an intensive multifactorial treatment on cognitive functioning in patients with type 2 diabetes. In **chapter 5** the results of the ADDITION-Cognition study are described.

DIAGNOSING COGNITIVE IMPAIRMENT IN PATIENTS WITH TYPE 2 DIABETES

The consequences of cognitive impairment in type 2 diabetes have become more and more known. Cognitive impairment however often remains unrecognized, even when patients or their relatives report symptoms.[17;18] Because of this underdiagnoses and the possible consequences of undiagnosed cognitive impairment, routine examination of cognitive impairment in elderly patients with type 2 diabetes has been advocated.[19] The

American Diabetes Association recommends to individualize diabetes treatment and to adjust management to the capacity of patients, thereby specifically taking into account cognitive functioning.[20] However, compared with other potential complications and co-morbid conditions of type 2 diabetes, the diagnostic evaluation of diabetes-associated cognitive impairment is underdeveloped.

In the diagnostic evaluation of cognitive impairment two situations should be distinguished. First, the situation in which a patient visits the general practice with complaints about cognitive functioning. Second, the situation in which patients are pro-actively approached for examination of cognitive functioning. For both situations a quick and reliable cognitive test is desirable, but the tradeoff between different aspects of a test and its preferred diagnostic properties are dependent on the prior probability of cognitive impairment. When the prior probability of dementia is high, based on a patients' signs and symptoms, a more elaborate test is allowed if this leads to a more certain diagnosis. However, when a patient without complaints is checked for cognitive impairment, the prior probability of cognitive impairment is lower. A simple and efficient test that makes cognitive impairment unlikely is than more appropriate. Currently, the Mini-Mental State Examination (MMSE) is used for all situations, independent whether the suspicion of cognitive impairment is high or low and whether complaints are present or not. The MMSE, however, is a relatively time consuming test and is mainly suitable for confirming a diagnosis of dementia. Other cognitive tests have been developed that seem more appropriate for quickly ruling out cognitive impairment, but a practical guide advising which test should be used based on the prior probability of cognitive impairment, is lacking for primary care. In **chapter 6** we try to fill this gap and describe a diagnostic algorithm for the evaluation of patients that visit the general practice with signs and symptoms of cognitive impairment.

Proactively approaching patients for examination of cognitive functioning is debated in the literature because no cure for cognitive impairment exists. Opponents of such case-finding or "screening" for cognitive impairment believe that diagnosing cognitive impairment when the patient visits the doctor when he/she thinks it is time (e.g. timely detection) is early enough.[21] However, as we argue in **chapter 7**, we believe that early detection of cognitive impairment in patients with type 2 diabetes is not only "gloom and doom", but evidence for an adequate procedure is needed.

Some of the recent developed cognitive tests are self-administered paper-and-pencil tests that the patient can fill out without much help of a professional. In a memory clinic setting two of these tests, the Test Your Memory test (TYM)[22] and the Self-Administered Gerocognitive Examination (SAGE)[23], have been shown to measure a broader range of cognitive domains than the MMSE and they were also able to detect mild cognitive impairment. These self-administered cognitive tests could be promising tests in a case-finding strategy for the detection of cognitive impairment in patients with type 2 diabetes in primary care, thereby facilitating tailoring of diabetes treatment. **Chapter 8**

describes the performance of the TYM and the MMSE compared to a comprehensive neuropsychological assessment in a sample of the ADDITION-Cognition population. **Chapter 9** reports the design of the Cognitive Impairment in Diabetes (Cog-ID) study. With the Cog-ID study we aim to establish an efficient stepped diagnostic procedure to detect undiagnosed cognitive impairment in patients with type 2 diabetes aged 70 years or over, starting with a self-administered cognitive test. In **chapter 10** we report the diagnostic accuracy of the TYM and the SAGE, as a first step in a case-finding strategy.

Finally, in **chapter 11**, we discuss our main findings and implications for clinical care and future research.

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PART I

COGNITIVE DYSFUNCTION IN

TYPE 2 DIABETES AND ITS DETERMINANTS

CHAPTER 2

COGNITIVE FUNCTION IN PATIENTS WITH DIABETES MELLITUS: GUIDANCE FOR DAILY CARE

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Guy E. H. M. Rutten, Geert Jan Biessels

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ABSTRACT

Diabetes mellitus is associated with an increase in the risk of dementia and the proportion of patients who convert from mild cognitive impairment (MCI) to dementia. In addition to MCI and dementia, the stages of diabetes-associated cognitive dysfunction include subtle cognitive changes that are unlikely to affect activities of daily life or diabetes self-management. These diabetes-associated cognitive decrements have structural brain correlates detectable with brain MRI, but usually show little progression over time. Although cognitive decrements do not generally represent a pre-dementia stage in patients below the age of 60-65 years, in older individuals these subtle cognitive changes might represent the earliest stages of a dementia process. Acknowledgement of diabetes-associated cognitive decrements can help to improve understanding of patients' symptoms and guide management. Future challenges are to establish the importance of screening for cognitive impairment in people with diabetes, to identify those at increased risk of accelerated cognitive decline at an early stage, and to develop effective treatment.

INTRODUCTION

Diabetes mellitus is a common metabolic disorder that can lead to chronic complications such as cardiovascular disease, nephropathy, retinopathy and peripheral neuropathy. Both type 1 and type 2 diabetes are characterised by hyperglycaemia, but their pathophysiology, associated comorbidities and epidemiology are different (table 1). Type 1 diabetes accounts for 5-10% of diabetes cases and mostly develops in childhood or early adulthood.[1] Type 2 diabetes is caused by insulin resistance, which is often related to obesity, but also involves progressive ß-cell dysfunction.[2] Type 2 diabetes is typically a disease of older age, although its incidence has increased in young adults and even in adolescents during the past two decades.[3] The worldwide prevalence of diabetes has increased during the past five decades, with 382 million people with diabetes in 2013, and is likely to increase further, making diabetes and its complications important public health issues.[4]

Awareness is increasing of subtle structural and functional cerebral changes in diabetes, which can manifest themselves in cognitive dysfunction. This increasing awareness is shown by a steady increase in publications about topics ranging from detailed cognitive testing and advanced brain imaging to epidemiological surveys. However, little guidance is available for the application of available knowledge about the daily clinical management of cognitive dysfunction in patients with diabetes. In this Personal View, we provide a framework that links different stages of cognitive dysfunction in type 1 and type 2 diabetes with brain-imaging abnormalities, risk factors, and treatment options. Additionally, we address the issues surrounding early identification of patients at increased risk of accelerated cognitive decline, and suggest possible therapeutic approaches.

TYPE 1 DIABETES MELLITUS

Cognitive function

Neuropsychological studies in patients with type 1 diabetes consistently report subtle changes in cognitive performance compared with individuals without diabetes, particularly in general intelligence, psychomotor speed, and mental flexibility. In a systematic review,[5] performance on these domains in adult patients was on average half an SD (0.3-0.7 SDs) below that of people without diabetes. Additionally, overall cognition and the visual perception domain were slightly affected (0.3-0.4 SDs less than people without diabetes), but the domain learning and memory was not reduced.[5] In cross-sectional studies, the effect sizes of the cognitive decrements (decrements of SD) seem to be consistent across age groups, from young adults up to those aged up to 70 years (figure 1).[5,6]

Type 1 diabetes often has its onset in childhood or adolescence. Decreased cognitive

Table 1. Characteristics of type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Pathophysiology	Autoimmune disorder with destruction of pancreatic cells leading to insulin deficiency	Insensitivity to insulin and progressive ß-cell dysfunction
Age of onset	Childhood or early adulthood	Adulthood; prevalence increases with age
Cognitive dysfunction	Subtle changes in all age groups, resulting in reduced intelligence, processing speed, and mental flexibility, usually with slow progression over time; link with dementia not established yet	Subtle changes in all age groups, resulting in reduced memory, processing speed, and executive functioning, usually slowly progressive over time; relative risk for MCI and dementia increased
MRI findings in patients without dementia	Reduced brain volume, as a result of altered brain development or atrophy; altered structural and functional connectivity	Modest brain atrophy, increased burden small vessel disease; disturbed structural and functional connectivity

performance in adults might therefore be a result of changes in cognitive function that began in childhood. A meta-analysis[7] of studies comparing cognitive function in children (aged ≤19 years) with type 1 diabetes with that of children without diabetes reported reduced performance of about 0.2 SDs in the same domains as those affected in adults with type 1 diabetes.[7] Changes in cognitive function seem to develop soon after diabetes onset, with only slow progression thereafter.[8] Results of longitudinal studies confirm these trajectories. In 1144 participants from the Diabetes Control and Complications Trial (DCCT),[9] no clear deterioration of average cognitive performance (in overall performance or in particular domains) was reported during the course of 18 years (mean age at study entry 27 years). However, small subgroups of patients with type 1 diabetes might show accelerated cognitive decline, particularly those with advanced diabetic microvascular disease.[10]

Uncertainty still exists about the relation between diabetes and cognitive decline in patients with type 1 diabetes aged 70 or older, and about the link between type 1 diabetes and dementia risk. In view of the increasing longevity of people with type 1 diabetes, future studies should address this knowledge gap.

Brain imaging

Changes in cognitive function in people with type 1 diabetes are accompanied by structural brain abnormalities on MRI. Compared with people without diabetes, middle-aged patients with type 1 diabetes had reduced grey matter volumes in the frontal lobe (6-19% smaller) and the adjacent supramarginal and postcentral gyri (8-13% smaller).[11] In many patients these volumetric changes might have their origin in childhood, since

reductions in grey matter volume have been reported in children (roughly 4% reduction in volume)[12] and in young adults with childhood diabetes onset (roughly 10% reduction in volume).[13] In adult patients aged 20-40 years, diabetes onset before the age of 7 years was associated with larger ventricular volumes than in patients with a later diabetes onset (aged 7-17 years).[14] Reduced brain volume in people with type 1 diabetes has been linked to disturbed integrity of fibre tracts connecting the main cortical areas.[15] Additionally, structural (DTI)[16] and functional (fMRI)[17] imaging studies show disturbed brain networks in patients with type 1 diabetes compared with those without diabetes, which are associated with reduced cognitive performance.[15;18] These features make connectivity measures interesting brain imaging markers for type 1 diabetes. Thus far, few studies have addressed the relation between type 1 diabetes and cerebral small vessel disease, and results are inconclusive.[6;19]

Risk factors

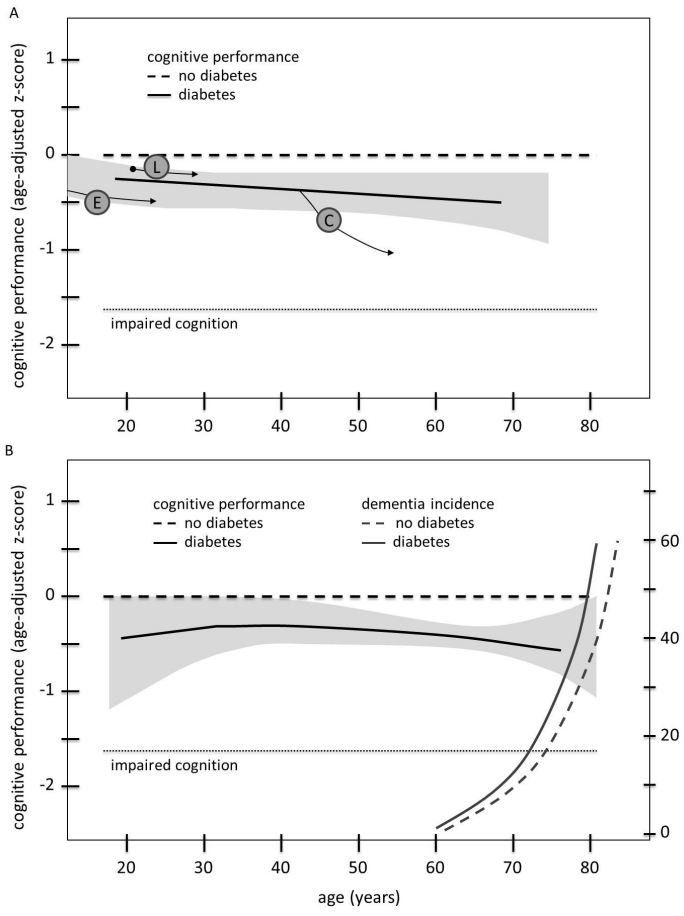
Early diabetes onset is one of the most consistent risk factors for reduced cognitive performance in adults with type 1 diabetes, probably as a result of the vulnerability of the developing brain to metabolic disturbances.[8] Moreover, patients with peripheral microvascular complications, especially retinopathy and nephropathy, show accelerated decline in psychomotor efficiency[10;20] and reorganisation of functional connectivity on fMRI,[17] compared with patients with diabetes but without these complications. Poor glycaemic control, as shown by increased haemoglobin A1c (HbA1c) concentrations, has been linked to accelerated decline in psychomotor efficiency[9] and disturbances of structural connectivity in DTI.[16] Severe hypoglycaemic episodes (ie, episodes severe enough to need help from others for recovery) have likewise been associated with cognitive decline in small case series.[8] However, neither the findings from a meta-analysis[5] of cross-sectional studies nor those from the 18 years of follow-up[9] of DCCT participants showed a relation between the occurrence of severe hypoglycaemic episodes and cognitive dysfunction.

Vascular risk factors, such as smoking, hypertension and high body-mass index are associated with decreased cognitive function in middle-aged adults with type 1 diabetes.[10;20;21] Moreover macrovascular disease, which is defined as a composite measure of coronary artery disease, peripheral artery disease, and carotid intima-media thickness, predicted reduced psychomotor efficiency.[10;20]

Management

The DCCT is the only randomised trial in patients with type 1 diabetes thus far with cognition as an outcome measure. In the DCCT,[9] intensive therapy, with three or more daily insulin injections or continuous subcutaneous insulin infusion, was compared with conventional therapy with one or two daily insulin injections. Prevention and slowing of progression of microvascular complications was the primary endpoint. Additionally,

Figure 1. Trajectories of cognitive dysfunction in type 1 and type 2 diabetes



(A) Cognitive dysfunction in patients with type 1 diabetes. Cognitive decrements can be detected soon after onset of diabetes, often in childhood. The width of the shaded area indicates the uncertainty of the estimates, which is larger in older age groups (>65 years for type 1, >80 for type 2 diabetes) because of the small number of studies. In young adults with type 1 diabetes, cognitive decrements are largest in individuals with an early diabetes onset (black arrow E), and smaller in individuals with a later onset (arrow L). Estimates of the diabetes-associated decrements do not clearly increase with age, consistent with slow progression of the decrements over time. However, some individuals, particularly those with severe microvascular complications (arrow C), might show accelerated decline. (B) In patients with type 2 diabetes, estimates of mean cognitive decrements are likewise mostly independent of age. By contrast, the incidence of dementia (grey lines), which is increased in people with diabetes, is strongly dependent on age. Modified from Biessels and colleagues.[40]

cognition was monitored closely, because of an expected (and observed) increase in incidence of severe hypoglycaemic episodes with intensive therapy (around 40 severe hypoglycaemic episodes per 100 patient-years). Cognitive function was similar in the two treatment groups, showing that intensive therapy was safe with regard to cognitive performance, but also that the intensive therapy group had 2% lower concentrations of HbA1c (20mmol/mol), maintained for an average of 6.5 years, which did not lead to improved cognitive outcomes in the intensively treated group.[22]

TYPE 2 DIABETES MELLITUS

Cognitive function

Compared with people without diabetes, patients with type 2 diabetes perform slightly worse at a range of cognitive tasks. For memory, processing speed, and executive function cognitive performance is on average 0.3-0.4 SDs lower than that of people without diabetes.[23;24] These subtle changes in cognitive performance have been reported from adolescence[25] up to the age of 80 years (figure 1). Because several domains are affected in patients with type 2 diabetes, a diminished ability to efficiently process unstructured information might be a common feature, resulting in decreased performance on neuropsychological tasks and difficulties in memory tasks.[26] This profile of cognitive dysfunction is thought to be a result of a decline in efficiency or effectiveness of processing resources, which is likewise seen in cognitive aging.[27]

Patients with newly identified type 2 diabetes detected by screening, people with impaired fasting glucose and people with metabolic syndrome (but without type 2 diabetes) show cognitive decrements in the same domains as patients with manifest type 2 diabetes.[28-30] The processes underlying cognitive dysfunction seem to start in the prediabetic stages and progress subtly over time (figure 1). Results of longitudinal studies show that the speed of cognitive decline in patients with type 2 diabetes is in the same range or up to two times faster than that of normal aging.[31-34]

Results of prospective population-based studies link diabetes to an increased risk of mild cognitive impairment (MCI) compared with people without diabetes.[35-37] This increased risk involves both amnestic and non-amnestic MCI (textbox 2), although the relation with the non-amnestic MCI is attenuated if other vascular risk factors are taken into account.[35;36] In people with amnestic or non-amnestic MCI, the proportion of patients who convert from MCI to dementia is 1.5-3 times higher for those with diabetes compared with those without.[38;39]

Results of epidemiological studies also link type 2 diabetes to an increased dementia risk. A meta-analysis including data from 11 studies of more than 30 000 people, of whom 16% had type 2 diabetes, showed that the relative risk (RR) for dementia was 1·51 (95% CI 1·31–1·74) in people with diabetes compared with those without.[37] Therefore,

the diabetes-attributable risk of dementia of 6-7% (ie, one in 15 cases of dementia is attributable to diabetes). This attributable risk might be even higher in populations in which diabetes is more common, and might increase with increasing diabetes prevalence.[4] The increased dementia risk in people with diabetes includes both vascular dementia, with an RR of 2·48 (2·08–2·96), and Alzheimer's disease, with a RR of 1·46 (1·20–1·77).[37] Nevertheless, because the absolute risk of development of Alzheimer's disease is higher than that of development of vascular dementia, Alzheimer's disease is the most common type of dementia in people with diabetes.[37]

Indications that the risk of dementia is increased in the prediabetic stages are clear, since prediabetes is associated with an increased incidence of dementia.[40;41] This finding raises the question of whether diabetes (ie, factors implicated in glucose dysregulation) increases the risk of dementia, or whether this risk is attributable to other diabetes-associated factors, particularly an adverse vascular risk-factor profile. In population-based cohort studies of older individuals (average age >65 years), adjustment for vascular risk factors did not weaken the association between diabetes and dementia.[42] Nevertheless, the role of an adverse vascular risk-factor profile – even before diabetes onset – in the dementia risk in patients with diabetes will require further study.

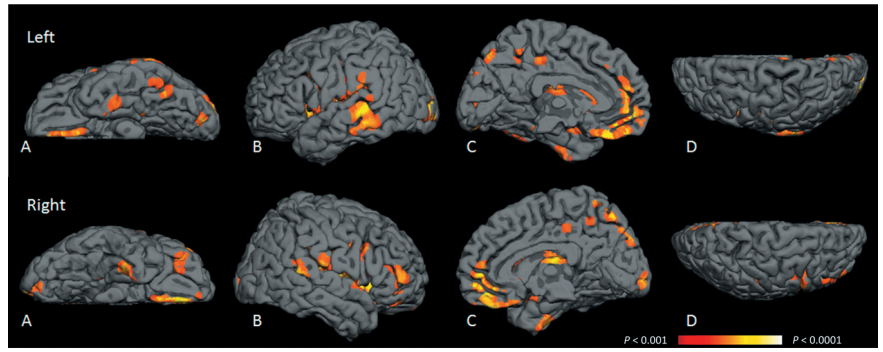
Whether increased risk of Alzheimer's disease in people with diabetes involves an interaction between glucose dysregulation and the core molecular processes – ie, aberrant amyloid-ß processing, involving generation of small toxic amyloid-ß oligomers, and aggregation of the microtubule-associated protein MAPT– that are thought to underlie Alzheimer's pathological changes is debated.[43] Despite the epidemiological link between diabetes and a clinical diagnosis of Alzheimer's disease, and many studies with experimental models linking aberrant cerebral insulin homeostasis to disturbances in amyloid and MAPT processing,[44] autopsy studies have reported a decreased burden of Alzheimer's pathological changes in the brains of people with diabetes compared with those in people without diabetes, whereas the burden of vascular pathological changes is clearly increased.[45;46] These post-mortem findings have been complemented by results of PET imaging studies showing that diabetes is associated with an Alzheimer's-like pattern of glucose hypometabolism in the bilateral angular gyri, posterior cingulate and precuneus, and inferior temporal cortical regions from both hemispheres, but not with increased amyloid deposition.[47]

Brain imaging

Type 2 diabetes is associated with a reduced brain volume.[48-51] Grey matter loss was most prominent in the medial temporal, anterior cingulate, and medial frontal lobes, and white matter loss was most prominent in frontal and temporal regions (figure 2).[52]

Results from longitudinal studies[48;53;54] show that reductions in brain volume occur slowly during the course of years, at a speed that only modestly exceeds normal age-related loss of brain-volume. Smaller grey and white matter volumes were associated

Figure 2. Probability map of location of grey matter atrophy attributable to type 2 diabetes



Voxel-based morphometric analysis was used to create a probability map of areas of grey matter atrophy attributable to type 2 diabetes, when adjusted for age, sex, education, and total intracranial volume. Highlighted voxels are the areas most likely to have grey matter atrophy attributable to type 2 diabetes. (A) Inferior region. (B) Temporal region. (C) Medial region. (D) Superior region. Reproduced from Moran and colleagues,[52] by permission of American Diabetes Association. For details, see original paper.

with, and mediated, reduced executive function, processing speed, and memory,[51;52] in patients with type 2 diabetes, but not in all studies.[48] Progression of cerebral atrophy in patients with type 2 diabetes has been linked to accelerated cognitive decline.[55]

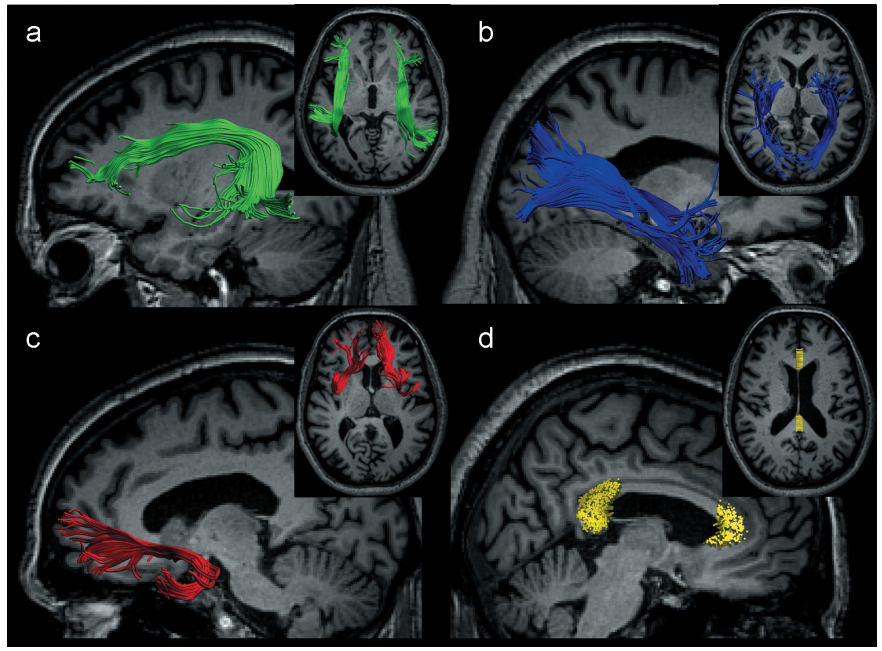
In view of the links between type 2 diabetes and cerebrovascular disease, particularly ischaemic stroke,[56] many studies have investigated the association of diabetes with damage to the brain vasculature as a potential mediator of cognitive dysfunction. Lacunar infarcts on MRI occur about twice as often in people with type 2 diabetes than in those without diabetes.[51;57] Although several studies report that the burden of white matter hyperintensities is not increased in patients with type 2 diabetes,[49;52] other studies report a modest increase (around 20%) in the volume of white matter hyperintensities compared with people without diabetes.[48;51;54;58]

Alterations in structural and functional connectivity have been identified as possible brain imaging markers of type 2 diabetes (figure 3).[59;60] Although abnormalities in these connectivity markers are not specifically associated with particular signs or symptoms, they are clearly linked to cognitive function in people with type 2 diabetes.[60] Longitudinal studies should further investigate the prognostic usefulness of connectivity markers in prediction of accelerated cognitive decline.

Risk factors

The subtle cognitive changes reported in people with type 2 diabetes do not necessarily have the same risk factors as those for MCI and dementia.[40] Risk factors for the subtle

Figure 3. White matter tracts reconstructed from diffusion tensor imaging scans



Reconstructed tracts: (A) the superior longitudinal fasciculus, (B) the inferior longitudinal fasciculus, (C) the uncinate fasciculus, and (D) the genu and splenium of the corpus callosum. In patients with type 2 diabetes, diffusion metrics within these tracts differed significantly from age-matched and sex matched controls. Within the type 2 diabetes group diffusion metrics in specific tracts were related to specific cognitive deficits. Reproduced from Reijmer and colleagues.[60] For details see original paper.

cognitive changes in patients with type 2 diabetes have mostly been investigated in cross-sectional studies with modest sample sizes. Identification of risk factors for dementia and MCI in people with type 2 diabetes is complex and requires large cohort studies with prolonged follow-up.

Studies that have addressed the relation between glycaemic control (as measured by HbA1c concentrations) and cognitive dysfunction in type 2 diabetes have reported mixed results.[40] The largest studies[61;62] thus far reported that the relation between HbA1c and performance of different cognitive domains or in tests of cognitive performance was either weak or absent. Only very high HbA1c concentrations (>10% or >86 mmol/mol) are associated with a moderately increased risk of dementia.[63] Peripheral microvascular complications of diabetes, which develop as a result of long-term exposure to hyperglycaemia, have also been linked to cognitive dysfunction in type 2 diabetes.

Albuminuria, as a marker of nephropathy, is associated with accelerated cognitive decline,[64;65] and the result of several studies have linked diabetic retinopathy to cognitive decline[66] and to an increased risk of dementia in patients with type 2 diabetes.[67]

By contrast with the aforementioned studies in patients with type 1 diabetes, the occurrence of (incident) severe hypoglycaemic episodes is associated with accelerated cognitive decline and an increased risk of dementia in patients with type 2 diabetes older than 65 years.[63;68-70] This link is likely to be bidirectional, as cognitive impairment increases the risk of hypoglycaemia probably through failure of diabetes self-management leading to medication errors.[70-72]

Cerebral and peripheral macrovascular disease (eg, stroke, myocardial infarction, cardiovascular disease, peripheral arterial disease) has consistently been shown to be related to cognitive decline[73] and to increased risk of dementia in patients with type 2 diabetes.[63;74] However, findings about the relation between vascular risk factors and cognition are more heterogeneous.[40;75] This heterogeneity might be due to the complex relation between vascular risk, cognitive decline and age, for which midlife, rather than late-life, exposure to vascular risk factors shows the strongest relation to late-life cognitive decline and dementia.[76] Hence, studies done in older individuals (age >60-70 years) might not be able to identify the relation between these factors, cognitive decline and dementia. A bidirectional association exists between depression and type 2 diabetes –depression can be predictive of the development of diabetes, and diabetes can be associated with future depression.[77] Although the exact biological processes underlying these associations are still debated,[77] depression is clearly an important factor in the relation between type 2 diabetes and cognitive dysfunction, because depressive and cognitive symptoms overlap, and depression is linked to late-life cognitive decline and dementia.[78] In the ACCORD-MIND study,[79] for example, depression in patients with type 2 diabetes was associated with increased cognitive decline in all cognitive domains compared with patients with type 2 diabetes without depression. Moreover, results from two large cohort studies showed that depression is associated with a doubled risk of dementia in patients with type 2 diabetes.[80;81] However, cognitive dysfunction and depressive symptoms have been shown to occur independently in patients with type 2 diabetes, with no difference in cognitive function in patients with or without mild depressive symptoms.[82]

Management of diabetes and vascular risk factors

Several weeks or months of intensive metabolic treatment, with either rosiglitazone or glyburide in addition to metformin, have been shown to improve memory and concentration in patients with type 2 diabetes and high HbA1c concentrations (a reduction in fasting glucose of 2.1-2.3 mmol/L was seen for both treatment groups).[83] However, several large randomised trials did not report a longer-term benefit of intensive glycaemic control on cognitive function in people with type 2 diabetes (table 2).

The ACCORD-MIND study[86] is the only study thus far that has specifically assessed

the potential effects of antihypertensive or lipid-lowering treatment on cognitive decline in patients with type 2 diabetes. Intensive therapy for hypertension (<120 mm Hg vs <140 mm Hg) and combination therapy with a statin plus a fibrate for 40 months did not improve cognition, but intensive blood-pressure lowering was, unexpectedly, associated with accelerated brain atrophy.[86] Results of observational studies in the general population indicate that cardiovascular risk management might reduce the risk of cognitive impairment.[78] Thus far, however, the results of randomised trials have been mixed, and many reported no significant benefit of intensified cardiovascular risk management.[78] In the ONTARGET and TRANSCEND studies, for example, blood-pressure lowering in 25 271 patients –35% of whom had diabetes– treated with ramipril, telmisartan, or both, did not change the incidence of cognitive impairment during a mean follow-up of 56 months (incidence was 7-9%).[87]

DIAGNOSIS OF COGNITIVE DYSFUNCTION IN DIABETES

Classification of stages of cognitive dysfunction

The data discussed in the preceding sections show that diabetes is associated with changes in cognitive function, ranging from subtle cognitive changes to MCI and dementia. In our view, differentiation between these different stages of cognitive dysfunction in clinical practice is essential, because they are likely to have a different prognosis and might require different management (panel 1).[40]

The same diagnostic criteria apply to cognitive impairment –ie, MCI and dementia– in people with diabetes as in people without diabetes (panel 2). An overlooked issue is how the subtle cognitive changes that occur in association with diabetes should be classified and managed in clinical practice. Outside the specialty of diabetes, efforts have been made to create a lexicon defining the earliest stages of cognitive dysfunction that precede dementia, particularly Alzheimer's disease.[88] The concept of MCI originates from this effort, as do terms as prodromal, preclinical or presymptomatic Alzheimer's disease.[88] So-called subjective cognitive decline in preclinical Alzheimer's disease has also received increasing attention, and international efforts are being made to develop criteria for that condition.[89] These terms, however, are not well suited for classification of subtle diabetes-associated cognitive changes. These subtle changes occur in all age groups, change slowly over many years, and are, in most patients, unlikely to indicate the earliest stage of a dementia process.[40] We propose to classify these subtle changes as diabetes-associated cognitive decrements. This classification can be considered if a patient with diabetes expresses concerns about his or her cognitive function, typically involving increased mental effort, but with mostly preserved social or occupational function. For a classification of diabetes-associated cognitive decrements, there should be no alternative explanations for the complaints, and there should be no cognitive deficits severe enough

Table 2. Trials of the effect of glucose-lowering treatment on cognitive functioning in diabetes

Study	Study population	Intervention	Control	Follow-up	Difference between intervention and control
Type 1 diabetes					
DCCT/EDIC[9]	1441 patients aged 13-39 years	Intensive control (HbA1c≤42 mmol/mol)	Standard control of blood glucose	Trial 6·5 years; total follow-up 18 years	No difference in cognitive decline
Type 2 diabetes					
ACCORD-MIND[84]	2977 patients aged >55 years	Intensive treatment (HbA1c<42 mmol/mol)	Standard treatment (HbA1c 53-63 mmol/mol)	2·8 years	No difference in both cognitive performance and cognitive decline. Reduced rate of brain atrophy
ADDITION-Cognition[32]	183 patients aged 50-70 years	Intensive multifactorial treatment of hyperglycaemia, blood pressure and lipids	Standard treatment following guidelines	3·2 years	No difference in cognitive performance and cognitive decline
ADVANCE[85]	11140 patients ≥55 years with a history of major macrovascular or microvascular disease, or one other cardiovascular risk factor	Perindopril-indampide for blood pressure control and intensive glucose control (HbA1c<48 mmol/mol with gliclazide)	Routine blood-pressure lowering and standard glucose control	5 years	No difference in risk of cognitive decline or dementia

DCCT/EDIC: Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications; ACCORD-MIND: Action to Control Cardiovascular Risk in Diabetes- Memory in Diabetes; ADVANCE: Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation; ADDITION: Anglo-Danish-Dutch study of Intensive Treatment In PeOple with screeN detected diabetes in primary care

to be classified as MCI. In our view, classification of cognitive complaints as diabetes-associated cognitive decrements is important in such cases because it acknowledges the subtle but real changes in cognitive function that people with diabetes might experience. Moreover, diagnosis of diabetes-associated cognitive decrements has prognostic implications, because progression of the underlying cognitive changes is usually slow.

Panel 1. Proposed stages of diabetes-associated cognitive dysfunction in diabetes

Diabetes-associated cognitive decrements

- Subtle changes in cognitive function in one or several domains, typically 0·3-0·5 SDs lower than in people without diabetes
- Might result in cognitive complaints (usually expressed only by the patient), but activities of daily life are preserved; unlikely to affect diabetes self-management
- Occur in all age groups in people with type 1 and type 2 diabetes
- Slow progression over time

Mild cognitive impairment (MCI)[90;91]*

- Impaired cognitive function of one or several domains, typically 1-1.5 SDs below normative data
- Can be subdivided into amnestic (memory-impaired) and non-amnestic type MCI (other domain affected, memory preserved)
- Results in cognitive complaints (by patient or informants), but activities of daily life are mostly preserved; might affect diabetes self-management
- Occurs predominantly over the age of 60-65 years.
- Can progress to dementia, but can be stable or even revert to normal
- No data specifically for relation with type 1 diabetes

Dementia[103]*

- Impaired cognitive function, affecting multiple cognitive domains
- Results in cognitive complaints (by patient or informants); activities of daily life are affected; often affects diabetes self-management
- Occurs predominantly (>95% of cases) over the age of 60-65 years
- Cognitive decline is generally progressive over time
- No data specifically for relation with type 1 diabetes

* For MCI and dementia, the same diagnostic criteria apply in people with diabetes as in those without.

Panel 2. Typical case histories

Patient A

A retired accountant aged 75 years known to have type 2 diabetes for 15 years who is on a basal bolus insulin regimen, is presented at the emergency room service with reduced consciousness. His blood glucose is 2·3 mmol/L, which seems to be caused by administration of a wrong dose of insulin. After restoration of normoglycaemia, further history taking is done, and information from his partner is gathered. Medication errors seem to happen more often lately, because the patient is forgetful. Other activities of daily living need a lot of attention, and the patient has been having increasing problems with his memory over the past 2-3 years. His partner has already taken over several administrative and financial tasks. One week later, a Mini-Mental State Examination (MMSE) is done, and he has a score of 20/30 (indicative of dementia). On the basis of the history taken from the patient and his caregiver, combined with the MMSE, the physician considers a diagnosis of dementia probable (panel 1), and does a further assessment according to local guidelines.

Patient B

A lawyer aged 48 years, known to have had type 2 diabetes for 3 years, has complained of cognitive difficulties for the past year. He still works fulltime at the office, but his tasks need more time and energy than before, and he experiences difficulties with his workload. He is afraid his complaints are the beginning of dementia. The patient's spouse confirms that her husband has complaints, although neither she nor his colleagues have noted shortcomings in his professional and social activities. He has no evidence of depression, and additional laboratory testing shows no abnormalities. The physician decides to do a neuropsychological examination, because careful documentation of the cognitive performance of the patient is important for potential insurance and legal difficulties related to his profession, and the examination will also help to definitely rule out mild cognitive impairment. The neuropsychological examination shows slight decrements in information-processing speed and executive function (around the 20-25th percentile), whereas performance of the other domains is average or above average. The physician explains that diabetes-associated cognitive decrements (panel 1) could be the cause of his complaints, and reassures the patient that these decrements are expected to show little progression over time. He is advised to monitor his complaints at work to gain insight into the distribution of his mental energy during the day. A reassessment is scheduled after 1 year. If the difficulty with his workload persists, consultation with a (cognitive) rehabilitation specialist is recommended.

Diagnosis of cognitive dysfunction

To differentiate between diabetes-associated cognitive decrements and cognitive impairment (MCI and dementia), detailed information is needed about the severity and type of cognitive complaints, their changes over time, and their effects on activities of daily life and occupational function. Confirmation by an informant is recommended. The severity of the complaints is a key distinguishing feature and should be proportional to the presumed underlying functional deficit. The magnitude of diabetes-associated cognitive decrements is on average 0.3-0.5 SDs greater than that of people without diabetes, which is the equivalent to a reduced cognitive performance of 10-15 percentile points relative to the normative mean.[5;23;24] The magnitude of cognitive deficits that meet the criteria for MCI (a performance deficit of >40-45 percentile points relative to the normative mean) is much larger.[90;91] Prior probability is another issue to consider. Diabetes-associated cognitive decrements can occur in all age groups, whereas MCI and dementia are quite rare in people younger than 65 years even in those with diabetes, with a prevalence that doubles every 5 years after the age of 65 years.[40]

When MCI or dementia is suspected, the diagnostic assessment for people with diabetes is the same as for people without diabetes and should be done according to local guidelines. When the cognitive decrements match the pattern of diabetes-associated cognitive decrements, a tailored diagnostic assessment is recommended (panel 2). In such cases, performance on cognitive screening tests like the Mini-Mental State Examination (MMSE) will be in the normal range. Ceiling effects limit the usefulness of such tests. A neuropsychological examination might formally distinguish between decrements and MCI. Domain scores in the normal range (higher than the 5th-10th percentile) rule out MCI. As a result of the subtlety of the cognitive changes, neuropsychological examination might often have insufficient sensitivity to provide evidence for the presence of diabetes-associated cognitive decrements. Therefore, if the existing likelihood of MCI is thought to be low, the clinician might decide not to do a full neuropsychological assessment. Nevertheless, a neuropsychological assessment might be needed if other sources of uncertainty are present (panel 2).

Depression is an important differential diagnosis to consider, because it can also present as cognitive complaints. Other possible explanations such as hypothyroidism, vitamin deficiency, anaemia, and renal or liver dysfunction should likewise be considered. When present, these disorders should be treated accordingly, and cognitive function should be re-examined after the disorder has resolved.

Brain imaging will generally not yield important diagnostic information for assessment of diabetes-associated cognitive decrements because the changes on brain MRI that have been linked to these decrements at the group level cannot be reliably detected and classified in an individual patient. Chance findings, such as mild white matter hyperintensities, that have little clinical relevance in an individual might also be made.

CURRENT MANAGEMENT

Cognitive impairment in diabetes

No specific treatments exist for people with diabetes and MCI or dementia, and clinicians should treat MCI or dementia according to the same principles as in people without diabetes. Nevertheless, cognitive dysfunction in patients with diabetes is associated with poor glycaemic control[92] –especially in the case of impaired executive functioning[93]– with an increased frequency of hospital admissions and, as mentioned in a previous section, with an increased occurrence of severe hypoglycaemic episodes.[72] Therefore, diagnosis of cognitive impairment should be reason for the diabetes care provider to re-assess the patient's capacities for self-management and treatment adherence, and to consider additional measures (panel 2).[94;95] First, the increased risk of medication errors should be addressed by use of medication dispensers or the involvement of caregivers can be considered. Second, the physician should assess whether perfect glycaemic control is still possible and desirable or whether more lenient glycaemic targets are better to prevent hypoglycaemia. Finally, appointments at the surgery should be made easier, for example with reminders of appointments.

Diabetes-associated cognitive decrements

When complaints are classified as diabetes-associated cognitive decrements, no specific therapeutic interventions are warranted. For patients with high concerns or insecurity, psychotherapy or cognitive rehabilitation therapy by a psychologist might be considered, to alleviate anxiety and acquire means to cope with cognitive decrements.

Because of the slow progression over time, the prognosis of diabetes-associated cognitive decrements is generally favourable, particularly for patients younger than 60-65 years.[40] The patient should be informed of this usually benign course. In patients older than 65 years, however, the incidence of dementia is higher. Cognitive decrements might be the first signs of further cognitive decline, and the prognosis is therefore less certain. In all patients, irrespective of age, a follow-up assessment is recommended to verify that the symptoms develop as expected (panel 2).

FUTURE PERSPECTIVES

Awareness of diabetes-associated cognitive dysfunction is increasing. However, important questions still need to be answered. Should cognitive impairment be routinely screened for in patients with diabetes, just like other diabetic complications? Can people at risk of accelerated cognitive decline be identified at an early stage, and how should these people be treated to prevent deterioration?

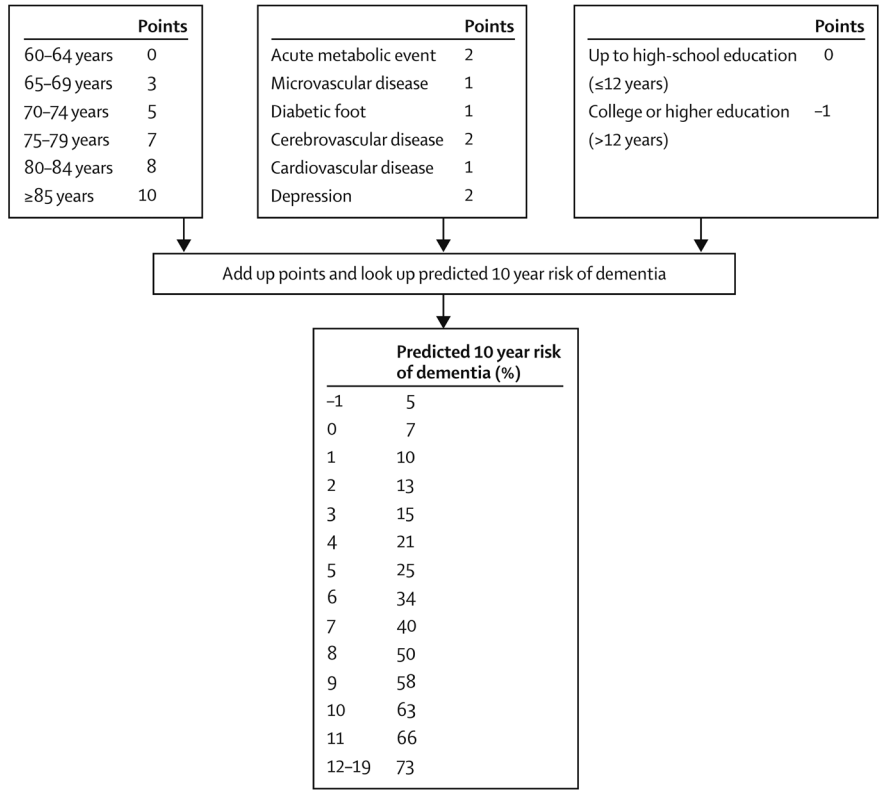
Screening

Outside of the field specialty of diabetes, the advantages and disadvantages of screening for cognitive disorders are debated intensively. Individuals opposed to screening argue that the benefit of an early diagnosis of dementia does not outweigh potential harm, because no treatment for dementia is yet available.[96] This view assumes that, as long as people do not complain, detection of cognitive impairment is not relevant. This assumption might not be correct, particularly in the context of diabetes, where unrecognised cognitive dysfunction can, apart from affecting many other aspects of life, affect diabetes self-management with potentially serious results.[72;97] Moreover, health-care professionals often overlook or discard the early signs of dementia in patients with cognitive complaints. From the initial presentation of patients' symptoms, voicing of family concerns, or both, confirmation of a diagnosis of dementia can take months to years.[98] Reasons for this slow diagnosis might be that physicians do not deem disclosure of a diagnosis relevant or that a diagnosis of cognitive impairment has only negative effects.[99] We propose that a case-finding strategy, combined with appropriate support for diabetes management, can lead to improved quality of life and quality of care for patients. Such case-finding strategies should focus on detection of MCI and dementia, since these disorders are most likely to have implications for daily function and diabetes self-management. Evidence for the benefits of this approach might guide the debate between those who advocate an early diagnosis of cognitive impairment and those who are sceptical of case-finding strategies. As a result of the increasing number of elderly patients with diabetes, the need for knowledge about the optimum approach for, and advantages and disadvantages of, case-finding for cognitive impairment is becoming increasingly urgent and relevant. For now a case-finding strategy could be considered in diabetes-specific scenarios in which cognitive impairment could play a part, for example, in patients with frequent hypoglycaemic events or in patients who need to start a new treatment because treatment targets are insufficiently reached with standard treatment.

Identification of who is at risk

In addition to identification of patients with existing cognitive impairment, prediction of which patients are most likely to become impaired in the future is also relevant. As indicated in this Personal View, only a subgroup of patients with diabetes will develop accelerated cognitive decline, MCI or dementia. Novel treatments to prevent these adverse cognitive outcomes might be most effective if they can be applied at an early stage of the process in high-risk individuals. A risk score has been introduced that predicts the 10-year dementia risk specifically for patients with type 2 diabetes mellitus of 60 years or older (figure 4).[63] The risk score consists of several clinical and demographic variables that are readily available from every patient, and ranges from a 10-year dementia risk of 5% for those with the lowest score up to a risk of 73% for

Figure 4. Risk score for individualised prediction of 10-year dementia risk



The risk score was developed for in patients with type 2 diabetes aged 60 years or older. Reproduced from Exalto and colleagues,[63] for details see original paper.

the highest scores (figure 4). An advantage of this risk score is that it can readily be implemented to select patients for prevention programmes. A limitation is that specific disease processes in dementia cannot be targeted. Biomarkers that not only predict risk of impairment, but are also indicative of a specific modifiable treatment target, are clearly needed. Such biomarkers could then be integrated into a prediction model combining risk estimates on the basis of a clinical profile, which identifies the individuals at risk, with a biomarker panel that identifies optimum individualized interventions.

Treatments

Treatments are clearly needed to prevent or delay cognitive decline, particularly MCI and dementia, in people with diabetes. Such treatments might be generic (ie, they

target dementia but are not specifically developed for people with diabetes[100]) or might specifically target diabetes-related disease processes. In the context of this Personal View, we focus on treatments specifically for people with diabetes. Although diabetes is a risk factor for, rather than a primary cause of, MCI and dementia, targeting diabetes-related disease processes might have a substantial effect. First, processes that ultimately lead to dementia develop over many years, even decades. Even part slowing of these processes could effectively postpone dementia onset and thus reduce lifetime risk. This slowing could be achieved by prevention of diabetes-related brain changes, but better insight is needed into the pathophysiology of cognitive dysfunction in diabetes, which is likely to be multifactorial. Second, cross-talk seems to occur between processes involved in the pathophysiology of diabetes and dementia, particularly in Alzheimer's disease. Insulin, for example, has direct effects on the brain and, in people with Alzheimer's disease, the brain seems to be insulin resistant.[44] These insights have spurred investigations into novel therapeutic approaches, such as intranasal insulin administration, aiming to normalise brain insulin concentrations in people with Alzheimer's disease, with or without diabetes (Clinicaltrials.gov, numbers NCT01767909 and NCT01595646).[44] A proof-of-concept study[101] that used this approach in patients with or without type 2 diabetes, reported acute improvements in cognitive function, potentially mediated by an insulin-induced increase in cerebral perfusion. Finally, several antidiabetic drugs – including metformin, thiazolidinediones, and incretin-based therapies – have direct effects on the brain, independent of their glucose-lowering effects. These pleiotropic actions, including effects on brain metabolism, neuroinflammation, and neuronal viability and survival are of clear interest.[102] Randomised trials should identify whether such effects also result in improved cognitive outcomes for people with diabetes.

CONCLUSIONS AND FUTURE DIRECTIONS

Diabetes is linked to different stages of cognitive dysfunction, ranging from diabetes-associated cognitive decrements to dementia. These stages are not necessarily part of one continuous process, and might have different prognoses. Moreover, different stages require different management. We present a framework that helps to distinguish between different stages of cognitive dysfunction in patients with diabetes. No treatment exists to reduce or prevent diabetes-associated cognitive dysfunction, but a diagnosis of cognitive impairment should be reason for the clinician to adjust diabetes treatment to the capacities of the patient (reduction of risk of medication errors, prevention of hypoglycaemia, arrangement of support when necessary). Hopefully, increasing awareness of the links between cognitive dysfunction and diabetes will help to support development of targeted treatment.

Search strategy and selection criteria

We searched PubMed from Jan 1, 1990 to May 15, 2014, with the terms (and synonyms) "dementia", "Alzheimer's disease", "cognitive impairment", "diabetes" and "metabolic syndrome", in combination with the key terms "epidemiology", "risk factors", "brain MRI", "prevention", "diagnosis", "treatment" and "screening". We only searched for papers published in English. We also searched reference lists of papers identified and extracted relevant papers from our records. Furthermore, we searched ClinicalTrials.gov. Subsequently, we selected mainly observational studies, systematic reviews or meta-analyses, and randomised controlled trials published in core clinical journals during the past 5 years. Our final selection was made on the basis of originality and relevance to topics covered in this Personal View. Where possible, we refer to reviews rather than to original studies.

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CHAPTER 3

MILD DEPRESSIVE SYMPTOMS DO NOT INFLUENCE COGNITIVE FUNCTIONING IN PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Introduction: Type 2 diabetes (T2DM) is associated both with cognitive decrements and with depressive symptoms. Since depression in itself has been associated with cognitive decrements we aimed to investigate the influence of depressive symptoms on the relation between T2DM and cognitive functioning.

Methods: Data were derived from three independent studies on cognitive functioning in patients with T2DM (n=366) and controls without diabetes (n=204), two with longitudinal and one with only cross-sectional assessments. Depressive symptoms were measured with self-report inventories (CES-D or BDI-II). The composite z-score of the domains memory, information-processing speed, and attention and executive function was the primary cognitive outcome measure. Mixed linear regression analyses were used in a stepped approach to compare cognitive functioning between 1) patients with T2DM and controls (cross-sectionally and longitudinally), 2) participants with and without depressive symptoms, separately for patients and controls, and 3) patients and controls after adjustment for depressive symptoms. In addition the mediating effect of depressive symptoms was assessed with a bootstrapping technique.

Results: Depressive symptoms were present in 11% of the patients with T2DM and in 7% of controls (p=0.15). Cognitive performance in patients with T2DM was worse than in controls (overall difference composite z-score -0.13). However, T2DM was not associated with accelerated cognitive decline over three years of follow-up relative to controls. Controls with depressive symptoms performed worse than those without depressive symptoms, although not statistically significant. Performance in patients with T2DM with and without depressive symptoms was similar. Adjustment for depressive symptoms and estimation of the mediating effect showed that the difference between patients and controls was not mediated by depressive symptoms.

Conclusions: The modest cognitive decrements that are associated with T2DM are not due to the presence of mild depressive symptoms.

INTRODUCTION

In patients with type 2 diabetes (T2DM) small decrements in cognitive functioning are consistently found on the domains memory, information-processing speed, and attention and executive functioning.[1] Diabetes is also an established risk factor for dementia, with an up to twofold increased risk.[2;3] In addition, depressive symptoms are more common among patients with T2DM[4-7] with depression occurring twice as often in patients with diabetes compared to individuals without diabetes.[5]

In the general population, depressive symptoms are associated with lower cognitive performance and an increased risk for dementia.[8;9] In people with depressive symptoms impairments are found in the domains memory and information-processing speed.[10-12] Therefore, the question arises whether depressive symptoms play a mediating role in the relation between T2DM and cognitive functioning and cognitive decline. In a meta-analysis of three studies, all with the same detailed standardized neuropsychological assessment, we studied the influence of depressive symptoms on the relation between T2DM and cognitive functioning in a cross-sectional and longitudinal design.

METHODS

Data were derived from three studies that assessed cognitive functioning in patients with T2DM relative to controls: the ADDITION-Netherlands study,[13] the UDES[14] and the Hoorn study.[15]

Design of the studies

The ADDITION study (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care) was a cluster-randomised trial in patients with screen-detected T2DM that compared the effectiveness of an intensive multifactorial treatment with routine care on cardiovascular outcome.[16] The study started with a population-based screening for diabetes followed by inclusion of newly diagnosed patients with diabetes in the trial. In a subgroup of patients from the Netherlands cognition was assessed through two standardised neuropsychological assessments, in 2006-2007 and again in 2009-2010.[13] Control participants without diabetes were recruited among spouses and acquaintances of the patients.

The UDES (Utrecht Diabetic Encephalopathy Study) was a longitudinal study on determinants of impaired cognition in patients with T2DM in the Netherlands.[14] Patients were recruited through their general practitioner. Controls were recruited among spouses and acquaintances of the patients. They were first examined between 2002 and 2004 and again four years later (2006-2009).

The Hoorn study was a population-based cohort study on glucose metabolism, which started in 1989 in the middle-sized town of Hoorn, the Netherlands.[17] A random

sample of inhabitants of Hoorn was invited to participate in the study. Over the years three follow-up examinations were performed.[15;17;18] In the third follow-up examination cognitive functioning was assessed.[15] For the present study participants of the Hoorn study were reclassified based on their fasting glucose of the last follow-up examination in patients with T2DM and control subjects.

The ADDITION study and the UDES were approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands. The Hoorn study was approved by the medical ethics committee of the VU University Medical Center, Amsterdam, the Netherlands. Written informed consent was obtained from all participants.

Study populations

Figure 1 represents a flowchart demonstrating drop-out and follow-up of the three studies. The first neuropsychological assessment in the ADDITION study was performed in 183 patients with screen-detected T2DM, aged between 50 and 70 years. Their diabetes was screen-detected approximately three years before, following a standardized protocol.[19] Classification was done according to the WHO-criteria.[20] Of these patients 135 were re-examined three years later. During the second examination eight patients did not complete a depressive symptoms questionnaire and were therefore excluded for the longitudinal analyses. In the UDES 122 patients aged between 56 and 80 years, known with T2DM for at least one year, underwent the first neuropsychological assessment. Twenty-three patients were excluded from the present analyses as sixteen patients had no baseline depressive symptoms questionnaire and seven had no estimated level of (crystallized) intelligence. Four years later 68 patients completed the second neuropsychological assessment. Participants of the Hoorn study were aged 50 to 75 years at recruitment. For a diagnosis of diabetes fasting blood glucose was measured and subsequently an oral glucose tolerant test (OGTT) was administered and classified according to the WHO-criteria.[20] Participants already known with diabetes and/or using glucose-lowering therapy were categorized as having diabetes. Eighty-six patients fulfilled the criteria for diabetes at the third examination and received a neuropsychological assessment. One person with a missing baseline depressive symptoms questionnaire and one without estimated level of (crystallized) intelligence measured were excluded.

Sixteen control participants of the UDES were also used as controls in the ADDITION-study. For the present pooled analyses these sixteen controls were only included in the population of the UDES. From all three studies only control participants with a fasting glucose ≤ 5.6 mmol/L were included. This left 39, 33 and 132 controls from the ADDITION, UDES and Hoorn study respectively for inclusion in the present pooled analysis.

All participants were functionally independent and Dutch speaking. None of them had a history of neurological or psychiatric disorders that could influence cognitive

functioning or a history of alcohol or substance abuse. Individuals with a previous non-disabling stroke (i.e. without interference with usual daily activities) could participate.

Neuropsychological assessment

The neuropsychological assessments in all three studies included the same nine tests addressing three cognitive domains, that are most consistently affected in T2DM in previous studies[1]: memory, information-processing speed, and attention and executive functioning. The division in cognitive domains was made a priori, according to neuropsychological practice and cognitive theory.[21] The domain 'memory' was subdivided in four domains: working memory, immediate memory and learning rate, forgetting rate, and incidental memory. Working memory was assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale –3rd edition (WAIS-III)[22] and the Corsi Block-tapping Task.[23] The product scores of both measures (number correct times span length) were used. Immediate memory and learning rate was assessed with the Rey Auditory Verbal Learning Test (RAVLT)[24] and the Location Learning Test (LLT).[25] For the RAVLT the mean of the total number of words remembered in five learning trials was recorded and a learning index was calculated. For the LLT the total number of displacements over five trials and a learning index was calculated. Forgetting rate was calculated in the RAVLT and the LLT by correcting the scores in the delayed recall condition for the score obtained in the fifth learning trial. Incidental memory was measured with the delayed recall of the Rey-Osterrieth Complex Figure Test.[26] This score was also corrected for the score obtained in the copy condition. The domain 'information-processing speed' was assessed by the Trail-making Test Part A (TMT-A),[27] the Stroop Color-Word Test (part 1 and 2)[28] and the subtest Symbol Digit Substitution of the WAIS-III (SS-WAIS-III). Time to complete the TMT-A task was recorded in seconds; the mean of the total time needed to complete part I and II of the Stroop was calculated and for the SS-WAIS-III the total correct numbers of copied symbols within two minutes was recorded. The domain 'attention and executive functioning' was assessed by the Trail-making Test Part B (ratio score),[27] the Stroop Color-Word Test (part 3; ratio score), the Brixton Spatial Anticipation Test[29] recording the number of errors, and a letter fluency test using the letters 'N' and 'A' and a category fluency test (animal naming) recording the total number of correct responses.[30] The Dutch version of the National Adult Reading Test was used to estimate level of (crystallized) intelligence.[31] The tests were administered in a fixed order by neuropsychologists and neuropsychologists in training and took about 90 minutes to complete.

Raw test scores at first and second neuropsychological assessment were standardized into z-scores per test, using the pooled mean of baseline scores of all control participants of the three studies. The z-scores of each domain were calculated by averaging the test scores comprising that domain. The primary cognitive outcome measure was defined as the mean composite z-score of the domains memory,

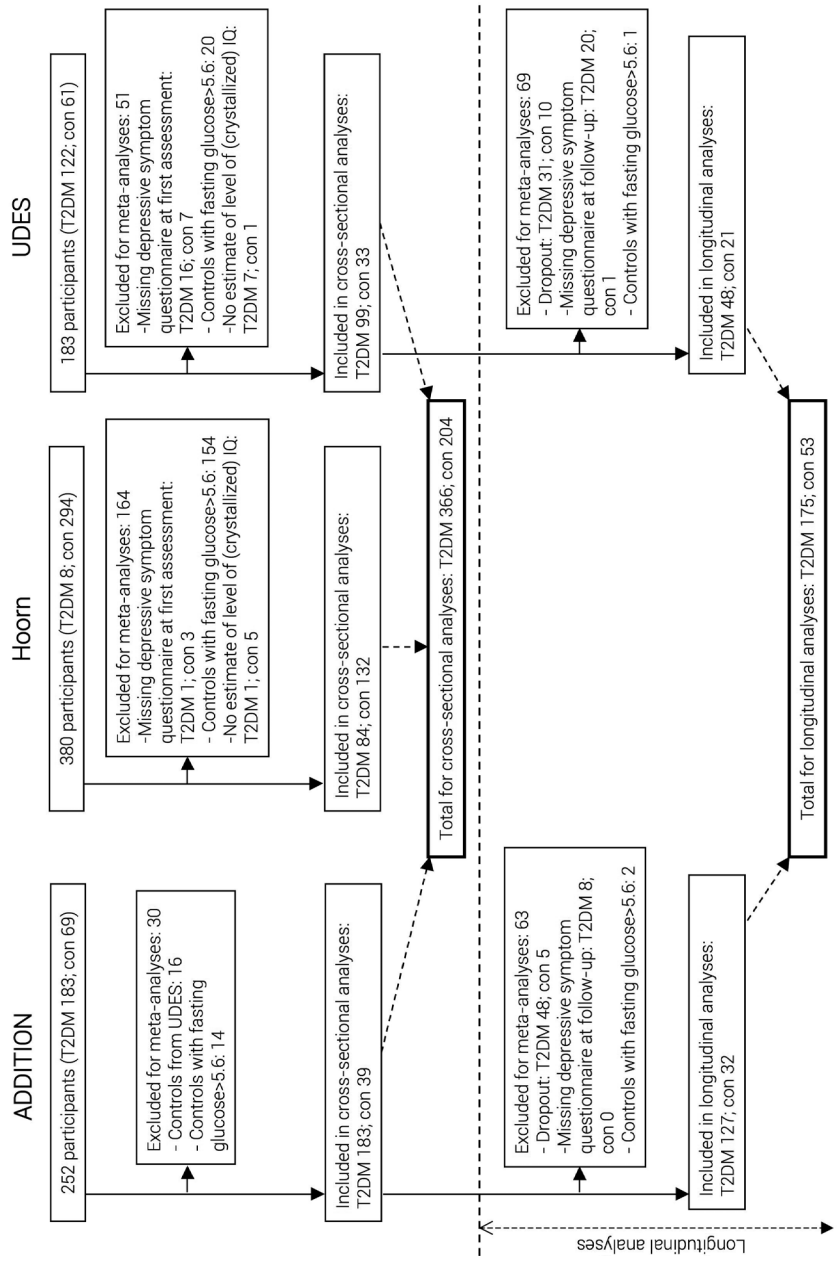


Figure 1. Flowchart of study participants

information-processing speed and attention and executive function.

In the ADDITION and Hoorn study depressive symptoms were assessed with the validated Dutch version of the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D)[32] and in the UDES with the Dutch version of the Beck Depression Inventory 2nd Edition (BDI-II).[33] Both are self-report questionnaires to measure the presence of depressive symptoms on a four-point scale. Higher scores indicate more depressive symptoms. A score ≥ 16 on the CES-D and a score of > 13 on the BDI is generally accepted as the cut off score for the presence of depressive symptoms.[34;35] The accuracy of these depressive screening instruments was examined by Katz et al, who found comparable sensitivities and specificities for the CES-D and the BDI when the cut off scores were respectively ≥16 and >13.[36] Therefore these cut off scores were used to classify depressive symptoms as absent or present.

Clinical characteristics

At the time of the neuropsychological assessments body weight, height, waist circumference and blood pressure were measured and body mass index (BMI) was calculated. Demographic variables and medical history were recorded in a standardized interview. Venous blood samples were drawn after an overnight fast to determine fasting blood glucose, HbA1c and total cholesterol. The specific protocols are described in the separate studies.[13-15]

Statistical analyses

Categorical variables are reported as numbers and percentages, continuous variables as means with standard deviations (SD) and not normally distributed variables as median with interquartile range (IQR). Within the studies, differences between the patients with diabetes and control subjects were analyzed with Chi-square tests for categorical variables, independent t-tests for normally distributed continuous variables and Mann-Whitney tests for not normally distributed continuous variables.

Mean cognitive domain scores were calculated by averaging the test scores comprising that domain and comparisons between groups were made using mixed linear regression analyses adjusted for age, sex and estimated level of (crystallized) intelligence. First, cognitive performance and depressive symptoms were compared between the diabetic and the control groups. Next, cognitive performance was compared between participants with and without depressive symptoms, separately for the diabetic and the control groups. Finally, to examine whether the relation between cognitive performance and diabetes status was mediated by depressive symptoms, we added the presence of depressive symptoms as a covariate in the first comparison. In addition, we estimated the possible mediating effect of depression and corresponding 99%-confidence interval (CI) with a bootstrapping technique.[37] During bootstrapping the data set is sampled repeatedly to estimate the mediating effect in each resampled data

set and reconstruct a 99%-CI. When the CI does not contain zero a mediating effect is present. We computed bootstrapped confidence intervals (5000 samples) for the size of the specific mediating effects using SPSS macros provided by Preacher and Hayes.[37]

In the longitudinal analyses, mean change in cognition per year was compared between the groups with and without diabetes using mixed linear models adjusted for age, sex, estimated level of (crystallized) intelligence. Because these analyses did not show accelerated cognitive decline in the group with diabetes, no further analyses on the possible modulating effects of depression were performed.

Secondary analyses were performed for each of the cognitive domains. In addition, to examine the influence of cardiovascular disease, two post hoc analyses were performed. In the first analyses participants with a history of stroke were excluded. The second additionally adjusted the primary comparisons for hypertension (defined by the use of antihypertensive medication or a blood pressure above 160 mmHg systolic and/or 95 mmHg diastolic) and hypercholesterolemia (defined by the use of cholesterol lowering medication or total cholesterol above 6.5 mmol/L). The analyses were performed per study and then combined in a fixed-effect model (Review Manager 5, Cochrane Collaboration). The i-squared (I^2) statistic was calculated to quantify the percentage of total variation across studies due to heterogeneity.[38] In case of an I^2 above 50% a random-effect model was used. To minimize the possibility of type 1 errors, a p-value of less than 0.01 was considered statistically significant; therefore results are reported with a 99%-confidence interval.

RESULTS

Table 1 shows the characteristics for the control group and patients with T2DM per study at the first neuropsychological assessment. Participants in the Hoorn study were older and T2DM patients in the UDES had a longer history of diabetes. Depressive symptoms were present in 10% to 13% of the patients with T2DM compared to 0% to 10% of the control participants (Table 1). Overall, depressive symptoms were present in 11% of the patients with T2DM and in 7% of controls (p=0.15).

Cognitive performance

In all three studies, patients with T2DM showed worse cognitive performance than control participants with an overall difference in composite z-score of -0.13 (99%-CI -0.22 to -0.04; p<0.001) (Figure 2). Secondary analyses for the separate cognitive domains showed overall differences of -0.08 (memory), -0.14 (attention and executive function) and -0.18 (information-processing speed).

Because the UDES had no control participants with depressive symptoms, this study could not be included in the meta-analysis for the comparison of controls with

Table 1. Patient characteristics per study of patients with type 2 diabetes and controls

	ADDITION		Hoorn	
	Type 2 diabetes	Controls	Type 2 diabetes	Controls
n	183	39	84	132
Age (yr)	63.0 ± 5.4	62.3 ± 6.5	74.5 ± 6.0	73.6 ± 6.1
Sex (% male)	61.2	28.2*	51.2	42.4
Estimated level of (crystallized) IQ	96.8 ± 19.4	106.4 ± 16.1*	96.4 ± 13.2	100.8 ± 12.8
BMI (kg/m^2)	30.6 ± 4.8	26.2 ± 3.6*	28.1 ± 4.2	26.1 ± 3.4*
Systolic blood pressure (mmHg)	143.7 ± 19.6	145.1 ± 24.9	151.9 ± 22.4	145.5 ± 21.6
Diastolic blood pressure (mmHg)	82.0 ± 10.4	83.1 ± 11.8	75.4 ± 11.8	73.8 ± 11.9
HbA1c (%)	6.2 ± 0.5	5.4 ± 0.2*	6.4 ± 0.8	5.5 ± 0.3*
Total cholesterol (mmol/L)	4.1 ± 1.0	5.7 ± 0.8*	4.8 ± 1.0	5.4 ± 1.1*
Depressive symptoms present (%)	9.8	10.3	12.9	7.6
CES-D/BDI-score†	4 (1-8)	6 (2-11)	6 (2-10)	4 (1-8)
Diabetes duration (yr)	3.6 ± 0.6	NA	6.2 ± 2.6	NA
Hypoglycemic medication (%)				
Metformin	48.6		61.6	29.8
Sulfonylurea	18.0		55.6	22.6
Thiazolidinediones	12.6		6.1	9.5
Insulin	0		29.3	4.8

* p-value < 0.01 within a study between patients with T2DM and control subjects

† Median with interquartile range. In the ADDITION and Hoorn-study the CES-D was used; in the UDES the BDI

Figure 2. Cognitive scores in T2DM versus controls adjusted for age, gender and IQ

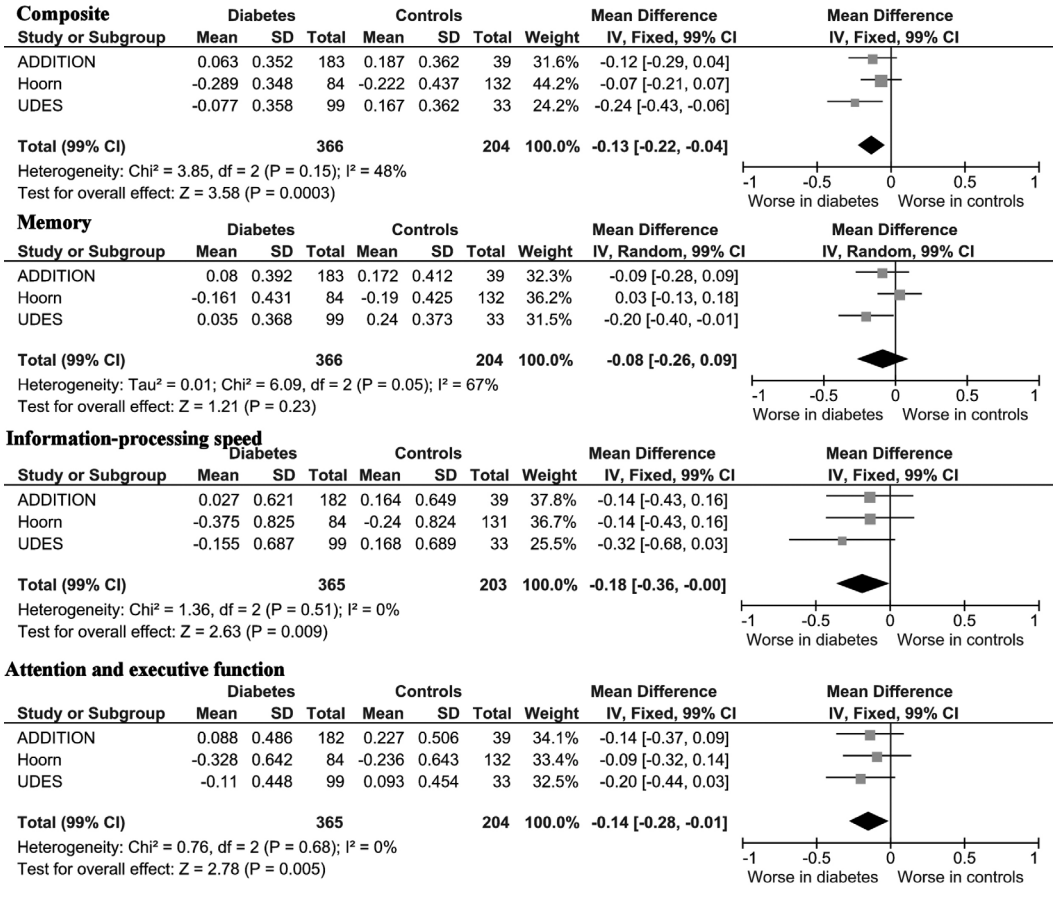


Figure 3. Cognitive scores in controls: depressive symptoms versus no depressive symptoms, adjusted for age, gender and IQ

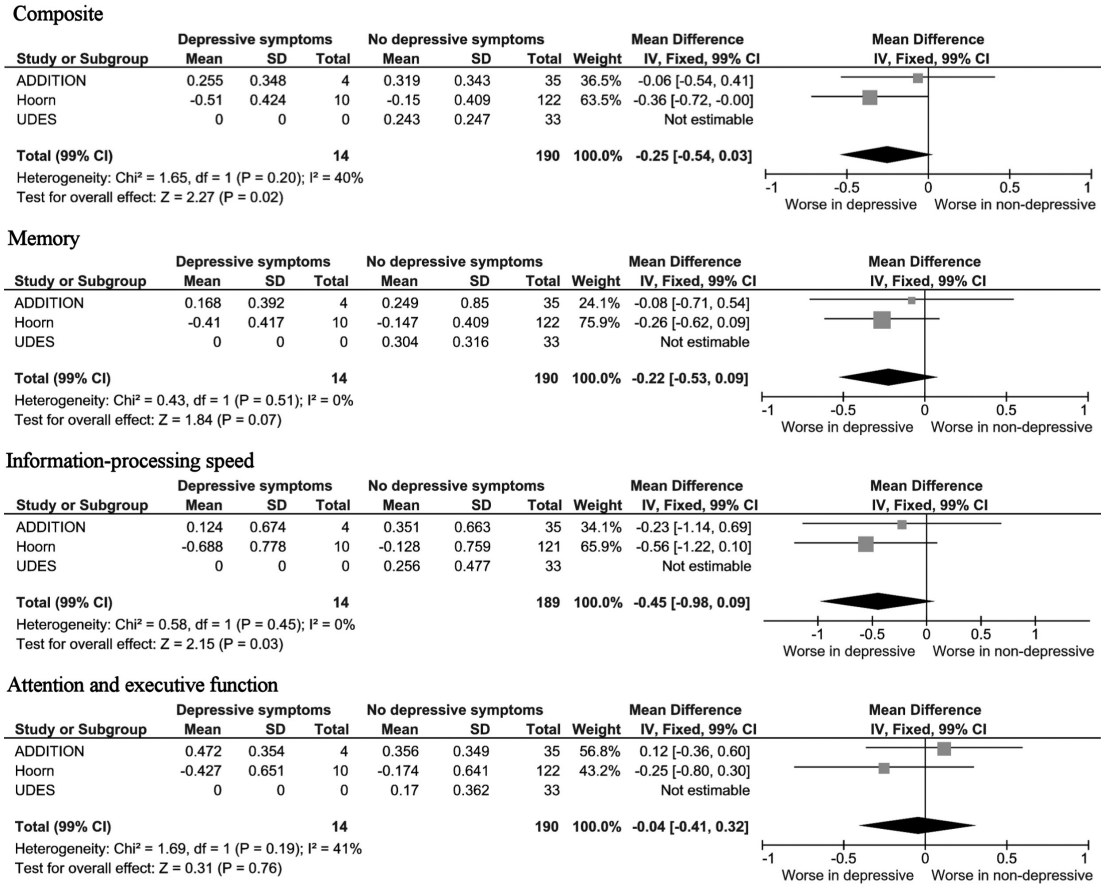


Figure 4. Cognitive scores in T2DM: depressive symptoms versus no depressive symptoms, adjusted for age, gender and IQ

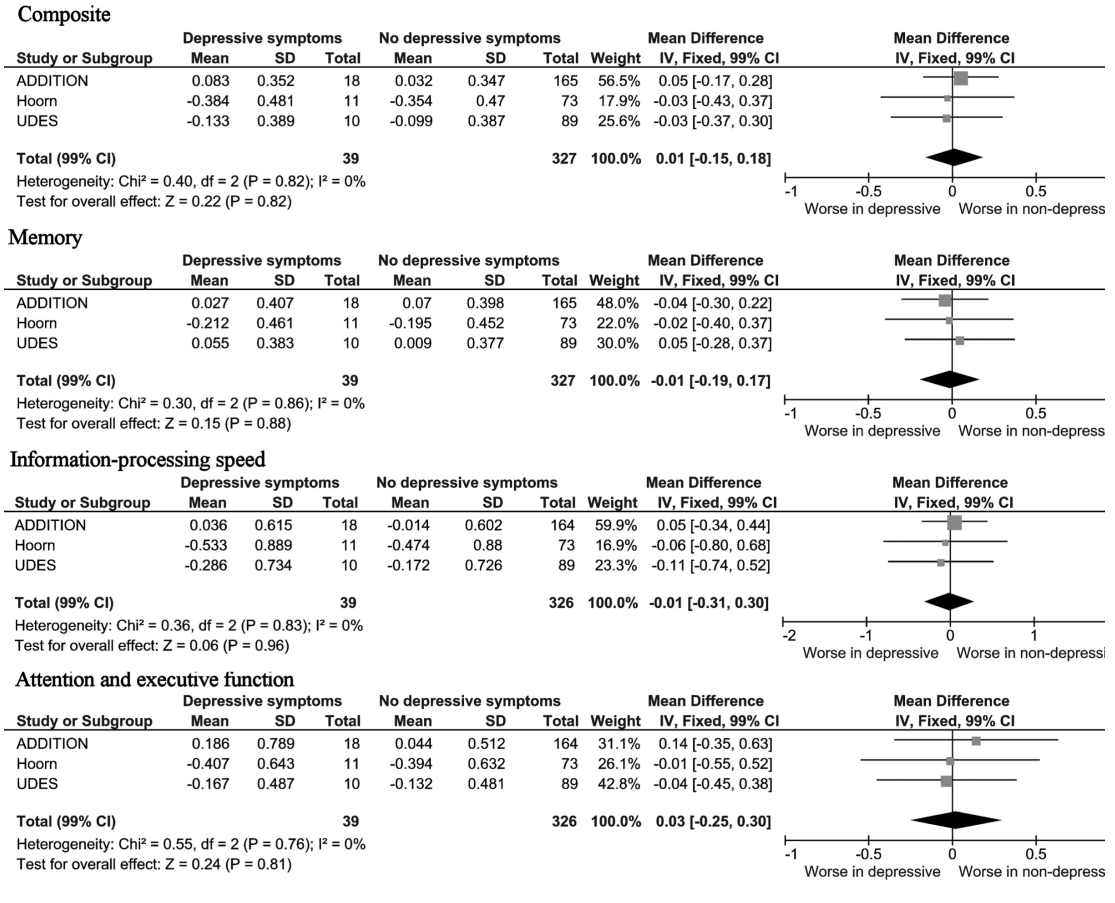
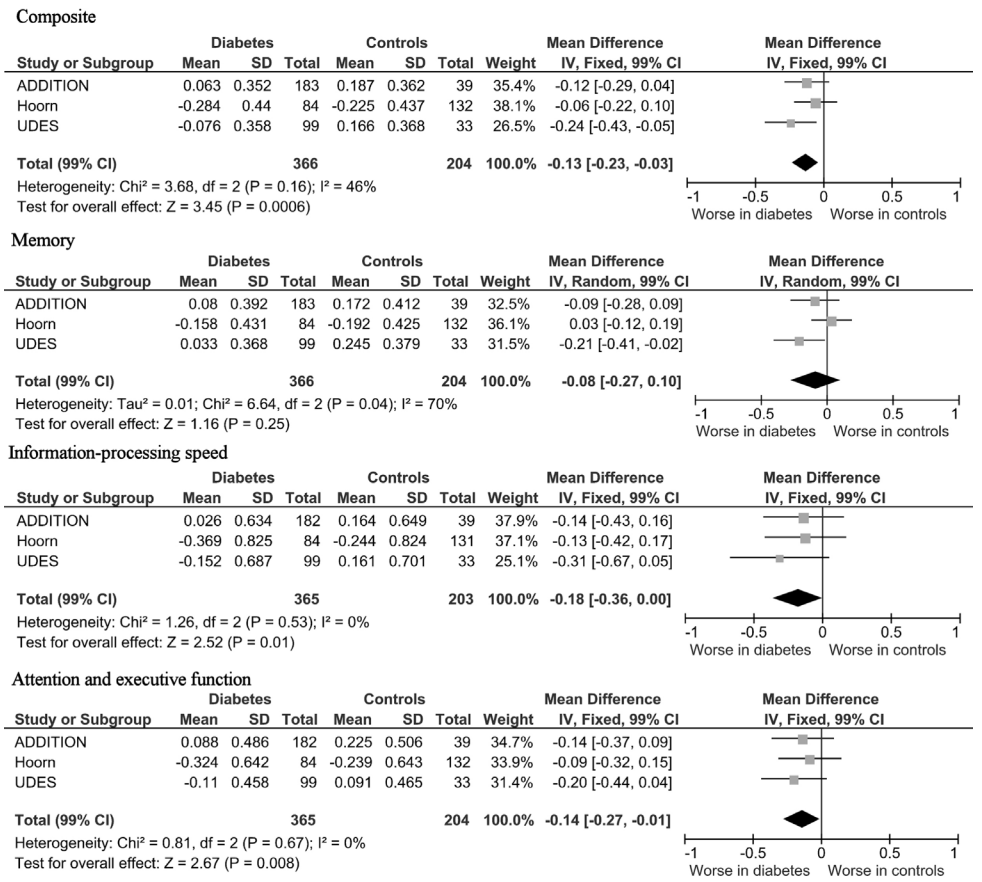


Figure 5. Cognitive scores in T2DM versus controls adjusted for age, gender, IQ and depressive symptoms



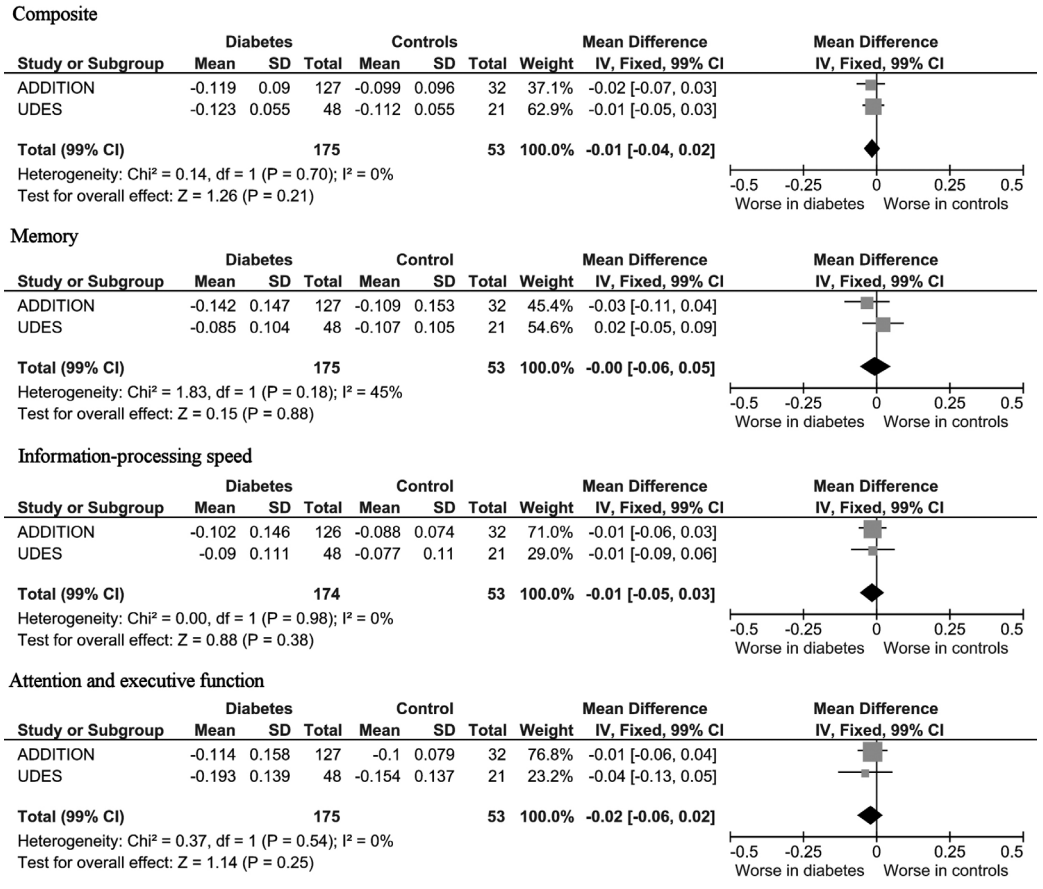


Figure 6. Cognitive decline per year in patients with T2DM versus controls adjusted for age, gender and IQ

and without depressive symptoms. In the other two studies the controls with depressive symptoms performed worse than those without depressive symptoms, although not significantly (overall difference composite z-score -0.25; 99%-CI -0.54 to 0.03; p=0.02) (Figure 3). Secondary analyses for the separate domains showed similar results. Also, no difference was found between patients with T2DM with and without depressive symptoms in any of the three studies on any of the domains (overall difference composite z-score 0.01; 99%-CI -0.15 to 0.18; p=0.82) (Figure 4).

Adjustment for depressive symptoms did not influence the difference in cognitive performance between patients with diabetes and controls; the difference in overall composite score remained -0.13 (99%-CI -0.23 to -0.03; p<0.001) (Figure 5). These results were confirmed by bootstrapping the mediating effect, with a mediating effect of depressive symptoms below 0.01 for all cognitive domains in all three studies (results not shown).

Post hoc analyses, one excluding participants with a history of stroke, another adjusting for hypertension and hypercholesterolemia, did not change the results (results not shown).

Cognitive decline

Cognitive decline was assessed in a pooled analysis of the ADDITION study and the UDES. Over a period of three to four years patients with T2DM showed no greater decline than control participants (overall difference in decline per year on composite score -0.01; 99%-CI -0.04 to 0.02; p=0.21) (Figure 6). We did not perform further longitudinal analyses on the mediating effect of depressive symptoms as no accelerated decline was found.

DISCUSSION

The present study demonstrated more cognitive decrements in diabetes patients compared to controls. Controls with depressive symptoms performed worse than those without depressive symptoms, although not statistically significant, but performance in diabetes patients with and without depressive symptoms was similar. The pooled analysis, including over 350 patients and 200 controls, showed that cognitive decrements in patients with T2DM are not influenced by the presence of depressive symptoms.

Previous studies reported similar prevalence rates of co-morbid depressive symptoms in patients with T2DM compared to our sample. In a review examining the prevalence of co-morbid depression in diabetes, measured by self-report questionnaires, prevalence rates ranged from 8 to 31% in patients with T2DM with an overall prevalence of 18%[4] and between 5 to 24% in people without diabetes, with an average of 10%. A study in the Netherlands that administered the CES-D to a community-based sample

of older adults, aged 55-85 years, found an overall prevalence of depressive symptoms (CES-D ≥ 16) of 17% in patients with T2DM.[39] In the three included studies, the prevalence rates of depressive symptoms were in the low range of other studies and were not significantly different between diabetes patients and controls, which might have been influenced by selection bias. People with a depressive disorder often do not participate in research. Besides, they are often excluded from the analyses due to their depressive symptomatology. The latter was also the case in the ADDITION study and the UDES; people with a diagnosis of severe depression were excluded.

Over the three studies, the difference in cognitive functioning between patients with T2DM and controls was at the lower end of the range of differences reported in other studies.[1;40] Diabetes-associated decrements are often reported in other studies with effect sizes up to 0.6.[1;40] In accordance with the literature the domains information-processing speed and attention and executive functioning are most affected in the pooled analyses. In contrast, the domain memory showed no significant difference between patients and controls in our study.[1;40;41] Several factors may have attenuated the differences in effect sizes. First of all, in our three cohorts patients with diabetes were well controlled for their diabetes and for vascular risk factors relative to control participants. Controls were not excluded if they had elevated vascular risk factor levels, therefore the contrast between participants with and without diabetes may be attenuated, as also hypertension and elevated lipid levels play a role in cognition.[40] Another explanation might be that patients with modest cognitive decrements were reluctant to participate in research.

Both longitudinal studies found no difference in rate of cognitive decline between diabetes patients and controls which is in agreement with recent publication of a large study.[42] In this study participants were followed for three years and no accelerated decline was found for both those with diabetes and those with elevated fasting glucose or insulin resistance.[42] Other studies however found an up to 1.5 to two times increased decline in cognition compared to normal ageing.[43-45]

Little research has been done on the effect of depressive symptoms on cognitive functioning in patients with T2DM.[1] Most previous studies have adjusted their analyses for the presence of depressive symptoms[11;12;46] and reported that the association between diabetes and cognitive functioning did not change after this adjustment.[44;47] One study compared cognitive functioning between patients with T2DM with and without a major depressive disorder.[48] Comparable to our study, they found no difference in cognitive performance between the two groups. Probably, diabetes-associated cognitive decrements and depressive symptoms emerge independently from each other and have different risk factors and etiologies.

In this article we included three studies that investigated cognitive functioning in patients with T2DM through an extensive neuropsychological assessment which was similar in all studies. This gave us the opportunity to examine the influence of depressive symptoms in a large group of patients with diabetes. Participants with comorbid

conditions associated with type 2 diabetes (e.g. hypertension, dyslipidemia) were included in the analyses to form a representative group of diabetes patients. Nevertheless, our findings remained the same after adjusting for these potential confounders. The mean age of the participants over the three studies varied. This might be a reason for the variation in prevalence rates of depressive symptoms as elderly people more often have mild depressive symptoms. To minimize the number of statistical tests, we choose to divide the tests into cognitive domains instead of analyzing the effect of depressive symptoms per test. We cannot exclude the possibility that a different approach might have lead to different result. Furthermore, it should be emphasized that cognitive functioning in the study populations was within the range of normal aging and that we only included people with mild depressive symptoms. The results therefore might not be generalizable to people with major depression or pathological cognitive decline.

In conclusion, the cognitive decrements in patients with T2DM compared to people without diabetes are not influenced by the mild depressive symptoms that are known to be present in one out of six of these patients.

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CHAPTER 4

UNDIAGNOSED COGNITIVE IMPAIRMENT, HEALTH STATUS AND DEPRESSIVE SYMPTOMS IN PATIENTS WITH TYPE 2 DIABETES

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Submitted

ABSTRACT

Aim: Type 2 diabetes is associated with cognitive impairment. We aimed to examine whether undiagnosed cognitive impairment in patients with type 2 diabetes is associated with a reduced health status and depressive symptoms.

Methods: 225 type 2 diabetes patients aged ≥70 years were examined in an observational study, at their homes and (some of them) at a memory clinic, for undiagnosed cognitive impairment (dementia or mild cognitive impairment [MCI]). Dementia and MCI were defined according to internationally accepted criteria. Questionnaires assessing health status (SF-36, EQ-5D and EQ-VAS) and depressive symptoms (CES-D) were filled out. Health status and depressive symptoms were compared between patients with and without cognitive impairment.

Results: Patients with cognitive impairment (n=57) showed significantly lower scores on the SF-36 on six out of the eight domains, on the physical and mental summary scores, and on both the EQ-5D and the EQ-VAS scores. CES-D scores were significantly higher in patients with cognitive impairment (9.2 ± 7.1 versus 12.7 ± 8.5; p=0.009). Depression (CES-D≥16) occurred almost twice as often in patients with cognitive impairment (RR 1.8; 95%-CI: 1.1-3.0).

Conclusions: Undiagnosed cognitive impairment in patients with type 2 diabetes is associated with a reduced health status and more depressive symptoms. Detection of cognitive impairment in type 2 diabetes patients identifies a vulnerable group of patients that could benefit from integrated and tailored treatment and care.

INTRODUCTION

Patients with type 2 diabetes develop cognitive impairment twice as often as patients without diabetes.[1;2] Cognitive impairment in type 2 diabetes might lead to impaired self-management and an increased incidence of diabetes-related complications, such as hypoglycaemia.[3;4] Although we know that in type 2 diabetes patients there is a relation between cognitive impairment and depression,[5-7] the relation of cognitive impairment with health status is unclear. Although the terms health status and health-related quality of life are often used interchangeably they have different meanings. A reduced health status may lead to a reduced quality of life but this is not always the case.[8] Assessment of health status is important because diabetes patients have to cope with a variety of advice, recommendations and medications which may be burdensome.[9]

Physicians often assume that informing the patient about a diagnosis of cognitive impairment will influence health status, quality of life and depressive symptoms negatively.[10] However, one could also argue that undiagnosed cognitive impairment, for which the patient or a family member did not yet ask professional help, might cause a reduced health status and depressive symptoms, because it is likely to bother patients. If patients with type 2 diabetes and undiagnosed cognitive impairment have a lower health status and experience more depressive symptoms than patients with only diabetes, this could be an argument to detect cognitive impairment in an early stage in order to organise support, adjust diabetes treatment and to try to improve health status and maybe quality of life.

The Cognitive Impairment in Diabetes (Cog-ID) study aims to establish a diagnostic procedure to detect undiagnosed cognitive impairment in patients with type 2 diabetes ≥70 year.[11] During the first examinations - before any suspicion of cognitive impairment was raised - health status and depressive symptoms were assessed. In the present study we examined whether undiagnosed cognitive impairment is associated with a reduced health status and with more depressive symptoms.

METHODS

Design

Between August 2012 and September 2014 patients were invited to participate by their own general practitioner (GP). After informed consent they underwent a stepwise diagnostic procedure. All participants were visited at home by a research physician (a trainee GP) and filled out two self-administered cognitive tests, the TYM (Test Your Memory)[12] and SAGE (Self-Administered Gerocognitive Examination)[13]). They also filled out questionnaires assessing health status (Short Form-36 (SF-36), EuroQol 5-Dimensions (EQ-5D) and EuroQol Visual Analogue Scale (EQ-VAS)) and depressive symptoms (CES-D).

Secondly, the research physician, blinded for the TYM- and SAGE-scores, performed an evaluation with a structured interview and the Mini-Mental State Examination (MMSE). Patients suspected of cognitive impairment (mild cognitive impairment (MCI) or dementia) on either the cognitive tests (TYM<40; SAGE<15) or based on the GP-evaluation were evaluated at a memory clinic. Besides, a random sample of 30% of patients not suspected of cognitive impairment based on the three test results, was also evaluated at the memory clinic.

In the last step, medical and neuropsychological examinations and an MRI were performed at the memory clinic to establish or rule out a diagnosis of MCI or dementia.[11]

Study population

Participants were ≥70 years and known with type 2 diabetes. Exclusion criteria were a previous dementia diagnosis or a previous memory clinic evaluation and inability to write or read Dutch. Patients with a disorder that might influence cognitive functioning, like substance abuse or a psychiatric or neurological disorder, but without a diagnosis of cognitive impairment were not excluded, as we were interested in the presence of unknown cognitive disorders regardless of the cause. After applying these criteria, 225 patients were eligible for inclusion in the analysis (see Results section for patient flow).

Measurements

The SF-36 is a self-report questionnaire measuring eight domains: physical functioning, role limitations due to physical problems, bodily pain, social functioning, mental health, role limitations due to emotional problems, vitality and general health. Two summary subscales can be calculated: the Physical Component Score (PCS) and the Mental Component Score (MCS).[14] Higher scores indicate more favourable levels of functioning.

The EQ-5D covers five dimensions of health: mobility, self-care, daily activities, pain/discomfort and anxiety/depression; each with three levels of functioning: no problems, some problems and severe problems.[15] Answers were used to compute an index value based on a Dutch valuation study,[16] ranging between +1 and −0.329, where 0 means death.

The EQ-VAS is a graded, vertical line ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The patient was asked to mark a point on the EQ-VAS that best reflects his/her actual health state.

Depressive symptoms were assessed with the validated Dutch version of the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D),[17] a self-report questionnaire measuring the presence of depressive symptoms on a four-point scale. Higher scores indicate more depressive symptoms. A score ≥16 is generally accepted as the cut-off score for the presence of depression.

Information on age, gender and educational level was gathered during the home visit. Medical data with respect to diabetes complications and duration, medication use and values of the last yearly diabetes monitoring visit (HbA1c, lipids, creatinine, weight, height, blood pressure) were collected from the patient's medical record.

Cognitive impairment

The diagnosis cognitive impairment, i.e., MCI or dementia, was established by a multidisciplinary team with a (resident) neurologist and a neuropsychologist after the visit to the memory clinic. For the diagnosis of dementia the DSM-IV criteria were used. Dementia was defined as memory impairment and impairment in at least one other cognitive domain (aphasia, apraxia, agnosia, executive functioning) that significantly affects social or occupational functioning compared to the previous level of functioning and not caused by a delirium.[18] MCI was defined as not normal, not demented, with cognitive complaints that could be objectified as a disorder (i.e. performance <5th percentile on normative values) by a neuropsychological assessment and/or evidence of decline over time, and preserved basic activities of daily living.[19]

Statistical analysis

Participants were divided in two groups: those with cognitive impairment (MCI or dementia) and those with 'normal cognition'. For participants not visiting the memory clinic, because they did not fulfil the above mentioned criteria to be invited or because they were unable to attend, a diagnosis of the memory clinic (cognitive impairment yes/no) was imputed. Ten imputed databases were generated with the predictors TYM, SAGE, MMSE, GP-evaluation, age, gender, educational level, living situation and score on the EQ-5D-domain mobility. The latter two were chosen because they could be associated with attending the memory clinic.

Categorical variables are reported as numbers and percentages, continuous variables as means with standard deviations (SD) and not normally distributed variables as median with interquartile range (IQR). Differences between the groups were analysed with the Fisher's exact test for categorical variables and with independent t-tests for continuous variables. Spearman correlation analysis was used to assess correlations between the total depressive symptom score and the health status scores PCS, MCS, EQ-5D index score and EQ-VAS.

Although the health status and depressive scores were skewed, we decided to report means and SDs, which were calculated using Rubin's rule,[20] and analysed with independent t-tests to be able to include the data from all imputed databases. A p-value<0.05 was considered significant.

Dementia can only be diagnosed when there are problems in daily functioning, because one of the DSM-IV criteria is a significant impairment in social or occupational functioning. One of the items assessed in health status questionnaires is whether patients experience problems in daily functioning, therefore including patients with dementia could disturb the results. For that reason we performed a sensitivity analysis excluding patients with dementia.

Regulation statement and ethical approval

The Cog-ID study was conducted according to the principles of the declaration of Helsinki

and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO). This study was approved by the medical ethics committee of the University Medical Centre Utrecht, the Netherlands. Written informed consent was obtained from all patients.

RESULTS

Study population

Between August 2012 and September 2014, 1243 patients from 22 general practices were invited by a letter from their GP to participate in the Cog-ID study. 959 patients (77%) responded of which 228 agreed to participate (18%). Three patients were excluded because of a previous memory clinic evaluation (n=2) or inability to write (n=1), leading to a study population of 225 subjects. In total 107 patients were selected for a memory clinic evaluation because of suspected cognitive impairment. Another 34 patients were invited as part of the random sample of patients with three negative results. Of all invited patients, 14 were unable to attend the memory clinic. From the 127 patients actually visiting the memory clinic 44 patients received a diagnosis of cognitive impairment (MCI: 41; dementia: 3). For the 84 patients without suspicion of cognitive impairment after the home visit and for the 14 patients that were unable to attend the memory clinic, a diagnosis of the memory clinic was imputed. Cognitive impairment was thus present in 57 patients. Table 1 describes the patient characteristics for the total population and per group. Patients with cognitive impairment had significantly less years of education and more macrovascular complications, namely a history of stroke. In addition, patients with cognitive impairment showed a trend for more microvascular complications, and for more often use of insulin and antihypertensive medication.

Health status - SF-36

The separate SF-36 domain scores could be calculated in 220 patients (Table 2). The two summary scales, the physical and mental component score, could be calculated in 212 patients. Patients with cognitive impairment showed lower scores on all SF-36 domains; in six out of the eight domains and in the summary scales PCS and MCS this difference reached statistical significance (Table 2). The largest differences between the groups were found for the domains role limitations due to physical and emotional problems (19.8 (95%-CI 6.5–33.0, p<0.01) and 14.7 (95%-CI 3.3–26.1, p=0.01) respectively). The differences between the scores on the PCS and MCS were of similar magnitude (3.5 (95%-CI 0.7–6.3, p=0.02) versus 2.9 (95%-CI 0.3–5.6; p=0.03).

Health status - EQ-5D and EQ-VAS

The proportion of patients with problems is higher on each EQ-5D domain in patients with cognitive impairment. The largest difference between the two groups was found for

Table 1. Patient characteristics

	N	Total population (n=225)	N	Normal cognition (n=168)	N	Cognitive impairment (n=57)
Age (years)	225	76.8 ± 5.0	168	76.5 ± 8.9	57	77.9 ± 5.8
Gender (% male)	225	60%	168	61%	57	58%
Education (median (IQR))	225	5 (4-6)	168	5 (4-6)	57	4 (4-5)*
Diabetes duration (years)	221	9.0 ± 7.9	166	8.6 ± 8.0	55	10.2 ± 9.0
HbA1c (mmol/mol)	216	52.1 ± 9.6	161	51.6 ± 10.3	55	53.2 ± 11.7
Systolic blood pressure (mmHg)	206	139.0 ± 17.5	154	138.7 ± 18.6	52	139.8 ± 18.4
Diastolic blood pressure (mmHg)	206	74.7 ± 11.2	154	74.3 ± 11.3	52	75.8 ± 13.6
Total cholesterol (mmol/L)	216	4.3 ± 1.1	162	4.3 ± 1.2	54	4.2 ± 1.2
Creatinine (mmol/L)	218	92.8 ± 29.9	162	90.8 ± 30.8	56	98.8 ± 35.2
BMI (kg/m^2)	211	29.0 ± 4.6	157	28.7 ± 4.6	54	29.9 ± 5.4
Microvascular complications	225	26%	168	24%	57	32%
Macrovascular complications	225	44%	168	40%	57	56%*
Myocardial infarction	225	18%	168	17%	57	19%
Angina pectoris	225	15%	168	14%	57	16%
Stroke	225	16%	168	9%	57	26%*
TIA	225	7%	168	7%	57	9%
Vascular surgery	225	26%	168	24%	57	33%
Medication use						
Glucose lowering medication	225	85%	168	86%	57	83%
Insulin	225	24%	168	23%	57	30%
Oral medication	225	79%	168	81%	57	72%
GLP1	225	0%	168	0%	57	2%
Antihypertensive medication	225	86%	168	83%	57	93%
Lipid lowering medication	225	75%	168	75%	57	74%
Antithrombotic medication	225	55%	168	54%	57	58%

Cognitive impairment was diagnosed at the memory clinic in 44 patients. Additionally, 13 patients were classified with cognitive impairment by multiple imputation. Data are presented as means (± standard deviation) or proportions (%).

* p-value < 0.05 for difference between patients with normal cognition and with cognitive impairment

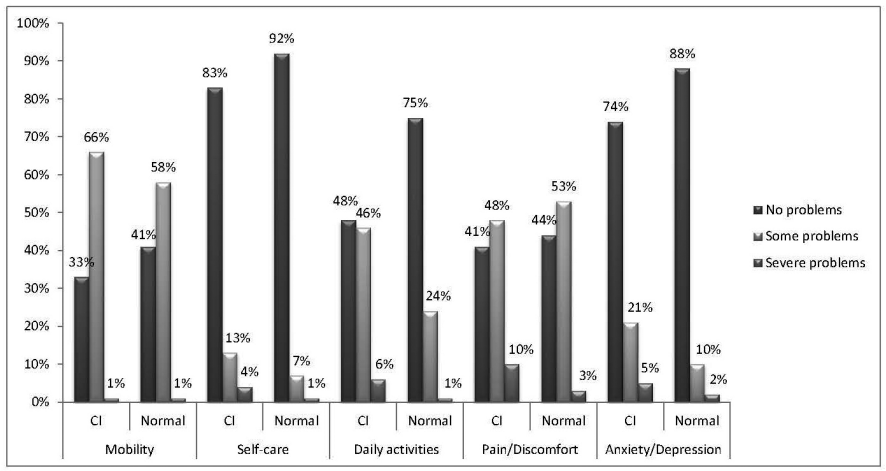
IQR: interquartile range; HbA1c: haemoglobin A1c; BMI: body mass index; TIA: transient ischemic attack; GLP1: glucagon-like-peptide 1-agonist.

Table 2. Health status scores for total population and patients with and without cognitive impairment (mean ± SD)

	N	Total population (n=225)	N	Normal cognition (n=168)	N	Cognitive impairment (n=57)
Physical functioning	224	63.6 ± 26.4	167	67.1 ± 25.5	57	53.2 ± 30.4*
Role limitations due to physical problems	223	67.7 ± 39.1	166	72.7 ± 28.5	57	53.0 ± 45.4*
Bodily pain	224	73.0 ± 24.2	167	74.6 ± 23.8	57	68.3 ± 27.0
General health	220	58.2 ± 18.8	165	59.3 ± 19.3	55	54.7 ± 20.5
Social functioning	225	79.2 ± 19.9	168	81.7 ± 19.7	57	71.8 ± 24.5*
Mental health	222	79.5 ± 14.5	167	80.9 ± 14.6	55	75.2 ± 17.9*
Role limitations due to emotional problems	221	80.7 ± 34.1	166	84.3 ± 32.0	55	69.6 ± 42.6*
Vitality	221	66.3 ± 18.5	167	68.5 ± 17.9	54	59.7 ± 22.1*
Physical Component Score (PCS)	212	51.2 ± 8.3	161	52.1 ± 8.3	51	48.6 ±8.9*
Mental Component Score (MCS)	212	52.5 ± 7.3	161	53.2 ± 7.2	51	50.2 ± 8.8*
EuroQol 5 Dimensions	219	0.80 ± 0.2	165	0.83 ± 0.2	54	0.73 ± 0.3*
EuroQol Visual Analogue Scale	222	73.8 ± 14.0	167	75.5 ± 12.9	55	68.8 ± 17.4*
CES-D	223	10.0 ± 7.1	167	9.2 ± 7.1	56	12.7 ± 8.5*
CES-D ≥ 16	223	45 (20%)	167	28 (17%)	56	17 (30%)*

* p-value < 0.05 for difference between patients with normal cognition and with cognitive impairment

Figure 1. Proportion of patients per EQ-5D domain in patients with normal cognition (normal) and patients with cognitive impairment (CI)



the domain 'daily activities' (52% vs 25%; p<0.001). The proportion of patients with 'pain/discomfort' was almost equal over the groups (59% vs 56%; p=0.76), but patients with cognitive impairment more often had severe problems on this subscale (Figure 1). The EQ-5D index value and EQ-VAS scores were significantly lower in patients with cognitive impairment (Table 2).

Depressive symptoms

CES-D scores were significantly higher in patients with cognitive impairment compared with patients with normal cognition. Thirty percent of the patients with cognitive impairment had a depression (CES-D≥16), which was almost twice as often as patients without cognitive impairment (RR 1.8; 95%-CI 1.1–3.0, p=0.03)(Table 2).

Depressive symptoms were moderately correlated with health status scores, with correlations ranging from 0.43 to 0.48 (all p-values<0.001).

Sensitivity analysis: excluding patients with dementia

Excluding patients with dementia slightly increased all SF-36 domain scores for the resulting group of patients with MCI, thus reducing the difference with the scores of the group with normal cognition. As a result, the differences between the two groups for the domain 'mental health' and the summary scale MCS did not reach statistical significance anymore. The scores for patients with cognitive impairment, however, remained below the scores of patients with normal cognition on all SF-36 domains. The EQ-5D, EQ-VAS and CES-D scores did not change.

DISCUSSION

The present study shows that detection of cognitive impairment in patients with type 2 diabetes identifies a vulnerable patient group who are more likely to suffer from a reduced health status and depressive symptoms. This group of patients, of which >90% had MCI, was still capable of maintaining a reasonable cardiometabolic control and the number of micro- and macrovascular complications was, aside from stroke, not significantly increased compared to patients without cognitive impairment.

In the general population, health status has, to our knowledge, not been compared between people with and without cognitive impairment. Nevertheless, patients with cognitive impairment are believed to have a lower quality of life than people without cognitive impairment.[21-24] In patients with type 2 diabetes, a significantly lower EQ-5D index was found for patients with lower cognitive functioning.[25] In our study, patients felt particularly limited in their daily and social functioning, represented by the largest effect on the role limitations of the SF-36 and the EQ-5D domain 'daily activities'. In this respect, patients might also experience feelings of falling too short with respect to their

diabetes self-management. One could argue that this is a self-fulfilling prophecy as a criterion for dementia is a significant impairment in social or occupational functioning, but the sensitivity analysis demonstrated that also patients with MCI experience more problems in these domains. Apparently these problems do not yet justify the diagnosis dementia, possibly because they are not yet severe enough or because coping strategies of the patient and/or family members reduce their impact on daily life, for example because the spouse took over household tasks. Our results, however, indicate that the coping strategies are not sufficient to diminish for example the depressive symptoms to a level comparable to patients without cognitive impairment.

The prevalence of depressive symptoms in our study population was comparable with the 17% prevalence in a Dutch sample of type 2 diabetes patients, aged 55-85 years.[26] A review examining depression in patients with dementia, not specifically with type 2 diabetes, showed prevalence rates of 10-62% for depression. In our study 30% of patients with cognitive impairment had a CES-D≥16, which was almost twice as often as patients without cognitive impairment. This doubled prevalence of depression is in line with other studies in patients with cognitive impairment versus those without, both in the general population[27] and in patients with type 2 diabetes.[5;6]

Diabetes patients identified with cognitive impairment may need extra attention. The diagnosis itself might explain difficulties that patients experience in performing tasks in daily life, diabetes self-management included. Detection of cognitive impairment gives the physician the opportunity to tailor diabetes treatment, which might reduce treatment-related complications and relieve patients from the feeling of falling too short; and consequently reduce depressive symptoms. Examples of measures to tailor treatment could be medication dispensers to reduce medication errors, more lenient glycaemic targets to prevent hypoglycaemia, and memory cards to remind patients of appointments. Further research however should indicate whether these measures can indeed be beneficial.

A strength of our study is the use of the memory clinic evaluation to define patients with cognitive impairment. The timing of the assessment of health status and depressive symptoms, shortly before people's cognitive performance was examined, gave us the opportunity to assess them as if patients were attending a medical clinic after being invited by a third party. Health status was therefore not yet influenced by receiving a formal diagnosis of cognitive impairment.

Due to our cross-sectional design, we could only assess associations and we cannot draw conclusions about causality. We also did not study the interaction between depression and health status, although this is reported to be an important determinant in both the relation between type 2 diabetes and health status and between cognitive impairment and health status.[28;29]

To conclude, undiagnosed cognitive impairment in patients with type 2 diabetes is associated with a reduced health status and with depressive symptoms. Detection

of cognitive impairment identifies a vulnerable patient group that could benefit from integrated and tailored treatment. Further research should examine what supportive measures should be taken and what their effect on health status and depressive symptoms is.

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CHAPTER 5

INTENSIVE MULTIFACTORIAL TREATMENT AND COGNITIVE FUNCTIONING IN SCREEN-DETECTED TYPE 2 DIABETES – THE ADDITION-NETHERLANDS STUDY: A CLUSTER-RANDOMIZED TRIAL

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ABSTRACT

Aim: To assess whether an intensive multifactorial treatment can reduce cognitive decrements and cognitive decline in screen-detected type 2 diabetes.

Methods: The multinational ADDITION-study, a cluster-randomized parallel group trial in patients with screen-detected type 2 diabetes, compared the effectiveness of intensive multifactorial treatment (IT; lifestyle advice and strict regulation of metabolic parameters) with routine care (RC) on cardiovascular outcome. In The Netherlands randomization was stratified according to practice organization. Allocation was concealed from patients. The present study assessed the effect of IT on cognition through two neuropsychological assessments (NPA) on two occasions. The assessments took place three and six years after the start of the intervention. Non-diabetic controls served as reference group. The first NPA was performed in 183 patients (IT: 97; RC: 86) and 69 controls. The second NPA was performed in 135 patients (IT: 71; RC: 64) and 55 controls. Primary outcome was a composite score, including the domains memory, information-processing speed and attention and executive function. Comparisons between the treatment groups were performed with multi-level analyses.

Results: The first NPA showed no differences between the treatment groups (mean difference composite z-score: 0.00; 95%-CI -0.16 to 0.16; IT vs RC). Over the next three years cognitive decline in the diabetic groups was within the range of the reference group and did not differ between the treatment arms (difference decline between diabetic groups -0.12; -0.24 to 0.01; IT vs RC).

Conclusions: Six years of IT in screen-detected type 2 diabetes had no benefit on cognitive functioning over RC.

INTRODUCTION

With the increasing incidence of type 2 diabetes, the prevalence of associated complications increases as well. Besides well-known complications, diabetes is also associated with decrements in learning and memory, mental flexibility and information-processing speed[1-3] and with an increased risk of developing dementia.[4-6] These cognitive decrements may already start to develop in pre-diabetic stages[7] and are slowly progressive over the years.[3]

The ADDITION study (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care),[8] started with a population-based screening for type 2 diabetes. In those identified through screening, the effectiveness of intensive multifactorial treatment on cardiovascular outcome was compared with routine care according to national guidelines. At start of the ADDITION-study it was known that patients with type 2 diabetes have a twofold increased risk for developing dementia. Studies also suggested that cognitive functioning in patients with type 2 diabetes might benefit from several months of improved glycemic control.[9;10] It was unknown, however, what the rate of cognitive decline was in people with early type 2 diabetes relative to controls. It was also unknown whether we could prevent or diminish cognitive decline in patients with screen-detected type 2 diabetes with for example lifestyle advice and strict regulation of glucose levels, blood pressure and lipid levels. Therefore we performed an add-on study in a subgroup of patients of the ADDITION-Netherlands study in which cognition was assessed on two occasions. The assessments took place three and six years after start of the intervention. Our aim was to investigate whether cognitive functioning benefited from intensive multifactorial treatment compared to routine care after three years and whether a further three years of intensive treatment attenuated cognitive decline.

METHODS

Embedding

The ADDITION study is a pragmatic multinational cluster-randomized parallel group trial that compared screening plus intensive multifactorial treatment to screening and routine care. Mean follow-up was 5.3 years.[8] Between 2002 and 2004, a population-based screening among 79 general practices in The Netherlands, screened 56 978 individuals between 50 and 70 years for type 2 diabetes. In total 586 patients were identified with type 2 diabetes according to the WHO-criteria.[11;12] To avoid contamination, randomization was done on the level of the general practice. Before screening, general practices were therefore randomly allocated to intensive multifactorial treatment or routine care using computer-generated random numbers, stratified according to practice organization

(single-handed vs. group practice) (Figure 1). Allocation was concealed from patients throughout the trial. Exclusion criteria for participation in the intervention study were: life expectancy of less than twelve months, being housebound, or psychological or psychiatric problems that were likely to invalidate informed consent.[13] Sixty-nine patients declined participation and nineteen did not meet the eligibility criteria. Subsequently, 498 individuals were included in the Dutch part of the ADDITION intervention study.[14] Patients started the intervention within six weeks after screening.

Treatment protocols

Intensive multifactorial treatment consisted of lifestyle advice regarding diet, physical activity and smoking and promotion of protocol-driven strict regulation of metabolic parameters.[8] HbA1c level had to be kept <53 mmol/mol (7.0%). Glucose-lowering therapy with a biguanide, prandial glucose regulator or sulphonylurea had to be altered when HbA1c was >48 mmol/mol (6.5%). Antihypertensive treatment with an ACE inhibitor was prescribed if blood pressure was >120/80 mmHg. When blood pressure was >135/85 mmHg calcium channel blockers, thiazides or beta-blockers were added in a stepwise approach. Patients receiving antihypertensive treatment were also treated with aspirin 80 mg/day. Treatment with a statin was indicated if total cholesterol was >3.5 mmol/L; dose needed to be increased when total cholesterol was >5.0 mmol/L or >4.5 mmol/L in patients with known cardiovascular disease (CVD). Although targets were specified and classes of medication recommended, decisions about medication were made by general practitioners and patients.

In the routine care group, general practitioners were only informed about diagnostic test results. Patients received treatment according to the current guidelines of the Dutch College of General Practitioners. At start of ADDITION the guideline from 1999 was followed with target levels for HbA1c, blood pressure and cholesterol below 69 mmol/mol (8.5%), 150/85 mmHg and 5.0 mmol/L respectively.[15] In 2006 a new guideline was introduced with stricter goals for HbA1c and systolic blood pressure respectively being below 53 mmol/mol (7.0%) and 140 mmHg.[16] Furthermore a statin was advised for almost all patients. Patients with CVD received aspirin 80 mg/day. Education and lifestyle advice were also given.

Study population and cognitive assessment

In the present add-on study, patients were invited to participate in a project in which cognition was assessed. We intended to include approximately one hundred patients per treatment group, allowing to detect a difference between the groups of an effect size of 0.3 standard deviation units, which is considered to be a small to medium effect in neuropsychological studies,[17] with 80% power and α of 5%. Patients were not eligible for the cognition sub-study if they had a known psychiatric or neurological disorder

that could influence cognitive functioning, history of alcohol or substance abuse or were unable to complete a neuropsychological assessment (NPA). Individuals with a previous non-invalidating stroke could participate. Patients were randomly sampled from both groups, after their records had been checked for exclusion criteria, and subsequently invited to participate. A reference group of participants without diabetes was recruited among spouses and acquaintances of the patients, matched for age, sex and educational level. An additional exclusion criterion for control participants was a fasting blood glucose >7.0 mmol/L. Because some of the exclusion criteria only became evident at a face to face interview (e.g. alcohol abuse), a second assessment against exclusion criteria was done after the first NPA by investigators unknown to group allocation and cognitive status. 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.

Neuropsychological assessment

Participants underwent a detailed NPA on two occasions, in 2006-2007 and 2009-2010. Both NPAs consisted of twelve verbal and nonverbal tasks addressing six cognitive domains. The division in cognitive domains was made a priori, according to standard neuropsychological practice and cognitive theory.[18] For the present study we focused on the domains which have previously been shown to be affected in type 2 diabetes, namely the domains memory, information-processing speed and attention and executive function.[1-3] The domain 'memory' was assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale –3rd edition (WAIS-III),[19] the Corsi Block-tapping Task,[20] the Rey Auditory Verbal Learning Test,[21] the Location Learning Test[22] and the delayed recall of the Rey-Osterrieth Complex Figure Test.[23] The domain 'information-processing speed' was assessed by the Trail-making Test Part A,[24] the Stroop Color-Word Test (part 1 and 2)[25] and the subtest Symbol Digit Substitution of the WAIS-III. The domain 'attention and executive function' was assessed by the Trail-making Test Part B (ratio score),[24] the Stroop Color-Word Test (part 3; ratio score), the Brixton Spatial Anticipation Test,[26] a letter fluency test using the letters 'N' and 'A' and category fluency (animal naming).[27] Furthermore, premorbid level of intelligence (IQ) was estimated by the Dutch version of the National Adult Reading Test.[28] Educational level was divided into seven categories (1,<6 years of education; 2, 6 years; 3, 8 years; 4, 9 years; 5, 10-11 years; 6, 12-18 years and 7,>18 years). The tests were administered in a fixed order at the patients' home by neuropsychologists and neuropsychologists in training. The entire battery took about 90 minutes to complete.

To assess possible selective loss to follow-up at the second NPA we invited all non-participants and participants of the second NPA to take part in the modified Dutch version of the Telephone Interview for Cognitive Status (TICS-m), a 12 item screening instrument designed to identify persons with dementia (maximum score 50).[29]

Timeline

The first NPA took place three and a half years (mean 3.6 ± 0.6 (±SD)) after screening and start of the intervention (Figure 2). The second NPA was performed 6.8 (± 0.6) years after the screening, at the end of the main ADDITION study, and 3.2 (± 0.3) years after the first NPA. There was a mean interval of 4.6 (± 3.6) months between the second NPA and the last measurements of the main ADDITION study.

Risk factor assessment

At time of the NPAs body weight, height and blood pressure were measured and BMI was calculated. Systolic and diastolic blood pressures were measured at the beginning and the end of the NPA with an automatic tonometer (Omron M6, Omron Healthcare Europe, Hoofddorp, The Netherlands); measurements were averaged. Demographic variables and medical history were recorded in a standardized interview. Smoking was classified as current, past or never. 'Any macrovascular event' was defined as self-reported history of myocardial infarction, stroke or surgery or endovascular treatment for carotid, coronary or peripheral arterial disease.

Venous blood samples were drawn after an overnight fast to determine HbA1c and total cholesterol. HbA1c was analyzed by DCCT aligned ion-exchange high-performance liquid chromatography using Menarini 8160 (A.Menarini Diagnostics, Florence, Italy). Lipids were measured using standard enzymatic techniques using a Beckman LX-20 (Beckman Coultier inc., USA) until November 2008 and thereafter a Roche Hitachi Modular P (Roche Diagnostics, USA). Because the second NPA was not performed simultaneously with the close-out of the intervention, we reassessed some risk factors (i.e. blood pressure, height, weight) during the NPA.

Analysis

Non-parametric data and proportions were analyzed respectively with Wilcoxon test and McNemar test for changes over time and Mann-Whitney test and Chi-square test for differences between groups. Normally distributed continuous data on risk factors levels were analyzed with multi-level linear regression analyses.

Raw test scores at first and second NPA were standardized into z-scores per test, using the pooled mean of the first NPA scores of the reference group. The individual's z-score reflects the number of standard deviations a measurement deviates from the mean of this group. The z-score of each domain was calculated by averaging the test z-scores comprising that domain. In between group comparisons, a mean difference in z-score below 0.2 is considered a small, between 0.2 and 0.8 a medium and above 0.8 a large effect.[17] The primary outcome measure was defined a priori, as the mean difference between the intensive treatment group and the routine care group in the composite z-score of the domains memory, information-processing speed and attention and executive function. These three domains were selected because they are most

consistently affected in type 2 diabetes.[1,3] The z-score on each of the separate domains was the secondary outcome measure. For the first NPA we calculated the z-scores per diabetic group compared to the reference group and the difference between the diabetic groups. To asses cognitive decline from the first to the second NPA we calculated a mean change over time per group and a difference between the groups in change over time. Again the performance of the non-diabetic group served as reference. Analyses were done with multi-level linear regression analyses to take into account the cluster-randomization at the general practice level. Analyses for differences between groups were adjusted for IQ-score as the reference group had a higher premorbid estimated intelligence. The change over time was additionally adjusted for time between the end of the intervention and the second NPA.

RESULTS

Study population

For the reference group 75 participants without diabetes underwent the first NPA. Six were excluded after the first NPA, because they were discovered to meet an exclusion criterion at the standardized face to face interview, leaving 69 controls for the analyses. The mean age of this group was 63 years, 48% were male and the mean IQ was 104. Further characteristics have been described elsewhere.[2] As this group acted as reference group, their mean z-scores at the first NPA were zero. At the second NPA two participants from the reference group had died, one could not be contacted, nine declined to participate and two had developed a fasting glucose above 7.0 mmol/L (Figure 1). The decline on the composite score over the three years was -0.07 (95%-CI -0.14 to 0.01).

From the intensive treatment group 101 patients underwent the first NPA. Four were excluded after checking the results of the interview against the exclusion criteria, leaving 97 patients for the first analyses. From the routine care group 96 patients were examined of which ten were excluded, leaving 86 patients for the analyses. At the second NPA 24 patients from the intensive treatment group declined to participate and two patients could not be contacted. In the routine care group two patients had died and 20 patients declined to participate (Figure 1). The second NPA was performed between February 2009 and September 2010, with a mean interval of 3.2 ± 0.3 years after the first NPA. Participants and non-participants at the second NPA did not differ with respect to age (63.2 vs 62.8 yr; p=0.69), sex (53.4% vs. 58.9% male; p=0.47) and estimated premorbid IQ (97.4 vs 99.2; p=0.53), but cognitive performance at the first NPA differed with a mean difference on the composite z-score of -0.18 (95%-CI -0.31 to -0.04; participants are reference). The TICS-m was obtained in 34 of the 58 surviving non-participants (58.6%) and in 143 of the 192 participants at the second NPA (74.5%). Within each of

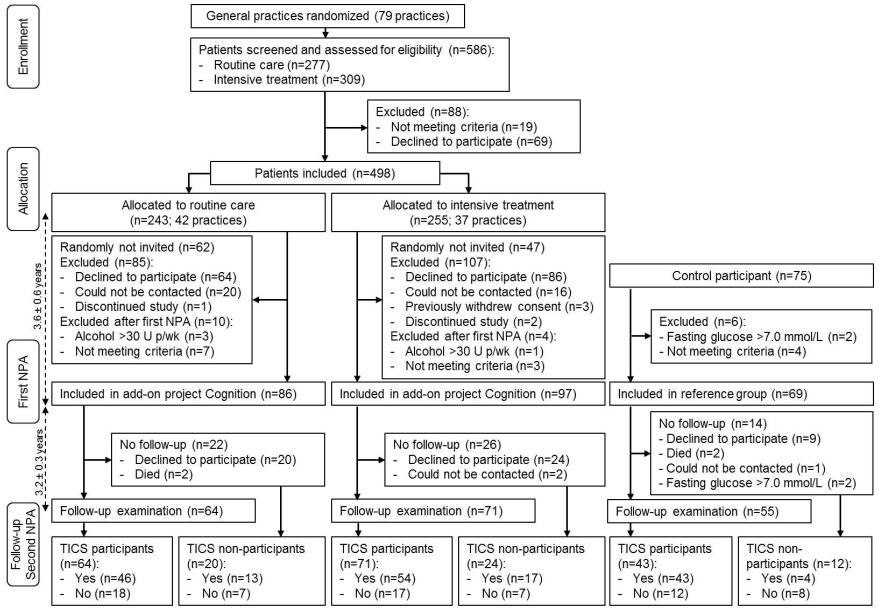

Figure 1. Flow diagram participants

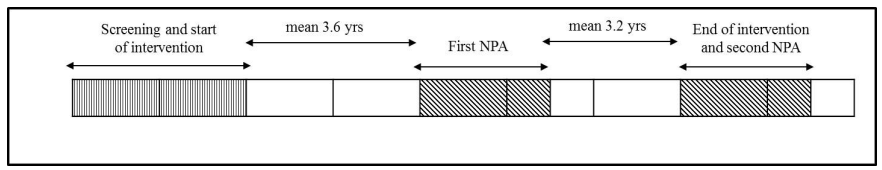

Figure 2. Study timeline

the three groups no difference was found between participants and non-participants at the second NPA with respect to age, sex and estimated premorbid IQ. For participants and non-participants at the second NPA from the reference group both the composite score of the first NPA (0.03 ± 0.4 vs -0.2 ± 0.6) and the TICS-score at follow-up (37.4 ± 3.8 vs 35.0 ± 4.4) were comparable. In the intensive treatment group participants of the second NPA scored higher than non-participants on the composite score of the first NPA (-0.2 ± 0.5 vs -0.6 ± 0.8), but TICS-scores at follow-up were similar (35.1 ± 4.7 vs 33.1 ± 5.8). In the routine care group the composite z-scores of the first NPA were comparable (-0.2 ± 0.5 vs -0.2 ± 0.5), but the TICS-score at follow-up was slightly lower

Table 1. Patient characteristics of diabetic patient groups

	Intensive treatment group			Routine care group			p-values		
	Baseline	First NPA	Final[a]	Baseline	First NPA	Final[a]	Group difference first NPA	Group difference final	Difference in change from first NPA to final
N	97		71	86		64			
Sex (% males)	57.7		62.0	64.3		62.5	0.37	0.91	
Age (years)	59.3 ± 5.6	62.9 ± 5.6	66.0 ± 5.7	59.5 ± 5.3	63.1 ± 5.2	66.3 ± 5.6	0.83	0.71	
Educational level (median (IQR))	4 (4–5)		4 (4–5)	5 (4–5)		5 (4–5)	0.19	0.79	
Estimated premorbid intelligence	95.2 ± 19.4		96.5 ± 19.3	98.6 ± 19.4		98.8 ± 20.5	0.24	0.82	
BMI (kg/m^2)	31.4 ± 4.9	30.8 ± 4.8[b]	31.4 ± 5.3	30.4 ± 4.3	30.2 ± 4.9	30.8 ± 5.1	0.38	0.50	0.88
Systolic blood pressure (mmHg)	164.7 ± 22.8	140.7 ± 20.7[b]	136.9 ± 17.6	162.4 ± 20.5	147.0 ± 17.7[b]	148.4 ± 19.4	0.08	<0.01	0.06
Diastolic blood pressure (mmHg)	89.6 ± 10.9	81.3 ± 10.6[b]	75.9 ± 8.5	89.8 ± 9.3	82.7 ± 10.2[b]	81.2 ± 10.1	0.44	<0.01	<0.01
Use of antihypertensive drugs (%)	25.8	89.7[b]	94.4	26.5	72.1[b]	78.1	<0.01	<0.01	
Current smoking (%)	22.7	20.0	19.4	19.8	22.6	14.3	0.67	0.63	
HbA1c (mmol/mol; %)	56.2 ± 14.4; 7.3 ± 1.3	43.4 ± 4.5; 6.1 ± 0.4[b]	44.2 ± 4.9; 6.2 ± 0.4	56.1 ± 17.0; 7.3 ± 1.6	45.9 ± 5.8; 6.4 ± 0.5[b]	47.2 ± 6.3; 6.5 ± 0.6	0.15	<0.01	0.99
Total cholesterol (mmol/L)	5.5 ± 1.1	3.9 ± 0.8[b]	4.0 ± 0.8	5.5 ± 1.2	4.4 ± 1.1[b]	4.3 ± 0.8	<0.01	0.04	0.84
Use of lipid-lowering medication (%)	16.5	91.8[b]	90.1	18.1	64.0[b]	81.3	<0.01	0.13	
Any macrovascular event (%)	13.4	13.4	17.6	11.6	16.3	21.9	0.58	0.66	

Data are presented as mean ± SD or percentage unless otherwise specified
[a] Physical and laboratory measurements measured at end of intervention; medication use, smoking and 'any macrovascular event' assessed during second NPA
[b] Significant difference between baseline measurement and first NPA

Table 2. Raw test scores of the reference group and the two diabetes groups at the first and second examination (mean ± SD)

		Intensive treatment group		Reference group	
Cognitive domain	Cognitive test	First NPA (n=97)	Second NPA (n=71)	First NPA (n=69)	Second NPA (n=55)
Memory	WAIS-III Digit Span forward	49.1 ± 21.2	40.4 ± 24.4	57.3 ± 27.8	47.7 ± 19.4
	WAIS-III Digit Span backward	24.1 ± 13.6	23.0 ± 18.5	29.3 ± 18.7	27.9 ± 18.1
	Corsi Block-Tapping Test forward	37.3 ± 10.5	35.7 ± 12.2	37.9 ± 12.4	39.7 ± 13.1
	Corsi Block-Tapping Test backward	38.7 ± 17.1	35.3 ± 14.7	40.8 ± 15.3	41.3 ± 15.4
	RAVLT total trials 1-5	35.5 ± 9.4	41.1 ± 11.8	41.3 ± 10.6	46.6 ± 11.1
	RAVLT delayed recall	6.6 ± 2.6	8.3 ± 3.5	7.8 ± 3.1	10.0 ± 3.3
	RAVLT recognition	27.1 ± 3.2	28.5 ± 2.2	28.4 ± 1.6	29.0 ± 1.4
	LLT total trails 1-5[a]	15.1 ± 16.7	25.4 ± 21.5	15.9 ± 20.8	15.6 ± 18.1
	LLT learning index	0.8 ± 0.3	0.6 ± 0.3	0.8 ± 0.3	0.7 ± 0.3
	LLT delayed trial[a]	1.5 ± 3.0	2.6 ± 4.9	1.5 ± 3.0	5.7 ± 12.4
	Complex Figure Test - Delay	16.5 ± 5.6	16.5 ± 6.3	19.4 ± 5.2	18.6 ± 6.4
Information processing speed	Stroop Color Word Test I[a]	48.1 ± 7.1	50.2 ± 8.4	44.9 ± 8.5	47.3 ± 9.0
	Stroop Color Word Test II[a]	62.7 ± 10.5	62.3 ± 10.6	59.9 ± 12.9	61.2 ± 13.7
	TMT Part A	48.2 ± 20.7	41.5 ± 11.8	42.1 ± 17.1	39.5 ± 16.5
	WAIS-III Digit Symbol	56.0 ± 14.7	55.6 ± 17.4	61.8 ± 17.0	64.3 ± 16.6
Attention and executive functioning	Stroop Color Word Test III[a]	115.8 ± 29.4	110.8 ± 27.1	105.4 ± 37.2	107.6 ± 39.0
	TMT Part B	101.2 ± 44.9	93.5 ± 39.4	89.7 ± 29.2	81.6 ± 29.4
	Letter fluency (mean of N+A)	10.2 ± 4.0	11.2 ± 4.9	11.8 ± 4.4	12.4 ± 3.9
	Category fluency (animals)	29.9 ± 8.1	30.0 ± 9.4	34.5 ± 8.8	35.5 ± 8.8
	Brixton Spatial Anticipation Test[a]	16.2 ± 6.9	17.6 ± 5.6	14.6 ± 5.4	16.4 ± 5.2

RAVLT, Rey Auditory Verbal Learning Test; LLT, Location Learning Test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale – Third edition
[a] Higher test scores reflect worse performance

Table 3. Mean difference per group compared to the reference group without diabetes in cognitive domain z-scores first NPA and difference between the groups corrected for estimated premorbid intelligence (95%-CI)

	Intensive treatment group (n=97)	Routine care group (n=86)	Difference between groups
Composite score	-0.15 (-0.31 to -0.01)	-0.15 (-0.31 to -0.01)	0.00 (-0.16 to 0.16)
Memory	-0.11 (-0.27 to 0.04)	-0.17 (-0.33 to -0.01)	0.06 (-0.09 to 0.21)
Information-processing speed	-0.19 (-0.42 to 0.03)	-0.04 (-0.27 to 0.18)	-0.15 (-0.36 to 0.06)
Attention and executive function	-0.13 (-0.42 to 0.15)	-0.19 (-0.48 to 0.09)	0.06 (-0.21 to 0.33)

Composite score was the primary outcome measure. Secondary analyses were done for the separate domains. Negative z-score indicates worse performance

in those participating at the second NPA (34.8 ± 4.4 vs 37.8 ± 5.4).

Among the whole group of non-participants, those participating in the TICS (n=34) did not differ from those that did not perform a TICS (n=26) with respect to age (63.7 ± 5.0 vs 62.4 ± 6.7; p=0.40), sex (54.5% vs 52% male; p=0.85), estimated premorbid IQ (99.9 ± 19.1 vs 94.1 ± 16.3; p=0.22) and cognitive performance at first NPA (mean difference composite z-score 0.02; 95%-CI -0.36 to 0.39; participants are reference).

Patient characteristics

Table 1 shows the patient characteristics of the routine care and intensive treatment group at baseline of the ADDITION-study, at first NPA and at the final measurements. The groups were similar in age, sex and IQ. Both groups improved significantly on blood pressure, HbA1c and total cholesterol during the first three years. Although the risk factor levels in the intensive treatment group decreased more, the differences between the groups were not significant, except for total cholesterol. In both groups the proportion of patients using antihypertensive and lipid-lowering medication increased. Over the next three years the group difference for total cholesterol remained and significant between group differences developed for blood pressure and HbA1c.

Cognitive functioning

Raw test scores of the reference group and the two diabetes groups at the first and second examination are presented in table 2. At the first NPA there was no difference between the groups with respect to the primary cognitive outcome measure (mean difference composite z-score 0.00; 95%-CI -0.16 to 0.16) (Table 3). Similar results were found in secondary analyses for the separate domains with mean differences ranging from -0.15 to 0.06 (Table 3). In the following three years the patients showed a slight

Table 4. Mean change over time in z-scores per group and difference in change over time between the groups (95%-CI)

	Intensive treatment group (n=71)	Routine care group (n=64)	Adjusted difference between groups in change over time[a]
Composite score	-0.14 (-0.23 to -0.06)	-0.02 (-0.12 to 0.07)	-0.12 (-0.24 to 0.01)
Memory	-0.27 (-0.38 to -0.15)	-0.05 (-0.17 to 0.07)	-0.22 (-0.38 to -0.05)
Information-processing speed	-0.05 (-0.17 to 0.07)	-0.13 (-0.27 to 0.00)	0.09 (-0.09 to 0.26)
Attention and executive function	-0.15 (-0.28 to -0.02)	0.07 (-0.07 to 0.21)	-0.21 (-0.41 to -0.02)

Composite score was the primary outcome measure. Secondary analyses were done for the separate domains. Negative z-score indicates worse performance

[a] Adjusted for time between end of intervention and second NPA and estimated premorbid intelligence

decline in cognition (mean change composite z-score intensive treatment: -0.14 (-0.23 to -0.06); routine care: -0.02 (-0.12 to 0.07)). The mean difference between the groups in change over time for the composite score was -0.12 (-0.24 to 0.01) (Table 4). Secondary analyses on the separate domains showed mean differences between the groups in change over time between -0.22 to 0.09 (Table 4).

DISCUSSION

In this study with cognitive assessments after three and six years of intensive treatment we could not show a positive effect above routine care on cognitive functioning in patients with screen-detected type 2 diabetes. After the first three years of treatment both diabetic groups had similar but modest decrements compared to the non-diabetic reference group. Over the next three years cognitive decline in the diabetic groups was within the range of the reference group and did not differ between the treatment arms.

To the best of our knowledge, this was the first study that compared the effect of six years of intensive multifactorial treatment with routine care on cognition in screen-detected type 2 diabetes. Strengths of our study are the extensive NPA, which was performed in a substantial number of patients with type 2 diabetes, and the longitudinal assessment of cognition over a period of three years. Moreover, treatment could be initiated at an early stage of type 2 diabetes. A limitation of our study is the timing of the NPAs. We were not able to perform a NPA at baseline. As a result we may have missed a change in cognition in the first three years of treatment. Nevertheless, there is no indication that the groups differed in cognition at baseline, as they were comparable

in demographic variables and IQ. The second NPA and the final measurements of the main ADDITION study were not administered simultaneously; however we found no differences in the contrast in risk factors between the groups at the two time points (data not shown). Other potential limitations are possible selection bias at the first NPA and possible selective attrition during follow-up. Although the lost to follow up was random and equally divided over the two treatment groups it might have led to an over- or underestimation of the cognitive functioning in one of the groups. The latter we examined with the TICS-m, which demonstrated no differences in cognitive functioning between participants and non-participants.

We previously reported that this population of screen-detected type 2 diabetes patients has mild cognitive decrements compared to people without diabetes (effect sizes up to -0.2).[2] Other cross-sectional studies found similar results with respect to impaired cognitive function in type 2 diabetes (effect sizes -0.3 to -0.6).[1] In agreement with our study, recent longitudinal studies demonstrated that the rate of cognitive decline in people with type 2 diabetes is generally slow and only slightly exceeds the rate of decline in normal ageing.[3;30] Probably, the process of cognitive decrements starts already in (pre-)diabetic stages and the decrements progress only slowly thereafter. Nevertheless, people with type 2 diabetes are overrepresented in the subgroup of individuals that show frank cognitive decline or progress to dementia[4-6] These recent insights into the course of development of cognitive decrements in people with type 2 diabetes do have important implications for future intervention studies. Possibly such studies should target the prevention of accelerated decline rather than average change in cognition across a whole population of patients, but this will require much larger study cohorts.

The intensive treatment in the main ADDITION-study resulted in a small but significant difference in change from baseline for several risk factors relative to routine care. In addition the intensive multifactorial treatment was associated with a non-significant 17% reduction of cardiovascular events. We did not find an effect of the six years intervention on cognitive functioning. In addition to the relative benign course of cognitive decline in the patients with diabetes, this might be caused by the well-controlled cardiovascular risk factors in both groups. At time of the first NPA, risk factor levels in our participants had already dropped significantly in both the routine care and the intensive treatment group, with minor differences between these groups. After six years of treatment the differences between the groups did become significant. Both groups however were treated well, which is probably the result of the high standard of care in general practice for patients with type 2 diabetes. In The Netherlands routine care improved by a new evidence based guideline in 2006.[16]

Some previous studies did report effects of improved glycemic control on cognitive functioning in people with type 2 diabetes.[9;10] However, these studies did not include a non-diabetic reference group, the follow-up time in these studies was short (≤24 weeks)

and the HbA1c levels before the intervention were relatively high (>60 mmol/mol (7.6%)). Because of the interval between start of treatment at baseline of the ADDITION study and first NPA we may have missed improvement of cognition with lowering of HbA1c. Furthermore, other studies indicate that mid-life hypertension might affect cognitive functioning later in life[31] and that hypertension is one of the factors involved in diabetes-associated cognitive decline.[32] Therefore strict control of blood pressure in mid-life might be a way to prevent cognitive decline. In our study the intensive treatment protocol resulted in a significantly lower blood pressure at close-out compared to routine care, but our follow-up time may have been too short to result in a significant effect on cognition.

It should be emphasized that cognitive functioning in our study population was within the range of normal ageing. The observed treatment effects on cognitive functioning may therefore not be generalizable to prevention of pathological cognitive decline, such as (early) dementia.

In conclusion, patients with screen-detected type 2 diabetes did not suffer from accelerated decline compared to participants without diabetes. In addition, we could not demonstrate that intensive multifactorial treatment had a beneficial effect on decline of cognitive functioning above routine care.

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PART II

DIAGNOSING COGNITIVE IMPAIRMENT

IN TYPE 2 DIABETES

CHAPTER 6

THE EVALUATION OF SIGNS AND SYMPTOMS OF COGNITIVE IMPAIRMENT IN PRIMARY CARE

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Submitted

INTRODUCTION

Cognitive functioning ranges from normal cognitive performance to subtle cognitive changes, mild cognitive impairment (MCI), and ultimately to frank dementia. The extremes are usually easy to establish. However, differentiating between subjective cognitive changes and cognitive impairment, i.e. MCI and dementia, can be difficult.[1] A policy of 'wait and see' in this situation can result in unsatisfactory outcomes.[2] Therefore, it is important to evaluate cognitive symptoms with a reliable and efficient diagnostic procedure including history taking, an informant interview and a formal assessment of cognitive performance.[3]

A wealth of research is devoted to individual components of this diagnostic procedure, especially regarding cognitive tests. However, the literature provides limited guidance on which and how cognitive tests should be used when cognitive impairment is suspected. The Mini-Mental State Examination (MMSE) is often recommended, because of extensive experience with this test, but alternative tests have been developed that are more suitable for use in primary care.[4]

In daily care, cognitive tests are only one component of the diagnostic procedure. It is essential to realise that the true value of a test is determined by the extent to which it provides diagnostic information on top of the information that has already been gathered.[5] With this paper we aim to translate available evidence on cognitive tests into a practical diagnostic algorithm for the evaluation of signs and symptoms of cognitive impairment in a primary care setting.

'Screening' for cognitive impairment, tests to assess the underlying cause of cognitive impairment and assessment of the needs of care are outside the scope of this article.

What is cognitive impairment?

The term cognitive impairment refers to abnormal cognitive functioning that can be objectified, regardless of severity, and thus includes both MCI and dementia. Dementia is commonly diagnosed with the DSM-IV criteria (box 1).[6] MCI refers to cognitive impairment that does not interfere with activities of daily living (ADLs) and does not meet the criteria for dementia. The Petersen criteria or the criteria by Winblad are commonly used for the diagnosis of MCI (box 1).[7;8]

Does this patient have cognitive impairment?

The algorithm in figure 1 provides a practical guide to evaluate cognitive signs and symptoms in a primary care setting. It can be used in the situation where a patient or relative visits the general practitioner (GP) with complaints about cognitive functioning, or in the situation where the GP suspects cognitive impairment. Each step will be explained in more detail in the next sections.

Box 1. Diagnostic criteria for dementia and MCI

DSM-IV criteria for dementia[6]:

A. The development of multiple cognitive deficits manifested by both:
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The deficits do not occur exclusively during the course of a delirium.

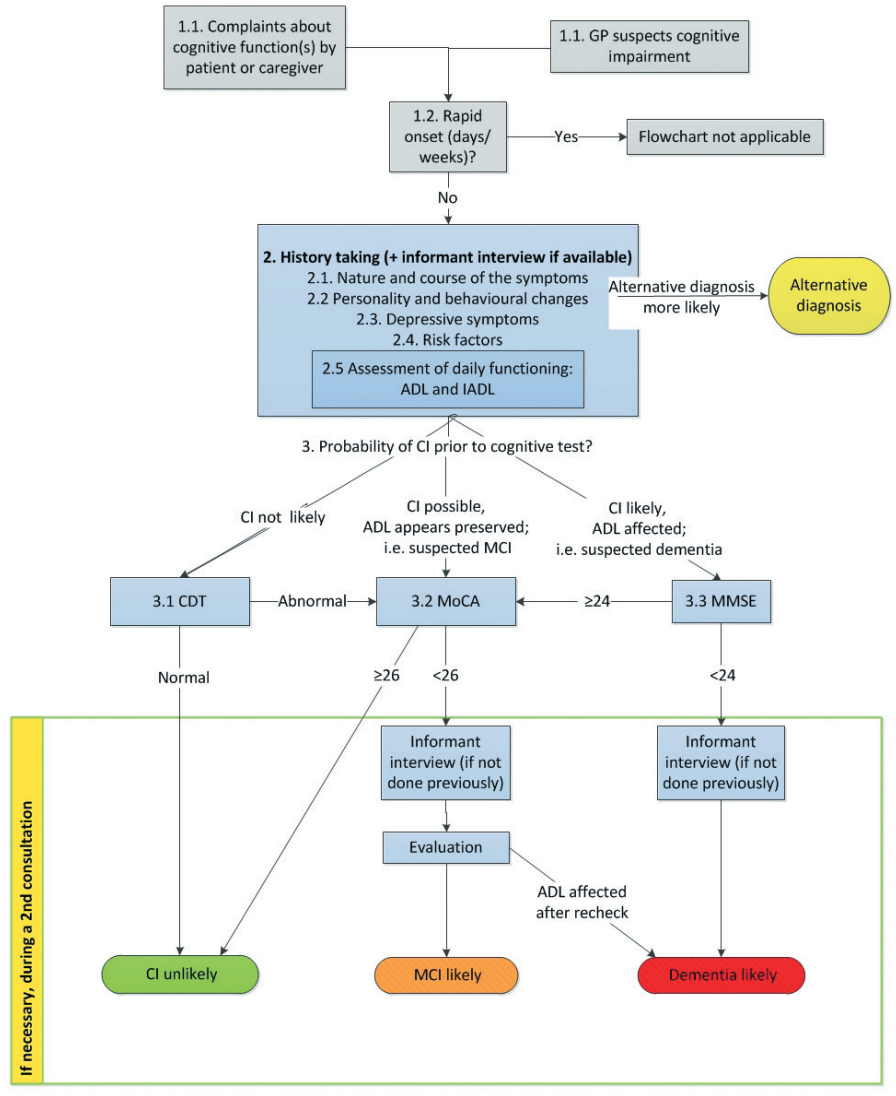
Petersen criteria for amnestic MCI[7]:

- Memory complaint usually corroborated by an informant
- Objective memory impairment for age
- Essentially preserved general cognitive function
- Largely intact functional activities
- Not demented

General criteria for MCI by Winblad et al[8]:

- Not normal, not demented (does not meet criteria(DSM IV, ICD 10) for dementia)
- Cognitive decline:
  - Self and/or informant report and impairment on objective cognitive tasks *and/or*
  - Evidence of decline over time on objective cognitive tasks
- Preserved basic activities of daily living/minimal impairment in complex instrumental functions

Figure 1. Diagnostic algorithm



Abbreviations: GP=General Practitioner; ADL=Activities of Daily Living, IADL= Instrumental Activities of Daily Living; CI=Cognitive Impairment (includes MCI and dementia); MCI=Mild Cognitive Impairment; CDT=Clock Drawing Test; MoCA = Montreal Cognitive Assessment; MMSE=Mini Mental State Examination.

1.1.What are the signs and symptoms of cognitive impairment?

Memory problems are typically one of the first signs of cognitive impairment, but other cognitive domains may also be affected (box 2).[9] Of note, concerns expressed by a close informant are more predictive of cognitive impairment than self-reported symptoms.[3;10]

Box 2. Signs and symptoms of cognitive impairment

Memory impairment
- Repetitive questions or conversations
- Hesitations, inconsistencies, omissions or confabulations
- Head turning sign (to verify answers with a caregiver)
- Misplacing personal belongings
- Forgetting events or appointments
- Getting lost on a familiar route

Aphasia
- Difficulty thinking of common words while speaking or using incorrect words
- No fluent production of words

Apraxia
- Difficulties in performing or imitating simple tasks (such as combing hair or brushing teeth) with intact comprehension, motor skills and perception

Agnosia
- Impaired ability to recognise faces or common objects or to find objects in direct view despite good acuity (visual agnosia)
- Impaired ability to recognise or identify objects by touch alone (tactile agnosia)

Disturbance in executive functioning
- Not correcting mistakes
- Difficulty learning how to use a new gadget or machine around the house
- Inability to manage finances
- Loss of abstract thinking, logical reasoning and/or visuoconstruction (e.g. drawing a clock)
- Lack of insight in own functioning
- Loss of initiative, increased impulsivity or uninhibited behaviour
- Inappropriate social behaviour or personality changes

1.2.What is the mode of onset?

In MCI and dementia, cognitive impairment has a slowly progressive onset. The diagnostic algorithm is not applicable to cognitive symptoms that develop within days or weeks. In that situation other diagnoses, such as a delirium or other neurological conditions, are more likely.

2.WHAT SHOULD BE ASSESSED DURING HISTORY TAKING AND THE INFORMANT INTERVIEW?

History taking and an informant interview are fundamental for diagnosing cognitive impairment.[3] An informant interview is preferably performed with a close informant separately from the patient. If an informant is not available and diagnostic uncertainty persists after the initial visit, the patient should bring an informant to a follow-up visit. The following topics should be addressed:

2.1.Nature and course of the symptoms

The GP should ascertain when and how the symptoms started and how these developed over time. Both the patient and the informant should be asked about memory and other cognitive functions (box 2).

2.2.Personality and behavioural changes

Changes in personality and behaviour are common in people with cognitive impairment and can cause considerable distress for both the patient and the caregiver. The Neuropsychiatric Inventory Questionnaire (NPI-Q)[11] is frequently recommended to assess severity and impact of behavioural changes.[12;13] The score of this 12-item informant questionnaire ranges from 0 to 36 with higher scores indicating more behavioural disturbance.[12]

2.3.Depressive symptoms

GPs should be alert for depressive symptoms in patients with suspected cognitive impairment. Depression can be a prodromal symptom of dementia but depressive symptoms can also follow cognitive decline. Besides, depressive symptoms can mimic symptoms of cognitive impairment and vice versa.[14] A table with typical presentations of mood symptoms in dementia and depression can be helpful to distinguish between the two.[15]

Depression can influence cognitive testing. If a depression is likely, focus should be on diagnosing and treating depression first. For this a depression scale, such as the 15-item Geriatric Depression Scale (GDS-15),[16] can be used. Cognitive symptoms should always be re-evaluated after the depression is treated.[15;17]

2.4.Risk factors

Age is the most important predisposing factor for cognitive impairment with estimated prevalence rates around 1% at the age of 60 and 30-60% in individuals of ≥90 years.[18] Lower intelligence, education and occupational attainment are associated with a higher risk of developing cognitive impairment.[19] Additional risk factors for cognitive impairment are a positive family history (especially early-onset cases), Down syndrome or Parkinson's disease.[20] Diabetes and cardiovascular risk factors, such as smoking and hypertension are other predisposing factors.[20]

2.5.Daily functioning

Daily functioning comprises ADLs and instrumental activities of daily living (IADLs). ADLs are basic daily self-care activities including feeding, bathing, dressing, mobility, toileting and continence. IADLs are more advanced activities including telephone use, shopping, food preparation, house-keeping, laundry, transportation, responsibility for medication and handling finances. In patients with MCI, ADLs are preserved while there can be minimal impairment in IADLs. In patients with dementia (I)ADLs are affected by definition.[6] It should be noticed that the boundaries between "normal" and "impaired" daily functioning are not always evident and influenced by pre-existent activity levels. The Katz ADL[21] and the Lawton IADL[22] scales are frequently recommended to assess (I)ADL.[13;23] Both scales can be completed by the patient or an informant.

3. IS COGNITIVE IMPAIRMENT UNLIKELY, POSSIBLE OR LIKELY?

After the first steps in the diagnostic procedure, where information is gathered through history taking and the informant interview, the GP will be able to estimate the probability that the patient has cognitive impairment. This probability affects the negative or the positive predictive value of the diagnostic test that should be used to make a diagnosis. Therefore, we selected the most suitable cognitive test for each of the following three situations separately:

- 1: Cognitive impairment not likely
- 2: Cognitive impairment possible, ADL appears to be preserved; i.e. suspected MCI
- 3: Cognitive impairment likely, ADL affected; i.e. suspected dementia

3.1. Which cognitive test should be used if cognitive impairment is unlikely?

The main issue in this situation is to rule out cognitive impairment and to reassure the patient. A high negative predictive value (NPV) for cognitive impairment is therefore most important. Three cognitive tests, studied for MCI, were considered. Since the GP feels cognitive impairment is unlikely the prevalence of cognitive impairment is expected to

be low in this situation. Both the Clock Drawing Test (CDT)[24] and the Montreal Cognitive Assessment (MoCA)[25] provide a high (≥ 90%) NPV in populations with low prevalence rates of MCI. Studies of at least fair quality that have assessed the use of the MMSE for MCI in populations with low prevalence rates of MCI are lacking (table 1).[26]

Because the average consultation time in general practice is approximately 10 minutes and cognitive impairment is deemed unlikely, brevity is an important advantage if NPV values are equal.[17] The short administration time of the CDT (1-3 minutes) relatively to the MoCA (10 minutes) may therefore lead to a preference for the CDT in this situation. It should however be noted that the CDT, in contrast to the MoCA, does not test all cognitive domains.

3.2.Which cognitive test should be used if MCI is suspected?

This is the most challenging situation, namely the "grey zone". To find out whether MCI or perhaps dementia is present, both the NPV and the positive predictive value (PPV) for MCI and dementia are important. We prioritised the NPV above the PPV to avoid false reassurance and accepted a somewhat lower PPV. A cognitive test with a high NPV for MCI will automatically lead to a high NPV for dementia since cognitive performance is expected to be worse in dementia.

Since cognitive impairment can involve different domains, the test should not be restricted to memory. Aphasia, agnosia and apraxia rarely occur in isolation and may be ascertained during history taking and the informant interview. In contrast, executive functioning can be affected in isolation and this domain is more difficult to assess during history taking.[27] The cognitive test in this situation, therefore, must at least test memory and executive functioning.

We considered the three cognitive tests that can be used to assess MCI or cognitive impairment by examining both memory and executive functioning and that have a well-established cut-off score (Table 1 and 2).[26] Taken together, the NPV and the PPV of the Mini-COG[28] and the MMSE[29] are less favourable than those of the MoCA which has a high NPV (cognitive impairment:94%; MCI:94-100%) and a fair PPV (cognitive impairment:56%; MCI:39-46%).In our view, the MoCA is the most suitable test for this situation.

3.3 Which cognitive test should be used if dementia is suspected?

When the GP suspects dementia, a cognitive test with a high PPV is needed to confirm the diagnosis. Again, the test needs to examine at least memory and executive functioning. Only two cognitive tests, the MMSE and the Mini-COG met this requirement and also have a well-established cut-off score (table 3).[26]

Table 1. Evidence summary of cognitive tests for MCI (MCI versus normal cognition, dementia not included)

Test	Studies (n)	Test time (min)	Cut-off score	% MCI (in study pop.)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC	Tests key cognitive domains?
CDT	3	1-3	≤ 9	48	41 (34, 47)	83 (78, 88)	69 (60, 77)	60 (55, 65)	0,65	No
			< 9	15	58 (54, 63)	57 (55, 59)	19 (17, 22)	89 (87, 90)	0,60	
			≤ 9	14	69 (56, 81)	63 (58, 68)	23 (17, 30)	93 (89, 96)	0,66	
MMSE	2	7-10	< 28	84	47 (36, 59)	73 (45, 92)	90 (76, 97)	22 (11, 35)	0,67	Yes
			< 28	44	45 (39, 52)	80 (75, 84)	64 (56, 71)	66 (60,70)	NR	
MoCA	2	10	< 26	24	100 (91, 100)	50 (41,59)	39 (29, 50)	100 (94, 100)	0,94	Yes
			< 26	20	80 (56, 94)	76 (65, 85)	46 (29, 63)	94 (85, 98)	NR	

Only the studies reporting a cut-off score that was studied more than once are depicted in the table. The following tests were not depicted in the table since a cut-off score was examined in only one study: HVLT, TMT, FOME, SLUMS and SAGE. We refer to the comprehensive research report of Kaiser Permanente for the U.S. Preventive Services Task Force for detailed information about (the evidence for) these tests. **Abbreviations:** CI=Confidence Interval; MCI=Mild Cognitive Impairment; NR=Not Reported; Sens=Sensitivity; Spec=Specificity; NPV=Negative Predictive Value; PPV=Positive Predictive Value; AUC=Area Under the Curve. **Abbreviations cognitive tests:** CDT=Clock Drawing Test; HVLT=Hopkins Verbal Learning Test; FOME=Fuld Object Memory Evaluation; MMSE=Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; SLUMS=Saint Louis University Mental Status; SAGE=Self-Administered Gerocognitive Examination; TMT=Trail Making Test.

Table 1. Evidence summary of cognitive tests for cognitive impairment (dementia and MCI versus normal cognition)

Test	Studies (n)	Test time (min)	Cut-off score	% dementia/ % MCI (in study pop.)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC
MMSE	3	10	< 24	9 / 47	77 (67,85)	70 (58, 80)	77 (67,85)	70 (58, 80)	0,82
			< 24	4 / 26	53 (43, 64)	92 (88, 95)	71 (59, 81)	85 (80, 89)	0,84
			< 24	4 / 5	72(62, 81)	89 (65,99)	39 (32, 47)	97 (96, 98)	NR
MoCA	1	10	< 26	8 / 19	86 (67, 96)	76 (65, 85)	56 (40, 71)	94 (85, 98)	NR
Mini-Cog	2	3-4	< 3	40 / 12	84 (79, 89)	88 (81, 93)	92 (87, 95)	77 (70, 83)	NR
			< 3	3 / 39	39 (34, 45)	78 (73, 82)	57 (49, 64)	63 (59, 68)	NR

Only the studies reporting a cut-off score that was studied more than once are depicted in the table. Cognitive tests were not depicted in the table if they did not test memory and executive functioning. The following tests were not depicted in the table since a cut-off score was examined in only one study: SAGE, MIS and MF-2. We refer to the comprehensive research report of Kaiser Permanente for the U.S. Preventive Services Task Force for detailed information about (the evidence for) these tests. **Abbreviations:** CI=Confidence Interval; MCI=Mild Cognitive Impairment; NR=Not Reported; Sens=Sensitivity; Spec=Specificity; NPV=Negative Predictive Value; PPV=Positive Predictive Value; AUC=Area Under the Curve. **Abbreviations cognitive tests:** MMSE=Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; SAGE=Self-Administered Gerocognitive Examination; MIS=Memory Impairments Screen; MF-2=Memory Function 2.

Table 3. Evidence summary of cognitive tests for dementia (dementia versus no dementia)

Test	Studies (n)	Test time (min)	Cut-off score	% dementia (in study pop.)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC
Mini-Cog	2	3-4	< 3	40	97 (93, 99)	71 (65, 77)	71 (64, 77)	97 (93, 99)	NR
			< 3	3	76 (54, 90)	73 (69, 76)	9 (5, 14)	99 (97,100)	NR
MMSE	5	7-10	< 24	4	91 (78, 98)	87 (85, 89)	23 (17, 29)	100 (99, 100)	NR
			< 24	1	87 (78, 95)	89 (86, 92)	52 (44, 60)	98 (96, 99)	0,95
			< 24	4	77 (46, 95)	97 (94,98)	46 (24, 68)	99 (97, 100)	NR
			< 24	6	88 (74, 96)	88 (85, 90)	32 (24, 42)	99 (98, 100)	NR
			< 24	28	84 (75, 90)	88 (84, 92)	73 (64, 81)	94 (90, 96)	0,93

Only the studies reporting a cut-off score that was studied more than once are depicted in the table. Cognitive tests were not depicted in the table if they did not test memory and executive functioning. The following tests were not depicted in the table since a cut-off score was only examined in one study : 7MS, CAST. GPCOG, MoCA and SAGE. We refer to the comprehensive research report of Kaiser Permanente for the U.S. Preventive Services Task Force for detailed information about (the evidence for) these tests. **Abbreviations:** CI=Confidence Interval; MCI=Mild Cognitive Impairment; NR=Not Reported; Sens=Sensitivity; Spec=Specificity; NPV=Negative Predictive Value; PPV=Positive Predictive Value; AUC=Area Under the Curve. **Abbreviations cognitive tests:** MMSE=Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; SAGE=Self-Administered Gerocognitive Examination; 7MS=Seven Minute Screen; CAST=Cognitive Assessment Screening Test; GPCOG=General Practitioner Assessments of Cognition.

The NPV's for both the MMSE (94-100%) and the Mini-Cog (97-99%) are high. The MMSE has a fair PPV (23-73%) for dementia with the established cut-off score of <24. However, these PPV's of the MMSE are from studies with a relatively low prevalence of dementia. In the situation that all patients are suspected of dementia, the prevalence of dementia and consequently the PPV will be higher. The PPV of the Mini-Cog is less than that of the MMSE in study populations with a high prevalence of dementia. In addition, the MMSE is well-studied and also well known. We selected the MMSE as the best available test.

What if the cognitive test result does not match the GPs expectations?

The steps in the proposed diagnostic algorithm will guide the GP towards the most probable diagnosis (figure 1). If expectations are confirmed, this strengthens the diagnosis. However, if there is a mismatch between the findings of history taking and the test, the results need to be reconsidered.

In the situation that cognitive impairment was deemed unlikely but both the CDT and MoCA are abnormal it is important to perform an informant interview if not done previously. The GP should reconsider the presence of cognitive impairment and consider alternative diagnoses. In such cases the GP may also decide to refer the patient for a more comprehensive cognitive assessment.

If the GP suspects MCI and the patient falls short on the MoCA (scores <26) it is important to ascertain whether criteria for dementia are met. Because impaired ADL discriminates between MCI and dementia, it is recommended to assess daily functioning in more detail.

If the GP suspects MCI, but the MoCA score is normal (≥26) and no alternative explanation is found, the GP may consider re-evaluating the patient in 6-12 months or earlier in case of progressive symptoms.

In the situation that the GP suspects dementia but both the MMSE and the MoCA are normal, a possible explanation should be sought (e.g. high initial cognitive performance). If the suspicion of dementia persists it is recommended to refer for a more comprehensive cognitive assessment.

Is this all?

If a diagnosis of cognitive impairment is made after going through this algorithm the diagnostic process is not yet completed. Other components of the diagnostic process are ruling out treatable causes of cognitive impairment (through physical examination and laboratory tests), establishing an aetiological diagnosis, assessment of care needs and communicating findings to the patient and caregiver(s). As mentioned above,

these aspects remain outside the focus of this article, but are addressed in other literature.[12;13;30-42]

Box 3. Summary points

- Cognitive functioning ranges from normal cognitive performance to subtle cognitive changes, mild cognitive impairment and ultimately to frank dementia
- Differentiating between these stages can be challenging and requires a diagnostic procedure including history taking, an informant interview and cognitive testing
- A wealth of research is devoted to brief cognitive tests. However, a cognitive test should be integrated in a stepwise diagnostic procedure where its value is determined by the extent to which it provides diagnostic information in addition to preceding components of the diagnostic procedure
- This review provides a practical guide including a diagnostic algorithm for the evaluation of signs and symptoms of cognitive impairment in primary care
- To our knowledge this is the first review that recommends cognitive tests based on the probability that the patient has cognitive impairment, after history taking and an informant interview on cognitive functioning has taken place
- The straightforward algorithm provides patients, caregivers and general practitioners with quick and clear answers to questions regarding the presence and severity of cognitive impairment
- Future research is needed to increase knowledge on the exact value of these diagnostic tests in addition to history taking and an informant interview.

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Appendix 1. Methods

- Guidelines and consensus documents for diagnosing cognitive impairment in primary care were used to establish a diagnostic algorithm
- We conducted a search using MEDLINE, EMBASE, PsychINFO, CINAHL and Cochrane databases for reviews, published after January 2000, written in English, addressing cognitive tests for use in primary care. Keywords: 'dementia' and 'cognitive impairment' combined with 'diagnosis'.
- The search retrieved 12 reviews[26;43-51] which assessed cognitive tests for use as a screening test in primary care; none evaluated them as part of a diagnostic procedure.
- Lin et al. published a review providing information on both cognitive tests and studies assessing them.[26] Using this information we determined which tests are most suitable for our diagnostic algorithm.
- We only considered tests which are suitable for administration during a GP-consultation. Tests were required to have a cut-off score studied in ≥2 studies of at least fair quality.

Appendix 2. Tips for non-specialists

- History taking and the informant interview are key elements of the evaluation of patients with signs and symptoms of cognitive impairment
- Brief cognitive tests can be used to objectify the findings from history taking and the informant interview
- Which cognitive test is most useful depends on the prior probability of cognitive impairment
- If you expect cognitive impairment to be unlikely the clock drawing test (CDT) can be used to rule out cognitive impairment
- If you suspect mild cognitive impairment, the Montreal Cognitive Assessment (MoCA) can be used to assess whether cognitive impairment is present or not
- If you suspect the patient to have dementia the Mini-Mental State Examination (MMSE) can be used to make dementia more likely
- When the cognitive test results do not match your initial suspicion a more comprehensive cognitive assessment or a re-evaluation after 6 to 12 months is recommended

CHAPTER 7

EARLY DETECTION OF DEMENTIA:

NOT ONLY DOOM AND GLOOM

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With great interest we read the letter by Brunet et al. in which the authors state that there is no evidence for the dementia screening proposed by the health secretary.[1] Overall, we agree with the authors that screening of all patients above 75 years of age may not be desirable. There are however some additional comments to be made.

Firstly, there is a difference between screening for an asymptomatic disease and early detection of problems that people are already suffering from but that have not been identified as a medical condition yet. The former is the case in many cancer-screenings, which aim to identify the disease before symptoms are present in order to try to improve survival, for example the breast cancer screening. In dementia, the situation is quite different, as, by definition, dementia can only be diagnosed if there are notable cognitive complaints (by the patient or relatives) and objective cognitive dysfunction severe enough to influence daily functioning.[2] Hence, screening for dementia is not looking for asymptomatic patients, but concerns early recognition of significant problems that people are already suffering from, but have not yet been classified as a medical problem. Early signs of dementia are often overlooked or even discarded, despite the impact on affected individuals. There is an average delay of 18 months between the first presentation of symptoms to the general practitioner and a diagnosis of dementia.[3] This indicates that the timely diagnosis mentioned by Brunet et al.[1] in which the patient marks the right time for diagnosis is not always recognized or acknowledged by the doctor.

Secondly, it is believed that the benefits of early diagnosis of dementia do not outweigh potential harms, because early detection cannot alter the course of the disease. In some groups of patients however, an early diagnosis of dementia might actually prevent further medical problems. An example are patients with type 2 diabetes, as stated by the Health Secretary.[4] Type 2 diabetes is associated with modest cognitive decrements[5] but also with an increased risk of marked cognitive deficits and dementia.[6] Patients with type 2 diabetes themselves play the central role in the, often complex, management of their own disease. Cognitive impairment can have a serious impact on this self-management. Patients with type 2 diabetes and a lower MMSE-score were found to be less involved in diabetes self-care and diabetes monitoring[7] and are more likely to experience severe hypoglycemic episodes,[8;9] and an increased number of hospital admissions.[10] The ACCORD-MIND study found that poor cognitive performance increased the risk of severe hypoglycemia, regardless of the glycemic targets.[11] On the other hand, a higher level of social support for patients with cognitive impairments has been shown to ameliorate their glycemic control,[9] possibly preventing these complications. These studies indicate that we should take cognitive functioning into account in patients with complex diseases, such as diabetes, and adjust treatment and monitoring to the preserved capacity of individual patients to assure safe self-management and prevent adverse events, especially in elderly with long-standing or more complicated disease.

To enable early recognition of dementia in at risk patient groups and to create the possibility to include cognitive functioning in the treatment plan, a valid and feasible stepped diagnostic procedure must be available, with a reliable but quick cognitive test as a first step. This stepped approach is recommended by the Health Secretary and we fully agree with it. The most commonly used cognitive test is the Mini-Mental State Examination (MMSE), but this test may not be reliable to detect cognitive problems in the primary care setting[12] and may not be feasible to perform in a large group of at-risk patients due to the time a healthcare professional needs to invest to take the MMSE. The past few years a lot of new cognitive screenings tests, that can be easily administered, have become available, but their performance in the general practice population has not yet been proven.[13] The validity of such instruments needs to be established in the primary care setting. Then, the next step would be to combine timely detection with an evidence-based treatment program and to assess whether this combination is better than watchful waiting.

However, first the taboo on diagnosing dementia must be lifted and possibilities must be created to perform the necessary investigations. Patients with dementia and their caregivers are probably less reluctant than doctors to accept and to deal with a diagnosis of dementia.[14] The diagnosis, although confronting, is also often a relief because it provides an explanation for the problems people experience in daily life; it is never a diagnosis that comes out of the blue.[14] This should persuade doctors and researchers to establish a diagnosis of early dementia.

Looking after our patients with type 2 diabetes and other complex medical conditions, good clinical practice requires to be alert for cognitive impairments. Even the suspicion of cognitive impairment in patients with longstanding diabetes might keep the physician from prescribing insulin to achieve strict HbA1c goals. Stringent control in this group has not proven to reduce vascular complications and does increase treatment complications like hypoglycemic episodes with the risk of hip fractures due to falling.[15] The example of diabetes lights that screening for dementia in vulnerable groups by the use of a stepped diagnostic procedure, as proposed by the Health Secretary, is not only doom and gloom, although we have a long way to go before we can do it evidence-based.

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CHAPTER 8

THE "TEST YOUR MEMORY" TEST PERFORMS BETTER THAN THE MMSE IN A POPULATION WITHOUT KNOWN COGNITIVE DYSFUNCTION

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ABSTRACT

Aim: To examine the relation of performance on the self-administered Test Your Memory-test (TYM) and the Mini-Mental State Examination (MMSE) with a comprehensive neuropsychological assessment in a population sample including people with modest cognitive decrements.

Methods: Eighty-six participants (aged 56-77 years), without known cognitive dysfunction, performed a neuropsychological assessment including MMSE, and were asked to fill out the TYM. The relation between both the TYM and the MMSE and a neuropsychological assessment was examined by means of correlation analyses, area under the ROC curves for discriminating between a "normal" and "modest decrements"(≥1SD below the sample mean) group, and Bland-Altman plots.

Results: Correlation with the full neuropsychological assessment was significantly stronger for the TYM than the MMSE (r=0.78 versus r=0.55; Steiger's Z=2.66, p<0.01). The TYM showed an area under the ROC-curve of 0.88 (95%-CI 0.80 to 0.97) for differentiating between "normal" and "modest decrements" compared with 0.71 (0.53 to 0.90) for the MMSE. Bland-Altman plots showed limits of agreement for the TYM of -1.10 to 1.10 and for the MMSE of -1.39 to 1.38.

Conclusions: The TYM showed good correlation with a neuropsychological assessment; performed better in discriminating between variations of cognition and showed more agreement with a neuropsychological assessment than the MMSE.

INTRODUCTION

Brief cognitive tests are increasingly implemented in both clinical and research settings. They are not only used for early recognition of cognitive deficits and dementia,[1] but also for measuring differences in cognitive functioning between groups, for assessment of treatment effects and for the detection of cognitive decline over time. For these purposes such an instrument should not only discriminate between dementia and normal cognitive functioning, but should also be able to measure more subtle variations in cognitive functioning.

The most widely used brief cognitive screening test is the Mini-Mental State Examination (MMSE).[22] A recent addition to the available instruments is the Test Your Memory (TYM) test.[3] This test is self-administered by patients, takes about five minutes to complete, and intends to measure a broad range of cognitive domains.[3] In a memory clinic setting, the TYM showed good diagnostic value compared with the MMSE.[4;5] Therefore, the TYM is a potentially interesting instrument to use, particularly in settings where little time is available for the assessment of cognitive functioning. One of those settings could be the practice of a general practitioner. The range of subtle cognitive decrements in a primary care population, however, is different from patients at the memory clinic, with more people performing in the range of "normal" cognitive functioning. The present study aimed to examine the relation of the performance on the TYM and the MMSE with a comprehensive neuropsychological assessment in a population sample including people with modest cognitive decrements.

METHODS

Study population

Participants took part in a cluster-randomized trial in primary care in patients with screen-detected type 2 diabetes that compared the effectiveness of an intensive treatment versus standard care on cardiovascular outcome (the ADDITION-Netherlands study).[6;7] Cognition was assessed in an add-on project of the main study in a subgroup of participants with type 2 diabetes,[8] in people with an impaired fasting glucose and in people with a normal glucose level. Participants were aged between 50 and 70 years and participants had been screened for type 2 diabetes. Participants with normal glucose levels were relatives of participants with diabetes. Exclusion criteria were previously diagnosed dementia, a known psychiatric or neurological disorder that could influence cognitive functioning, a history of alcohol or substance abuse or the inability to complete a neuropsychological assessment. Participants with a previous non-invalidating stroke could participate. During the neuropsychological examination participants were asked to fill out the TYM after they had completed a full neuropsychological assessment that also included the

MMSE. The present study included all participants who completed the TYM (n=86). The ADDITION-study was approved by the medical ethics committee of the University Medical Center Utrecht, The Netherlands, and was completed in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants.

Neuropsychological assessment

The neuropsychological assessment consisted of twelve verbal and nonverbal tasks addressing six cognitive domains. The division in cognitive domains was made a priori, according to standard neuropsychological practice and cognitive theory.[9] The domain "abstract reasoning" was assessed by Raven Advanced Progressive Matrices. The domain "memory" was assessed by the subtest Digit Span of the Wechsler Adult Intelligence Scale –3rd edition (WAIS-III),[10] the Corsi Block-tapping Task,[11] the Rey Auditory Verbal Learning Test,[12] the Location Learning Test[13] and the delayed recall of the Rey-Osterrieth Complex Figure Test.[14] The domain "information-processing speed" was assessed by the Trail-making Test Part A,[15] the Stroop Color-Word Test (part 1 and 2)[16] and the subtest Symbol Digit Substitution of the WAIS-III.[10] The domain "attention and executive function" was assessed by the Trail-making Test Part B (ratio score),[15] the Stroop Color-Word Test (part 3; ratio score),[16] the Brixton Spatial Anticipation Test,[17] a letter fluency test using the letters "N" and "A" and category fluency (animal naming).[18] The domain "visuoconstruction" was assessed by the copy trial of the Rey-Osterrieth Complex Figure Test. Finally, the domain "language comprehension" was assessed with the Token Test (short form).[19] Subsequently the MMSE was administered. Educational level was recorded in seven categories[20] and subsequently translated into years of education.[21] The tests were administered in a fixed order at the patients" home by neuropsychologists and neuropsychologists in training. The entire battery took about 90 minutes to complete.

Raw test scores of the neuropsychological assessment were standardized into z-scores per test, based on the mean and the pooled standard deviation (SD) of the whole sample that was included in these analyses. The individual's z-score reflects the number of SDs a measurement deviates from the mean of this sample. The z-score of each domain was calculated by averaging all separate test z-scores comprising that domain. The cognitive domains in the neuropsychological assessment were determined a priori and theory-based, instead of with factor analysis. Previous studies by our group have shown that modest differences can be detected with these predefined domains.[22;23] We preferred this procedure above factor analysis on the data from the neuropsychological assessment. A composite score was also calculated by averaging the z-scores of the six domains, representing a "global cognition" score.

The Test Your Memory test

The TYM was developed to test a range of cognitive functions and consists of 10 subtasks.[3] It is a paper-and-pencil, self-administered test and takes a person approximately five

minutes to fill out. The tasks include orientation (10 points), ability to copy a sentence (2 points), semantic knowledge (3 points; assessed by the questions "who is the prime minister" and "in what year did the first world war start"), calculation (4 points), verbal fluency (4 points), similarities (4 points), naming (5 points), visuo-spatial abilities (2 tasks, total 7 points) and recall of a copied sentence (6 points). The ability to complete the test without help provides an 11th score (5 points). The maximum score is 50 points with lower scores indicating worse cognitive performance. The TYM was translated into Dutch after which a bilingual native English speaker back-translated the Dutch version into English, which resulted in a version almost identical to the original version.

Statistical analyses

Categorical variables are reported as numbers and percentages, continuous variables as means with SD and not normally distributed variables as median with interquartile range (IQR). Differences between groups in demographic variables and cognitive scores were analyzed with Chi-square tests for categorical variables, independent t-tests for normally distributed continuous variables and Mann-Whitney tests for not normally distributed continuous variables.

The relation between both the TYM and the MMSE and the neuropsychological assessment, which were administered consecutively, was examined in three steps. First, the correlations between both the TYM and the six domains of the neuropsychological assessment and between the MMSE and the six domains as well as the composite score of the neuropsychological assessment were examined using Spearman correlation coefficients, as the results from the TYM and the MMSE were not normally distributed. Differences between the correlations of the two brief cognitive tests with the neuropsychological assessment were statistically tested by means of the Steiger's Z-test.[24] In the primary analyses, no distinction was made between different categories of glucose regulation (diabetes, impaired fasting glucose, normal glucose level). However, because patients with type 2 diabetes were overrepresented in our sample and type 2 diabetes has been associated with modest cognitive decrements,[25] a sensitivity analysis was performed adjusting the correlations for diabetes status.

Second, the sample was divided into two groups based on the scores of the neuropsychological assessment. Participants performing 1 SD or more below the mean of the whole sample on the composite z-score were defined as the group with "modest decrements"; those with a score above -1 SD were defined as "normal cognition". This dichotomization translates into a "below average" performance (lowest 16%) of the total sample for the "modest decrements" group. Based on the discrimination of these two groups, a receiver operating characteristics (ROC) curve was plotted to assess the discriminative power of the TYM and the MMSE respectively.

Bland and Altman illustrated that a high correlation between two measures does not necessarily imply that they give an equally high or low estimation of true values.[26]

Therefore, in the third step agreement between performance on the TYM, respectively the MMSE, and the neuropsychological assessment was examined with Bland-Altman plots. The mean of the measurements (x-axis) was plotted against the difference between the two measurements (y-axis); both expressed as standardized z-scores with the accompanying corrected 95% limits of agreement.[26] These plots quantify the difference between performances on the TYM and the MMSE on the one hand and the neuropsychological assessment on the other. They create an interval in which 95% of the differences between the two instruments are expected to lie. A narrow 95% interval indicates greater agreement between the tests.

RESULTS

Study population

The TYM was completed by 86 persons of whom 46 were known with type 2 diabetes, 11 were diagnosed with impaired fasting glucose and 29 had a normal fasting glucose. Eighty-one participants also completed the MMSE. Due to time constraints five participants were not able to complete a MMSE. The mean age of participants was 65.8 ± 5.4 years, 59% was male and the average years of education was 11 ± 3 years. No differences were found for age and sex between participants with type 2 diabetes and impaired fasting or normal glucose. Patients with diabetes had less years of education. Table 1 shows the raw neuropsychological test scores for the total sample. The TYM and the MMSE scores were not normally distributed (Kolmogorov-Smirnov: TYM z = 0.21, p <0.001; MMSE z = 0.16, p <0.001). The total sample had a median TYM-score of 44 (IQR 42-48) and a MMSE-score of 29 (IQR 28-30). None of the patients had a MMSE-score below 22 points or showed signs of dementia on the neuropsychological assessment.

Correlations with a neuropsychological assessment

The correlation coefficients of the TYM and the MMSE with the full neuropsychological assessment and the individual domains are presented in Table 2. The TYM showed a strong correlation with the full neuropsychological assessment ($r = 0.78$; $p < 0.001$). Correlations with the individual domains ranged from 0.44 to 0.67, all were statistically significant, with the strongest correlation for language comprehension and the weakest for memory and visuoconstruction. The relation between the MMSE and the full neuropsychological assessment was weaker in all separate domains, ranging from 0.27 to 0.52, with the strongest correlation for language comprehension and the weakest for visuoconstruction. In a direct comparison, the TYM showed a statistically significant stronger correlation with the full neuropsychological assessment than the MMSE (Steiger's $Z = 2.66$; $p = 0.008$). The sensitivity analyses with adjustment for type 2 diabetes yielded similar correlation coefficients (data not shown).

Table 1. Raw neuropsychological test scores of the total sample

Domain	Test	Mean ± SD	Total range
Global	TYM-score	44.1 ± 4.6	24-48
Memory	MMSE-score	28.8 ± 1.3	22-30
	WAIS-III Digit Span forward[b]	49.5 ± 21.3	20-108
	WAIS-III Digit Span backward[b]	28.8 ± 18.8	9-96
	Corsi Block-Tapping Test forward[b]	41.5 ± 13.3	12-77
	Corsi Block-Tapping Test backward[b]	42.3 ± 13.7	12-96
	RAVLT total trials 1-5	44.0 ± 10.7	20-67
	RAVLT delayed recall	8.9 ± 3.3	2-15
	RAVLT recognition	28.6 ± 2.1	21-30
	LLT total trails 1-5[a]	22.8 ± 18.9	0-86
	LLT learning index	0.6 ± 0.3	0.1-1
	LLT delayed trial[a]	1.9 ± 3.5	0-14
	Complex Figure Test - Delay	17.7 ± 6.4	5-33
Information-processing speed	Stroop Color Word Test I[a]	49.8 ± 10.6	32-87
	Stroop Color Word Test II[a]	62.7 ± 12.2	43-112
	TMT Part A	42.0 ± 17.2	16-107
	WAIS-III Digit Symbol	62.1 ± 16.9	20-98
Attention and executive functioning	Stroop Color Word Test III[a]	108.3 ± 28.9	64-220
	TMT Part B	88.1 ± 42.8	37-272
	Letter fluency (mean of N+A)	12.3 ± 4.4	4-26
	Category fluency (animals)	32.2 ± 8.9	9-53
	Brixton Spatial Anticipation Test[a]	16.1 ± 4.6	5-31
Abstract reasoning	Raven APM	7.7 ± 2.4	1-12
Visuoconstruction	Complex Figure Test - Copy	33.5 ± 2.9	20-36
Language comprehension	Token test	19.0 ± 2.2	12-21

RAVLT, Rey Auditory Verbal Learning Test; LLT, Location Learning Test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale – Third edition; Raven APM, Raven Advanced Progressive Matrices;

[a] Higher test scores reflect worse performance

[b] product score; span length x number of correct items

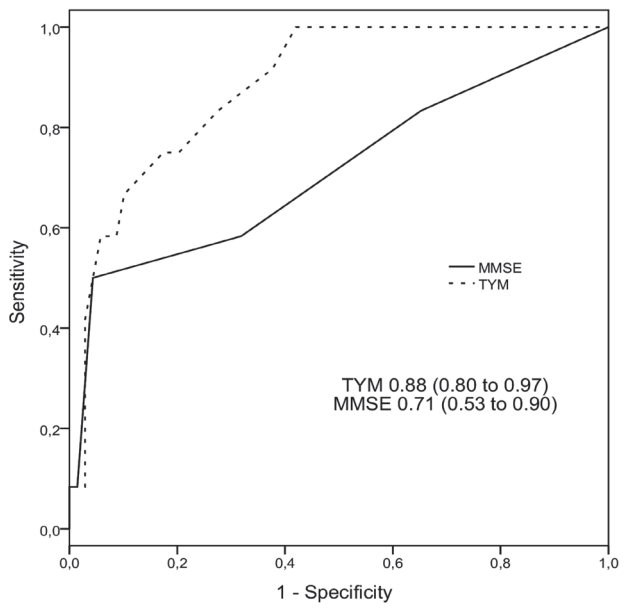
Table 2. Correlations of TYM and MMSE with neuropsychological assessment within the total sample

	TYM		MMSE	
	r	p-value	r	p-value
Composite	0.78	< 0.001	0.55	< 0.001
Memory	0.44	< 0.001	0.38	< 0.001
Information-processing speed	0.66	< 0.001	0.38	0.001
Attention and executive function	0.61	< 0.001	0.37	0.001
Abstract reasoning	0.54	< 0.001	0.42	< 0.001
Visuoconstruction	0.44	0.001	0.27	0.02
Language comprehension	0.67	< 0.001	0.52	< 0.001
MMSE	0.49	< 0.001	-	-

TYM: Test Your Memory test; MMSE: Mini-Mental State Examination

r = Spearman correlation coefficient

Figure 1. Receiver operating characteristic curve for TYM (dotted line) and MMSE (straight line) differentiating between normal cognition and modest decrements



Discriminative values of TYM and MMSE

The participants were divided in two groups to assess the discriminative values of the tests for detecting mild cognitive decrements. Compared to the "normal cognition" group (n = 73) participants in the "moderate decrements" group (n = 13) were older (65.1 ± 5.4 versus 69.8 ± 3.9; p = 0.001) and more often male (54.8% versus 84.6%; p = 0.04). Both the TYM and the MMSE score were significantly lower in the "modest decrements" group: TYM 38 (36-43) versus 46 (43-48), p < 0.001; MMSE 28 (27-29) versus 29 (28-30), p = 0.01. The area under the ROC curve was higher for the TYM with 0.88 (95%-CI 0.80 to 0.97) compared with 0.71 (95%-CI 0.53 to 0.90) for the MMSE (Figure 1).

Agreement of TYM and MMSE with a neuropsychological assessment

Figure 2 shows Bland-Altman plots comparing agreement between the TYM and the MMSE respectively and the full neuropsychological assessment, with accompanying 95% limits of agreement. The plots show limits of agreement for the TYM of -1.10 to 1.10 and for the MMSE of -1.39 to 1.38, indicating that the agreement of the TYM with the neuropsychological assessment was higher than between the MMSE and the full assessment.

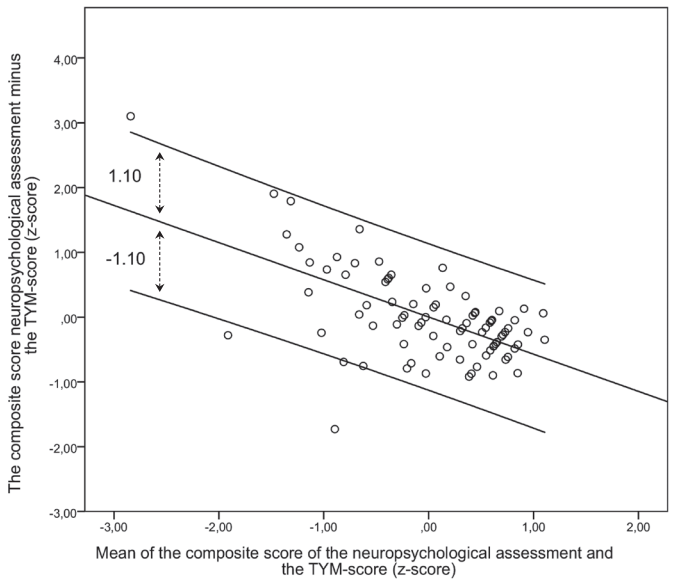
The plot of the TYM shows a negative relation between the TYM and the neuropsychological assessment indicating that the TYM tends to slightly underestimate the performance at lower cognitive functioning (upper left quadrant) and slightly overestimate performance at better cognitive functioning (lower right quadrant).

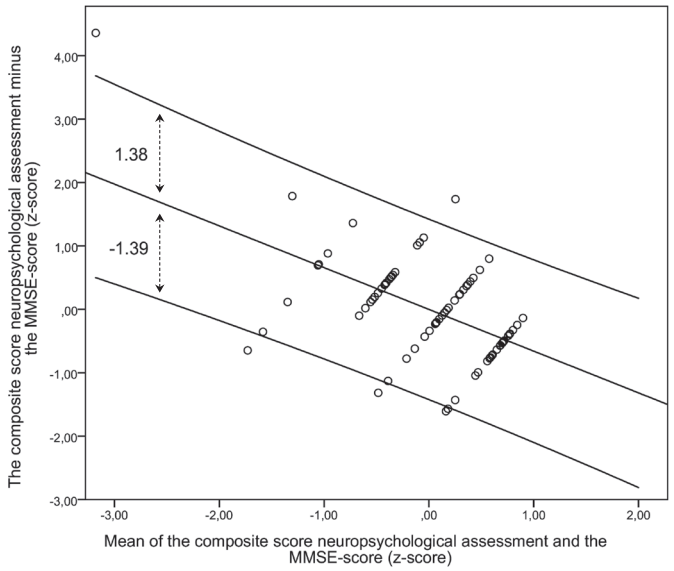
DISCUSSION

The present study provides a detailed examination of the relation between a comprehensive neuropsychological assessment and the TYM in a population of people without dementia and compared this to the MMSE. The results showed that the TYM test had a stronger correlation with a full neuropsychological assessment and its separate cognitive domains than the MMSE. In addition, the TYM had more discriminative power to distinguish people with modest decrements from normal cognitive functioning. Analysis of agreement indicated better agreement between the TYM and the neuropsychological assessment as compared with the MMSE.

After the index-study by Brown et al., who determined the accuracy of the TYM for discriminating patients with Alzheimer's disease from controls in a memory clinic setting,[3] two other studies also examined its diagnostic utility in a memory clinic population.[4,5] All found good diagnostic properties for the TYM, with two out of three finding superior values compared to the MMSE.[3;5] Brown et al. presented normal scores for the TYM of 47 and 46 points for respectively people aged between 18 to 70 and 70 to 80 years and a cut off score of ≤ 42 points for Alzheimer's disease.[3] Hancock et al. revised the optimal cut off score to ≤ 30 points to obtain increased accuracy for the detection of

Figure 2. Bland-Altman plots comparing TYM (a) and MMSE (b) with a neuropsychological assessment





Differences (y-axis; neuropsychological assessment minus TYM/MMSE) are plotted against means of the neuropsychological assessment and the TYM/MMSE (x-axis). All data are expressed as standardized z-scores.

dementia.[4] Since the present study was performed in a population without dementia the cut offs that were previously established for the detection of early dementia could not be validated in our sample. Importantly, however, our primary aim was to compare the TYM to the MMSE in measuring variation in cognitive functioning in non-demented people, rather than validation of the cut off scores for the detection of dementia. In many studies the MMSE is used to give a global measure of cognitive functioning when examining the relation between risk factors and cognition or investigating the effects of treatment on cognition.[27-29] A meta-analysis, examining the performance of the MMSE, found that the MMSE has limitations when used for this purpose.[30] In this meta-analysis the MMSE distinguished only 63% of the people with mild cognitive impairment (MCI) from healthy subjects indicating that the MMSE is insufficient measuring relatively small decline in cognition. To examine whether the TYM could discriminate between small decrements within the normal cognitive spectrum, we divided the sample into two groups. People performing in the lowest 16% of the study population were categorized as those with modest decrements. The cut-off value, namely one SD, was to some extent arbitrary and based on the sufficient number of people in the modest decrements group to allow the analyses. Nevertheless, the areas under the ROC curve did not change significantly with other cut off points (data not shown). Our results suggest that the TYM is a good alternative for examining global cognitive performance as it is more sensitive to mild decrements and it shows higher correlation and agreement with a neuropsychological assessment. The performance of the MMSE in measuring variation in normal cognitive functioning has not been previously examined. The still relatively wide limits of agreement of the Bland-Altman plots however showed that these tests cannot simply replace a comprehensive neuropsychological assessment.

The present study used a comprehensive neuropsychological assessment in a relatively healthy population aged between 56 and 77 years. Hence, the performance of the TYM was assessed in a population with at most mild cognitive decrements. Whether the TYM has similar qualities in a population that also includes patients with more severe cognitive impairment requires further examination. Another limitation might be the overrepresentation of patients with diabetes. However, by including this group of patients with more variation in cognitive functioning, we increased the contrast in the performance range in both the neuropsychological assessment and the screening instruments leading to valuable insight in the relation between the instruments and a neuropsychological assessment. Moreover, sensitivity analyses indicate that the high proportion of individuals with diabetes did not influence our results.

In conclusion, the TYM showed good correlation with a comprehensive neuropsychological assessment in people without clinically relevant cognitive decrements. The TYM had more discriminative power in discriminating between variations of cognition and showed more agreement with a neuropsychological assessment than the MMSE.

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CHAPTER 9

RATIONALE AND DESIGN OF THE COGNITIVE IMPAIRMENT IN DIABETES (COG-ID) STUDY

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ABSTRACT

Background: Cognitive impairment frequently co-occurs with type 2 diabetes, but is often undiagnosed. Cognitive impairment affects self-management leading to treatment-related complications.

Objective: This paper describes the Cognitive Impairment in Diabetes (Cog-ID) study which aims to develop a stepped diagnostic procedure, consisting of a screening test complemented by an evaluation by a general practitioner to detect undiagnosed cognitive impairment in older people with type 2 diabetes.

Methods: The accuracy of two self-administered cognitive tests, the "Test Your Memory" (TYM) and "Self-Administered Gerocognitive Examination" (SAGE) alone, and in combination with an evaluation by a general practitioner will be assessed. A diagnosis of mild cognitive impairment (MCI) or dementia at a memory clinic will serve as reference standard.
The Cog-ID study will include 513 people from primary care aged ≥70 with type 2 diabetes. First, participants fill out the TYM and SAGE. Second, a standardized GP-evaluation for cognitive impairment, including a MMSE, will be performed. Subsequently, participants suspected of cognitive impairment (on either test or general practitioner assessment) and a random sample of 15% of participants without suspicion will be referred to the memory clinic. In the last step, the memory clinic, a medical examination, neuropsychological examination and MRI will be performed. Participants also fill out questionnaires assessing health status and depressive symptoms at baseline and after 6 and 24 months.

Conclusion: With the results physicians will be able to detect cognitive impairment that is already bothering patients through case-finding and can apply tailored care to reduce complications. In addition the results will form a base for the discussion whether early recognition of cognitive impairment is desirable.

INTRODUCTION

Patients with type 2 diabetes have an increased risk of cognitive impairment and a doubled risk of dementia compared with people without diabetes.[1;2] Cognitive impairment often remains unrecognized by physicians, even when patients or their relatives express complaints.[3;4] This is an important problem since in patients with type 2 diabetes, cognitive impairment is associated with impaired self-management and an increased incidence of diabetes-related complications.[5;6] If cognitive impairment would be recognized earlier, this might help the general practitioner to take appropriate personalized measures in diabetes management to prevent complications.[7]

Routine screening for cognitive impairment in elderly patients with type 2 diabetes has been advocated.[8] The American Diabetes Association advises to individualize diabetes treatment and to adjust management to the preserved capacity of patients, thereby specifically taking into account cognitive functioning.[9] However, compared with other potential complications and co-morbid conditions of type 2 diabetes, the diagnostic evaluation of diabetes-associated cognitive impairment is underdeveloped. Screening algorithms have been established for microvascular complications, such as retinopathy or nephropathy, but there is as yet no established method to detect undiagnosed cognitive impairment. The ideal procedure for assessment of possible disturbances of cognitive functioning should be easy and quick to perform. The procedure should readily identify people who require further, more elaborate and time consuming, evaluation by the general practitioner or possibly referral to a memory clinic. Unfortunately, administration of most cognitive tests already requires a lot of time from a physician, nurse or other health care worker. In addition, currently available tests with the shortest administration times tend to cover only certain aspects of cognition, particularly those affected in Alzheimer's disease. Moreover, these tests are much less accurate in identifying people with other conditions, in particular vascular cognitive impairment.[10] These issues may be resolved by the recent introduction of self-administered cognitive tests, such as the Test Your Memory test (TYM)[11] and the Self-Administered Gerocognitive Examination (SAGE).[12] In a memory clinic setting these tests have been shown to measure a broader range of cognitive domains than the Mini-Mental State Examination (MMSE) and they were also able to detect mild cognitive impairment (MCI). Therefore, in our view, these self-administered cognitive tests could be promising tools for the detection of cognitive impairment in type 2 diabetes in primary care.

The ultimate goal of a diagnostic procedure for cognitive impairment is to improve clinical outcomes and patients' quality of life. But before the effect of a diagnostic procedure can be evaluated, it first needs to be clear which tests should be included in such a procedure. The latter is examined in the Cognitive Impairment in Diabetes (Cog-ID) study, which we describe in this paper. The Cog-ID study aims to establish a reliable, valid and efficient stepped diagnostic procedure to detect cognitive impairment in patients of at least 70 years of age with type 2 diabetes, starting with the TYM and the SAGE. It is unknown which of the two

tests is best suited for application in a primary care setting; therefore we assess the accuracy and feasibility of both tests. In addition, we will describe how early detection of cognitive impairment affects treatment and quality of life in an observational study that is part of Cog-ID. The results will form a base for future studies that should answer the unresolved, but increasingly relevant and heavily debated question,[13] whether early recognition of cognitive impairment in patients with type 2 diabetes will help the general practitioner to take appropriate measures in diabetes management that might prevent treatment-related complications. After the Cog-ID study, future studies are needed to assess the effect of the established diagnostic procedure on clinical outcomes in a randomized controlled trial.

KEY OBJECTIVE

Our overall aim is to establish a reliable, valid and efficient stepped diagnostic procedure to detect undiagnosed cognitive impairment in patients of at least 70 years of age with type 2 diabetes, consisting of a self-administered cognitive test and an evaluation by a general practitioner. In addition, we will describe how early detection of cognitive impairment affects treatment and quality of life in participating patients, in an observational study that is part of Cog-ID.

SPECIFIC OBJECTIVES

1. To assess the validity of two self-administered cognitive tests (TYM and SAGE) to detect undiagnosed cognitive impairment in elderly patients with type 2 diabetes in a primary care setting and to select the best instrument;
2. To assess the diagnostic accuracy of a standardized evaluation by a general practitioner in detecting undiagnosed cognitive impairment in patients with type 2 diabetes;
3. To estimate the accuracy and efficiency of the combination of the best cognitive test combined with the evaluation by the general practitioner;
4. To describe the effect of the diagnostic procedure on several aspects of diabetes care (i.e., treatment targets and appointment schedules) and patients' quality of life.

METHODS

Study participants

General practitioners in the surroundings of Utrecht, the Netherlands, will be asked to select patients with type 2 diabetes mellitus aged 70 years or older. Exclusion criteria

are a diagnosis of dementia or a previous investigation at a memory clinic and the inability to write or read in Dutch. Patients with a disorder that might influence cognitive functioning, like substance abuse or a psychiatric or neurological disorder, but without a diagnosis of cognitive impairment are not excluded as we are interested in the presence of unknown cognitive impairment regardless of the cause. Eligible patients will receive a letter from their general practitioner with information regarding the study. Patients will be asked to return the response form on which they can mark whether or not they are willing to participate. In case of non-response, one reminder will be sent.

Screening tests

Test Your Memory test

The TYM is developed to test a range of cognitive functions and consists of 10 subtasks.[11] It is a self-administered test and takes a patient around five minutes to fill out. The tasks include orientation (10 points), ability to copy a sentence (2 points), semantic knowledge (3 points), calculation (4 points), verbal fluency (4 points), similarities (4 points), naming (5 points), visuospatial abilities (2 tasks, total 7 points) and recall of a copied sentence (6 points). The ability to complete the test without help is an 11th task (5 points); due to our study design all patients will receive these 5 points. The maximum score is 50 points. A score of 39 or below is suggestive for dementia.[11] The TYM was translated into Dutch after which a bilingual native English speaker back-translated the Dutch version into English, which resulted in a version almost identical to the original version.

Self-Administered Gerocognitive Examination

The SAGE measures cognitive functioning in the domains of orientation (4 points), language (4 points), memory (2 points), executive function (4 points), calculations (2 points), abstraction (2 points) and visuospatial abilities (4 points).[12] Furthermore, the SAGE includes several questions on demographic information, medical and family history and current status. The maximum score is 22 points. A score of 14 or below is suggestive for dementia.[12] The SAGE was translated into Dutch after which a bilingual native English speaker back-translated the Dutch version into English, which resulted in a version almost identical to the original version.

The diagnostic strategy

Part 1: home-visit

Participants will be visited at home by a research physician (a trainee general practitioner). The home-visit takes about one hour. The participant will be asked to fill out the TYM, the SAGE and a questionnaire assessing health status and depressive symptoms, including the Short Form Health Survey (SF-36),[14] EuroQol (EQ)-5D and EQ-VAS[15] and the Center for Epidemiologic Studies Depression scale (CES-D).[16] The research physician will be blinded for the scores on the TYM and the SAGE and does not help with filling out these

questionnaires. Next, the research physician will administer a standardized diagnostic interview based on the Dutch guideline for case finding of dementia by general practitioners to both the participant and (if possible) a close informant,[17] representing an evaluation by the general practitioner. This interview includes demographic variables, educational level and living conditions as well as a medical history and a list of cognitive complaints (Table 1). After the interview the MMSE will be administered. The MMSE consists of eleven tasks including the domains orientation in time (5 points), orientation in space (5 points), registration of three words (3 points), concentration and calculation (5 points), recall of three words (3 points), language (8 points) and visuospatial abilities (1 point). The maximum score is 30 points with a higher score indicating a higher level of cognitive functioning. A score of 24 or below is suggestive for dementia.

Based on the history taking, the research physician will decide whether the participant should be classified as 'suspected of cognitive impairment' or 'no cognitive impairment' according to the criteria for MCI and dementia.[18;19] If the MMSE-score is 24 or below the participant will always be classified as 'suspected of cognitive impairment'.

Part 2: selection criteria for memory clinic visit

After the home-visit an independent physician, neither involved in the home visit nor in the memory clinic, will determine whether the participant will be selected for a visit to the memory clinic of the University Medical Centre Utrecht. To minimize the influence of the increasing experience of the research physician because of the growing number of home visits during the study period, the research physician who has visit the participant at home will not be informed about the results of the memory clinic. Three criteria will be used to decide whether a participant will be invited to the memory clinic: 1. a classification of "suspected of cognitive impairment" by the research physician, 2. a score of ≤ 39 on the TYM, and 3. a score of ≤ 14 on the SAGE. When a participant scores positive on one of these three criteria the participant will be invited to the memory clinic. In addition a random sample of 15% of participants with negative scores on all three criteria will be invited to the memory clinic (see sample calculation below and Figure 1).

Part 3: the visit to the memory clinic

All professionals involved in the memory clinic will be blinded to the results of the TYM and the SAGE. The visit to the memory clinic will take half a day and will consist of a standardized memory clinic workup.

Medical examination

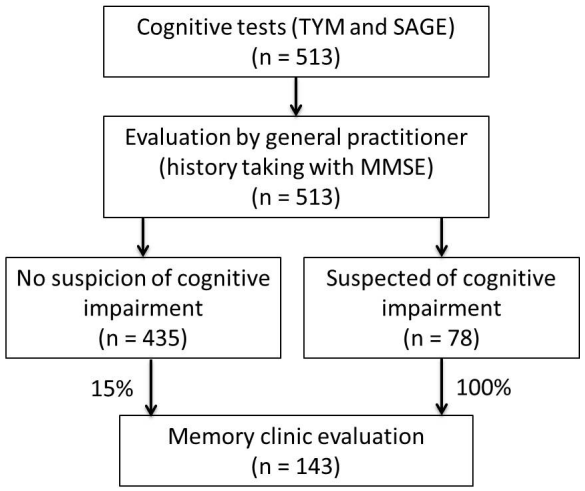
Participants will be examined by a (trainee) neurologist who performs a diagnostic interview, a neurological examination, administers the Cambridge Cognitive Examination (CAMCOG),[20] and measures body weight, height and blood pressure. Body mass index (BMI) is calculated. In addition the Disability Assessment for Dementia (DAD)[21] and

Table 1. List of questions for acquired cognitive symptoms to both the participant and an informant

Questions	Patient	Informant
Do you have memory problems?		
Do other people think you are forgetful?		
Do you forget names of relatives or peers?		
Do you often lose things?		
Do you have to write more things down to remember it than you were used to?		
Are there activities you stopped doing in the past five years (and why)?		
Do you visit friends or family less often?		
How does cooking, grocery shopping and the household go?		
Do you have trouble managing your finances?		
Do you have trouble driving a car or using public transport?		
Do you need help getting dressed?		
Do you sometimes forget what month or year it is?		
Can you independently manage your medication?		
Can you follow the news in the paper or on television?		
Do you have problems with walking or holding your balance?		
Did you lose weight unintentionally in the past years?		
Has your smell or taste changed in the past years?		
Are you depressive?		
Can you still have pleasure in things?		
Do you have problems with hearing or vision?		
Do you think his/her personality has changed?		
Did you take over tasks from the participant (and why)?		
Does he/she repeat things often?		

Observational points	Yes	No
Inability to find the correct words		
Many repetitions or hesitations		
Often does not understand the question		
Head turning sign		
Inconsistencies or confabulation		
Poor grooming		

Figure 1. Flowchart



the Neuropsychiatric Inventory (NPI)[22] will be administered to a caregiver to measure functional abilities of daily living and to assess the presence of neuropsychiatric symptoms.

Neuropsychological assessment

A neuropsychologist will administer a standardized neuropsychological assessment of 90 minutes examining memory, information-processing speed, attention and executive functioning and visuoconstruction. The division in cognitive domains is made a priori, according to standard neuropsychological practice and cognitive theory.[23] The domain 'memory' will be assessed by the subtest Digit Span of the Wechsler Adult Intelligence Scale –3rd edition (WAIS-III) , the Rey Auditory Verbal Learning Test and the delayed recall of the Rey-Osterrieth Complex Figure Test. The domain 'information-processing speed' will be assessed by the Trail-making Test Part A, the Stroop Color-Word Test (part 1 and 2) and the subtest Symbol Digit Substitution of the WAIS-III. The domain 'attention and executive function' will be assessed by the Trail-making Test Part B (ratio score), the Stroop Color-Word Test (part 3; ratio score), the visual elevator test, a letter fluency test using the letters 'N' and 'A' and category fluency (animal naming). The domain 'visuoconstruction' will be assessed by the copy trial of the Rey-Osterrieth Complex Figure Test, the Judgement of Line Orientation (JLO) and the Visual Object and Space Perception Battery (VOSP). Furthermore, premorbid level of intelligence (IQ) will be estimated by the Dutch version of the National Adult Reading Test. Educational level will be recorded in seven categories and subsequently translated into years of education. Frailty will be examined with the short physical performance battery (SPPB).

Additional examinations

MRI data will be acquired on a Philips 3.0 Tesla scanner using a standardized protocol and consists of a T2*-weighted scan (48 continuous slices, reconstructed voxel size: 0.99 × 0.99 × 3.00 mm^3), a 3D T1 scan (192 continuous slices, reconstructed voxel size: 1.00 × 1.00 × 1.00 mm^3), a fluid attenuated inversion recovery (FLAIR) scan (48 continuous slices, reconstructed voxel size: 0.96 × 0.95 × 3mm^3), and diffusion-weighted MRI data using a single-shot spin echo planar imaging sequence (48 contiguous slices, acquired isotropic voxel size 2.50 mm, 45 isotropically distributed diffusion-sensitizing gradients with a b-value of 1200 s/mm^2, and one b = 0 s/mm^2).

Venous blood samples will be drawn to determine non-fasting blood glucose, HbA1c, blood count, lipid-levels (HDL, LDL, total cholesterol, triglycerides), thyroid function, liver functions and kidney function.

The diagnosis 'cognitive impairment'

Within two weeks after the visit to the memory clinic a multidisciplinary team meeting will be planned with a neurologist, the neurology resident and the neuropsychologist to establish the diagnosis. Cognitive impairment, i.e., MCI or dementia, is our primary outcome. For the diagnosis of dementia the DSM-IV criteria are used.[18] In short, dementia is defined as memory impairment and impairment in at least one other cognitive domain (aphasia, apraxia, agnosia, executive functioning) that significantly affects social or occupational functioning compared to the previous level of functioning and that is not caused by a delirium. MCI will be diagnosed according to the criteria by Winblad et al. and defined as not normal, not demented, with cognitive complaints that can be objectified by a neuropsychological assessment and/or evidence of decline over time, and preserved basic activities of daily living.[19] In addition, the presumed etiology of dementia will be specified (e.g. Alzheimer's disease). Guided by the diagnosis a tailored treatment advice will be given to the participants' general practitioner regarding management of the diabetes treatment and cognitive impairment. Advice for the diabetes treatment consists of re-evaluation of the proper glycaemic target and the risk of insulin treatment and advice to evaluate the need for extra support to participants that are unable to meet treatment goals or that need extra tools, for example a memory aid for appointments or medication.

After the diagnosis

The results of the visit to the memory clinic and the treatment advice will be sent to the participants' own general practitioner who will discuss the results with the participant. Subsequently, the general practitioner and the participant decide together what actions will be taken. Further support by the memory clinic is available if considered desirable by the general practitioner and the participant.

Follow-up

Six months after the home-visit participants will receive a follow-up questionnaire,

Table 2. Follow-up questions for the general practitioner

Questions
1. Did the result came as a surprise to you or did you expect it? and why?
2. Do you agree with the result of the memory clinic? and why?
3. Did you adjust diabetes treatment or management because of the results? and why?
4. Did the results have consequences for your overall medical treatment of the patient? and why?

including the SF-36, EQ-5D, EQ-VAS and the CES-D, to evaluate the course of their health status, quality of life and depressive symptoms. A questionnaire asking whether and how many hypoglycemic events, visits to emergency services and hospital admissions they experienced will also be included. In addition participants will be asked whether they regret their participation in the study and whether they would again participate in the study. After twenty-four months a second follow-up questionnaire will be sent with the same questions.

Six months after the home-visit the medical record of participants will be scrutinized to obtain information on medical history, values of recent diabetes controls (HbA1c, lipids, creatinine, weight, height, blood pressure) and complications – hypo- or hyperglycemic events - and visits to emergency services and hospital admissions in the year before and six months after participation in the study.

To further assess the impact of the study on participants' treatment, the general practitioner of participants that attended the memory clinic will receive a questionnaire six months after the evaluation at the memory clinic to assess whether the study led to new insights and whether it changed their treatment plan (Table 2).

Statistical analysis

The diagnosis of cognitive impairment (MCI or dementia) at the memory clinic will be used as the reference standard. To address the first two objectives participants will be classified as true positive (TP), false positive (FP), false negative (FN) or true negative (TN) separately for the evaluation by the general practitioner, the TYM and the SAGE.

Not all patients in our study receive the reference standard, which could lead to partial verification bias.[24] If only the patients with the reference standard would be included in the analysis (complete case analyses) the results would be biased because the selection of the patients with the reference standard will not be at random.[24] A reliable method to reduce this bias is to impute the reference standard.[24] A diagnosis of the memory clinic (cognitive impairment yes/no) will therefore be imputed for patients who did not attend the memory clinic. Ten imputed databases will be generated with the predictors TYM, SAGE, MMSE, GP-evaluation and age, gender, educational level, living situation and score on the domain mobility of the EQ-5D. The latter two are chosen because they

can play a role in the reason why patients do not attend the memory clinic. With these imputed numbers the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) will be calculated.

The extent to which the cognitive tests and the evaluation by the general practitioner are discriminating between participants with and without cognitive impairment will be determined by the area under the receiver operating characteristic (ROC) curve. Next, the optimal cut-off values of the tests for this population will be assessed according to the best combination of corresponding sensitivity and specificity assessed with the Youden index. The Youden index measures the effectiveness of a diagnostic marker and enables the selection of an optimal cut-off point.[25] By means of the ROC curve and the best combination of diagnostic values the optimal instrument will be selected.

For assessing the accuracy and efficiency of the diagnostic procedure (i.e., the cognitive test combined with history taking; objective 3) the result of the best cognitive test and the result of the evaluation by the general practitioner will be combined into one test result. This should reflect the future implementation of the stepped diagnostic procedure, in which a general practitioner will only evaluate those patients with a positive test result. Participants will be categorized in the "test positive" group when both the best cognitive test and the evaluation by the general practitioner are positive. This combination will probably have a higher PPV than the cognitive test or the evaluation by the general practitioner alone, leading to a more efficient diagnostic procedure. The added value of the general practitioner's evaluation will be assessed by calculating the adjusted ROC curve and the net reclassification index.[26]

The fourth objective will be addressed by comparing the difference in health status and depressive symptoms between those with and without a diagnosis of cognitive impairment, both at baseline and after six and 24 months of follow-up, taking into account potential baseline differences of relevant parameters. In addition we will describe the changes that were made in diabetes care by comparing the diabetes management before and after study participation (changes in treatment, number of hypo- or hyperglycemic events, emergency and hospital visits).

Sample size calculation

For our sample size calculations we assumed a prevalence of undiagnosed cognitive impairment of 8%. This assumption is based on the following considerations:

- The prevalence of dementia in the Dutch population above the age of 65 is around 16%.[27] The prevalence of cognitive impairment will be even higher if MCI is also considered.
- Around half of all patients with cognitive impairment are undiagnosed
- Prevalence of cognitive impairment is higher in people with diabetes
- The oldest old, in whom dementia prevalence is highest, are least likely to participate in research projects.

In previous research in adults aged above 59 years recruited from geriatric and memory clinics and facilities for seniors, the SAGE had a PPV of 64%, a NPV of 95%, a sensitivity of 79% and a specificity of 95% with regard to diagnosing cognitive impairment.[12] In a memory clinic population the TYM had a specificity of 95%, a sensitivity of 81%, a PPV of 64% and a NPV of 98% at a cutoff score of 39 points for Alzheimer's disease. In our view a new cognitive test should at least have a PPV comparable with that of the most commonly used instrument, the MMSE, which has a PPV for the diagnosis of dementia in primary care of 53.6%.[28] Therefore, for our sample size calculation, we set the lower margin for the estimated PPV at 53% (i.e. 11% below the previously established PPV of 64%). With this margin, an α of 5% and one-sided testing (we are only interested in the lowest 5% of cognitive scores), 52 participants with a positive test result (0.11 = 1.65* √(0.64*(1-0.64)/n) n=52) are needed to have reliable results for relevant interpretation. To achieve this number of test positive participants, given an assumed prevalence of 8% and a sensitivity of 79%, we need to test 513 participants. Given the test features of the TYM this sample size should also be sufficient to determine the accuracy of the TYM. As participants will be referred to the memory clinic based on the results of all of the three tests (TYM, SAGE and evaluation by the general practitioner), and the results of the tests will probably not completely overlap, the group 'suspected of cognitive impairment' will be larger than the group that will be tested positive on the SAGE alone. We estimate that the former group will be 50% larger than SAGE-positive group, i.e., 78 people are estimated to be in the group "suspected of cognitive impairment". All these 78 participants will be invited to attend the memory clinic, to establish the true and false positive rates of each of the tests. In addition a sample (15%; 65 out of 435) of the participants in which all three tests are negative (the screen-negatives) will be invited to the memory clinic, to establish the true and false negative rates of each test. Hence, 143 participants in total will be evaluated at the memory clinic (Figure 1).

Because of uncertainty on the actual prevalence of undiagnosed cognitive impairment in our cohort, an interim analysis is planned after the inclusion of 80 participants. During this interim analysis only the proportion of participants that is classified as 'suspected of cognitive impairment' will be checked, without unblinding the test scores or the findings at the memory clinic. If the proportion deviates significantly from our assumptions we will adjust the sample size of the study population accordingly.

Regulation statement

This study will be conducted according to the principles of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO).

Ethics committee approval

The Cog-ID study is approved by the medical ethics committee of the University Medical Centre Utrecht, the Netherlands. Written informed consent will be obtained from all participants.

DISCUSSION

The Cog-ID study will provide a stepped diagnostic procedure to identify patients with type 2 diabetes and undiagnosed cognitive impairment, which can be readily implemented in daily practice. This is essential to improve the care for this vulnerable patient group. We will have information on the diagnostic accuracy of two new cognitive tests, the TYM and the SAGE, and whether these tests can be used in a diagnostic procedure - combining a cognitive test with history taking by the general practitioner - to detect cognitive impairment in primary care. In addition, we collect observational data on the impact of such diagnostic procedure on several aspects of patients' life's (health status, depressive symptoms, complications, diabetes treatment) after six and 24 months.

A potential bias in diagnostic studies in which not all patients receive the reference standard is partial verification bias.[24] We however try to reduce this verification bias by imputing the reference standard in participants that do not visit the memory clinic. This method has shown to give reliable estimates of missing reference data.[24]

With the information from this study, we can advise general practitioners how to assess cognitive functioning in their patients so they can adjust diabetes treatment to the preserved capacities of their patients, as advocated by the American Diabetes Association, and consequently might prevent treatment-related complications. In addition, the results will form a base for the discussion whether early recognition of cognitive impairment in patients with type 2 diabetes with a case-finding strategy is desirable.

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CHAPTER 10

CASE-FINDING FOR COGNITIVE IMPAIRMENT WITH THE TYM AND SAGE QUESTIONNAIRES IN TYPE 2 DIABETES IN PRIMARY CARE - THE COG-ID STUDY

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ABSTRACT

Objective: To evaluate two cognitive tests for case-finding for cognitive impairment in older patients with type 2 diabetes.

Methods: From 1243 invited type 2 diabetes patients aged ≥70, 228 participated in a prospective cohort study. Exclusion criteria were a diagnosis of dementia, previous investigation at a memory clinic, and inability to write or read. Patients first filled out two self-administered cognitive tests (Test Your Memory(TYM) and Self-Administered Gerocognitive Examination(SAGE)). Secondly a primary care physician(PCP), blinded for TYM and SAGE, performed a structured evaluation with MMSE. Subsequently, patients suspected of cognitive impairment (on either the cognitive tests or PCP-evaluation) and a random sample of 30% of patients not suspected of cognitive impairment were evaluated at a memory clinic. Diagnostic accuracy and AUC were determined for the TYM, SAGE and PCP-evaluation compared with a memory clinic evaluation to detect cognitive impairment (mild cognitive impairment or dementia).

Results: 44 patients were diagnosed with cognitive impairment. The TYM and SAGE showed a NPV of 81% and 85% respectively. Positive predictive values were 39% and 40%. The PCP-evaluation had a NPV of 83% and PPV of 64%. The AUC was around 0.70 for all tests.

Conclusions: Both tests can easily be used in case-finding strategies for cognitive impairment in patients with type 2 diabetes in primary care. The SAGE has the best diagnostic accuracy and therefore a slight preference. Applying the SAGE would considerably reduce the number of patients in whom the PCP needs to evaluate cognitive functioning to tailor diabetes treatment.

INTRODUCTION

According to the guideline of the American Diabetes Association physicians should individualize diabetes treatment to the cognitive capacities of a patient.[1] In type 2 diabetes the incidence of dementia is doubled compared to people without diabetes.[2] When cognitive function is deteriorating, self-management capacities will diminish, resulting in problems with diabetes self-management, treatment adherence and monitoring.[3] Therefore, it is necessary to take cognitive functioning into account when establishing a treatment plan.

Usually the primary care physician (PCP) evaluates cognitive functioning when a patient visits the surgery with cognitive symptoms, e.g., memory complaints. The PCP takes a history and when considered necessary administers a cognitive test, most often the Mini-Mental State Examination (MMSE). The literature shows that many cases of cognitive impairment remain undiagnosed in this way.[4;5] Because of this underdiagnosis and the possible consequences of undiagnosed cognitive impairment, case-finding for cognitive impairment in elderly patients with type 2 diabetes has been advocated.[6] However, it is time consuming for a PCP to take a history to evaluate cognitive functioning and administer a cognitive test in every patient with type 2 diabetes. A cognitive screening test that is administered first and that identifies patients who require an evaluation by the PCP could make case-finding more feasible. If such a test should be easy and quick to perform and could reliably make a diagnosis of cognitive impairment unlikely, it could minimize the number of patients the PCP needs to examine. Self-administered tests, like the Test Your Memory test (TYM)[7] and the Self-Administered Gerocognitive Examination (SAGE)[8], seem appropriate for this purpose. The TYM and SAGE are paper-and-pencil tests that can be used in settings in which limited time is available. At the memory clinic both the TYM and the SAGE are able to reliably differentiate patients with dementia and mild cognitive impairment (MCI) from those with normal cognitive functioning.[7;8;9] Their usefulness in this respect in a primary care setting is however not yet assessed.

The Cognitive Impairment in Diabetes (Cog-ID) study was designed to examine a stepped diagnostic procedure, starting with a self-administered cognitive test (TYM or SAGE), to detect undiagnosed cognitive impairment in elderly patients with type 2 diabetes.[10] Because it was unclear whether the TYM or the SAGE is most suitable, both tests were evaluated. Here we report the diagnostic accuracy of the TYM and the SAGE, as a first step in the diagnostic procedure, in patients aged 70 years or older with type 2 diabetes.

METHODS

Study design

The study design of the Cog-ID study has been reported previously.[10] Briefly, patients aged 70 years or older with type 2 diabetes were recruited from primary care.

Participants underwent a stepwise diagnostic procedure to detect undiagnosed cognitive impairment (see further). Exclusion criteria were a diagnosis of dementia, a previous investigation at a memory clinic and the inability to write or read in Dutch. Patients with a disorder that might influence cognitive functioning, like substance abuse or a psychiatric or neurological disorder but without a diagnosis of cognitive impairment were not excluded as we were interested in the presence of unknown cognitive disorders regardless of the cause.

Cognitive tests

Both the TYM and the SAGE were translated into Dutch after which a bilingual native English speaker back-translated the Dutch version into English, which resulted in versions almost identical to the original version.

Test Your Memory test

The TYM is a self-administered test consisting of 10 subtasks, which can be filled out in around five minutes.[7] It is a self-administered test and takes a patient around five minutes to fill out. The tasks include orientation (10 points), ability to copy a sentence (2 points), semantic knowledge (3 points), calculation (4 points), verbal fluency (4 points), similarities (4 points), naming (5 points), visuospatial abilities (2 tasks, total 7 points) and recall of a copied sentence (6 points). The ability to complete the test without help is an 11th task (5 points). The maximum score is 50 points. A score below 40 is suggestive of dementia.[7]

Self-Administered Gerocognitive Examination

The SAGE is a self-administered test, filled out in ten to fifteen minutes, that measures cognitive function in the domains of orientation (4 points), language (4 points), memory (2 points), executive function (4 points), calculations (2 points), abstraction (2 points) and visuospatial abilities (4 points).[8] Furthermore the SAGE includes several questions on demographic information, medical and family history and current status. The maximum score is 22 points. A score below 15 is suggestive of dementia.[8]

The diagnostic strategy

Part 1: home-visit

Patients were visited at home by a research physician (a trainee PCP) and were, during the home-visit of one hour, first asked to fill out the TYM, the SAGE and questionnaires assessing health status (Short Form-36 (SF-36), EuroQol 5-Dimensions (EQ-5D) and EuroQol Visual Analogue Scale (EQ-VAS)) and depressive symptoms (CES-D). The research physician remained blinded for the scores on the TYM and the SAGE and did not help with filling out these questionnaires, nor did anyone else help with filling out the questionnaires. Next, the research physician administered a standardized interview based on the Dutch guideline for PCPs to the patient and a close informant,[11] representing

an evaluation by the PCP. After the interview the MMSE was administered. The MMSE consists of eleven tasks including the domains orientation in time (5 points), orientation in space (5 points), registration of three words (3 points), concentration and calculation (5 points), recall of three words (3 points), language (8 points) and visuospatial abilities (1 point).[12] The maximum score is 30 points with a higher score indicating a higher level of cognitive functioning. A score below 25 is suggestive of dementia.

Based on the history taking and MMSE, the research physician decided whether the patient should be classified as "suspected of cognitive impairment" or "no suspicion of cognitive impairment" according to the criteria for MCI and dementia.[13;14] In case of a MMSE-score below 25 the patient was always classified as 'suspected of cognitive impairment'.

Part 2: selection for memory clinic visit

After the home-visit, an independent physician, neither involved in the home visit nor at the memory clinic, determined whether the patient should be selected for a visit to the memory clinic. Three criteria were used: 1. classification of "suspected of cognitive impairment" by the research physician; 2. a TYM score below 40;[7] and 3. a score below 15 on the SAGE.[8] When a patient scored positive on one of these three criteria the patient was invited to the memory clinic at the University Medical Center Utrecht. In addition a random sample of 30% of patients with negative scores on all three above mentioned criteria, every third patient, was invited to the memory clinic.

Part 3: the memory clinic – the diagnosis

All professionals involved in the memory clinic were blinded to the results of the TYM and the SAGE. The visit to the memory clinic took half a day and consisted of a standardized memory clinic workup. Patients were examined by a (resident) neurologist and a neuropsychologist, a MRI-scan of the brain was performed and venous blood samples were taken. The neuropsychological assessment focused on memory, information-processing speed, attention and executive functioning and visuoconstruction. In addition the premorbid level of intelligence, educational level and activities of daily living were assessed. Educational level was divided into seven categories (1,<6 years of education; 2, 6 years; 3, 8 years; 4, 9 years; 5, 10-11 years; 6, 12-18 years and 7,>18 years).[15] More details of the memory clinic evaluation have been described previously.[10]

Cognitive impairment, i.e., MCI or dementia, was our primary outcome. The diagnosis was established in a multidisciplinary team meeting with the neurologist, neurology resident and the neuropsychologist. For the diagnosis of dementia the DSM-IV criteria were used.[13] In short, dementia was defined as memory impairment and impairment in at least one other cognitive domain (aphasia, apraxia, agnosia, executive functioning) that significantly affected social or occupational functioning compared to the previous level of functioning and that was not caused by a delirium. MCI was diagnosed

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according to the criteria of Winblad et al. and defined as not normal, not demented, with cognitive complaints that could be objectified as a disorder (i.e. performance below the 5th percentile on normative values) by a neuropsychological assessment and/or evidence of decline over time, and preserved basic activities of daily living.[14] During the study a category "cognition otherwise disturbed" appeared necessary. Patients in this group did show cognitive decrements but did not fulfill the criteria of MCI because they had no (progressive) cognitive complaints or because their decrements were not severe enough to be labeled as a disorder.

Statistical analyses

The diagnosis of cognitive impairment (MCI and dementia) at the memory clinic was used as the reference standard. For that reason, in our primary analyses the patients with "cognition otherwise disturbed" were categorized in the group of 'normal cognitive functioning'.

Because the number of patients with dementia was limited, the outcomes MCI and dementia were combined. Patients were classified as true positive (TP), false positive (FP), false negative (FN) or true negative (TN) with regard to the PCP-evaluation, the TYM and the SAGE separately.

Not all patients in our study received the reference standard and selection of the patients with the reference standard was not at random. Performing a complete case analysis could lead to partial verification bias.[16] A reliable method to reduce this bias is to impute the reference standard.[16] A diagnosis of the memory clinic (cognitive impairment yes/no) was therefore imputed for patients who did not attend the memory clinic. Ten imputed databases were generated with the predictors TYM, SAGE, MMSE, PCP-evaluation and age, gender, educational level, living situation and score on the domain mobility of the EQ-5D. The latter two were chosen because they could play a role in the reason why patients did not want to attend the memory clinic. With these imputed numbers the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The Clopper-Pearson method was used to calculate the 95%-confidence intervals.

Discrimination between patients with and without cognitive impairment for the cognitive tests and the PCP-evaluation was determined by the area under the receiver operating characteristic (ROC) curve (AUC). Next, the optimal cut-off scores of the tests were assessed with the Youden index. A Youden index that approaches 1 represents complete separation of the test values between the groups for that cut-off score and a Youden index of 0 represents complete overlap.[17] Rubin's rule was used to calculate the 95%-confidence intervals for the combined AUCs and Youden indices.[18]

Due to our study design all patients received five points for the last task of the TYM, performing the test without help. A sensitivity analysis in which all patients received zero points for this task was performed to check whether this influenced the results. Another

sensitivity analysis was performed, excluding patients with the diagnosis "cognition otherwise disturbed" to assess whether this changed the results.

Categorical variables are reported as numbers and percentages, continuous variables as means with standard deviation (SD) and not normally distributed variables as median with interquartile range (IQR). Differences between groups in demographic variables and cognitive scores were analyzed with Chi-square tests for categorical variables, independent t-tests for normally distributed continuous variables and Mann-Whitney tests for not normally distributed continuous variables. All statistical analyses were performed with SPSS Statistics version.[21]

Sample size calculation

The sample size calculation was described previously.[10] Because of uncertainty on the actual prevalence of undiagnosed cognitive impairment in our cohort, an interim analysis was planned and performed after the inclusion of 80 patients. During this interim analysis only the proportion of patients classified as "suspected of cognitive impairment" was checked, without unblinding the test scores or the findings at the memory clinic. Because this proportion (45%) deviated significantly from the assumed proportion (15%), less patients were needed to achieve reliable results. Therefore we reduced our study population from 513 to 228 patients. Subsequently we needed to increase the sampling of screen-negatives (i.e., patients with a negative TYM, SAGE and PCP-evaluation) from 15% to 30% to maintain a sufficient number of screen-negatives that also received the reference standard (memory clinic evaluation).

Regulation statement and ethical approval

The Cog-ID study was conducted according to the principles of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO). This study was approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands. Written informed consent was obtained from all patients.

RESULTS

Study population

Between August 2012 and September 2014, 1243 patients from 22 general practices were invited for participation. 959 patients (77%) responded of which 228 participated (18% of those invited; 24% of those responding). Six patients of those who were not willing to participate indicated that they did not want to know whether they had cognitive impairment or not. Frequently mentioned reasons to decline participation were feeling too old, presence of comorbidity or problems with attending the memory clinic (e.g.,

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Figure 1. Flowchart

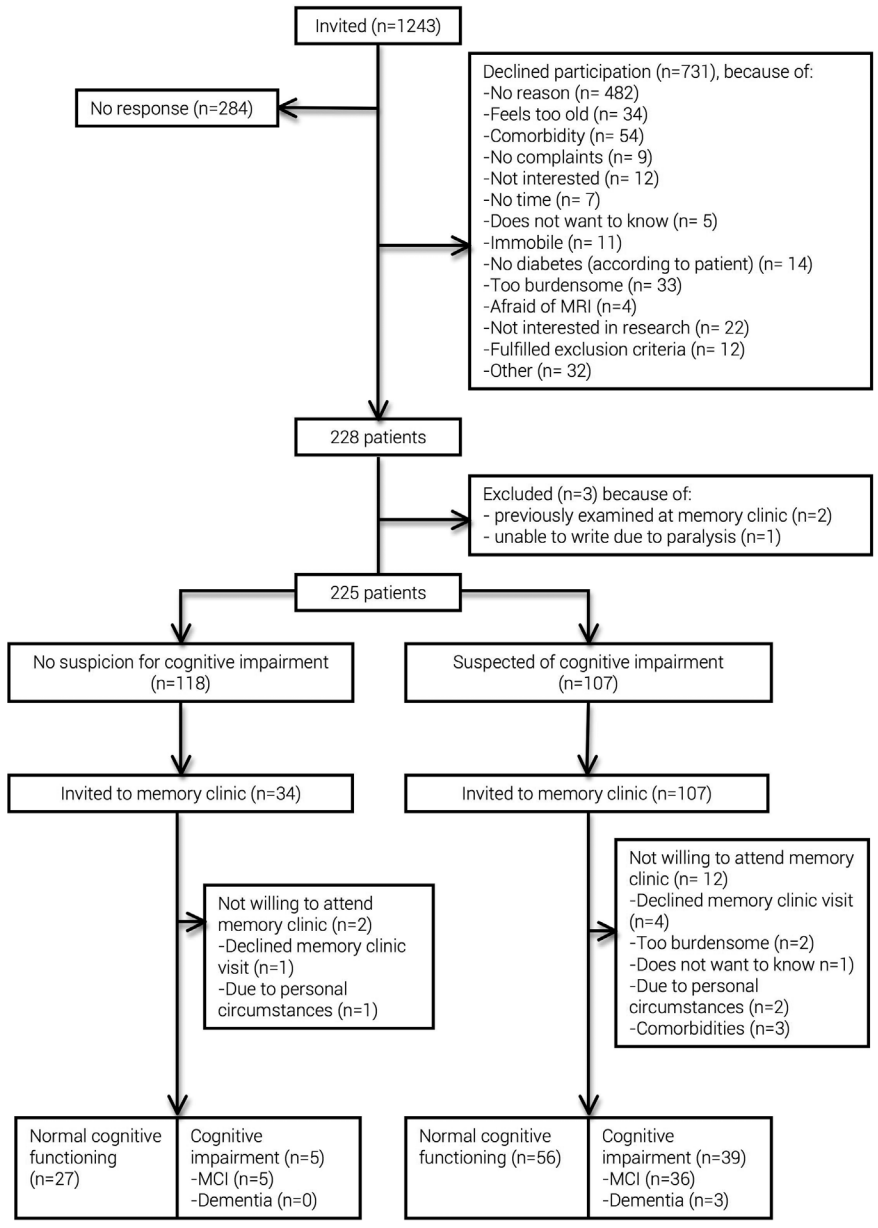

Table 1. Patient characteristics per test

	TYM		SAGE		PCP-evaluation	
	Positive (n=64)	Negative (n=157)	Positive (n=77)	Negative (n=141)	Positive (n=39)	Negative (n=186)
Age (years;mean ± SD)	77 ± 5	77 ± 5	77 ± 5	77 ± 5	78 ± 5	77 ± 5
Gender (male)	59%	61%	51%	67%*	56%	61%
Education (median(IQR))	4 (3-5)	5 (5-6) *	4 (3-5)	5 (5-6) *	4 (3-5)	5 (4-6) *
Living alone	42%	38%	38%	40%	36%	40%
EQ-5D mobility		*		*		
No problems	26%	44%	22%	49%	29%	41%
Some problems	74%	55%	76%	50%	71%	58%
Confined to bed	0%	1%	1%	1%	0%	1%
TYM (median(IQR))	35 (29-38)	44 (42-46) *	38 (31-42)	44 (41-46) *	37 (27-42)	43 (40-46) *
SAGE (median(IQR))	13 (10-15)	18 (15-20) *	12 (10-13)	18 (17-20) *	13 (9-16)	17 (14-20) *
MMSE (median(IQR))	28 (26-29)	29 (28-30) *	28 (26-29)	29 (28-30) *	27 (25-28)	29 (28-30) *

* significantly different between patients with a positive and a negative score ($p<0.05$)

TYM: Test Your Memory test; SAGE: Self-Administered Gerocognitive Examination; PCP: primary care physician; SD: standard deviation; IQR: interquartile range; EQ-5D: EuroQol 5-Dimensions

no transportation, a half day at the memory clinic too burdensome or afraid of MRI). After inclusion three patients had to be excluded because of a previous examination at a memory clinic (n=2) or inability to write (n=1)(Figure 1). Mean age of the remaining 225 patients was 76.8 years (range 70 to 92 years), 60% was male and median educational level was 5 (i.e., 10-11 years of education; IQR 4-6). 40% of the patients lived alone and 61% had some or severe problems with walking measured with the EQ-5D. Table 1 provides an overview of patient characteristics and median test values per test. Patients with a negative score on either of the three criteria were more often higher educated and had less mobility problems.

Results on cognitive tests and memory clinic evaluation

Four patients missed values on the TYM and seven patients did not complete the full SAGE; they were excluded for the analyses concerning the TYM and the SAGE respectively.

The median score on the TYM was 43 (IQR 39-46; range 14 to 49), with 64 patients (29%) scoring below 40. The median score on the SAGE was 16 (IQR 13-19; range 2 to 22), with 77 patients (35%) scoring below 15. In total 107 patients were selected for an evaluation at the memory clinic because of suspected cognitive impairment (Figure 1). Suspicion of cognitive impairment was based on both the tests and the PCP-evaluation in

Table 2. Results of TYM, SAGE, MMSE and PCP-evaluation, related to the memory clinic evaluation

		Cognitive impairment (n=55)	Normal (n=166)
TYM	Positive (n=64)	25	39
	Negative (n=157)	30	127
		Cognitive impairment (n=52)	Normal (n=166)
SAGE	Positive (n=77)	31	46
	Negative (n=141)	21	120
		Cognitive impairment (n=57)	Normal (n=168)
MMSE	Positive (n=7)	7	0
	Negative (n=218)	50	168
		Cognitive impairment (n=57)	Normal (n=168)
PCP-evaluation	Positive (n=39)	25	14
	Negative (n=186)	32	154

The number of people within each group is calculated after imputation of the memory clinic evaluation.

Test Your Memory (TYM): positive below 40 points

Self-Administerd Gerocognitive Examination (SAGE): positive below 15 points

Mini-Mental State Examination (MMSE): positive below 25 points

Primary care physician (PCP) evaluation: positive based on history taking and MMSE score (< 25 points); negative when no cognitive disorder suspected based on history taking and MMSE score > 24 points.

Table 3. Diagnostic accuracy (95%-confidence interval) TYM, SAGE, MMSE and PCP-evaluation for cognitive impairment

	Sensitivity	Specificity	PPV	NPV	AUC†	Youden index†
TYM (cut-off <40)	46 (32-59)	77 (69-83)	39 (27-52)	81 (74-87)	0.69 (0.63-0.75)	0.22 (0.13-0.32)
SAGE (cut-off <15)	60 (45-73)	72 (65-79)	40 (29-52)	85 (78-91)	0.74 (0.67-0.81)	0.33 (0.20-0.46)
MMSE (cut-off <25)	12 (5-24)	100 (98-100)	100 (59-100)	77 (71-83)	0.71 (0.65-0.77)	0.11 (0.06-0.16)
PCP-evaluation	44 (31-58)	92 (86-95)	64 (47-79)	83 (77-88)	-	-

† Mean over the ten imputed databases

PPV: positive predictive value; NPV: negative predictive value; AUC: area under the receiver operating curve; TYM: Test Your Memory; SAGE: Self-Administerd Gerocognitive Examination; MMSE: Mini-Mental State Examination; PCP: primary care physician

31 patients, on only the PCP-evaluation in 8 patients, and on only the tests in 68 patients (16 on TYM; 26 on SAGE; 26 on both TYM and SAGE). Besides, 34 patients were selected as part of the random sample of screen-negatives. They were comparable to the whole group of screen-negatives with respect to age, gender and education (data not shown).

At the memory clinic three patients were diagnosed with dementia and 41 patients with MCI (Figure 1). Five patients diagnosed with MCI were part of the random sample of screen-negatives. Seventeen patients received the diagnosis "cognition otherwise disturbed"; 15 of these patients had an abnormal score on the cognitive tests (3 on TYM; 4 on SAGE; 8 on both TYM and SAGE), four were also suspected by the PCP (in addition to the tests) and two were part of the random sample of screen-negatives. Table 2 summarizes the results of the cognitive tests with the results of the memory clinic evaluation, after imputation, as reference standard. Because of the imputation the numbers of patients with cognitive impairment as well as those with normal cognition differ from those in Figure 1.

Diagnostic accuracy TYM, SAGE, MMSE and PCP-evaluation

In Table 3 the diagnostic accuracy per test for cognitive impairment are presented. The TYM and the SAGE showed a NPV of 81% and 85% respectively, but the PPV of both tests was low. The PCP-evaluation showed a comparable NPV with a higher PPV. The MMSE showed a PPV of 100% and a NPV of 77%.

A sensitivity analysis giving all patients the minimum score for the 11th task of the TYM (i.e., zero points instead of 5 points), did not significantly change its predictive values, but the sensitivity increased from 45% to 85% and the specificity decreased from 77% to 43%.

Excluding patients with the diagnosis "cognition otherwise disturbed" increased the PPV for all tests with approximately 7% and reduced the specificity of the TYM and SAGE with 5%.

ROC-curve and Youden index

The AUC and the Youden index were calculated for each test in each imputed database, leading to ten AUCs and Youden indices for each test. The AUCs for the TYM ranged between 0.65 and 0.72, for the SAGE between 0.66 and 0.78, and for the MMSE between 0.69 and 0.76. The mean Youden indices for the used cut-off scores are presented in Table 3. Youden indices were calculated for all possible cut-off scores in each imputed database, leading to ten 'highest' Youden indices. The highest Youden index for the TYM ranged between 0.23 and 0.34 with corresponding cut-off scores between 40 and 44; for the SAGE between 0.23 and 0.38 with eight out of ten times for the cut-off scores <15/<16, and for the MMSE from 0.26 to 0.35 with optimal cut-off scores between 27 and 29.

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DISCUSSION

The present study demonstrates that both the TYM and the SAGE have adequate diagnostic accuracy to support a case-finding strategy for cognitive impairment in patients with type 2 diabetes in primary care. If the test is negative, the chance that the patient indeed has no cognitive impairment is 81% and 85% respectively. If a patient scores positive on the test there will be cognitive impairment in 40% of cases. Evaluation by the PCP should follow to rule out or establish cognitive impairment. The MMSE shows the opposite. If the MMSE is positive cognitive impairment is almost certainly present, but the MMSE misses 7 out of 8 cases of cognitive impairment in patients with type 2 diabetes. Moreover, the MMSE needs to be administered by a professional and is therefore more labor intensive. Although the PCP-evaluation alone might do just as well as the tests, the use of one of these tests would considerably reduce the number of patients in whom the PCP needs to evaluate cognitive functioning in a case-finding strategy to individualize diabetes treatment. The SAGE might be the most suitable test because it has the highest predictive values and the availability of four test versions of the SAGE prevents test-retest influences.

A strength of our study is the use of the memory clinic evaluation as reference standard and the population under study. The cognitive tests are evaluated in a setting and in patients in which case-finding should be performed: patients in primary care at risk of cognitive impairment – i.e. those aged 70 or above and with additional risk factors like type 2 diabetes – and not unwilling to know their cognitive functioning.

The response rate in the Cog-ID study was 74% and 24% of those responding agreed to participate, this might be considered a limitation since this might have induced selection bias. People that worried about their cognitive performance because they, or their relatives, experienced complaints might have been more willing to participate. On the other hand people with complaints could also be more reluctant to participate because they might be afraid of a diagnosis of cognitive impairment. Because the PPV and NPV are dependent on the prevalence of a disease in the population the diagnostic accuracy of the tests can only be extrapolated to populations and settings with a similar prevalence rate of cognitive impairment. The prevalence rate of dementia in the Dutch population above the age of 65 is around 16%.[19]

The PCP-evaluation was performed without knowledge of the test results, as is done in current practice. However, in light of our current findings, where the NPV of the SAGE is as good as the NPV of the PCP, the SAGE can be used for a first selection of patients that need further examination. The PCP would then only evaluate those patients with a positive result. Doing so, the prevalence of cognitive impairment in the group that needs to be evaluated by the PCP will be higher than the prior probability in our study population. As a result, the diagnostic accuracy of the stepped procedure starting with the TYM/SAGE and followed by the PCP-evaluation is likely to increase. We could not

test this added value due to the design of our study. If the patients were evaluated by their own PCP, who is in the position to determine a decline in cognitive functioning over time, the results of the PCP evaluation could have been better as well.

A potential bias in diagnostic studies in which not all patients receive the reference standard is partial verification bias.[16] We however reduced this verification bias by imputing the reference standard in patients that did not visit the memory clinic. This method has shown to provide reliable estimates of missing reference data.[16]

Due to the study protocol a modification of the TYM was needed to maintain blinding of the PCP. All patients received the maximum score for the ability to complete the test without help; executive functioning was therefore examined less thoroughly. Although the sensitivity analysis showed no difference in the PPV and the NPV, our strategy could have reduced the diagnostic accuracy of the TYM. In addition we chose to dichotomize our outcome in patients with and without cognitive impairment, which is often done, but is to some extent arbitrary. Due to this distribution, people with cognitive disorders that do not fulfill the criteria of MCI (the group "cognition otherwise disturbed") are placed in the group of "normal cognition". A number of these patients were detected by the tests and one can argue whether these results are really considered false-positives. However this is inherent to our study design and also applies to other studies examining diagnostic tests. It further underlines the importance of a stepped procedure in which the tests are complemented by an assessment by a physician.

The diagnostic accuracy of the TYM was previously examined at several memory clinics validating the test for different countries.[7;20-26] No study examined the accuracy of the TYM in a primary care population at risk of cognitive impairment, the setting in which the TYM could be most useful, and with a diagnosis at the memory clinic as reference standard. The SAGE was examined in a geriatric and memory clinic setting and as a screening tool in a community setting.[8;27] In the latter however the diagnosis of cognitive impairment was made based on the scores on the SAGE and was not checked at a memory clinic. Any comparison with these studies is therefore difficult.

One study, examining the TYM at a memory clinic, presented a Youden index of 0.61 at a cut-off score of ≤ 30 for detecting dementia.[20] The Youden indices in our study showed that the used cut-off score of <15 for the SAGE was close to the optimal cut-off score (<15/<16), but the optimal cut-off scores for the TYM and MMSE were higher than our used cut-off scores (<43 versus <40 and <27 versus <25 respectively). Changing these cut-off scores would reduce the number of false-negatives, but would also increase the number of false-positives, thereby increasing the number of people that need to be examined further by the PCP after filling out the cognitive test. We realize that these cognitive tests are not perfect and that patients with cognitive impairment are still missed. There is always a trade-off between the certainty of ruling out a diagnosis and the effort needed to be sure. A NPV of 85% is to our opinion sufficient for a case-finding tool for cognitive impairment in primary care, as missing some cases may not have a

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major impact on long-term patient outcomes. Cognitive impairment was present in 25% of the people who accepted our invitation to be tested for cognitive impairment. We think it could be worthwhile to routinely offer type 2 diabetes patients aged ≥70 a simple self-administered cognitive test to fill out. In case of a positive score, the PCP could then start a conversation to discuss possible signs and symptoms of cognitive impairment and evaluate diabetes treatment.

Conclusions

To conclude, we demonstrated that case-finding identifies a substantial number of patients with cognitive impairment among type 2 diabetes patients ≥70 years who are not unwilling to know their cognitive performance. For the first step in a case-finding strategy, the TYM and SAGE provide enough certainty to make cognitive impairment unlikely in case of a negative test, and identify patients that need further examination. This can save time for PCPs who want to follow the advice to tailor treatment to the preserved capacities of a type 2 diabetes patient. Further research should examine whether our suggested procedure results in an improvement in diabetes management and a reduction in treatment-related complications.

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CHAPTER 11

GENERAL DISCUSSION

This thesis focuses on cognitive dysfunction in patients with type 2 diabetes from a primary care perspective. First, it reports on cognitive dysfunction in type 2 diabetes and its relation with depression and health status, and the effect of intensive multifactorial treatment. Secondly, it evaluates tests that can be used in patients with and without complaints to detect cognitive impairment in a primary care setting.

Cognitive dysfunction in diabetes, what's in a name?

The research in this thesis shows that type 2 diabetes is associated with different stages of cognitive dysfunction (**chapter 2**). Over the past years, in performing the research projects that constitute the chapters of this thesis, we often struggled how to classify and name these different stages of cognitive dysfunction. Classifying the most severe stages of cognitive dysfunction, e.g. mild cognitive impairment and dementia, is – at least at first sight – reasonably simple, because the conventional terminology that is used in people without diabetes can also be used in patients with type 2 diabetes. Classification of the more subtle cognitive changes is more difficult, because these subtle cognitive changes do not fit within usual definitions. The subtle cognitive changes fall within the range of normal cognitive function (i.e. above the 5th percentile relative to the normative mean) and therefore do not meet the criteria of a disorder (i.e. below the 5th percentile relative to the normative mean).

Most of the available knowledge about these subtle stages of cognitive dysfunction in type 2 diabetes comes from research in groups of patients (e.g. **chapter 3 and 5**). Mean test results are compared between groups of type 2 diabetes patients and groups of people without diabetes. With this approach, patients with type 2 diabetes as a group generally show cognitive decrements with a mean performance of 0.3-0.5 SDs below that of people without diabetes, which is equivalent to a reduced cognitive performance of 10-15 percentile points relative to the normative mean.[1]

From these group studies we learned that the subtle cognitive changes occur in all age-groups[2] and are only slowly progressive over time (**chapter 5**). This is different from the cognitive changes that occur in mild cognitive impairment or dementia, which present particularly in people aged ≥65 years and are progressive over time.[3,4] Based on the literature subtle cognitive changes are likely to be common among patients with type 2 diabetes. Such cognitive changes may give rise to complaints. The question is, however, how these subtle cognitive changes can be recognized on an individual level. Although these subtle cognitive changes can be demonstrated on a group level, detection in an individual is difficult. Performance on cognitive screening tests like the Mini-Mental State Examination (MMSE) will be in the normal range and a neuropsychological examination might also have insufficient sensitivity to provide evidence for the presence of these cognitive changes.

In **chapter 8** we investigated if these subtle cognitive changes could be discriminated on a individual level with cognitive screening tests. To do this, we divided patients in

two groups based on an arbitrary threshold for the cognitive decrements of -1 SD. A disadvantage of this approach is that it does not take into account the presence and severity of complaints.

During my project our concept on these subtle cognitive changes evolved. In chapter 2 – our most recent work on this topic – we propose a classification that also included the presence and severity of complaints, and the impact of the cognitive decrements on social and occupational functioning. We proposed the classifying term 'diabetes-associated cognitive decrements', that can be considered if a patient with diabetes, from all ages, expresses concerns about his or her cognitive performance, typically this involves increased mental effort, but with largely preserved social or occupational functioning. In these patients there should be no alternative explanation for the complaints and there are no cognitive deficits severe enough to be classified as mild cognitive impairment. In our view the value of classifying cognitive complaints as 'diabetes-associated cognitive decrements' is that it acknowledges the subtle but realistic changes in cognitive function that patients with diabetes may experience. Moreover, it has prognostic implications, as progression of the underlying cognitive changes is usually slow.

Occurrence and treatment of diabetes-associated cognitive decrements

Patients with type 2 diabetes detected by screening, people with impaired fasting glucose and those with the metabolic syndrome (but without type 2 diabetes) already show mild diabetes-associated cognitive decrements in the same domains as patients with manifest type 2 diabetes, namely memory, information-processing speed and attention and executive functioning.[5-7] The rate of cognitive decline in patients with type 2 diabetes is in the same range as that of normal aging (**chapter 5**). Other longitudinal studies found the process of cognitive decline in the same range or up to two times faster than that of normal aging.[8-10] In the observational Atherosclerosis Risk in Communities (ARIC) study more than 13.000 people were categorized in no diabetes, prediabetes and type 2 diabetes at start of the study (at midlife) and at two time points, with 20 years in between, cognitive function was assessed.[11] This study reports that cognitive decline over these groups shows a sliding scale with the least cognitive decline in patients without (pre)diabetes and the most cognitive decline in patients with type 2 diabetes. Probably, the processes underlying cognitive dysfunction start already in prediabetic stages and progress insidiously over time.

Observational studies in the general population indicate that cardiovascular risk management may reduce the risk of cognitive decline.[12] Many randomized controlled trials, however, did not observe a significant benefit of intensified cardiovascular risk management.[12]

In the ADDITION-Cognition study (**chapter 5**) we were able to initiate intensive multifactorial treatment in screen-detected patients with type 2 diabetes, whereby a

large proportion of the patients already had hypertension and/or hypercholesterolemia.[13] We did not find a positive effect of six years of intensified multifactorial treatment on (the rate of) cognitive decline in this group as compared to patients who received diabetes care as usual. However, both the intensive and the usual care group were well-controlled with respect to cardiovascular risk factors. The good 'usual treatment', probably induced by the new diabetes guidelines that were launched during the ADDITION study, might have resulted in only small differences in both risk factors and cognitive function between the groups.

Two other large randomized controlled trials in people with longstanding diabetes (on average more than 8 years) – the results of which were published after the initiation of the ADDITION-Cognition study – observed no effect of intensive glycaemic control on cognitive performance. In the ADVANCE study five years of intensive glycaemic control, compared to usual care, had no effect on risk of cognitive decline.[14] In the ACCORD-MIND study intensive glycaemic control did result in significantly lower HbA1c levels than usual care, but no difference in cognitive performance between the treatment arms was found after 2.8 years, although intensive treatment did slow the rate of brain atrophy.[15]

The ACCORD-MIND study was the only study thus far specifically assessing the potential effects of antihypertensive or lipid-lowering treatment on cognitive decline in patients with type 2 diabetes.[16] Intensive therapy for hypertension – less than 120 mmHg versus less than 140 mmHg – and combination therapy with a statin plus a fibrate for 40 months did not change cognition.[16]

To conclude: patients with type 2 diabetes have diabetes-associated cognitive decrements in the domains memory, information-processing speed and attention and executive functioning. These diabetes-associated cognitive decrements are, on a group level, not influenced by intensive multifactorial treatment, possibly because the cognitive decrements evolve only slowly over time, leaving little room for a possible treatment effect. This does not answer the question, however, if intensive treatment has a protective effect against the increased incidence of cognitive impairment in individuals with type 2 diabetes. To investigate whether intensive treatment is effective in reducing the incidence of cognitive impairment in patients with type 2 diabetes, trials should be performed in subgroups of patients at high risk of developing cognitive impairment and maybe should start even before the early stages of type 2 diabetes.

Role of depression in cognitive functioning and type 2 diabetes

Depressive symptoms occur in about 17% of patients with type 2 diabetes,[17] with depression occurring twice as often as compared to people without diabetes.[18] A bidirectional association seems to be present between depression and type 2 diabetes, i.e. depression predicts the development of diabetes and diabetes is associated with future depression.[19] Depression is also an important factor in the relation between type

2 diabetes and cognitive dysfunction, because of the overlap between depressive and cognitive symptoms and links between depression and late-life cognitive decline and dementia.[12] The guideline on depression of the Dutch College of General Practitioners provides advice how to assess depressive symptoms in patients in primary care. The guideline advices to inquire after the core symptoms of depression: depressive mood and anhedonia.[20] In patients with dementia, these symptoms may also occur as part of the dementia process but then these symptoms develop more gradually over time and can be improved by stimulation and structure.[21] If a depression is likely, focus should be on diagnosing and treating depression first and cognitive symptoms should be re-evaluated after the depression is treated.

The relation between depressive symptoms and cognitive dysfunction does not seem to be linear in patients with type 2 diabetes. The severity of both the cognitive dysfunction and the depressive symptoms influence the strength of the association. In **chapter 3** we found that diabetes-associated cognitive decrements and mild depressive symptoms occurred independently from each other. Cognitive performance in people without diabetes differed between those with and without depressive symptoms. However, both the cognitive decrements and the severity of the depressive symptoms of the included patients were mild, which might have influenced the results. By contrast, in the ACCORD-MIND study depression – defined as a score ≥10 on the 9-item Patient Health Questionnaire – was associated with greater cognitive decline over time in all cognitive domains.[22] Moreover, in **chapter 4** we did find an association between cognitive impairment and depression in patients with type 2 diabetes, with depression occurring almost twice as often in patients with cognitive impairment.

This threshold effect between depression and cognitive function has previously been found for the general population.[23] In my view, a possible explanation for this threshold effect could be that depression and cognitive impairment are linked by shared etiologies, but also that cognitive impairment may cause depression and vice versa. By contrast, the processes that lead to subtle cognitive changes and mild depressive symptoms may be more diffuse and therefore less casually linked. Moreover, subtle cognitive changes are less likely to affect mood and vice versa (subtle mood changes are not likely to impact cognitive performance).

To conclude: it is important to be aware of co-occurring depressive symptoms in patients with cognitive dysfunction and vice versa, also in case-finding when a patient with a positive test result is analyzed further; history taking should therefore include assessment of depressive symptoms.

Detection of cognitive impairment

In the diagnostic evaluation of cognitive impairment two situations can be distinguished:

1. Detection of cognitive impairment in patients that visit the practice with complaints of possible cognitive impairment

2. Pro-active examination for cognitive impairment before a patient visits the practice with complaints, i.e. case-finding.

Below we will separately discuss detection of cognitive impairment for both situations.

Patients who visit the general practice with complaints of cognitive function

When a patient with type 2 diabetes attends the practice with complaints about cognitive function, the differential diagnosis consists of several conditions (e.g. depression, diabetes-associated cognitive decrements, cognitive impairment etc.). As mentioned in the general introduction a diagnostic procedure that distinguishes between possible conditions should include the prior probability of cognitive impairment to decide what test characteristics are important in different situations. Although the guideline on dementia of the Dutch College of General Practitioners is comprehensive[24] and many guidelines exist for diagnosing cognitive impairment,[25-27] no clear diagnostic procedure exists for use in primary care, not even for patients that visit their general practitioner with signs and symptoms of cognitive impairment. A policy of 'wait and see' in this situation can result in unsatisfactory outcomes.[28] Therefore, it is important to evaluate cognitive signs and symptoms with a reliable and efficient diagnostic procedure including history taking, an informant interview and a formal assessment of cognitive performance.[29] History taking is the most important tool in order to clarify the differential diagnosis. In history taking, information on the type and course of complaints, their effect on activities of daily life and occupational functioning, and mood is needed. Confirmation by an informant is recommended. Age should also be included in determining the prior probability of the different underlying conditions. For example, diabetes-associated cognitive decrements can occur in all age groups, whereas cognitive impairment (i.e. mild cognitive impairment or dementia) is quite rare below the age of 65 years. The results of **chapter 6**, in which we present a diagnostic algorithm in patients that attend the practice with signs and symptoms of cognitive impairment, can guide the general practitioner towards the most probable diagnosis. We assume that implementing this diagnostic algorithm will facilitate the general practitioner to establish a diagnosis of cognitive impairment and will reduce the time between initial presentation of patient symptoms and/or family concerns and confirmation of a diagnosis of dementia, which currently takes between 18 and 30 months, but can take up to 4 years.[30]

Case-finding for cognitive impairment

In case-finding (also called opportunistic screening), patients at risk for a disease, already attending the physician for another reason, are examined for the presence of a certain disease. This is different from population-based screening in which a group of unselected people is examined to distinguish healthy people from those with an asymptomatic disease. Patients with type 2 diabetes are at an increased risk for cognitive impairment and case-finding might therefore be indicated in patients with type 2 diabetes.

As mentioned before, the criteria for cognitive impairment in type 2 diabetes are not different from the criteria for cognitive impairment in patients without diabetes, but the clinical consequences might be greater in patients with type 2 diabetes. Cognitive impairment in patients with diabetes is associated with worse glycaemic control,[31;32] with an increased frequency of hospital admissions,[33] and with an increased occurrence of severe hypoglycemic episodes,[34] especially in case of impaired executive functioning.[35] In addition, as described in **chapter 4** cognitive impairment in type 2 diabetes, even when still undiagnosed, is associated with a reduced health status and more depressive symptoms. These problems might be ameliorated by taking appropriate measures that support patients in their, often complex, diabetes treatment.[32] Firstly, the increased risk of medication errors could be addressed; the use of medication dispensers or involvement of caregivers may be considered. Secondly, the physician could assess whether it is still possible and desirable to pursue perfect glycaemic control or whether more lenient glycaemic targets are better in order to prevent hypoglycemia. Third, appointments at the surgery could be facilitated, for example with reminders of appointments. For these reasons the most important argument against early detection, namely that no treatment exists for cognitive impairment, does not hold completely in type 2 diabetes. The latter is an important difference between case-finding for cognitive impairment in the general population and in patients with type 2 diabetes.

This opinion is supported by the guideline of the American Diabetes Association[36] and the guideline on diabetes of the Dutch College of General Practitioners[37] which advise to take into account cognitive function when establishing or adjusting a treatment plan. An expert working group to enhance the quality of life of older people with diabetes or dementia also stresses the need for detection of cognitive impairment in patients with type 2 diabetes.[38]

To conclude: we think there are a number of arguments to study (not yet implement!) systematic case-finding of cognitive impairment in older patients with type 2 diabetes.

Diagnostic issues in a case-finding strategy

Before we started the Cognitive Impairment in Diabetes (Cog-ID) study (described in **chapter 9**), we examined whether the Test Your Memory test (TYM) could be a useful test to diagnose cognitive impairment in primary care. In **chapter 8** we examined the sensitivity of the TYM for small variations in cognition and found that it could discriminate between these small variations in cognitive function. Additionally, the TYM could discriminate better than the MMSE between people with modest cognitive decrements and those with normal cognitive function. We therefore believed that the TYM was a promising tool for case-finding for cognitive impairment in primary care. At the same time, however, another promising self-administered test was published, the Self-Administered Gerocognitive Examination (SAGE).[39] This test was also not examined in primary care. We therefore decided to evaluate both tests in the Cog-ID study.

In **chapter 10** we report that both the TYM and the SAGE have adequate diagnostic accuracy to support a case-finding strategy for cognitive impairment in patients with type 2 diabetes in primary care. If the SAGE is negative, the likelihood that the patient indeed has no cognitive impairment is 85%. If a patient scores positive on the SAGE there will be cognitive impairment in 40% of cases and evaluation by the general practitioner should follow a positive SAGE to rule out or establish cognitive impairment. Due to the study design of the Cog-ID study, it is not possible to assess the formal diagnostic accuracy of the combination of a positive test result followed by an evaluation of the general practitioner, but such a procedure would likely have a higher diagnostic accuracy than the diagnostic accuracy of several tests alone. A limitation of our study is possible selection bias, which may have occurred because some patients were more willing to participate than others. People that worried about their cognitive performance because they, or their relatives, experienced complaints might have been more willing to participate. On the other hand, people with complaints could also be more reluctant to participate, because they might be afraid of a diagnosis of cognitive impairment. Of all invited patients, 18% was willing to participate and of these patients 25% received a diagnosis of cognitive impairment. When a similar case-finding strategy is offered to patients in daily practice, selection bias will probably occur in a similar pattern and a comparable mix of patients will participate; also leading to a comparable yield.

Importantly, case-finding is possible with a simple self-administered cognitive test and identifies a substantial number of patients with cognitive impairment in type 2 diabetes aged 70 years or over. This gives general practitioners the opportunity to tailor treatment to the individual patient.

Should we perform case-finding for cognitive impairment?

In previous paragraphs arguments for case-finding are presented, but does this mean that we should perform case-finding in clinical practice? Considering a case-finding strategy one often appraises its validity with the Wilson and Jungner criteria (see textbox 1).[40] As is shown in the textbox many but not all of the Wilson and Jungner criteria are met with respect to case-finding for cognitive impairment in patients with type 2 diabetes. The criteria assessing the yield of case-finding for cognitive impairment with respect to clinical and patient-relevant outcomes, and for society are still uncertain and need to be examined.

Based on the above mentioned criteria and their fulfillment, one could conclude that case-finding could at least alleviate the burden of complaints related to cognitive impairment in some diabetes patients. It is, however, important to realize that one of the most important factors in the success of a case-finding strategy is what the patient wants. Do they wish to be examined for cognitive impairment and do they want to know whether they have cognitive impairment? In the Cog-ID study, the participation rate was

24% of all patients that responded to the invitation (228 of 959 patients). 249 of the 731 patients (34%) that declined participation provided a reason for not participating. Frequently mentioned reasons to decline participation were feeling too old, presence of comorbidity or problems with attending the memory clinic (e.g., no transportation, a half day at the memory clinic too burdensome or afraid of MRI). Only six patients of those that were not willing to participate (0.8%; 6 out of 731), indicated that the reason to decline participation was because they were reluctant to know whether they had cognitive impairment or not (**chapter 10**). For the 482 patients that did not provide an explanation, we obviously do not know what the reason was, but it is possible that they were afraid to mention that they did not want to know whether they have cognitive impairment. But even when this is true, still a large number of patients might be eager to check their cognitive function. In the literature, when patients were asked whether they would want to be screened for Alzheimer's disease, the majority of primary care patients (71 to 90%) agreed to regular examination of cognitive function.[41;42] In addition, people with dementia preferred to know their own diagnosis.[43] Caregivers and even more clinicians, however, were reluctant to disclose a diagnosis of dementia to the patient, because of the perceived impact on the well-being of the patient.[43] The results of **chapter 4** also show that, although patients do not complain at the doctor's office, those with undiagnosed cognitive impairment are likely to encounter their limits on several domains that may be relevant for daily life. The follow-up of the Cog-ID study, in which health status and depressive symptoms are re-examined after six and twenty-four months, will provide observational data whether knowing the diagnosis ameliorates these conditions. Taking all this together, we believe that patients should be able to decide for themselves whether they want to be examined for cognitive impairment, but offering a cognitive test is currently only useful in patients in whom cognitive impairment might play a role in the management of their diabetes (e.g. in case of frequent hypoglycemic episodes or inability to reach treatment targets). If future research shows a positive effect of early detection of cognitive impairment in elderly patients with type 2 diabetes, followed by evidence-based interventions, case-finding could be implemented on a larger scale.

To conclude: General practitioners could offer patients with type 2 diabetes older than 70 years with treatment-related complications or difficulties in reaching treatment targets, an examination of cognitive functioning, for example with the SAGE. Patients that do not want to have their cognitive functioning examined, should not undergo such an examination.

Implications for primary care

For general practitioners it is important to know that type 2 diabetes is associated with several stages of cognitive dysfunction. In this thesis we have presented a classification for diabetes-associated cognitive dysfunction that can guide general practitioners in the discrimination between diabetes-associated cognitive decrements, which has

Textbox 1. Wilson and Jungner criteria for case-finding for cognitive impairment

Wilson and Jungner criteria	Fulfilled?	Comment
The condition sought should be an important health problem.	Yes	The number of (older) patients with type 2 diabetes and consequently the number of patients with type 2 diabetes and cognitive impairment is increasing. (Chapter 2)
There should be an accepted treatment for patients with recognized disease.	No	No cure is available, but measures might be taken to improve treatment. This however needs to be examined in further research.
Facilities for diagnosis and treatment should be available.	Yes	The TYM and SAGE can easily be administered by general practitioners which are consequently able to diagnose and treat patients with cognitive impairment. When necessary, additional support can be provided by the memory clinic. (Chapter 10)
There should be a recognizable latent or early symptomatic stage.	Yes	From the initial presentation of patient symptoms and/or family concerns, confirmation of a diagnosis of dementia takes between 18 and 30 months, but can take up to 4 years.
There should be a suitable test or examination.	Yes	Chapter 10 shows that the TYM and SAGE are suitable tests to support a case-finding strategy.
The test should be acceptable to the population.	Yes	In the Cog-ID study a simple self-administered questionnaire, like the TYM and SAGE, proved to be acceptable. (Chapter 10)
The natural history of the condition, including development from latent to declared disease, should be adequately understood.	Yes	The natural history of the condition is known and adequately understood. The ADDITION-Cognition study provides insight in the course of cognitive decline in patients with type 2 diabetes. (Chapter 5)
There should be an agreed policy on whom to treat as patients.	Yes	Patients with cognitive dysfunction that interferes with daily functioning (i.e. cognitive impairment) are considered as patients by health care providers.
The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	No	The cost-effectiveness needs to be assessed. Case-finding with a self-administered questionnaire, like in the Cog-ID study, is inexpensive.
Case-finding should be a continuing process and not a "once and for all" project.	Yes	Patients with type 2 diabetes regularly visit the general practice. A simple questionnaire could be added yearly to this examination.

a favorable prognosis, and cognitive impairment, including dementia (**chapter 2**). The understanding of the difference between these conditions can guide the general practitioner in establishing the most likely diagnosis and in the conversation with the patient about expectations and prognosis.

General practitioners should also be aware that patients with type 2 diabetes and cognitive impairment are at risk for treatment-related complications. General practitioners should be vigilant for patients that present with cognitive complaints or voicing of family concerns, and follow the diagnostic algorithm as presented in **chapter 6**. Additionally, general practitioners should be alert for the occurrence of cognitive impairment, particularly in older patients. In essence such increased alertness shows analogies to the screening for peripheral neuropathy, which is common practice in patients with type 2 diabetes. Although peripheral neuropathy by itself cannot be cured, the knowledge of its presence directs efforts to prevent complications (e.g. fool ulcers and amputations). Along these same lines general practitioners might consider to offer elderly patients with type 2 diabetes a self-administered cognitive test like the TYM or SAGE to evaluate cognitive function (**chapter 10**). The goal of such case-finding should be to tailor diabetes treatment to the cognitive capacities of the patient.

SUMMARY

Key findings:

Cognitive dysfunction in type 2 diabetes

- Type 2 diabetes is associated with several stages of cognitive dysfunction
- We propose a classification for diabetes-associated cognitive dysfunction that can guide physicians in the discrimination between diabetes-associated cognitive decrements, which has a favorable prognosis, and cognitive impairment, including dementia
- Diabetes-associated cognitive decrements are, on a group level, not influenced by intensive multifactorial treatment

Cognitive dysfunction and depression

- Depressive symptoms and cognitive function have a non-linear relationship in patients with type 2 diabetes. Frank cognitive impairment and depression are interrelated, whereas for subtle cognitive and mood symptoms the link is less clear
- Cognitive impairment in type 2 diabetes, even when still undiagnosed, is associated with a reduced health status and more depressive symptoms

Detection of cognitive impairment

- The TYM and the SAGE have adequate diagnostic accuracy to support a case-finding strategy for cognitive impairment in patients with type 2 diabetes in primary care
- General practitioners could offer a cognitive test to patients in whom cognitive impairment might play a role in the management of their diabetes

Future directions:

- The subgroup of diabetes patients that develops cognitive impairment should be identified at an early stage for the development of targeted prevention strategies
- Trials should investigate whether intensive treatment is effective in reducing the incidence of cognitive impairment in patients with type 2 diabetes with a high risk for cognitive impairment
- Future studies should examine what measures should follow a positive result of a diagnostic procedure for cognitive impairment
- The effect of a diagnostic procedure, starting with the TYM or SAGE and followed by supportive interventions, on clinical outcomes and especially patient-relevant outcomes (e.g. health status) should be examined

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SUMMARY

Type 2 diabetes (T2DM) is associated with cognitive dysfunction. In the first part of this thesis we evaluated cognitive dysfunction in patients with T2DM and its relation with depression and health status, and we investigated the effect of intensive multifactorial treatment on cognitive deterioration. In the second part we evaluated tests that can be used in patients with and without cognitive complaints to detect cognitive impairment in a primary care setting.

PART I: COGNITIVE DYSFUNCTION IN T2DM

In *chapter 2* we summarised the literature on cognitive function in T2DM and make recommendations with respect to diagnosis and treatment for clinical practice. The literature shows that diabetes is linked to different stages of cognitive dysfunction, ranging from diabetes-associated cognitive decrements to dementia. The risk for dementia is increased 1.5 times in patients with T2DM. The cognitive changes are associated with changes in brain structure. Several risk factors have been linked to cognitive performance in diabetes.

How to best recognise and classify the different stages of cognitive dysfunction in patients with T2DM is not clear. Diagnostic criteria for cognitive impairment (i.e. mild cognitive impairment (MCI) and dementia) are similar in people with and without diabetes. The classification and management of subtle cognitive changes however is different between these two groups. We propose the term 'diabetes-associated cognitive decrements' for subtle cognitive changes in patients with T2DM, from all ages, that express concerns about their cognitive performance, typically increased mental effort, but with largely preserved social or occupational functioning. In these patients there should be no alternative explanation for the complaints and there are no cognitive deficits severe enough to be classified as MCI. The different stages of cognitive dysfunction require different management. No specific treatment is warranted for diabetes-associated cognitive decrements, but this classification could re-assure patients due to the generally favourable prognosis. Treatment of cognitive impairment is similar for patients with and without T2DM. A diagnosis of cognitive impairment in T2DM however should be reason for the clinician to adjust diabetes treatment to the capacities of the patient (reduction of risk of medication errors, prevention of hypoglycaemia, arrangement of support).

Besides cognitive changes patients with T2DM also more frequently have depressive symptoms. Depressive symptoms can influence cognitive function. We hypothesised that depressive symptoms might play a role in the relation between cognitive function

and T2DM. We investigated this in *chapter 3*, where we report a meta-analysis of three studies examining cognitive function on the domains memory, information-processing speed and attention and executive function and a composite score of these three domains. This study compared patients with (n=366) and without (n=204) T2DM (aged 50-75 years). Patients with T2DM showed cognitive decrements compared to people without diabetes (difference composite z-score -0.13; 95%-CI -0.22- -0.04). Cognitive function in patients with T2DM was similar between those with and without depressive symptoms (difference composite z-score 0.01; 95%-CI -0.15-0.18). On the contrary, cognitive function in people without diabetes differed between those with and without depressive symptoms (difference composite z-score -0.25; 95%-CI -0.54-0.03). We concluded that mild cognitive decrements in patients with T2DM are not influenced by the presence of mild depressive symptoms.

Physicians often assume that informing the patient about a diagnosis of cognitive impairment will influence health status, quality of life and depressive symptoms negatively. However, one could also argue that undiagnosed cognitive impairment (i.e., cognitive impairment for which the patient or relatives have not yet asked professional help), might cause a reduced health status and depressive symptoms, because it is likely to bother patients before it is formally diagnosed. We examined in *chapter 4* in 225 patients with T2DM aged ≥70 years whether undiagnosed cognitive impairment was associated with a reduced health status and with more depressive symptoms. Patients were visited at home and filled out questionnaires assessing cognitive function (Test Your Memory test (TYM) en Self-Administered Gerocognitive Examination [SAGE]), physical and mental health status (SF-36, EQ-5D, EQ-VAS) and depressive symptoms (CES-D). Additionally, a physician examined cognitive function. Patients suspected of cognitive impairment and a selection of patients not suspected of cognitive impairment also visited the memory clinic of the UMC Utrecht. Cognitive impairment was present in 57 of the 225 patients (25%). Patients with cognitive impairment showed lower scores on all health status domains (difference between the groups on physical scale 3.5 out of 100 points; on mental scale 2.9 points) and 30% of the patients with cognitive impairment had a depression, which was almost twice as often as patients without cognitive impairment (RR 1.8; 95%-CI 1.1-3.0). The results indicate that we should realise that other domains than cognitive function are affected in these people and that the more frequent depressive symptoms in people with cognitive impairment is not the result of discussing the diagnosis of cognitive impairment, but could also be associated with the presence of cognitive impairment itself. Detection of cognitive impairment at an early stage may identify a vulnerable patient group that could benefit from integrated and tailored treatment.

The literature showed that improving diabetes treatment might improve cognitive

function. In the ADDITION-Cognition study, of which the results are described in *chapter 5*, we examined whether an intensive multifactorial treatment (with strict targets for blood glucose, blood pressure and lipids and with lifestyle advices), improves cognitive function or prevents accelerated cognitive decline. In this study 183 patients with screen-detected T2DM were randomised to standard treatment (n=86, 64% male, mean age 60 years) or an intensive multifactorial treatment (n=97, 58% male, mean age 59 years). Cognitive performance was examined three and six years after randomisation at home by a neuropsychological assessment. Cognitive performance of 69 people without diabetes was also examined (48% male, mean age 63 years). Three years after the diagnosis and start of treatment, both the patients in the intensive and the usual care group showed cognitive decrements in the domains memory, information-processing speed, and attention and executive function compared to people without diabetes. Over the next three years, cognitive decline in patients with T2DM was within the range of people without diabetes and did not differ between the groups (decline compared to people without diabetes for intensive group -0.14 (95%-CI -0.23--0.06); for standard group -0.02 (95%-CI -0.12-0.07)). Both the intensive and usual care group, however, were well-controlled with respect to cardiovascular risk factors. The good usual treatment, probably induced by the new diabetes guidelines that were launched during the ADDITION-study, might have resulted in only small differences in both risk factors and cognitive function between the groups.
The progression of diabetes-associated cognitive decrements are, on a group level, not influenced by intensive multifactorial treatment, possibly because the cognitive decrements evolve only slowly over time, leaving little room for a possible treatment effect. Future studies should identify patients at high risk for cognitive impairment and examine whether intensive treatment is effective in reducing the incidence of cognitive impairment in these patients.

PART II: DETECTION OF COGNITIVE IMPAIRMENT IN T2DM

In the diagnostic evaluation of cognitive impairment two situations should be distinguished. First, the situation in which a patient visits the general practice with complaints about cognitive function. Second, the situation in which patients are pro-actively approached for examination of cognitive function when visiting the general practitioner for another reason (i.e. case-finding).
Cognitive impairment often remains undiagnosed, even when patients or their relatives express complaints. In patients with T2DM cognitive impairment is associated with reduced self-management and diabetes complications. Guidelines therefore advice to take cognitive function into account when establishing a treatment plan. The diagnostic evaluation of diabetes-associated cognitive impairment, however, is underdeveloped. In

the second part of this thesis we evaluated tests that can be used in patients with and without cognitive complaints to detect cognitive impairment in a primary care setting.

Chapter 6 describes a diagnostic algorithm, composed after a literature search, that can guide the general practitioner towards the most probable diagnosis in case of cognitive complaints. History taking is the most important tool in order to clarify the differential diagnosis and should include information on type and course of complaints, their effect on activities of daily life and occupational functioning, and mood. We propose to adjust the test that the general practitioner administers to the probability that cognitive impairment is present. If cognitive impairment is not likely, a test with a high negative predictive value (NPV) is used to rule out cognitive impairment. The clock drawing test is than the most suitable test, with a NPV of 60-93%. If the clock drawing test is positive, impairment is not certainly present (positive predictive value (PPV) 19-69%), but further investigation is recommended. If cognitive impairment is possible, the Montreal Cognitive Assessment (MoCA) can be filled out to distinguish normal cognitive function from mild cognitive impairment. If cognitive impairment is likely, the Mini-Mental State Examination (with a high PPV) can be administered to make a diagnosis of dementia likely.

The advantages and disadvantages of case-finding for cognitive impairment in the general population are debated intensively. In *chapter 7* we discussed that case-finding for cognitive impairment is different from the standard screening programs in for example breast cancer, because cognitive impairment can only be diagnosed when patients suffer from it. Additionally, there is a difference between case-finding for cognitive impairment in the general population and in patients with T2DM. In patients with T2DM, cognitive impairment is associated with more complications, which might be reduced by tailoring treatment. We acknowledge that up to now evidence for case-finding in patients with T2DM is lacking, but the yield of case-finding for cognitive impairment and its consequences for optimal diabetes treatment should be studied, since the number of elderly people with T2DM – and therefore the number of people with T2DM and cognitive impairment – will increase.

The best method to detect cognitive impairment in patients with T2DM in a reliable and efficient way is lacking. The literature indicated that the self-administered test 'Test Your Memory' (TYM) could discriminate between cognitive impairment and normal cognition at a memory clinic. We examined this for primary care. In *chapter 8* we compared the relation of the TYM and the Mini-Mental State Examination (MMSE) with a neuropsychological assessment in 86 participants of the ADDITION-Cognition study. We found that the TYM showed good correlation with a neuropsychological assessment (r=0.78 versus 0.55 for the MMSE) and performed better in discriminating between variations of cognition than the MMSE (ROC 0.88 vs 0.71). We concluded that the TYM is a promising test for the detection of undiagnosed cognitive impairment in

primary care and decided to evaluate this test in the Cognitive Impairment in Diabetes (Cog-ID) study.

The Cog-ID study, described in *chapter 9*, aimed to establish a stepped diagnostic procedure to detect undiagnosed cognitive impairment in patients with T2DM aged ≥70 years. Participants were examined for undiagnosed cognitive impairment in three steps. At their homes, participants first filled out the TYM and Self-Administered Gerocognitive Examination (SAGE) questionnaires and were examined by a trainee general practitioner with history taking and a MMSE. Afterwards, participants suspected of cognitive impairment, and a random sample of 30% of participants not suspected of cognitive impairment, were tested at the memory clinic. The results of the Cog-ID study are reported in *chapter 10*. From 22 general practices 1243 patients were invited and 228 agreed to participate. Subsequently, three patients were excluded because they fulfilled the exclusion criteria. Cognitive impairment was present in 57 patients (25%). The results showed that if the TYM or SAGE is negative, the chance is high that the patient indeed has no cognitive impairment (NPV 81% and 85%). If the TYM or SAGE is positive, the chance of cognitive impairment is 39% for the TYM and 40% for the SAGE, requiring further investigation by the general practitioner. We concluded that both tests have adequate diagnostic accuracy to support a case-finding strategy for cognitive impairment in patients with T2DM in primary care in order to reduce the work load of the general practitioner.

In the closing *chapter 11* we conclude that physicians should be aware of the association between T2DM and the different stages of cognitive dysfunction, because the stage of cognitive dysfunction has consequences for the prognosis of cognitive complaints and the risk for complications. Additionally, the general practitioner should be aware of co-occurring depressive symptoms. In the literature there are a number of arguments for case-finding for cognitive impairment in patients with T2DM. We found that case-finding with the TYM or SAGE is possible, but the yield of case-finding for cognitive impairment with respect to clinical and patient-relevant outcomes, and for society are still uncertain and need to be examined. Until future studies show a beneficial effect of case-finding, followed by supportive interventions, case-finding is only useful in patients in whom cognitive impairment might play a role in diabetes management.

NEDERLANDSE SAMENVATTING

Diabetes mellitus type 2 (DM2) is geassocieerd met cognitieve functiestoornissen (stoornissen in functies die te maken hebben met het opnemen en verwerken van informatie; bijvoorbeeld aandacht en concentratie, oriëntatie, waarnemen, denken, herinneren, plannen maken, problemen oplossen, vaardigheden). In het eerste deel van dit proefschrift onderzochten we de relatie tussen enerzijds het cognitief functioneren van patiënten met DM2 en anderzijds depressie en de algemene gezondheidstoestand. Ook bestudeerden we het effect van een zes jaar durende intensieve multifactoriële behandeling op het cognitief functioneren van mensen bij wie door screening DM2 werd vastgesteld. In het tweede deel onderzoeken we verschillende cognitieve testen voor het opsporen van cognitieve stoornissen in de huisartsenpraktijk.

DEEL 1: COGNITIEVE DISFUNCTIE BIJ DM2

In *hoofdstuk 2* hebben we de literatuur over cognitief functioneren bij diabetes samengevat en doen we op basis daarvan aanbevelingen voor diagnostiek en behandeling in de dagelijkse praktijk. Uit de literatuur bleek dat diabetes mellitus geassocieerd is met verschillende stadia van cognitieve disfunctie, van lichte cognitieve tekorten tot ernstige cognitieve stoornissen. Zo is het risico op dementie anderhalf keer verhoogd bij patiënten met DM2. De cognitieve veranderingen gaan gepaard met structurele veranderingen in de hersenen. Verschillende cardiovasculaire risicofactoren lieten een relatie zien met het cognitief functioneren.

De vraag is hoe die verschillende stadia van cognitieve disfunctie bij patiënten met DM2 het best te herkennen en benoemen zijn. Naar onze mening kunnen de gangbare termen 'mild cognitive impairment' (MCI) en dementie ook bij mensen met diabetes worden gebruikt. Voor de lichtere cognitieve tekorten vonden wij in de literatuur geen passende terminologie. Wij stellen voor om deze te classificeren als 'diabetes-geassocieerde cognitieve tekorten'. Deze classificatie is van toepassing op lichte cognitieve tekorten die langzaam ontstaan, voorkomen op alle leeftijden, en niet voldoen aan de criteria voor MCI. Patiënten met diabetes-geassocieerde cognitieve tekorten hebben vaak lichte cognitieve klachten, maar ervaren daarvan geen problemen in het dagelijks leven.

De verschillende stadia van cognitieve disfunctie geven richting aan de te volgen aanpak. Er bestaat geen specifieke behandeling voor diabetes-geassocieerde cognitieve tekorten, maar vanwege de gunstige prognose kunnen patiënten vaak gerustgesteld worden en kunnen zij tips krijgen hoe het beste om te gaan met hun klachten. De behandeling van cognitieve stoornissen is gelijk bij mensen met en zonder DM2. Het vaststellen van een cognitieve stoornis zou bij DM2 echter aanleiding kunnen zijn voor de behandelend arts om de diabetesbehandeling beter af te stemmen op de patiënt, bijvoorbeeld door het

risico op medicatiefouten te verminderen, strenger toe te zien op het voorkomen van hypoglykemie, of inschakeling van mantelzorgers.

Naast veranderingen in de cognitie, hebben patiënten met DM2 ook vaker een depressie. We wisten dat depressieve symptomen invloed kunnen hebben op cognitie en vroegen ons af of depressieve symptomen een rol zouden kunnen spelen in het verschil in cognitief functioneren tussen mensen met en zonder DM2. We vergeleken daarvoor patiënten met (n=366) en zonder (n=204) DM2. Deze deelnemers (50-75 jaar) kwamen uit drie studies waarin het cognitief functioneren op de domeinen geheugen, informatieverwerkingssnelheid en aandacht en uitvoerende functies en een samengestelde score van deze drie domeinen vergeleken werd. Hieruit bleek dat patiënten met DM2 lichte cognitieve tekorten hebben vergeleken met mensen zonder DM2 (verschil samengestelde z-score -0.13; 95%-BI -0.22- -0.04). Het cognitief functioneren van patiënten met DM2 verschilde niet tussen patiënten met en patiënten zonder depressieve klachten (depressieve klachten gemeten met de CES-D en BDI vragenlijsten; verschil samengestelde z-score 0.01; 95%-BI -0.15-0.18). Mensen zonder DM2 scoorden echter slechter op het cognitief functioneren als ze wel depressieve klachten hadden (verschil samengestelde z-score -0.25; 95%-BI -0.54-0.03). Wij concludeerden dat depressieve klachten geen invloed hebben op de aanwezigheid van lichte cognitieve tekorten bij patiënten met DM2.

Artsen denken vaak dat het melden van een cognitieve stoornis aan een patiënt een negatief effect kan hebben. Het zou kunnen leiden tot depressieve symptomen en negatieve effecten hebben op de algemene gezondheidstoestand en hun kwaliteit van leven. Het is echter ook mogelijk dat patiënten al een slechtere gezondheidstoestand en meer tekenen van een depressie hebben omdat zij een cognitieve stoornis hebben, zonder dat deze al formeel gediagnosticeerd is. Wij onderzochten in *hoofdstuk 4* bij 225 70-plussers met DM2, of een nog niet gediagnosticeerde cognitieve stoornis (dat wil zeggen cognitieve stoornissen waarvoor de patiënt of zijn/haar familie nog niet bij de dokter is geweest) samenhangt met een slechtere gezondheidstoestand (gemeten met de SF-36, EQ-5D en EQ-VAS) en met meer depressieve symptomen (CES-D). Patiënten werden thuis bezocht en vulden vragenlijsten in waarbij hun cognitie werd getest ('Test Your Memory test' (TYM) en 'Self-Administered Gerocognitive Examination' [SAGE]) en waarbij hun fysieke en mentale gezondheidstoestand en de aanwezigheid van depressieve symptomen werden gemeten. Ook werd hun cognitief functioneren onderzocht door een arts. Patiënten bij wie een cognitieve stoornis werd vermoed en een deel van de patiënten bij wie dit niet werd gevonden, werden onderzocht op de geheugenpolikliniek van het UMC Utrecht. Cognitieve stoornissen waren aanwezig bij 25% van de patiënten. Patiënten met cognitieve stoornissen hadden een lagere gezondheidstoestand (verschil tussen de groepen op de fysieke schaal 3.5 punten op een schaal van 0-100; op de

mentale schaal 2.9 punten) en 30% van de patiënten met cognitieve stoornissen had een depressie, wat ongeveer twee keer zo hoog is als patiënten zonder een cognitieve stoornis (RR 1.8; 95%-BI 1.1-3.0). Dit onderzoek toonde aan dat we ons moeten realiseren dat bij mensen die cognitief niet meer optimaal functioneren andere aspecten van de gezondheid ook vaker aangedaan zijn. Het vaker voorkomen van depressieve klachten bij mensen met cognitieve stoornissen hoeft dan ook niet het gevolg te zijn van het bespreken van de diagnose, maar kan ook goed samenhangen met de aanwezigheid van de cognitieve stoornissen zelf. Het vroegtijdig opsporen van cognitieve stoornissen kan daarom nuttig zijn omdat het een groep identificeert die baat kan hebben bij een aangepaste behandeling.

In de literatuur is beschreven dat een betere diabetesbehandeling het cognitief functioneren van diabetespatiënten zou kunnen verbeteren. In de ADDITION-Cognitie studie, beschreven in *hoofdstuk 5*, onderzochten wij of een intensieve multifactoriële behandeling (met strikte doelen voor glucose, bloeddruk en cholesterol en leefstijladvies), het cognitief functioneren inderdaad kon verbeteren of achteruitgang kon voorkomen. In deze studie werden 183 patiënten met door screening opgespoorde DM2 gerandomiseerd tussen de gebruikelijke behandeling volgens de meest recente NHG-Standaard (86 patiënten, 64% man, gemiddeld 60 jaar) en een intensievere diabetesbehandeling (97 patiënten, 58% man, gemiddeld 59 jaar). Patiënten kregen deze behandeling gedurende zes jaar. Hun cognitief functioneren werd drie en zes jaar na randomisatie thuis onderzocht met een neuropsychologisch onderzoek. Ook bij 69 mensen zonder DM2 werd het cognitief functioneren onderzocht (48% man, gemiddeld 63 jaar). Drie jaar na vaststellen van de diagnose en aanvang van de behandeling hadden de patiënten met DM2 lichte cognitieve tekorten op de domeinen geheugen, informatieverwerkingssnelheid en aandacht en executief functioneren, vergeleken met mensen zonder DM2. Echter, in de drie jaar daarna was de cognitieve achteruitgang van de patiënten met DM2, ongeacht hun behandeling, ongeveer gelijk aan de achteruitgang van mensen zonder DM2 (achteruitgang samengestelde score ten opzichte van mensen zonder DM2 voor intensieve groep -0.14 (95%-BI -0.23--0.06), voor standaard groep -0.02 (95%-BI -0.12-0.07)). Daarbij dienen we te bedenken dat na zes jaar ook het verschil in risicofactoren tussen de twee diabetesgroepen klein was, waarschijnlijk door de herziene NHG-Standaard, die gedurende het onderzoek gepubliceerd werd, met strengere doelstellingen voor bloeddruk en cholesterol. Mogelijk heeft dit invloed gehad op de resultaten. De progressie van cognitieve tekorten wordt dus niet beïnvloed door een iets intensievere behandeling. Dit komt mogelijk doordat de achteruitgang zich langzaam manifesteert waardoor er maar weinig ruimte is voor het vinden van een verschil. Verder onderzoek moet uitwijzen of er een bepaalde groep diabetespatiënten is met een hoog risico op cognitieve stoornissen die wèl baat heeft bij een intensievere multifactoriële diabetesbehandeling.

DEEL 2: DETECTEREN VAN COGNITIEVE STOORNISSEN BIJ DM2

Bij de diagnostiek naar cognitieve stoornissen kunnen twee situaties onderscheiden worden. In het eerste geval gaat het om patiënten die met klachten over hun geheugen naar de huisarts gaan. De tweede situatie betreft het actief benaderen van patiënten voor onderzoek van het cognitief functioneren die voor andere klachten op het spreekuur komen. Deze laatste situatie noemen we 'case-finding'.

Cognitieve stoornissen worden vaak niet gediagnosticeerd, zelfs als patiënten of hun familieleden klachten rapporteren. Bij patiënten met DM2 kunnen cognitieve stoornissen samenhangen met verminderd zelfmanagement en met het ontstaan van meer diabetescomplicaties. Richtlijnen adviseren daarom om bij de behandeling van diabetes rekening te houden met het cognitief functioneren van de patiënt. De mogelijkheden om cognitieve stoornissen te diagnosticeren bij patiënten met DM2 zijn echter onvoldoende onderzocht. In het tweede deel van dit proefschrift onderzochten wij eenvoudig toe te passen testen voor het opsporen van cognitieve stoornissen bij patiënten met DM2 in de huisartsenpraktijk.

Hoofdstuk 6 beschrijft een stappenplan, opgesteld aan de hand van een literatuurstudie, dat de huisarts kan helpen bij het vaststellen van de meest waarschijnlijke diagnose als er klachten zijn over zaken als geheugen, de weg weten, mensen herkennen enzovoorts. De anamnese is hierbij het belangrijkste. Door te vragen naar de aard, het beloop en het effect van de klachten op het dagelijks leven en tevens te exploreren of er sprake is van depressieve symptomen krijgt de huisarts inzicht in de aard en omvang van de problemen. Wij stelden voor dat de test die de huisarts vervolgens doet om uit te sluiten of aan te tonen of er daadwerkelijk cognitieve stoornissen zijn, afgestemd wordt op de kans dat er daadwerkelijk stoornissen zijn. Wanneer de huisarts op basis van de (hetero-) anamnese de kans op een cognitieve stoornis klein acht, neemt hij/zij een test af die goed is in het uitsluiten van een stoornis (hoge negatief voorspellende waarde (NVW)). De kloktekentest is hiervoor het meest geschikt, de test heeft een NVW van 60-93%. Is de kloktekentest positief dan is er niet zeker een stoornis (de positief voorspellende waarde (PVW) is 19-69%), maar is het verstandig om nog eens goed te kijken. Acht de huisarts de kans op MCI aanwezig, dan is de Montreal Cognitive Assessment (MoCA) meer geschikt. Denkt de huisarts dat er sprake is van dementie, dan kan de Mini-Mental State Examination (MMSE), met een hoge PVW, gebruikt worden om deze diagnose meer waarschijnlijk maken.

Over de voor- en nadelen van case-finding op cognitieve stoornissen in de algemene populatie wordt veel gediscussieerd. In *hoofdstuk 7* betogen wij dat er een belangrijk verschil is tussen case-finding op cognitieve stoornissen en de meer bekende

screeningprogramma's op bijvoorbeeld borstkanker. Daarnaast is er een verschil tussen case-finding op cognitieve stoornissen bij mensen uit de algemene populatie en bij patiënten met DM2. Patiënten met DM2 en cognitieve stoornissen hebben een hoger risico op complicaties. Een aangepaste behandeling kan dit risico mogelijk verlagen. We erkennen dat er momenteel onvoldoende wetenschappelijk bewijs is om case-finding bij mensen met DM2 te adviseren, maar vinden wel dat de voor- en nadelen hiervan goed onderzocht moeten worden. Het aantal (hoog-)bejaarde mensen met DM2 – en dus ook het aantal mensen met DM2 en cognitieve stoornissen – zal immers alleen maar toenemen.

Een goede methode om cognitieve stoornissen op een betrouwbare en efficiënte wijze op te sporen ontbrak in de huisartsenpraktijk. In de literatuur bleek de TYM, een test die patiënten zelfstandig kunnen invullen, op een geheugenpoli goed onderscheid te kunnen maken tussen cognitieve stoornissen en normaal cognitief functioneren. Wij wilden onderzoeken of dit ook het geval was in de huisartsenpraktijk. Daarom vergeleken wij in *hoofdstuk 8* de TYM en de MMSE met een neuropsychologisch onderzoek. Hiervoor gebruikten we gegevens van 86 deelnemers van de ADDITION-Cognitie studie. De resultaten lieten zien dat de TYM goed overeen komt met een neuropsychologisch onderzoek (correlatiecoëfficiënt 0.78 vs. 0.55 voor de MMSE). Ook onderscheidde de TYM lichte cognitieve tekorten beter dan de MMSE (ROC-curve 0.88 vs. 0.71). Hieruit concludeerden wij dat de TYM mogelijk een geschiktere test is voor case-finding in de huisartsenpraktijk dan de MMSE.
Om dit vervolgens te onderzoeken, hebben we de Cognitive Impairment in Diabetes (Cog-ID) studie opgezet, beschreven in *hoofdstuk 9*. Het doel van deze studie was het ontwikkelen van een diagnostische procedure voor het opsporen van ongediagnosticeerde cognitieve stoornissen bij 70-plussers met DM2. In de Cog-ID studie werden patiënten in drie stappen onderzocht op cognitieve stoornissen. Zij werden thuis bezocht door een arts-onderzoeker en vulden als eerste zelfstandig zowel de TYM als de SAGE in. Vervolgens werden een (hetero-)anamnese en de MMSE afgenomen. Patiënten die verdacht werden van een cognitieve stoornis op basis van de TYM, SAGE of de anamnese met MMSE werden uitgenodigd voor een bezoek aan de geheugenpoli. Ook een willekeurige steekproef van 30% van de patiënten zonder verdenking op cognitieve stoornissen werd daarvoor uitgenodigd.

In *hoofdstuk 10* beschrijven we de resultaten van de Cog-ID studie. Van de 1243 patiënten uit 22 huisartsenpraktijken die werden uitgenodigd wilden 228 patiënten deelnemen. Drie patiënten werden alsnog geëxcludeerd omdat ze niet bleken te voldoen aan de deelname criteria. Bij 57 patiënten (25%) werd een cognitieve stoornis vastgesteld. De resultaten lieten zien dat als de TYM of de SAGE negatief is, de kans groot is dat er inderdaad geen cognitieve stoornis aanwezig is (NVW 81% en 85%). Als de TYM of de

SAGE positief is, dan is de kans dat een cognitieve stoornis aanwezig is 39% voor de TYM en 40% voor de SAGE. Verder onderzoek is dan nodig. Hieruit concludeerden wij dat beide testen gebruikt kunnen worden bij case-finding op cognitieve stoornissen bij 70-plussers met DM2 in de huisartsenpraktijk. Door deze getrapte diagnostiek kan de werkbelasting van de huisarts verminderd worden.

In het afsluitende *hoofdstuk 11* concluderen we dat artsen op de hoogte moeten zijn van het verband tussen DM2 en de verschillende stadia van cognitieve disfunctie, aangezien dit gevolgen heeft voor de prognose van cognitieve klachten en het risico op complicaties. Ook is het goed dat de behandelend arts zich bewust is van mogelijk tegelijk voorkomende depressieve klachten. In de literatuur is een aantal argumenten voor case-finding op cognitieve stoornissen bij patiënten met DM2 te vinden. Case-finding met behulp van de TYM of SAGE is mogelijk, maar de opbrengst van case-finding met betrekking tot patiëntrelevante uitkomsten en de opbrengst voor de maatschappij zijn echter nog onduidelijk. Toekomstig onderzoek zal moeten laten zien of het vroegtijdig opsporen van reeds aanwezige cognitieve stoornissen, gevolgd door een ondersteunende interventie, nuttig is. Tot die tijd is het alleen zinvol om het cognitief functioneren te onderzoeken bij patiënten met DM2 bij wie een cognitieve stoornis mogelijk een rol speelt bij de diabetesbehandeling.

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LIST OF PUBLICATIONS

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1. **Paula S. Koekkoek**, L. Jaap Kappelle, Esther van den Berg, Guy E.H.M. Rutten, Geert Jan Biessels. Cognitive function in patients with diabetes mellitus: guidance for daily care. The Lancet Neurology. 2015;14:329-40
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3. **Paula S. Koekkoek**, Geert Jan Biessels, Minke Kooistra, Jolien Janssen, L. Jaap Kappelle, Guy E.H.M. Rutten, On behalf of the Cog-ID study group. Undiagnosed cognitive impairment, health status and depressive symptoms in patients with type 2 diabetes. Submitted.
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Other publications

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CURRICULUM VITAE

Paula Sophia Koekkoek was born on the 23th of September 1985 in Zwolle, the Netherlands. She attended secondary school at the Gymnasium Celeanum in Zwolle from which she graduated in 2003. Following, she started her study Medicine at Utrecht University. During this study she developed an interest for both the practice and research of primary care. After receiving her master's degree in Medicine in 2009, she decided to combine a PhD project with general practice training in an AIOTHO-program. In December 2009 she started her PhD project, leading to this thesis, at the Julius Center for Health Sciences and Primary Care and the department of Neurology at the University Medical Center Utrecht under the supervision of prof. dr. G.E.H.M. Rutten, prof. dr. L.J. Kappelle and prof. dr. G.J. Biessels. In March 2012 she started general practice training at Utrecht University from which she expects to graduate in 2016.
During the combined AIOTHO-program she also obtained her Master of Science degree in Clinical Epidemiology at Utrecht University in 2013.
She is married to Johan Boer and together they have one daughter: Tessa (2014).