COGNITIVE IMPAIRMENT IN TYPE 2 DIABETES

Opportunities for diagnosis, prevention and management

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COGNITIEVE STOORNISSEN BIJ TYPE 2 DIABETES

Mogelijkheden voor diagnostiek, preventie en behandeling
(met een samenvatting in het Nederlands)

Proefschrift

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Contents

CHAPTER 1

General introduction

In the Netherlands, over 1.1 million people were known to have diabetes in 2017, and due to ageing of the population and growing numbers of people with overweight and obesity these numbers are expected to increase further over the next decades.[1] Cognitive dysfunction is increasingly recognised as an important complication of type 2 diabetes.[2,3] There are different stages of cognitive dysfunction. Diabetes is associated with subtle changes in cognitive function, which are already present in pre-diabetes stages and evolve very slowly over the course of many years. These 'subtle diabetes-associated cognitive decrements' occur in patients of all ages.[4] In addition, people with diabetes -predominantly those over the age of 65 years- are also at risk for more severe stages of cognitive dysfunction, namely mild cognitive impairment and dementia. Indeed, the risk to develop dementia is doubled in those with type 2 diabetes.[2] Such cognitive deficits are already posing a tremendous economic, social, and public health burden. Yet, the number of people affected is expected to increase further.[1]

Throughout this thesis I will use the term cognitive impairment to refer to both mild cognitive impairment and dementia. The term cognitive dysfunction refers to all stages of cognitive dysfunction and thus also includes the subtle diabetes-associated cognitive decrements.[4] Cognitive impairment among people with type 2 diabetes is associated with reduced self-management skills and an increased risk of severe hypoglycaemic events.[5-8] Besides, the risk of cardiovascular events (e.g. stroke and myocardial infarction) and even death is increased.[9] This vulnerable group of patients with diabetes might therefore benefit from a tailored treatment and support. Hence, the American Diabetes Association (ADA) and the Dutch College of General Practitioners (NHG) recommend to take the cognitive abilities of a patient into account in defining the most adequate treatment.[10,11] However, identification of people with undiagnosed cognitive impairment is both difficult and also still a matter of discussion.[12,13] As a result, the diagnosis of cognitive impairment is prone to be missed or delayed.[14-16]

I focused on the following three questions in this thesis:

I. **What is the impact of cognitive impairment on people with type 2 diabetes?**
   We specifically looked at the impact of cognitive impairment on health status, depressive symptoms and the use of acute health care services.

II. **Are there ways to prevent cognitive impairment in patients with type 2 diabetes?**
   We were particularly interested in the etiologic role of dysglycaemia, insulin resistance and beta-cell function with regard to cognitive dysfunction in diabetes, as possible starting points for preventive strategies.

III. **How can we identify patients with type 2 diabetes and cognitive impairment who may benefit from a more tailored treatment and support?**

We investigated which cognitive tests are most suitable to diagnose cognitive impairment in primary care and we determined the diagnostic accuracy of two tests for a case-finding strategy in older people with type 2 diabetes.

Impact of cognitive impairment on people with type 2 diabetes

Health status and depressive symptoms

Health status refers to the problems that patients experience in daily life and includes both physical, mental and social domains. Patient-reported outcomes, such as health status, are increasingly used because they help us to understand the perspectives of patients better and they measure concepts that matter to the patient.[17] The same applies to depressive symptoms. Most importantly, depressive symptoms are very common in elderly with type 2 diabetes and they can affect self-efficacy and adherence to diabetes management.[18,19] The relation between diabetes, depression and cognitive impairment is complex and multidirectional.[20,21] **Chapter 2** describes to what extent patients with type 2 diabetes and undiagnosed cognitive impairment suffer from a reduced health status and depressive symptoms.

Use of acute health care services and falls

Utilisation of acute health care services accounts for a substantial proportion of health expenditures and is associated with compromised health in older people.[21] Adjustment of patient's treatment and enhancing patient's support could potentially reduce the need for visits to acute health care services.[22] Falls are another common and disabling problem among elderly, especially in vulnerable patients with comorbidities and use of multiple medications. Falls often lead to serious consequences such as (hip) fractures, pain, functional limitations and high health care costs.[23-25] Since hypoglycaemia can cause falls and hospitalisations,[26] one might assume that elderly patients with cognitive impairment (and associated hypoglycaemia risks) fall more often and use acute health care services more often compared to those without cognitive impairment. If this hypothesis can be confirmed, this would reinforce the need to timely identify cognitive impairment in people with type 2 diabetes, because hypoglycaemia is a common, but preventable complication in diabetes. In **chapter 4** we describe the occurrence of unplanned hospitalisations, emergency room visits, visits to general practitioner (GP) out of hours services and self-reported falls. We compared people with type 2 diabetes and screen-detected cognitive impairment to those not suspected of cognitive impairment during screening.

Etiology and prevention of cognitive decline in type 2 diabetes

Etiology

To find effective prevention strategies for cognitive impairment in patients with type 2 diabetes, it is essential to know its underlying mechanisms. Previous studies suggest that both vascular risk factors and metabolic changes such as insulin resistance, beta-cell dysfunction, chronic hyperglycaemia and hypoglycaemic events may contribute to cerebral

damage in diabetes.[27] However, a comprehensive understanding is still lacking.

We choose to look in more detail into the role of dysglycaemia, insulin-resistance and beta-cell function. We used glycosylated haemoglobin (HbA1c) as a measure of dysglycaemia; it reflects the average blood glucose levels over the preceding two to three months. Chronic hyperglycaemia will result in a high HbA1c value, while a low HbA1c value increases the chance that the patient experienced hypoglycaemic episodes in the preceding months.[28] Previous studies reported a significant, but weak, linear association between higher HbA1c levels and worse cognitive function, while others found no association.[29] Since both low and high values might be related to worse cognitive functioning, it was of particular interest to investigate whether the association between HbA1c and cognition could be quadratic (bell-shaped). The above mentioned studies did not sufficiently take this possible nonlinearity into consideration.

Type 2 diabetes is characterised by insufficient insulin secretion from the beta-cells of the pancreatic islets (beta-cell dysfunction) as well as by impaired insulin action in target tissues such as muscle, liver and fat (insulin resistance).[30] Accumulating evidence indicates that insulin has also important functions in the brain and that insulin resistance in the brain is associated with cognitive impairment.[31] It is however not clear if and how peripheral insulin resistance and beta-cell dysfunction, as in type 2 diabetes, contribute to insulin resistance in the brain and to cognitive impairment.[29,32] **Chapter 6** describes the relation between HbA1c and indices of insulin-resistance and beta-cell function with cognition in individuals with type 2 diabetes.

Prevention
Because the relation between diabetes and cognitive impairment seems to be multifactorial, the chances of success of a prevention strategy will probably increase when it engages different starting points. Promising targets include life style changes to beneficially influence cardiovascular risk factors and optimising diabetes treatment to avoid long-term hyperglycaemia. However, intervention studies investigating the effect of stricter glycaemic control, as single factor or in combination with stricter targets for blood pressure and lipid levels, on cognitive functioning in patients with diabetes, could not show a decrease in cognitive decline.[33]

An increase in hypoglycaemic events due to intensified glycaemic control could play a role in this respect.[33] Another possible reason could be that the primary outcome measure used in most of these studies, namely the mean change in cognitive performance, was not the most appropriate one. Using this outcome measure, the investigators looked at cognitive decline across the total study population, including both patients witch accelerated cognitive decline and (many) patients with no or very little decline. In the past years, it has become clear that the average cognitive decline among people with type 2 diabetes over

the years is relatively slow.[4] It might therefore be more appropriate to focus on patients whose cognitive function declines most rapidly. Such an approach would also be more clinically relevant, because accelerated cognitive decline may progress to dementia and tailored treatment and care are likely to be most urgent in this category of patients. Such an approach is used in the CAROLINA® cognition sub-study.

The CAROLINA® cognition sub-study investigates whether the dipeptidyl peptidase-IV (DPP-IV) inhibitor linagliptin can prevent accelerated cognitive decline in patients with diabetes. In this regard, DPP-IV inhibitors are an interesting class of glucose-lowering agents. In contrast to many other glucose-lowering drugs, DPP-IV inhibitors do usually not provoke hypoglycaemic events. Besides, preclinical studies suggest beneficial neuroprotective effects.[34] **Chapter 5** describes the design of the CAROLINA® cognition sub-study.

Diagnosing cognitive impairment

Diagnostic process in primary care

Currently, diagnosing cognitive impairment in primary care, also outside the specific context of diabetes, is usually initiated in case of clinical suspicion based on patients' symptoms or the concerns of a relative. Primary care guidelines recommend to go through a stepwise diagnostic process when dementia is suspected.[35-40] This process starts with history taking and is followed by an informant interview, physical examination and lab tests. The GP can complete this information with cognitive tests to obtain more certainty about the presence or absence of cognitive impairment. A wealth of research is devoted to the performance of individual cognitive tests. However, it remains unclear which and how cognitive tests should be used in the context of a stepwise diagnostic procedure. **Chapter 7** proposes a practical diagnostic algorithm to guide GPs in their choice of a cognitive test for the evaluation of cognitive complaints. The first steps in this algorithm, history taking and the informant interview, are used to estimate the likelihood that the patient has cognitive impairment. Subsequently, this likelihood is used to determine which cognitive test is most suitable for the individual patient.

Case-finding (opportunistic screening) in patients with type 2 diabetes

In the field of diabetes, screening for cognitive impairment is increasingly advocated.[41] In fact, annual screening for cognitive impairment in elderly people with type 2 diabetes is recommended by recent ADA guidelines.[10] Screening is defined as 'a process of identifying apparently healthy people who may be at increased risk of a disease or condition' and is aimed at offering people information, further tests and appropriate treatment to reduce associated problems or complications.[42] Routine screening may identify patients with cognitive impairment who might benefit from a personalised intervention.

In contrast to a population-based screening strategy, screening can also be performed

as case-finding, also called 'opportunistic screening'. In the latter policy, only patients at risk are eligible for screening, regardless of cognitive complaints. Ideally, a case-finding strategy in type 2 diabetes patients should identify people who require further, more elaborate evaluation by the general practitioner or possibly referral to a memory clinic. Starting with history taking and an informant interview in all patients is time consuming. A (self-administered) cognitive test as first step to identify those in whom further testing for cognitive impairment is indicated could be an efficient alternative.

Most current available cognitive tests target certain aspects of cognition, particularly those affected in Alzheimer's disease, the most common cause of dementia. These tests are less accurate in the identification of vascular cognitive impairment, which is more common in patients with type 2 diabetes.[27] These issues are taken into account in the design of the Cognitive Impairment in Diabetes (Cog-ID) study, as described in **chapter 8**. This study aims to establish a primary care based case-finding strategy to detect cognitive impairment in people with type 2 diabetes of 70 years or above. Cog-ID investigates the diagnostic accuracy of two candidate tests for such a case-finding strategy, the Test Your Memory (TYM) and the Self-Administered Gerocognitive Examination (SAGE), as reported in **chapter 9.**

Screening for cognitive impairment is, however, not (yet) widely implemented. Arguments commonly used against screening for cognitive impairment, not specifically in patients with diabetes, are the lack of cure, the risk of stigmatisation and the fear that the diagnosis of mild cognitive impairment or dementia might evoke depressive symptoms or even suicidal thoughts.[15,43] The same concerns may apply to screening for cognitive impairment in older people with type 2 diabetes, which might hamper its implementation. More insight into these potential negative effects of screening can be helpful in weighing the pros and cons of screening for cognitive impairment. **Chapter 3** describes the course of depressive symptoms and health status of patients with type 2 diabetes after screening and a subsequent diagnosis of cognitive impairment.

Finally, in **chapter 10,** we will discuss the findings and the implications of this thesis for clinical care and future research.

References

1. RIVM. 2017. Available at: https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/cijfers-context/huidige-situatie#node-prevalentie-diabetes-naar-leeftijd-en-geslacht (accessed 13a05-2019)
2. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J Diabetes Investig. 2013;4(6):640-650.
3. Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. Arch Neurol. 2007;64(4):570-575.
4. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol. 2015;14(3):329-340.
5. Bruce DG, Davis WA, Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. Diabetologia. 2009;52(9):1808-1815.
6. Feil DG, Zhu CW, Sultzer DL. The relationship between cognitive impairment and diabetes self-management in a population-based community sample of older adults with Type 2 diabetes. J Behav Med. 2012;35(2):190-199.
7. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care. 2012;35(4):787-793.
8. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. Diabetes Res Clin Pract. 2000;50(3):203-212.
9. Cukierman-Yaffe T, Gerstein HC, Miller ME, et al. The Relationship Between the Score on a Simple Measure of Cognitive Function and Incident CVD in People With Diabetes: A Post Hoc Epidemiological Analysis From the ACCORD-MIND Study. J Clin Endocrinol Metab. 2017;102(9):3218-3225.
10. Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers. Clin Diabetes. 2019;37(1):11-34.
11. Barents ESE Bilo HJG BM, Van den Brink-Muinen A, Dankers M, Van den Donk M, Hart HE, Houweling ST, IJzerman RG, Janssen PGH, Kerssen A, Palmen J, Verburg-Oorthuizen AFE, Wiersma Tj. The Dutch College of General Practitioners Standard on type 2 diabetes mellitus. In:2018.
12. Giezendanner S, Monsch AU, Kressig RW, et al. General practitioners' attitudes towards early diagnosis of dementia: a cross-sectional survey. BMC Fam Pract. 2019;20(1):65.
13. Sanford AM. Mild Cognitive Impairment. Clin Geriatr Med. 2017;33(3):325-337.
14. Connolly A, Gaehl E, Martin H, Morris J, Purandare N. Underdiagnosis of dementia in primary care: variations in the observed prevalence and comparisons to the expected prevalence. Aging Ment Health. 2011;15(8):978-984.
15. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Dis Assoc Disord. 2009;23(4):306-314.
16. Amjad H, Roth DL, Sheehan OC, Lyketsos CG, Wolff JL, Samus QM. Underdiagnosis of Dementia: an Observational Study of Patterns in Diagnosis and Awareness in US Older Adults. J Gen Intern Med. 2018.
17. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health. 2007;10 Suppl 2:S125-S137.
18. Maneze D, Everett B, Astorga C, Yogendran D, Salamonson Y. The Influence of Health Literacy and Depression on Diabetes Self-Management: A Cross-Sectional Study. J Diabetes Res. 2016;2016:3458969.
19. Schmitt A, Reimer A, Hermanns N, et al. Depression is linked to hyperglycaemia via suboptimal diabetes self-management: A cross-sectional mediation analysis. J Psychosom Res. 2017;94:17-23.
20. Mejia S. Promoting multilevel primary prevention of depression and diabetes during midlife may protect against dementia. Evid Based Ment Health. 2016;19(1):e4.
21. Paddock K, Hirdes JP. Acute health care service use among elderly home care clients. Home Health Care Serv Q. 2003;22(1):75-85.
22. Gagnon-Roy M, Hami B, Genereux M, et al. Preventing emergency department (ED) visits and hospitalisations of older adults with cognitive impairment compared with the general senior population: what do we know about avoidable incidents? Results from a scoping review. BMJ Open. 2018;8(4):e019908.
23. Delbaere K, Kochan NA, Close JC, et al. Mild cognitive impairment as a predictor of falls in community-dwelling older people. Am J Geriatr Psychiatry. 2012;20(10):845-853.
24. Heinrich S, Rapp K, Rissmann U, Becker C, Konig HH. Cost of falls in old age: a systematic review. Osteoporos Int. 2010;21(6):891-902.
25. Vinik AI, Vinik EJ, Colberg SR, Morrison S. Falls risk in older adults with type 2 diabetes. Clin Geriatr Med. 2015;31(1):89-99, viii.
26. Zhao Y, Kachroo S, Kawabata H, et al. Association between Hypoglycemia and Fall-Related Fractures and Health Care Utilization in Older Veterans with Type 2 Diabetes. Endocr Pract. 2016;22(2):196-204

27. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol. 2014;2(3):246-255.
28. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. Diabetes Care. 2013;36(11):3535-3542.
29. Geijselaers SLC, Sep SJS, Schram MT, et al. Insulin resistance and cognitive performance in type 2 diabetes - The Maastricht study. J Diabetes Complications. 2017;31(5):824-830.
30. Bergman RN, Finegood DT, Kahn SE. The evolution of beta-cell dysfunction and insulin resistance in type 2 diabetes. Eur J Clin Invest. 2002;32 Suppl 3:35-45.
31. Bello-Chavolla OY, Antonio-Villa NE, Vargas-Vazquez A, Avila-Funes JA, Aguilar-Salinas CA. Pathophysiological mechanisms linking type 2 diabetes and dementia: Review of evidence from clinical, translational and epidemiological research. Curr Diabetes Rev. 2019.
32. Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol. 2015;3(1):75-89.
33. Tuligenga RH. Intensive glycaemic control and cognitive decline in patients with type 2 diabetes: a meta-analysis. Endocr Connect. 2015;4(2):R16-R24.
34. Groeneveld ON, Kappelle LJ, Biessels GJ. Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus. J Diabetes Investig. 2016;7(1):5-16.
35. Adelman AM, Daly MP. Initial evaluation of the patient with suspected dementia. Am Fam Physician. 2005;71(9):1745-1750.
36. Cummings JL, Frank JC, Cherry D, et al. Guidelines for managing Alzheimer's disease: part I. Assessment. Am Fam Physician. 2002;65(11):2263-2272.
37. Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. J Am Board Fam Med. 2012;25(3):367-382.
38. Geldmacher DS, Kerwin DR. Practical Diagnosis and Management of Dementia Due to Alzheimer's Disease in the Primary Care Setting: An Evidence-Based Approach. Prim Care Companion CNS Disord. 2013;15(4).
39. Lee L, Weston WW, Heckman G, Gagnon M, Lee FJ, Sloka S. Structured approach to patients with memory difficulties in family practice. Can Fam Physician. 2013;59(3):249-254.
40. Luning-Koster M, Perry M, Moll van Charante EP, Vernooij-Dassen M, Wiersma T, Burgers JS. Dutch College of General Practitioners' (NHG) practice guideline 'Dementia'. Ned Tijdschr Geneeskd. 2012;156(49):A5323.
41. Sinclair AJ, Hillson R, Bayer AJ, National Expert Working G. Diabetes and dementia in older people: a Best Clinical Practice Statement by a multidisciplinary National Expert Working Group. Diabet Med. 2014;31(9):1024-1031.
42. Public Health England. https://www.gov.uk/guidance/nhs-population-screening-explained (accessed 01-06-2019)
43. Draper B, Peisah C, Snowdon J, Brodaty H. Early dementia diagnosis and the risk of suicide and euthanasia. Alzheimers Dement. 2010;6(1):75-82.

PART 1

Consequences of cognitive impairment in type 2 diabetes

CHAPTER 2

Undiagnosed cognitive impairment, health status and depressive symptoms in patients with type 2 diabetes

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Abstract

Aims
Type 2 diabetes (T2D) is associated with cognitive impairment. We examined whether undiagnosed cognitive impairment in T2D-patients is associated with a reduced health status and depressive symptoms.

Methods
In an observational study, 225 T2D-patients aged ≥70 years were examined at their homes and (some of them) at a memory clinic for undiagnosed cognitive impairment (dementia or mild cognitive impairment [MCI], defined according to internationally accepted criteria). Questionnaires assessing health status (SF-36, EQ-5D, 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 physical and mental summary scores of the SF-36 than patients with normal cognition (difference: 3.5 (95%-CI 0.7–6.3, p=0.02, effect size 0.41) and 2.9 (95%-CI 0.3–5.6; p=0.03, effect size 0.37). EQ-5D index and EQ-VAS scores were significantly lower in patients with cognitive impairment. 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 T2D-patients is associated with a reduced health status and more depressive symptoms. Detection of cognitive impairment in T2D-patients identifies a vulnerable patient group that could benefit from 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 patients with type 2 diabetes there is a relation between depression and risk of cognitive impairment,[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. Health status represents the problems that patients experience in daily life. Quality of life is a subjective appraisal of a patient's position in life in the context of all aspects of life.[8] A reduced health status may lead to a reduced quality of life but this is not always the case.[9] Assessment of health status is important because diabetes patients have to cope with a variety of advice, recommendations and medications which may be burdensome.[10]

Physicians often assume that informing the patient about a diagnosis of cognitive impairment will influence health status, quality of life and depressive symptoms negatively.[11] However, one could also argue that undiagnosed cognitive impairment, for which the patient or a family member did not yet ask professional help, might affect health status and generate depressive symptoms, because it is likely to bother patients. It has been proposed that screening strategies for cognitive impairment in patients with diabetes are warranted to provide personalized diabetes treatment - optimized to the capabilities and co-morbidities of the patient - and can prevent treatment-related complications.[4,12] If patients with type 2 diabetes and undiagnosed cognitive impairment also have a lower health status and experience more depressive symptoms than patients with only diabetes, this could be another argument to try to detect cognitive impairment in an early stage in order to organise support, 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 years.[13] During the first examinations - before any suspicion of cognitive impairment was raised - health status and depressive symptoms were assessed. In the present study we assess differences in health status and depressive symptoms between patients with type 2 diabetes with and without undiagnosed cognitive impairment.

Materials and 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)[14] and SAGE (Self-Administered Gerocognitive Examination).[15] 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.[13]

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 the 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 section ‘results; study population’ 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).[16] 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.[17] Answers were used to compute an index value based on a Dutch valuation study,[18] 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),[19] 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.[20] 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.[21]

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,[22] 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.

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%). Frequently mentioned reasons to decline participation were feeling too old, presence of comorbidity or considering a visit to the memory clinic to burdensome. Three patients, who agreed to participate, 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 of these patients were selected for a memory clinic evaluation because of suspected cognitive impairment.[23] Another 34 patients were invited as part of the random sample of patients with three negative screening tests. Of all invited patients, 14 were unable to attend the memory clinic. From the 127 patients that actually visited 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.

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

Patients with cognitive impairment had significantly less years of education and more macrovascular complications, predominantly due to a more frequent history of stroke than patients with normal cognition. In addition, patients with cognitive impairment showed a trend for more microvascular complications, and they more often used insulin and antihypertensive medication than patients with normal cognition. Cardiovascular risk factors, i.e. blood pressure, cholesterol and BMI, and HbA1c, were comparable between the groups.

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

	N	Total population (n=225)	N	Normal cognition (n=168)	N	Cognitive impairment (n=57)	Effect size (d)
Domains SF-36:							
Physical functioning	224	63.6 ± 26.4	167	67.1 ± 25.5	57	53.2 ± 30.4*	0.50
Role limitations due to physical problems	223	67.7 ± 39.1	166	72.7 ± 28.5	57	53.0 ± 45.4*	0.52
Bodily Pain	224	73.0 ± 24.2	167	74.6 ± 23.8	57	68.3 ± 27.0	0.25
General Health	220	58.2 ± 18.8	165	59.3 ± 19.3	55	54.7 ± 20.5	0.23
Social Functioning	225	79.2 ± 19.9	168	81.7 ± 19.7	57	71.8 ± 24.5*	0.45
Mental Health	222	79.5 ± 14.5	167	80.9 ± 14.6	55	75.2 ± 17.9*	0.35
Role limitations due to emotional problems	221	80.7 ± 34.1	166	84.3 ± 32.0	55	69.6 ± 42.6*	0.39
Vitality	221	66.3 ± 18.5	167	68.5 ± 17.9	54	59.7 ± 22.1*	0.44
Physical Component Score (PCS)	212	51.2 ± 8.3	161	52.1 ± 8.3	51	48.6 ±8.9*	0.41
Mental Component Score (MCS)	212	52.5 ± 7.3	161	53.2 ± 7.2	51	50.2 ± 8.8*	0.37
EQ-5D	219	0.80 ± 0.2	165	0.83 ± 0.2	54	0.73 ± 0.3*	0.39
EQ-VAS	222	73.8 ± 14.0	167	75.5 ± 12.9	55	68.8 ± 17.4*	0.44
CES-D	223	10.0 ± 7.1	167	9.2 ± 7.1	56	12.7 ± 8.5*	0.45
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. Scores on the Short Form-36 (SF-36) and the EuroQol Visual Analogue Scale (EQ-VAS) range from 0 to 100; scores on the EuroQol 5 Dimensions (EQ-5D)_range from 0 to 1; higher scores on these scales indicate better performance. Scores on the Centre for Epidemiologic Studies Depression Scale (CES-D) range from 0 to 48, higher scores on the CES-D indicate more depressive symptoms.*

Health status - SF-36

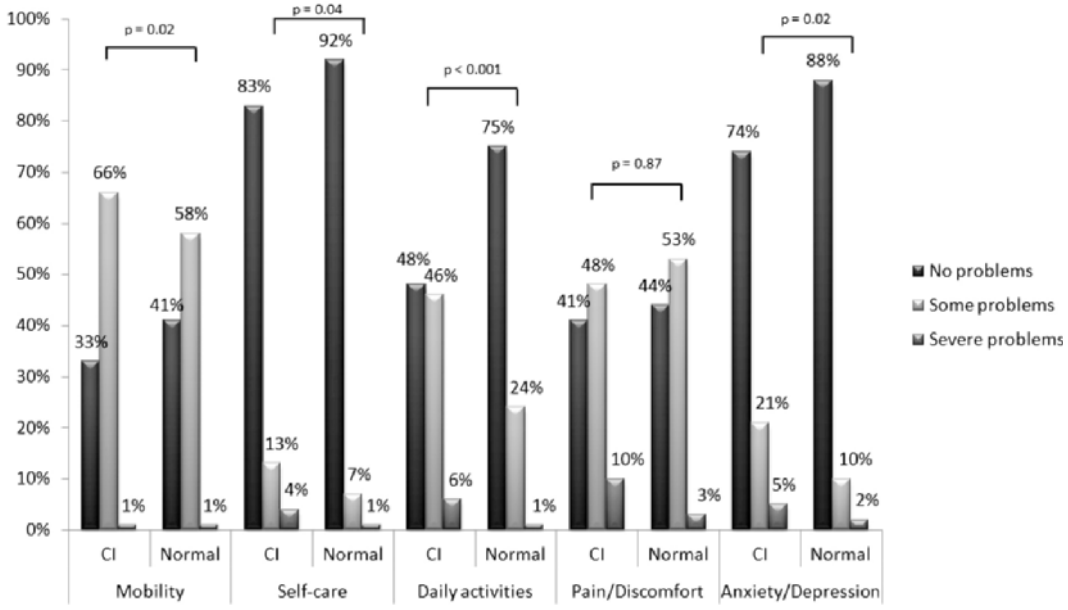
The separate SF-36 domain scores could be calculated in 220 patients (Table 2). The two summary scales, the physical and mental component score (PCS and MCS), could be calculated in 212 patients. Patients with cognitive impairment showed lower scores on all SF-36 domains; in six out of the eight domains and in the summary scales PCS and MCS this difference reached statistical significance (Table 2). The largest difference between the groups was found for the domain role limitations due to physical problems (19.8 (95%-CI

6.5–33.0, p<0.01, effect size 0.52)). 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, effect size 0.41) versus 2.9 (95%-CI 0.3–5.6; p=0.03, effect size 0.37).

Health status - EQ-5D and EQ-VAS

Both groups experienced the most problems in the domains mobility, pain and discomfort and daily activities (Figure 1). The proportion of patients with problems is higher on each EQ-5D domain in patients with cognitive impairment, with significant differences in four out of the five domains. The largest difference between the two groups was found for 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 (10% versus 3%, p= 0.03, Figure 1). The EQ-5D index value and EQ-VAS scores were significantly lower in patients with cognitive impairment (Table 2).

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



p-values are calculated for the difference between patients with and without cognitive impairment for those without problems versus those with some or severe problems.

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 scores indicative of 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 correlation coefficients ranging from 0.43 to 0.48 (all p-values<0.001).

Sensitivity analysis: excluding patients with dementia
Excluding the three 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.

It is generally assumed that cognitive impairment can affect quality of life,[24-27] but we could not identify previous studies that specifically compared health status between people with and without cognitive impairment in the general population (i.e. not specifically in patients with diabetes). In patients with type 2 diabetes, a significantly lower EQ-5D index was found for patients with lower cognitive functioning.[28] Comparable to our results, most problems were found in the domains mobility, daily activities and pain and discomfort.[28] In our study, patients felt particularly limited in their daily and social functioning, represented by the largest effect on role limitations of the SF-36 and the EQ-5D domain 'daily activities'. In this respect, patients with cognitive impairment might also experience feelings of falling to short with respect to their diabetes self-management, indicated by a doubled proportion of patients experiencing problems with daily activities (52% vs 25%) and self-care (17% vs 8%). 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.[29] 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[30] and in patients with type 2 diabetes.[6,7] These results indicate that attention for depressive symptoms is essential in patients with cognitive impairment and type 2 diabetes and that treatment of depressive symptoms might be an option to improve health status. Comparing the results of the CES-D with the domain anxiety/depression of the EQ-5D shows that the EQ-5D may underestimate problems in this domain and highlights the need for a domain specific questionnaire for depression.

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.[31] 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 to 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.

The participation rate in our study was relatively low (18%). Several reasons for this relatively low participation rate can be provided. First, the study population included patients aged ≥70; elderly patients are often less willing to participate in studies. Second, patients were examined for cognitive impairment, which might be threatening for people.

Third, examination of cognitive function first took place at home, but when patients were suspected for cognitive impairment they had to be examined at a memory clinic. This visit to the memory clinic was often mentioned as the reason to decline participation. These refusals to participate have led to selection bias. However, for the aim of the current study - describing differences in health status and depressive symptoms between patients with type 2 diabetes with and without cognitive impairment - selection bias will probably have minimal impact on the results.

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.[32,33]

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.

References

1. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64-74.
2. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 2012;42:484-491.
3. Bruce DG, Davis WA, Casey GP et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. Diabetologia 2009;52:1808-1815.
4. Punthakee Z, Miller ME, Launer LJ et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787-793.
5. Katon W, Lyles CR, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of depression with increased risk of dementia in patients with type 2 diabetes: the Diabetes and Aging Study. Arch Gen Psychiatry 2012;69:410-417.
6. Katon WJ, Lin EH, Williams LH et al. Comorbid Depression Is Associated with an Increased Risk of Dementia Diagnosis in Patients with Diabetes: A Prospective Cohort Study. J Gen Intern Med 2010;25:423-429.
7. Sullivan MD, Katon WJ, Lovato LC et al. Association of Depression With Accelerated Cognitive Decline Among Patients With Type 2 Diabetes in the ACCORD-MIND Trial. JAMA Psychiatry 2013;70:1041-1047.
8. Felce, D. , Perry, J., Quality of life: its definition and measurement. Res. Dev. Disabil. 1995;16:51-74.
9. Carr AJ, Higginson IJ. Are quality of life measures patient centred? BMJ 2001;322:1357-1360.
10. Kuznetsov, L., Long, G.H., Griffin, S.J., Simmons, R.K., Are changes in glycaemic control associated with diabetes-specific quality of life and health status in screen-detected type 2 diabetes patients? four-year follow up of the ADDITION-Cambridge cohort. Diabetes Metab Res. Rev. 2015;31:69-75.
11. Iliffe S, Manthorpe J, Eden A. Sooner or later? Issues in the early diagnosis of dementia in general practice: a qualitative study. Fam Pract 2003;20:376-381.
12. Inzucchi, S.E., Bergenstal, R.M., Buse, J.B., Diamant, M., Ferrannini, E., Nauck, M., et al., Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1577-1596.
13. Koekkoek P, Janssen J, Kooistra M et al. Cognitive Impairment in Diabetes: Rationale and Design Protocol of the Cog-ID Study. JMIR Res Protoc. 2015 Apr-Jun; 4(2): e69
14. Brown J, Pengas G, Dawson K, Brown LA, Clatworthy P. Self administered cognitive screening test (TYM) for detection of Alzheimer's disease: cross sectional study. BMJ 2009;338:b2030.
15. Scharre DW, Chang SI, Murden RA et al. Self-administered Gerocognitive Examination (SAGE): a brief cognitive assessment Instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord 2010;24:64-71.
16. Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-1068.
17. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-343.
18. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. Ned Tijdschr Geneeskd 2005;149:1574-1578.
19. Bouma J, Ranchor AV, Sanderman R et al..Measuring symptoms of despression with the CES-D; instructions Groningen, the Netherlands, Noordelijk Centrum voor Gezondheidsvraagstukken, 1995.
20. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington, DC, 2000.
21. Winblad B, Palmer K, Kivipelto M et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240-246.
22. Rubin DB. Multiple Imputations for Nonresponse in Surveys, in New York, John Wiley & Sons, 1987,
23. Koekkoek, P.S., Janssen, J., Kooistra, M., biesbroek, J.M., Groeneveld, O., van den Berg, E., et al., Case-finding for cognitive impairment with the Test Your Memory and Self-Administered Gerocognitive Examination questionnaires in type 2 diabetes in primary care - the Cog-ID study. Diabet Med. 2016 Jun;33(6):812-9.
24. Muangpaisan W, Assantachai P, Intalapaporn S, Pisansalakij D. Quality of life of the community-based patients with mild cognitive impairment. Geriatr Gerontol Int 2008;8:80-85.
25. Missotten P, Squelard G, Ylieff M et al. Relationship between quality of life and cognitive decline in dementia. Dement Geriatr Cogn Disord 2008;25:564-572.
26. Missotten P, Squelard G, Ylieff M et al. Quality of life in older Belgian people: comparison between people with dementia, mild cognitive impairment, and controls. Int J Geriatr Psychiatry 2008;23:1103-1109.
27. Barrios H, Narciso S, Guerreiro M, Maroco J, Logsdon R, de MA. Quality of life in patients with

mild cognitive impairment. Aging Ment Health 2013;17:287-292.
28. Rodriguez-Pascual C, Rodriguez-Justo S, Garcia-Villar E, Narro-Vidal M, Torrente-Carballido M, Paredes-Galan E. Quality of life, characteristics and metabolic control in diabetic geriatric patients. Maturitas 2011;69:343-347.
29. Pouwer F, Beekman AT, Nijpels G et al. Rates and risks for co-morbid depression in patients with Type 2 diabetes mellitus: results from a community-based study. Diabetologia 2003;46:892-898.
30. Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68:1596-1602.
31. Sinclair, A.J., Girling, A.J., Bayer, A.J., Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. Diabetes Res. Clin. Pract. 2000;50:203-212.
32. Banerjee S, Samsi K, Petrie CD et al. What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. Int J Geriatr Psychiatry 2009;24:15-24.
33. Ali S, Stone M, Skinner TC, Robertson N, Davies M, Khunti K. The association between depression and health-related quality of life in people with type 2 diabetes: a systematic literature review. Diabetes Metab Res Rev 2010;26:75-89

CHAPTER 3

Depressive symptoms and quality of life after screening for cognitive impairment in patients with type 2 diabetes: observations from the Cog-ID cohort study

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Abstract

Objectives
To assess changes in depressive symptoms and health related quality of life (HRQOL) after screening for cognitive impairment in people with type 2 diabetes.

Design
A prospective cohort study, part of the Cognitive Impairment in Diabetes (Cog-ID) study.

Setting
Participants were screened for cognitive impairment in primary care. People suspected of cognitive impairment (screen positives) received an evaluation at a memory clinic.

Participants
Participants ≥70 years with type 2 diabetes were included in Cog-ID between August 2012 and September 2014. The current study includes 179 patients; 39 screen positives with cognitive impairment, 56 screen positives without cognitive impairment and 84 participants not suspected of cognitive impairment during screening (screen negatives).

Outcome measures
Depressive symptoms and HRQOL assessed with the Centre for Epidemiologic Studies Depression Scale (CES-D), 36-Item Short-Form Health Survey (SF-36), European Quality of Life-5 Dimensions questionnaire and the EuroQol visual analogue scale. Outcomes were assessed before screening, and 6 and 24 months after screening. An analysis of covariance model was fitted to assess differences in score changes among people diagnosed with cognitive impairment, screen negatives and screen positives without cognitive impairment using a factor group and baseline score as covariate.

Results
Of all participants, 60.3% was male, the mean age was 76.3±5.0 years, mean diabetes duration 13.0±8.5 years. At screening, participants diagnosed with cognitive impairment had significantly more depressive symptoms and a worse HRQOL than screen negatives. Scores of both groups remained stable over time. Screen positives without cognitive impairment scored between the other two groups at screening, but their depressive symptoms decreased significantly during follow-up (mean CES-D: -3.1 after 6 and -2.1 after 24 months); their HRQOL also tended to improve.

Conclusions
Depressive symptoms are common in older people with type 2 diabetes. Screening for- and a subsequent diagnosis of- cognitive impairment will not increase depressive symptoms.

Introduction

Cognitive impairment in people with type 2 diabetes can result in problems with self-management, treatment adherence and monitoring,[1] in addition it increases the risk of severe hypoglycaemia.[2,3] Comorbidities such as cognitive impairment, must be taken into account to provide optimal care for people with type 2 diabetes.[4] It is well known that cognitive impairment often remains unrecognised by physicians. As a result, the prevalence of missed and delayed diagnoses of cognitive impairment is high.[5-7] The American Diabetes Association (ADA) guidelines recommend annual screening for cognitive impairment in older people with diabetes to facilitate patient-centred care aimed at optimising health outcomes and health related quality of life (HRQOL).[8] No data is available regarding the implementation of this recommendation.

Outside the field of diabetes, concerns have been raised regarding whole-population screening for cognitive impairment. Arguments commonly used against screening are the lack of cure, the risk of stigmatisation and the fear that the diagnosis might evoke depressive symptoms or even suicidal thoughts.[8-10] Targeting higher risk groups, such as those with type 2 diabetes is considered more clinically meaningful, but some of the same concerns may apply. To get the ADA guidelines implemented on a larger scale, it would be beneficial to have insight in possible negative outcomes. It would be particularly interesting to assess the potential impact of screening and a subsequent diagnosis of cognitive impairment on depressive symptoms in elderly with type 2 diabetes. Besides, assessing whether HRQOL is influenced by screening for cognitive impairment could be a good starting point to design targeted interventions for these vulnerable patients.

The Cognitive Impairment in Diabetes (Cog-ID) study aimed to establish a primary care based screening strategy to detect cognitive impairment in people with type 2 diabetes.[9] The study showed that self-administered cognitive screening tests can be used for this purpose and that the Self-Administered Gerocognitive Examination (SAGE) had the best diagnostic accuracy (negative predictive value of 85%; positive predictive value of 40%) with a memory clinic established diagnosis as a reference standard.[10]

As both the HRQOL and depressive symptoms were assessed prior to screening, after six months and after 24 months, the Cog-ID study is ideally suited to assess changes in depressive symptoms and HRQOL after participating in a screening program for cognitive impairment in older people with type 2 diabetes.

Methods

The design of the Cog-ID study has been described previously.[9] In brief, people ≥70 years with type 2 diabetes were invited by their general practitioner (GP) between August 2012 and September 2014. Exclusion criteria were a diagnosis of dementia, a previous memory clinic evaluation or the inability to read or write. After informed consent, participants underwent a stepwise diagnostic procedure as described below.

Screening

A research physician visited participants at home. First, participants completed HRQOL and depression questionnaires (see below). Thereafter, they completed two self-administered cognitive tests, the Test Your Memory (TYM)[11] and Self-Administered Gerocognitive Examination.[12] Lastly, the research physician, blinded for the HRQOL and depression scores, and for the TYM- and SAGE-scores, performed an evaluation with a structured interview and the Mini-Mental State Examination.[13] Participants suspected of cognitive impairment based on this evaluation or either of the cognitive tests (TYM<40; SAGE<15) were classified as screen positive and were invited for a memory clinic evaluation. For reasons out of the scope of this article, 30% of the screen negatives were randomly selected and were also invited to the memory clinic.[9]

Memory clinic

Cognitive impairment, that is mild cognitive impairment (MCI) or dementia, was established by a multidisciplinary team composed of a neurologist and a neuropsychologist, blinded for all results of the screening visit. Dementia was defined as memory impairment and impairment in at least one other cognitive domain (aphasia, apraxia, agnosia, executive functioning) significantly affecting social or occupational functioning compared to the previous level of functioning and not caused by a delirium, according to Diagnostic and Statistical Manual of Mental Disorders – 4th edition.[14] MCI was defined as not normal, not demented, with acquired cognitive complaints that could be objectified as a disorder (i.e. performance <5th percentile on normative values) by a neuropsychological assessment, with preserved basic activities of daily living.[15] Participants with objective cognitive impairment on neuropsychological testing, but who did not fulfil MCI or dementia criteria were labelled as 'cognition otherwise disturbed' and classified as screen positive patients without cognitive impairment. In most cases this was due to absence of accompanying acquired cognitive complaints, which are requested for a diagnosis of MCI or dementia.

Communicating the results

Screen negatives received a letter indicating that screening had not revealed signs of cognitive impairment. The memory clinic results and treatment advice of the screen positives were sent to the participants' own GP, who was requested to discuss them with the patient. The GP and the participant decided together what actions were necessary.

When desirable, further support by the memory clinic was available. When the participant was diagnosed with cognitive impairment, the GP also received advice on how to adjust their patient's diabetes care (Supplementary File 1).

Follow-up
Participants received follow-up questionnaires to assess depressive symptoms and HRQOL, 6 and 24 months after screening. Their opinion on study participation was also assessed.

Measures
Depressive symptoms were assessed with the Centre for Epidemiologic Studies Depression Scale (CES-D).[16] A score ≥16 is generally accepted as the cut-off score for the presence of depression.[17]

The 36-Item Short-Form Health Survey (SF-36) is a questionnaire measuring a patient's HRQOL. It consists of eight domains and two summary scales can be calculated: the Physical Component Score (PCS) and the Mental Component Scale (MCS). Higher scores indicate more favourable levels of functioning.[18] The European Quality of Life-5 Dimensions (EQ-5D) covers five dimensions of HRQOL: mobility, self-care, daily activities, pain/discomfort and anxiety/depression.[19] An index value was computed based on a Dutch valuation study,[20] ranging between 0 and 1, where 0 means death and 1 means full health. The EuroQol visual analogue scale (EQ-VAS) is a graded, vertical line ranging from 0 to 100 (worst to best imaginable health state). Participants were asked to mark a point best reflecting their actual health state.

Information about age, sex and educational level was gathered during screening. Information about participant's medical history, medication use, diabetes duration and laboratory results was collected from the participants' medical record.

Outcomes
The change from screening to follow-up in the total CES-D, PCS, MCS, and EQ-VAS scores and in the EQ-5D index value, both after six and after 24 months, were the most important outcomes. Secondary outcomes were the change in the SF-36 domain scores.

Groups
Participants were classified into three groups:

- 'Screen positives with cognitive impairment': participants suspected of cognitive impairment during screening and diagnosed with either MCI or dementia.
- 'Screen negatives without cognitive impairment': participants not suspected of cognitive impairment during screening.
- 'Screen positives without cognitive impairment': participants suspected of

cognitive impairment during screening, but not meeting MCI or dementia criteria.

Statistical analysis

An analysis of variance model has been fitted to compare the groups pairwise, using a factor group (as defined above). An analysis of covariance model has been fitted to assess change from baseline, using a factor group and baseline score as covariate. A p-value <0.05 was considered significant. Statistical analyses were performed using IBM SPSS statistics V.21.

Missing data

Twelve (7%) sets of questionnaires were missing after 6 months and 25 (15%) after 24 months. Of all the returned baseline and follow-up questionnaires 1% of the CES-D scores were missing, 1.4% EQ-VAS scores, 2.2% EQ-5D scores and 7% of the PCS and MCS scores. Because an incomplete questionnaire could be related to both depression, HRQOL and cognitive function, the missing data could introduce bias. A sensitivity analysis was therefore performed using multiple imputation by predictive mean matching.

Results

Study population

Out of 225 Cog-ID participants, 107 were suspected of cognitive impairment based on the screening visit (Figure 1). All screen positive participants were invited to the memory clinic, 12 (on average 2 years older, more often woman and living alone) were not willing to attend and were therefore not included in this study. Out of 95 screen positives who visited the memory clinic, 39 were diagnosed with cognitive impairment and 56 did not fulfil MCI or dementia criteria. These 56 screen positives without cognitive impairment included 15 participants who were labelled as 'cognition otherwise disturbed'.

Out of 118 screen negatives, 34 were invited to the memory clinic as part of the random sample and not included in this analysis. This resulted in a study population of 179 participants; 39 with cognitive impairment, 84 screen negatives and 56 screen positives without cognitive impairment. Table 1 describes the patient characteristics.

Figure 1 - Patient flow (CI; Cognitive Impairment)

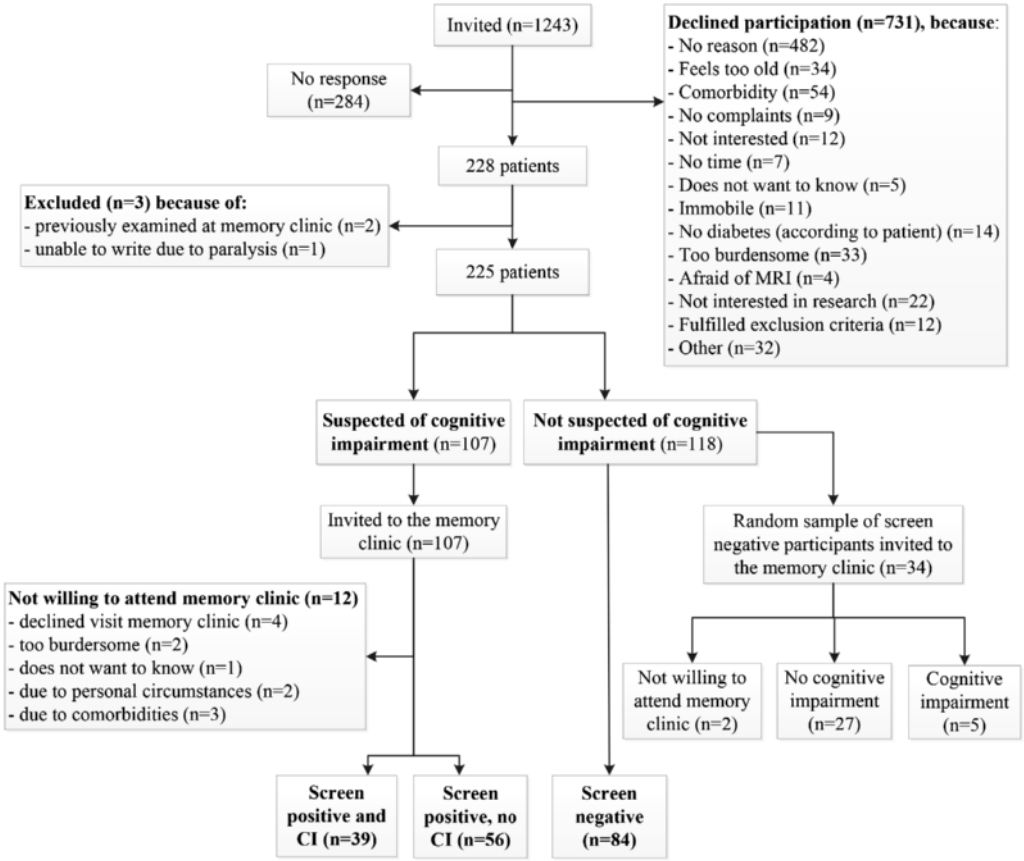


Table 1– Characteristics of participants at time of screening

	Total study population (n=179)	Screen positive and CI (n=39)	Screen positive, no CI (n=56)	Screen negative (n=84)
Age (years)	76.8 ± 5.0	77.7 ± 5.5	76.7 ± 4.4	76.4 ± 5.2
Female sex	71 (39.7%)	17 (43.6%)	23 (41.1%)	31 (36.9%)
Education*	4.6 ± 1.4	3.9 ± 1.5	4.1 ± 1.5	5.2 ± 1.1
Diabetes duration (years)	13.0 ± 8.5	14.6 ± 8.6	13.5 ± 7.7	12.0 ± 8.9
HbA1c (mmol/mol)	52.8 ± 9.8	54.1 ± 9.8	52.1 ± 9.2	52.7 ± 10.3
HbA1c (%)	7.0 ± 0.9	7.1 ± 0.9	6.9 ± 0.8	7.0 ± 0.9
Living alone	70 (39.1%)	12 (30.8%)	23 (41.1%)	35 (41.7%)
MMSE	28.2 ± 2.0	26.5 ± 2.9	28.3 ± 1.6	29.0 ± 1.0
TYME	40.5 ± 6.7	35.3 ± 8.7	38.2 ± 6.0	44.3 ± 2.6
SAGE	15.5 ± 4.3	11.5 ± 4.3	13.5 ± 3.1	18.6 ± 2.2

Data are presented as means (± standard deviation), or number and proportion in %. CI, cognitive impairment; HbA1c, Glycated Hemoglobin; MMSE, Mini-Mental State Examination; SAGE, Self-Administered Gerocognitive Examination; TYME, Test Your Memory

**Educational level is classified by the Dutch Verhage scale[31]; a seven point rating scale ranging from 1 (which equals a level of less than six years of elementary school) to 7 (equals a finished training at a university or technical college)*

Differences at baseline

At screening, participants with cognitive impairment had more depressive symptoms than screen negative participants (Table 2, Figure 2). Nine (11%) screen negative participants, 12 (22%) screen positive participants without cognitive impairment and 15 (40%) participants with cognitive impairment scored ≥16 on the CES-D, indicative for the presence of depression.

Participants with cognitive impairment scored worse at baseline compared to screen negatives on most HRQOL scores (Supplementary File 2, Table 2). All scores of the screen positives without cognitive impairment were between those of the screen negatives and those of participants with cognitive impairment.

Differences after 6 and 24 months
Time from screening until the memory clinic evaluation ranged between 12-126 (median 35) days. The first follow-up questionnaires were sent to all participants 6 months after the screening visit; 54-168 (median 145) days after the memory clinic evaluation. No association was observed between this time interval and mean CES-D and HRQOL scores (data not shown).

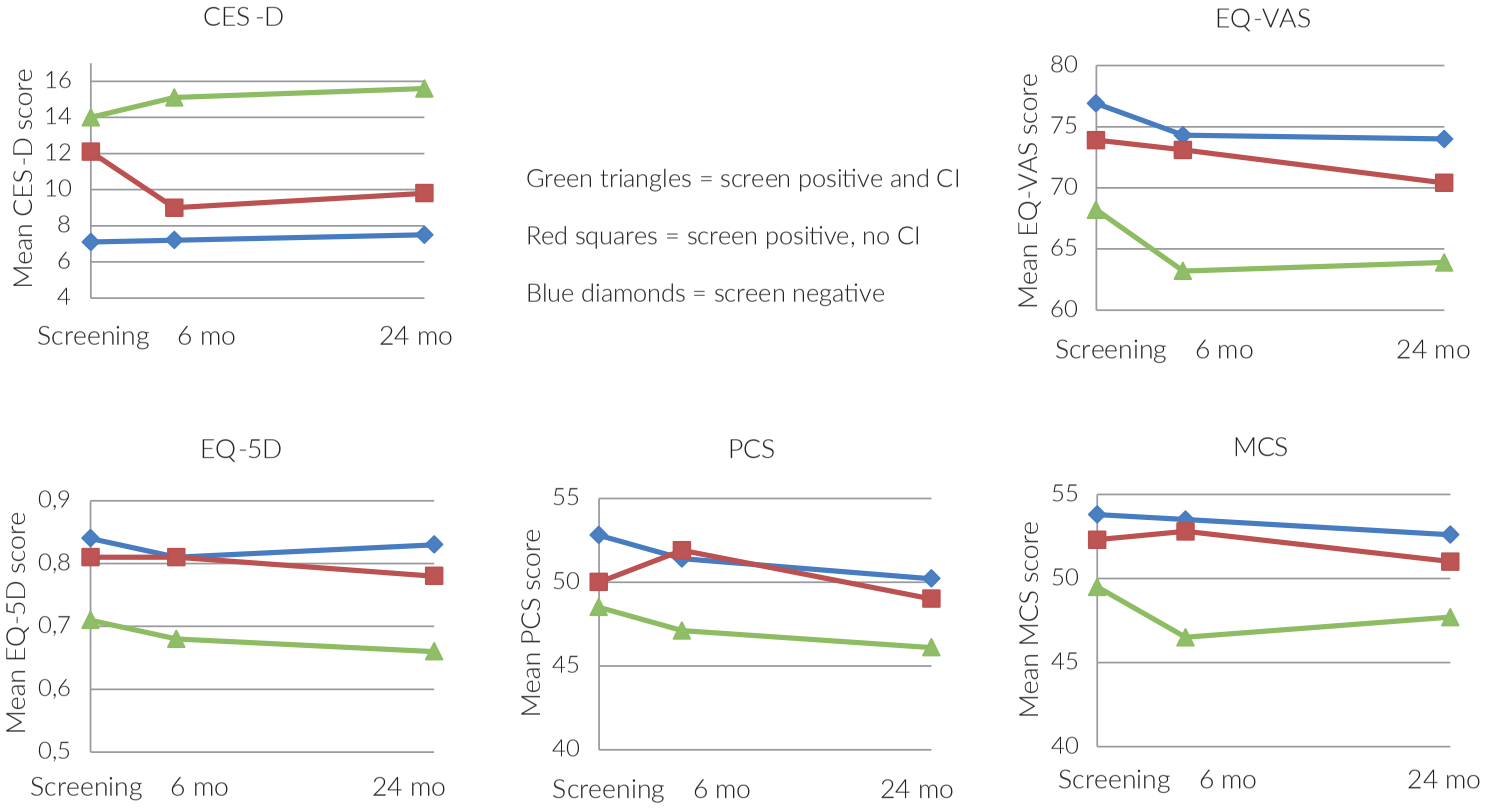
Depressive symptoms in screen negatives and in those with cognitive impairment remained quite stable over time. Unlike these two groups, the screen positives without cognitive impairment experienced a significant improvement in depressive symptoms after 6 months, which sustained after 2 years. This change in depressive symptoms differed significantly between the groups. The change in PCS after 6 months differed between screen negatives and screen positives without cognitive impairment; the PCS improved in the latter (Figure 2, Table 2).

The sensitivity analysis based on the imputed datasets showed results consistent with the primary analysis (data not shown).

Patient's opinion on study participation
Six months after screening, 165 (92%) participants completed the question 'do you regret your participation in this study?'. Most (161 (98%)) answered 'no', only four (2%) answered 'yes'.

Of the 163 (91%) participants answering the question 'would you be willing to participate again in this study?', 141(87%) answered 'yes', 22(13%) 'no'. None of the participants indicated that they would not have wanted to know the results of the study.

Figure 2 – Depressive symptoms and health related quality of life scores over time



CES-D, Center for Epidemiologic Studies Depression Scale; CI, cognitive impairment; EQ-VAS, EuroQol Visual Analogue Scale; EQ-5D, European Quality of Life-5 Dimensions; MCS, Mental Component Scale; Mo, month; PCS, Physical Component Scale.

Table 2 – Depressive symptoms and health related quality of life scores over time.

	Baseline				Mean change after 6 mo. follow-up				Mean change after 2 yr. follow-up			
	Screen positive and CI (n=39)	Screen positive, no CI (n=56)	Screen negative (n=84)		Screen positive and CI (n=39)	Screen positive, no CI (n=56)	Screen negative (n=84)		Screen positive and CI (n=39)	Screen positive, no CI (n=56)	Screen negative (n=84)	
CES-D	14.1±7.2	12.2±5.2	7.1±6.7	a, b	+0.2±6.1	-3.1±6.3	+0.2±5.7	c	+2.0±7.6	-2.1±6.1	+1.0±5.4	**b, c**
EQ-VAS	68.2±14.5	73.9±13.0	76.9±13.1	a	-4.2±15.5	-0.7±10.9	-3.0±10.8	c	-2.8±15.3	-3.9±16.7	-3.5±10.7	
EQ-5D	0.71±0.27	0.81±0.17	0.85±0.17	a, c	-0.01±0.20	-0.00±0.21	-0.03±0.16		-0.05±0.25	-0.03±0.22	-0.01±0.16	**a**
SF-36: PCS	48.4±8.1	50.2±7.4	52.9±8.3	a	-1.0±6.6	+1.7±6.2	-1.6±5.7	b	-3.2±5.4	-1.3±7.2	-3.1±5.7	
SF-36: MCS	49.4±8.2	52.3±7.8	53.8±6.4	a	-2.3±8.2	-0.6±6.6	-0.3±6.9	a	-2.9±9.0	-2.3±7.4	-1.1±5.6	

Data are presented as means ± standard deviation. CES-D, Center for Epidemiologic Studies Depression Scale; CI, cognitive impairment; EQ-VAS, EuroQol Visual Analogue Scale; EQ-5D, European Quality of Life-5 Dimensions; MCS, Mental Component Scale; PCS, Physical Component Scale; SF-36, 36-Item Short-Form Health Survey.

a = $p < 0.05$ for difference in (change) score between screen positives with CI and screen negatives.
b = $p < 0.05$ for difference in (change) score between screen positives without CI and screen negatives.
c = $p < 0.05$ for difference in (change) score between screen positives with CI and screen positives without CI.

Discussion

Summary

The present study shows that undiagnosed cognitive impairment in people with type 2 diabetes is associated with depressive symptoms and a reduced HRQOL, already prior to the diagnosis. Yet, neither participating in a screening program for cognitive impairment nor disclosure of a diagnosis led to a sustained increase in depressive symptoms. In contrast, we found a decrease in depressive symptoms after visiting the memory clinic in screen positives without cognitive impairment. Most HRQOL scores remained stable over time in all participants.

Interpretation of the results and comparison with existing literature

Depression is about twice as common in people with type 2 diabetes compared to those without.[21] Depression and diabetes are risk factors for one another, and both are associated with an increased risk of cognitive impairment.[22-24] The prevalence of depressive symptoms in our study population was comparable to a Dutch sample of type 2 diabetes patients, aged 55-85 years.[25] In our study 40% of patients with cognitive impairment had a CES-D score ≥16, compared to 11% of the screen negative participants and 22% of the screen positive participants without cognitive impairment. These differences are in line with other studies that assessed depressive symptoms in people with cognitive impairment versus those without cognitive impairment, both in the general population[26] and in patients with type 2 diabetes.[27,28] It is thus clear that depressive symptoms, diabetes and cognitive impairment often co-occur, but their relationship is complex and still not completely understood.[22,29]

A review of both longitudinal and cross sectional studies investigating the association between depression and cognitive impairment found evidence to support the assumption that early life depression can act as a risk factor for cognitive impairment, but also that depression can be a prodrome to cognitive impairment.[29] There are also studies suggesting that the relation between depression and diabetes is bidirectional. The psychological burden of living with a chronic disease could trigger depressive symptoms. Vice versa, depression is associated with a low self-esteem and self-neglect, which could increase the risk of an unhealthy lifestyle and, in turn, the risk of type 2 diabetes.[21] In line with our findings, a previous cross-sectional study in community dwelling patients, not specifically people with diabetes, reported lower HRQOL scores in participants with cognitive impairments compared to those without. Besides, depressive symptoms were strongly associated with both physical, as well as mental HRQOL.[30] Altogether, the psychological wellbeing of our study population at baseline can be considered typical for elderly people with type 2 diabetes who are willing to be screened for cognitive impairment.

Little is known about the impact of screening for cognitive impairment on depressive symptoms and HRQOL, both in people with and in those without diabetes. A systematic review found no studies that addressed the adverse psychological effects from screening for cognitive impairment.[31] A small study published since found no effect of screening on mental health.[32] Qualitative studies indicate that disclosure of a diagnosis of cognitive impairment can be stressful, but it can also end a period of uncertainty and facilitate acceptance and adaptation.[6,33,34] In this study, participating in a screening program for cognitive impairment did not lead to a sustained increase in depressive symptoms. Besides, none of the participants who received a diagnosis of cognitive impairment indicated afterwards that he or she did not want to know it. These findings support the evidence that fear of inducing depressive symptoms or even suicidal thoughts with disclosure of a diagnosis of cognitive impairment is unjustified for people who agree to be screened for cognitive impairment.

Surprisingly, we found that depressive symptoms decreased in screen positive participants without cognitive impairment, particularly in the first months after screening. Besides, their HRQOL scores were relatively high after 6 months of follow-up. It could be that the assessment at the memory clinic and its result, indicating that the patient did not have MCI or dementia, decreased depressive symptoms and had a positive effect on the HRQOL. However, we did not find evidence in literature that depressive symptoms or HRQOL could be improved by reassuring diagnostic results. Another explanation for these findings could be that the depressive symptoms of (a part of) these patients mimicked the symptoms of cognitive impairment during screening. This may have resulted in a high number of depressive symptoms in the group of screen positive participants without cognitive impairment at screening. Either as a result of the natural course or as a result of therapy depressive symptoms may have disappeared during follow-up, with a corresponding improvement of HRQOL scores. Unfortunately, we have not monitored the GP's therapy of the participants' depressive symptoms during the study period.

As discussed in the introduction, the ADA guidelines recommend annual screening for cognitive impairment in older people with diabetes to facilitate patient-centred care aimed at optimising health outcomes and HRQOL.[7] In the present study, HRQOL did not improve after disclosure of a diagnosis of cognitive impairment. In our opinion, optimising HRQOL, should not automatically be interpreted as improvement of HRQOL. Since HRQOL is likely to worsen over the years in the vulnerable group of people with both type 2 diabetes and cognitive impairment,[35,36] less decline in HRQOL might already be positive. However, our findings should be interpreted cautiously, because we were not in the position to compare our results to people who did not participate in our screening program for cognitive impairment and who were unknown with their diagnosis of cognitive impairment.

Strengths and limitations

A strength of this study is the use of a comprehensive neuropsychological assessment at the memory clinic to diagnose cognitive impairment. The timing of the assessments of depressive symptoms and HRQOL gave us the opportunity to assess these outcomes before they were influenced by the screening program, relatively short after the program, and in the long term. The response rate for the questionnaires was high (94% of the surviving participants after six months, 89% after 24 months), especially considering the vulnerability of this patient group.

As shown in Figure 1, the participation rate in the Cog-ID study was relatively low (18%). Most frequently mentioned reasons to decline participation were comorbidities, feeling too old and supposing the procedure will be too burdensome. The results of this study can therefore not be generalised to all older people with diabetes, but only to those who are willing to participate in a screening program for cognitive impairment. This does not hamper its relevance, because diabetes care should be personalised and a screening program for cognitive impairment will never be obligatory. All memory clinic results and treatment advice were sent to the patients' own GP. The GP was asked to discuss the results with the patient; however, we do not know which actions were actually taken and whether these influenced depressive symptoms and HRQOL. Finally, since only three participants were diagnosed with dementia, we cannot draw any firm conclusions on the effect of disclosure of a diagnosis of dementia.

Implications for practice

The high prevalence of depressive symptoms and the reduced HRQOL scores in people with type 2 diabetes identified with cognitive impairment indicate that these patients need extra attention. Both cognitive impairment and depressive symptoms in people with type 2 diabetes are associated with reduced self-management skills and increased diabetes-related complications such as hypoglycaemic events.[1,3,37] Early detection of depression and cognitive impairment can facilitate effective treatment and can help to minimise adverse effects of diabetes management.[38] Ongoing assessment of both cognitive function and depressive symptoms in older people with type 2 diabetes is therefore recommended.[8] Both in case of depressive symptoms and in case of suspicion of cognitive impairment physicians could tailor the patient's diabetes treatment. Older people are likely to benefit from individualised glycaemic goals and avoidance of overtreatment.[8,39] The harms and benefit of diabetes treatment should be balanced to minimise complications and to optimise well-being.[8] With the growing number of old and very old people with type 2 diabetes, such a policy may become increasingly relevant.

Conclusions

Undiagnosed cognitive impairment in patients with type 2 diabetes is associated with a reduced health status and with depressive symptoms. Screening for cognitive impairment in older patients with type 2 diabetes does not seem to affect depressive symptoms or HRQOL negatively. Detection of cognitive impairment identifies a vulnerable patient group that may need extra attention and tailored care.

References

1. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. Diabetes Res Clin Pract 2000;50:203-212
2. Bruce DG, Davis WA, Casey GP et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. Diabetologia 2009;52:1808-1815.
3. Punthakee Z, Miller ME, Launer LJ et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787-793.
4. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429-442.
5. Amjad H, Roth DL, Sheehan OC, Lyketsos CG, Wolff JL, Samus QM. Underdiagnosis of Dementia: an Observational Study of Patterns in Diagnosis and Awareness in US Older Adults. J Gen Intern Med 2018.
6. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Dis Assoc Disord 2009;23:306-314.
7. Connolly A, Gaehl E, Martin H, Morris J, Purandare N. Underdiagnosis of dementia in primary care: variations in the observed prevalence and comparisons to the expected prevalence. Aging Ment Health 2011;15:978-984.
8. Standards of Medical Care in Diabetes-2018 Abridged for Primary Care Providers. Clin Diabetes 2018;36:14-37.
9. Koekkoek PS, Janssen J, Kooistra M et al. Cognitive Impairment in Diabetes: Rationale and Design Protocol of the Cog-ID Study. JMIR Res Protoc 2015;4:e69.
10. Koekkoek PS, Janssen J, Kooistra M et al. Case-finding for cognitive impairment among people with Type 2 diabetes in primary care using the Test Your Memory and Self-Administered Gerocognitive Examination questionnaires: the Cog-ID study. Diabet Med 2016;33:812-819.
11. Brown J, Pengas G, Dawson K, Brown LA, Clatworthy P. Self administered cognitive screening test (TYM) for detection of Alzheimer's disease: cross sectional study. BMJ 2009;338:b2030.
12. Scharre DW, Chang SI, Murden RA et al. Self-administered Gerocognitive Examination (SAGE): a brief cognitive assessment Instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord 2010;24:64-71.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J.Psychiatr Res 12, 189-198. 1975.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. 2000.
15. Winblad B, Palmer K, Kivipelto M et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240-246.
16. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Measurem 1, 385-401. 1977.
17. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S454-S466.
18. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33:AS264-AS279.
19. Rabin R, de CF. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-343.
20. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. Ned Tijdschr Geneeskd 2005;149:1574-1578.
21. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. Lancet Diabetes Endocrinol 2015;3:461-471.
22. Danna SM, Graham E, Burns RJ, Deschenes SS, Schmitz N. Association between Depressive Symptoms and Cognitive Function in Persons with Diabetes Mellitus: A Systematic Review. PLoS One 2016;11:e0160809.
23. Guerrero-Berroa E, Ravona-Springer R, Schmeidler J et al. Depressive Symptoms Are Associated with Cognitive Function in the Elderly with Type 2 Diabetes. J Alzheimers Dis 2018;65:683-692.
24. Zheng F, Zhong B, Song X, Xie W. Persistent depressive symptoms and cognitive decline in older adults. Br J Psychiatry 2018;1-7.
25. Pouwer F, Beekman AT, Nijpels G et al. Rates and risks for co-morbid depression in patients with Type 2 diabetes mellitus: results from a community-based study. Diabetologia 2003;46:892-898.

26. Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology 2007;68:1596-1602.
27. Katon WJ, Lin EH, Williams LH et al. Comorbid depression is associated with an increased risk of dementia diagnosis in patients with diabetes: a prospective cohort study. J Gen Intern Med 2010;25:423-429.
28. Katon WJ, Young BA, Russo J et al. Association of depression with increased risk of severe hypoglycemic episodes in patients with diabetes. Ann Fam Med 2013;11:245-250.
29. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas 2014;79:184-190.
30. Pusswald G, Moser D, Pfluger M et al. The impact of depressive symptoms on health-related quality of life in patients with subjective cognitive decline, mild cognitive impairment, and Alzheimer's disease. Int Psychogeriatr 2016;28:2045-2054.
31. Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;159:601-612.
32. van den Dungen P, Moll van Charante EP, van de Ven PM, van Marwijk HW, van der Horst HE, van Hout HP. Case Finding of Mild Cognitive Impairment and Dementia and Subsequent Care; Results of a Cluster RCT in Primary Care. PLoS One 2016;11:e0156958.
33. Lee SM, Roen K, Thornton A. The psychological impact of a diagnosis of Alzheimer's disease. Dementia (London) 2014;13:289-305.
34. Mormont E, Jamart J, Jacques D. Symptoms of depression and anxiety after the disclosure of the diagnosis of Alzheimer disease. J Geriatr Psychiatry Neurol 2014;27:231-236.
35. Roehr S, Luck T, Pabst A et al. Subjective cognitive decline is longitudinally associated with lower health-related quality of life. Int Psychogeriatr 2017;29:1939-1950.
36. Schunk M, Reitmeir P, Ruckert-Eheberg IM et al. Longitudinal change in health-related quality of life in people with prevalent and incident type 2 diabetes compared to diabetes-free controls. PLoS One 2017;12:e0176895.
37. Pouwer F, Nefs G, Nouwen A. Adverse effects of depression on glycemic control and health outcomes in people with diabetes: a review. Endocrinol Metab Clin North Am 2013;42:529-544.
38. Young-Hyman D, de GM, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial Care for People With Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care 2016;39:2126-2140.
39. Hart HE, Rutten GE, Bontje KN, Vos RC. Overtreatment of older patients with type 2 diabetes mellitus in primary care. Diabetes Obes Metab 2018;20:1066-1069.

Supplementary File 1– Advice provided to the general practitioners of people diagnosed with MCI or dementia

Subject	Advice
HbA1c target	Strict glycaemic control is associated with hypoglycaemic events and associated falls. This risk is even higher in people with cognitive impairment. A beneficial effect of strict glycaemic control HbA1c < 8% (64 mmol/mol) in older people and those with a long duration of diabetes is not proven. An HbA1c target around 8% (64 mmol/mol) is probably best.
Prevention of hypoglycaemic events	The risk of hypoglycaemic events is higher when insulin is used, adequate use of insulin is more difficult than taking oral medication, perhaps you can replace insulin by an oral drug.
Medication adherence	The use of blister packing makes it easier for people with diabetes to use multiple drugs safely, in people with cognitive impairment this might be even more important.
Hyperglycaemia	If HbA1c is >10.4% (90 mmol/mol) and the patient experiences symptoms which could be due to hyperglycaemia you can explore how to support the patient with his or her treatment or to simplify the treatment.
Cardiovascular risk factors	Treat other cardiovascular risk factors according to corresponding guidelines, but take into account that patient's compliance can be affected.
Reminders	Patients may forget instructions and appointments; it might help to provide notes or written instructions.

Supplementary File 2– SF-36 domain scores over time

	Baseline				Mean change after 6 mo follow-up				Mean change after 2 yr follow-up		
SF-36 domains:	Screen positive and CI (n=39)	Screen positive, no CI (n=56)	Screen negative (n=84)		Screen positive and CI (n=39)	Screen positive, no CI (n=56)	Screen negative (n=84)		Screen positive and CI (n=39)	Screen positive, no CI (n=56)	Screen negative (n=84)
Physical functioning	52.4 ±28.1	60.5±24.0	72.0±25.1	a, b	-0.4±13.4	+2.3±15.5	-7.2±14.0	b	-8.2±16.9	-8.2 ±23.4	-10.4 ±14.2
Role limitations due to physical problems	50.6±40.8	66.9±39.2	75.0±36.6	a	-4.4±31.1	-1.0±54.1	-8.2 ±35.0		-9.2±36.8	-17.4±45.0	-16.4±38.3
Bodily Pain	69.2±26.0	71.7±25.1	75.9±22.1		-5.7±20.8	+7.7±24.2	-0.2 ±18.9	c	-5.0 ±24.7	-1.8 ±26.6	-3.7 ±21.1
General Health	54.9±17.6	56.0±16.8	61.5±19.8		-1.9±32.3	+4.3±14.9	-1.3±17.1		-5.3 ±15.9	-0.1±19.6	-2.7±14.1
Vitality	57.8±22.3	63.5±17.6	71.4±16.9	a	-4.5±13.6	-0.3±16.6	-3.8 ±16.9		-7.0 ±19.3	-6.5 ±20.0	-7.3 ±13.4
Social functioning	73.7±19.4	78.1±21.0	84.4±16.5	a	-5.4±15.8	+0.9 ±21.3	-1.4±20.3		-10.3±22.7	-12.0±28.3	-6.3±20.9
Role limitations due to emotional problems	66.7±40.8	80.0±36.1	87.6±27.9	a	-2.0±43.4	+0.7 ±41.8	-3.5±34.4		-8.0±45.1	-7.4±38.2	-3.9±24.8
Mental Health	74.1±16.1	80.3±14.7	82.2±12.9	a	-6.8±15.1	-0.2±14.8	-0.6 ±10.7	a	-3.0 ±15.9	-0.1 ±19.6	-2.7 ±14.1

Data are presented as means ± standard deviation.
a = p < 0.05 for difference in (change) score between screen positives with CI and screen negatives.
b = p < 0.05 for difference in (change) score between screen positives without CI and screen negatives.
c = p < 0.05 for difference in (change) score between screen positives with CI and screen positives without CI.

CHAPTER 4

People with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often: observations from the Cog-ID study

Janssen J, Koekkoek PS, Biessels GJ, Kappelle LJ, Rutten GEHM, on behalf of the Cog-ID study group

Diabetology & Metabolic Syndrome 2019;11:21

Abstract

Background
Patients with type 2 diabetes have an increased risk of cognitive impairment which can lead to impaired diabetes self-management and an increased risk of diabetes-related complications. Routine screening for cognitive impairment in elderly patients with type 2 diabetes is therefore increasingly advocated. The aim of this study is to investigate whether people with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often than patients not suspected of cognitive impairment.

Methods
People with type 2 diabetes ≥70 years were screened for cognitive impairment in primary care. Diagnoses in screen positives were established at a memory clinic. Information about acute health care use was collected for 2 years prior to and 2 years after screening and compared to screen negatives.

Results
154 participants (38% female, mean age 76.7±5.2 years, diabetes duration 8.7±8.2 years) were included, 37 patients with cognitive impairment, 117 screen negatives. A higher percentage of participants with cognitive impairment compared to screen negative patients used acute health care services; this difference was significant for general practitioner's out of hours services (56% versus 34% used this service over four years, p=0.02). The mean number of acute health care visits was also higher in those with cognitive impairment than in screen negatives (2.2±2.8 versus 1.4±2.2 visits in 4 years, $p<0.05$; 1.4±2.2 versus 0.7±1.5 visits in 2 years after screening, p=0.03). Factors that could have played a role in this increased use of acute health care services were a low educational level, the presence of depressive symptoms (CES-D score ≥ 16), self-reported problems in self-care and self-reported problems in usual activities.

Conclusions
People with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often.

Background

Patients with type 2 diabetes have an increased risk of cognitive impairment and dementia.[1,2] Cognitive impairment, already in its early stages, can lead to impaired diabetes self-management.[3,4] Patients with diabetes and cognitive impairment have increased risks of hypoglycemic events, cardiovascular events and even death compared to those without cognitive impairment.[5-7] In addition, cognitive impairment in diabetes is associated with a reduced health status and more depressive symptoms.[8] Therefore, recent guidelines recommend individualized diabetes treatment for patients with cognitive impairment.[9]

Since cognitive impairment often remains unrecognized,[10-12] routine screening for cognitive impairment in elderly patients with type 2 diabetes is increasingly advocated.[9] The argument is that routine screening may identify patients with cognitive impairment who might then benefit from a personalized intervention. It is however unknown how often people with type 2 diabetes and cognitive impairment identified through screening (screen-detected cognitive impairment) experience acute health problems (e.g. problems that require the use of acute health care services or falls) and if this is indeed more often than patients without cognitive impairment.

The Cognitive Impairment in Diabetes (Cog-ID) study aimed to establish a primary care based screening strategy to detect cognitive impairment.[13] The study showed that self-administered cognitive screening tests can be used for this purpose and that the Self-Administered Gerocognitive Examination (SAGE) had the best diagnostic accuracy (negative predictive value of 85%; positive predictive value of 40%) with a memory clinic established diagnosis as reference standard. Because health outcomes were recorded for the 2 years prior to and after screening, the Cog-ID study is ideally suited to investigate whether people with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often and if they report more falls than people without cognitive impairment.

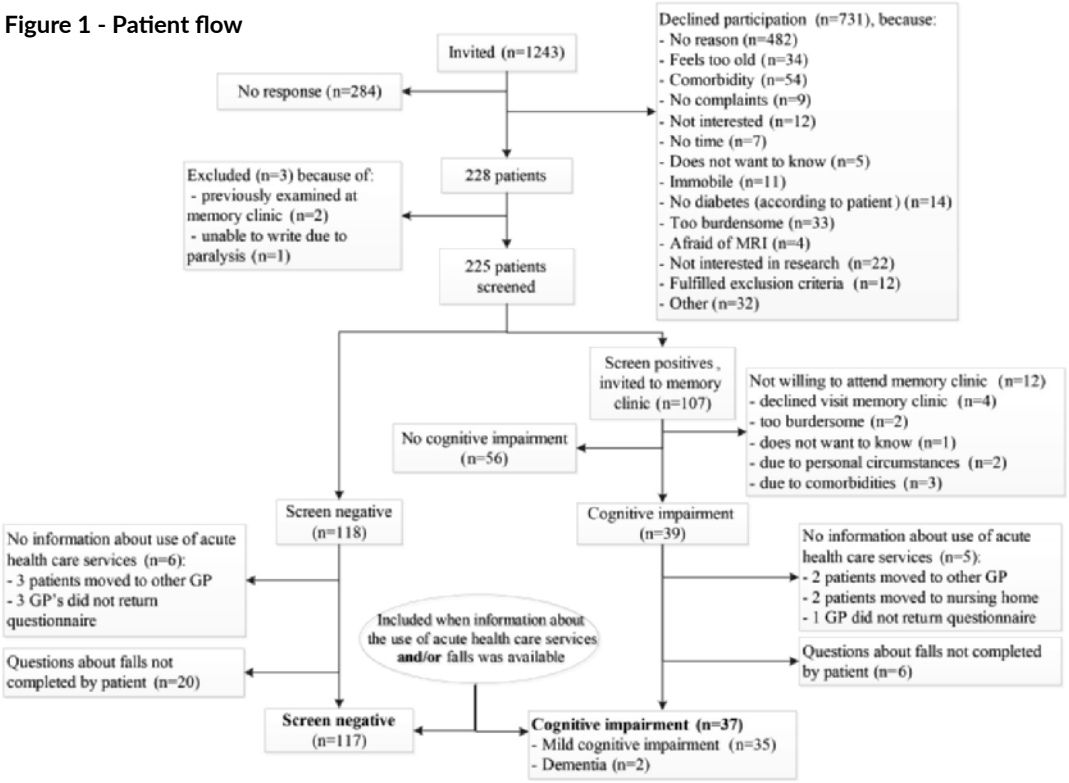
Methods

Design

The design of the Cog-ID study has been described in detail elsewhere.[13] In brief, people ≥70 years with type 2 diabetes were invited to participate by their general practitioner (GP) in the period August 2012 to September 2014. People with a previous diagnosis of dementia, a previous memory clinic evaluation or the inability to write or read Dutch were excluded. Written informed consent was obtained from all participants.

Participants were first visited at home by a research physician who screened for cognitive impairment with two self-administered cognitive tests (the SAGE and the 'Test Your Memory' (TYM)), the Mini-Mental state examination (MMSE) and a structured interview. People who were not suspected of cognitive impairment based on this screening visit are referred to as 'screen negatives' and those suspected of cognitive impairment as 'screen positives'. Screen positives received a standardized memory clinic evaluation as reference standard. Screen positives who fulfilled criteria for mild cognitive impairment (MCI) or dementia were subsequently diagnosed with cognitive impairment. The current study includes the screen positive patients diagnosed with cognitive impairment and all screen negative patients (Figure 1).

Figure 1 - Patient flow



The GPs of patients diagnosed with cognitive impairment at the memory clinic received information about the diagnosis, accompanied by a letter with a not binding advice on how to tailor patient's diabetes care in light of the cognitive problems (Additional file 1).

Use of acute health care services

Short questionnaires were sent to all general practices to collect information about the use of acute health care services, defined as any of the following: unplanned hospitalizations, emergency room visits and visits to GP out of hours services (between 5.00 p.m. and 8.00 a.m.). Consecutive acute health care visits within 48 hours for the same health problem were counted as one acute health care visit, e.g. when patients consulted the emergency room and were hospitalized one or two days afterwards. Calls to the GP out of hours services were not included. Hospitalizations were categorized as 'unplanned' (= acute) and 'other' (= not acute), as shown in Additional file 2. Unplanned hospitalizations were defined as 'an unexpected admission for the management of a disease or treatment-related event that cannot be controlled in the outpatient setting'. Patients who died within 24 months after screening were not excluded for the analysis, their use of acute health care services was registered until the day of their death.

Falls

Twenty-four months after the home screening visit participants received a follow-up questionnaire with the following questions, namely 1. 'Did you fall in the past year?' (yes or no) and 2. 'If yes, how many times did you fall in the past year?'. We chose to ask patients only about falls in the past year and not about falls in the past 2 years to minimize the risk of memory bias. Falls in the years prior to screening were not registered.

General practitioner questionnaires

To evaluate if and how GPs changed their patient's treatment after a diagnosis of cognitive impairment, we sent a questionnaire to the GPs with the following questions: 1. 'Did the result of the memory clinic came as a surprise for you?' (yes/no); 2. 'Did you change your patient's diabetes treatment as a result of the diagnosis of cognitive impairment?' (yes/no and open field) and 3. 'Did the results of the screening and the possible diagnosis of cognitive impairment have implications for the patient's treatment, that are not related to their diabetes?' (yes/no and open field).

Other measures

During the (screening) visit at home by the research physician, participants also completed questionnaires about depressive symptoms and health related quality of life (HRQOL). Depressive symptoms were assessed with the Centre for Epidemiologic Studies Depression Scale (CES-D). A score ≥16 is generally accepted as the cut-off score for the presence of depression. The European Quality of Life-5 Dimensions (EQ-5D) covers five dimensions of HRQOL: mobility, self-care, daily activities, pain/discomfort and anxiety/

depression.

Information about age, sex and educational level was gathered during the home screening visit. Information about participant's medication use, medical history, diabetes duration, BMI, MDRD and HbA1c was collected by the researchers from the participant's GP electronic medical record. HbA1c and MDRD values closest to the screening visit were taken, this could be up to 6 months prior or after the visit.

Statistical analysis
Our primary aim was to describe the differences between people with and without screen-detected cognitive impairment with regard to the use of acute health care services and not to model determinants of acute health care use. The proportion of patients with at least one time use of an acute health care service was compared between those with screen-detected cognitive impairment and screen negative patients with a Chi-square test. The mean number of acute health care visits was compared between the groups with a Mann-Whitney-U-test. The same tests were used to investigate fall accidents.

In addition, the proportion of patients with at least one time use of an acute health care service was compared between the years prior to and the years after screening using a Mc Nemar test, for each of the groups separately. The mean number of acute health care visits was compared between the years prior to and the years after screening with a Wilcoxon Signed-Rank-test, for each of the groups separately. The Mann-Whitney-U-test was used to test whether this increase or decrease in mean number of acute health care visits differed between the groups.

To explore whether other factors than cognitive impairment could explain between group differences, we looked whether the use of acute health care services differed between groups that were stratified based on baseline characteristics with an unequal distribution between the groups.

A p-value ≤ 0.05 was considered significant. All statistical analyses were performed using IBM SPSS statistics V.21.

Results

Study population

Of the 1243 patients eligible for the COG-ID study, 731 declined participation and 284 did not respond to the invitation (Figure 1). Of the 225 patients who participated and were screened for cognitive impairment, 118 were screen negative. Of the 107 patients who were screen positive, 39 were diagnosed with cognitive impairment at the memory clinic. Of the remaining screen positives, 12 were not willing to attend the memory clinic and 56 had no cognitive impairment compatible with MCI or dementia criteria; these patients were not included in the current analysis. Three patients (two with cognitive impairment, one screen negative patient) with missing information about both the use of acute heath care services and about falls were not included in the current analyses (Figure 1). The remaining 37 patients with cognitive impairment and 117 screen negative patients were included in this study, resulting in a study population of 154 individuals. Their baseline characteristics are summarized in Table 1.

Mean age was 76.7 ± 5.2 years, 58 (38%) were female and 57 (37%) were living alone. The mean duration of diabetes was 8.7 ± 8.2 years, mean HbA1c level 52.2 ± 9.7 mmol/l (6.9 ± 0.9%) and 30 (20%) of the patients used insulin. A higher percentage of people with screen-detected cognitive impairment had a low educational level, depressive symptoms, problems with self-care and problems with usual activities. In addition, this group had also lower MMSE, TYME and SAGE scores compared to the screen-negative participants (Table 1). Two (5%) patients with cognitive impairment and six (5%) of the screen negative patients died within two years after screening.

Table 1 - Characteristics of participants at time of screening

	Total study population (n=154)	Screen-detected cognitive impairment (n=37)	Screen negatives (n=117)
Age (years)	76.7 ± 5.2	77.8 ± 5.6	76.4 ± 5.0
Female sex	58 (38%)	15 (41%)	43 (37%)
Living alone	57 (37%)	10 (27%)	47 (40%)
Educational level[a]	5 (4-6)	4 (2-5)*	5 (5-6)*
Low educational level (Verhage scale 1 - 4)	46 (30%)	22 (60%)*	24 (20%)*
Diabetes duration (years)	8.7 ± 8.2	10.6 ± 8.1	8.1 ± 8.1
HbA1c (mmol/mol)	52.2 ± 9.7	53.8 ± 9.8	51.7 ± 9.6
HbA1c (%)	6.9 ± 0.9	7.1 ± 0.9	6.9 ± 0.9
Use of Metformin, yes	104 (78%)	22 (76%)	82 (80%)
Use of insulin, yes	30 (20%)	9 (24%)	21 (18%)
Use of Sulfonylurea, yes	45 (29%)	9 (24%)	36 (31%)
Use of lipid lowering drugs, yes	122 (80%)	29 (78%)	93 (81%)
Diabetic neuropathy, yes	15 (10%)	5 (14%)	10 (9%)
Diabetic retinopathy, yes	11 (7%)	4 (11%)	7 (6%)
MDRD	67.9 ± 19.2	64.9 ± 20.7	71.9 ± 18.5
BMI (kg/m^2)	28.6 ± 4.4	29.2 ± 4.8	28.4 ± 4.3
Systolic blood pressure (mm Hg)	139.8 ±17.4	140.4 ± 13.3	139.6 ± 18.6
Diastolic blood pressure (mm Hg)	75.4 ± 11.4	76.0 ± 12.1	75.3 ± 11.2
MMSE	28.4 ± 2.0	26.4 ± 3.0*	29.0 ± 1.1*
TYM score	42.4 ± 6.4	35.4 ± 8.8*	44.5 ± 2.6*
SAGE score	17.1 ± 4.1	11.5 ± 4.4*	18.6 ± 2.2*
EQ5D mobility, any problems (%)	83 (55%)	24 (65%)	59 (51%)
EQ5D self care, any problems (%)	17 (11%)	8 (22%)*	9 (8%)*
EQ5D usual activities, any problems (%)	49 (32%)	22 (59%)*	27 (23%)*
CES-D ≥ 16	27 (18%)	13 (36%)*	14 (12%)*

Data are presented as means (± standard deviation), median (interquartile range), or number and proportion in %. BMI, body mass index. CES-D, Centre for Epidemiologic Studies Depression Scale. EQ5D, EuroQol five-dimension scale. MDRD, Modification of Diet in Renal Disease. MMSE, Mini-Mental state examination. TYM, Test Your Memory, SAGE, Self-administered gerocognitive Examination.

** p ≤0.05 for comparison between the groups (chi-square test /t-test).*

[a]Educational level is classified by the Dutch Verhage scale [24]; a seven point rating scale ranging from 1 (which equals a level of less than six years of elementary school) to 7 (equals a finished training at a university or technical college)

Use of acute health care services
As shown in Figure 2, more participants with cognitive impairment than screen negative patients used acute health care services, this difference between the groups was only significant for general practitioners out of hours services (56% versus 34% used this service over 4 years, p=0.02).

The mean number of all acute health care visits and unplanned hospital admissions was significantly higher in those with cognitive impairment than in screen negative patients, both in the total four year period (2.2 ± 2.8 versus 1.4 ± 2.2, p<0.05) and in the two years after screening (1.4 ± 2.2 versus 0.8 ± 1.4, p=0.03), as depicted in Table 2. Again, this was most evident for visits to GP out of hours services. The mean number of GP out of hours visits was significantly higher in patients with cognitive impairment than in screen negative patients (1.4 ± 1.8 versus 0.7 ± 1.3 visits over the total four years, p=0.01; 0.8 ± 1.4 versus 0.3 ± 0.8 over the two years after screening, p=0.03).

Comparing the years after to the years prior to screening for each of the groups separately, there was no significant increase or decrease in the use of acute health care services. These changes (increase or decrease) in the use of acute health care services did also not differ significantly between the two groups (Table 2 and Figure 3). Table 3 shows that people with or without cognitive impairment and a relatively low educational level, or with self-reported problems in self-care, or with self-reported problems in usual activities or with depressive symptoms all tend to use acute health care services more often.

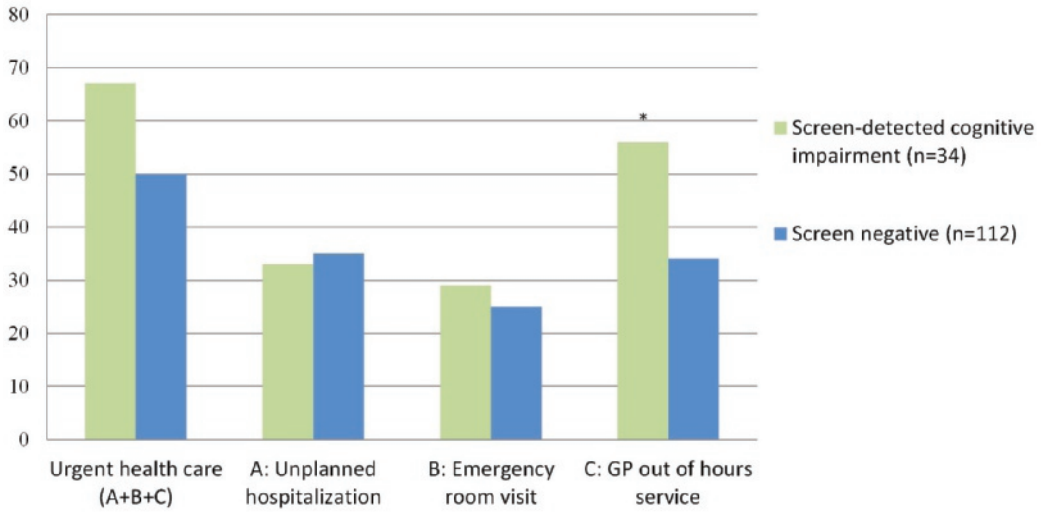
Falls
Twelve patients with cognitive impairment (36%) and 24 (25%) screen negative people reported at least one fall accident in the 12 to 24 months after screening (p = 0.186). The mean number of falls in that period did not differ between both groups (1.9 ± 4.6 versus 0.7 ± 1.7, p = 0.176).

Table 2 – Mean number of acute health care visits

	Screen-detected cognitive impairment (n=34)			Screen negative (n=112)		
	4 year period	2 yrs. prior	2yrs. after	4 year period	2 yrs. prior	2yrs. after
Acute health care services (A+B+C)	2.2±2.8*	0.8±1.2	1.4±2.2*	1.4±2.2*	0.7±1.2	0.7±1.5*
A: Unplanned hospitalization	0.6±1.2	0.2±0.6	0.5±1.0	0.6±1.1	0.3±0.6	0.3±0.8
B: Emergency room visit	0.6±1.1	0.2±0.7	0.4±0.7	0.4±0.8	0.2±0.6	0.2±0.5
C: GP out of hours service	1.4±1.8*	0.6±0.9	0.8±1.4*	0.7±1.3*	0.4±0.8	0.3±0.8*

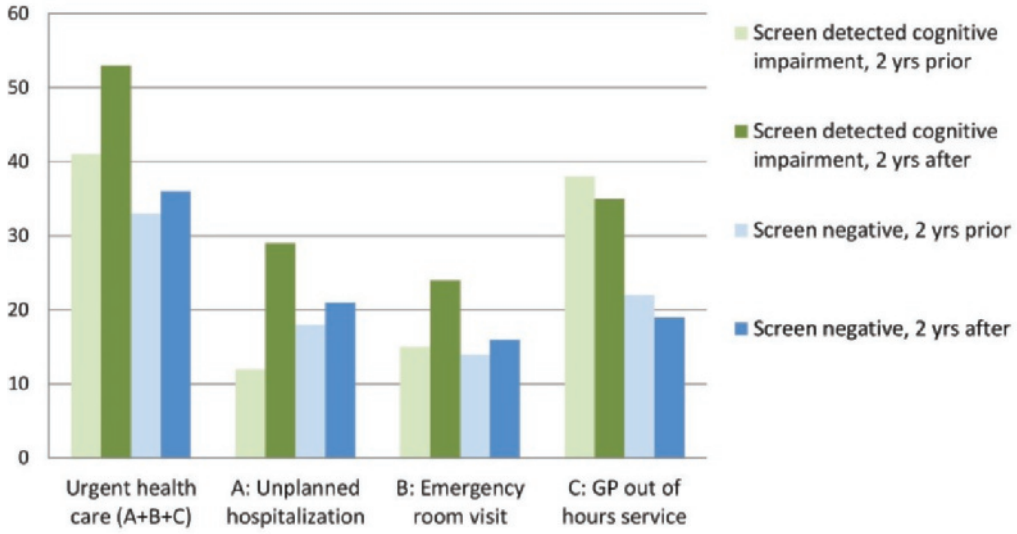
** p ≤ 0.05 for difference in mean number of acute health care visits between screen negatives and those with screen-detected cognitive impairment. GP, general practitioner.*

Figure 2 – Percentage of patients that used the acute health care service at least once in four years.



** p ≤ 0.05 for the difference in proportion of patients with at least one time use of an acute health care service. GP, General practitioner.*

Figure 3 – Percentage of patients that used the acute health care service at least once in the two years prior and in the two years after screening.



GP, General practitioner.

Table 3 – Living situation, educational level, EQ5D and CES-D and the use of acute health care services in the total study population

	Living situation		Educational level		EQ5D self-care		EQ5D usual activities		CES-D	
	Alone (n=54)	With others (n=92)	1-4** (n=43)	5-7* (n=103)	Any problem (n=13)	No problem (n=132)	Any problem (n=45)	No problem (n=101)	= > 16 (n=24)	<16 (n=121)
N(%) people that used GP out of hour services at least once in 4 years	25 (46%)	32 (35%)	21 (49%)	36 (35%)	8 (62%)	48 (36%)	24 (53%)	33 (33%)	13 (54%)	43 (36%)
Mean (± SD) number of visits to GP out of hour services in 4 years	0.8 ± 1.3	0.8 ± 1.6	1.2 ± 2.2	0.5 ± 0.9	1.5 ± 1.9	0.8 ± 1.4	1.4 ± 2.1	0.6 ± 1.0	1.5 ± 2.0	0.7 ± 1.3
Mean number (± SD) of acute health care visits in 4 years	1.6 ± 1.8	1.5 ± 2.6	2.3 ± 3.4	1.2 ± 1.7	2.5 ± 2.3	1.5 ± 2.4	2.5 ± 3.0	1.1 ± 1.9	2.9 ± 3.4	1.3 ± 2.1

Data are presented as means (± standard deviation) or number and proportion in %. GP, general practitioner. CES-D, Centre for Epidemiologic Studies Depression Scale.

*EQ5D, EuroQol five-dimension scale. *Educational level is classified by the Dutch Verhage scale;[24] a seven point rating scale ranging from 1 (which equals a level of less than six years of elementary school) to 7 (equals a finished training at a university or technical college).*

General practitioner questionnaires

In eleven (28%) of the 39 patients with screen-detected cognitive impairment their GP had not suspected the diagnosis. Only two (5%) GPs changed their patient's diabetes treatment as a result of the diagnosis of cognitive impairment (one increased the HbA1c target, one lowered the insulin dosage). In seven (18%) cases the diagnosis had other implications (treatment discussed with patient, situation at home discussed with daughter, more care in nursing home, close monitoring of the course of cognitive function (2x) and being more alert to problems at home (2x)).

Discussion

This study shows that patients with cognitive impairment, detected during a screening program in individuals with diabetes ≥70 years, more often use acute health care services than patients without cognitive impairment. These findings are in line with previous studies that demonstrate that patients with both type 2 diabetes and cognitive impairment experience more adverse health outcomes compared to patients without cognitive impairment.[5-8] The current study shows that this increased risk is already there when patients are diagnosed with cognitive impairment by screening, even if people are diagnosed with mild cognitive impairment and not with dementia.

We explored which factors could have played a role, besides cognitive impairment. Living alone may be a reason for people not being able to visit acute health care services. Ten out of 37 (27 %) participants with screen-detected cognitive impairment were living alone, compared to 47 out of 117 (40%) of the screen negatives. Table 3 shows that, in our total study population, living alone was not associated with a reduced number of visits to acute health care services and is therefore unlikely to account for the differences between the screen negatives and the screen positives. This finding is in line with a recent study among 1447 older people in the UK; those living alone had a higher probability of utilising emergency department and general practitioner services.[14]

Depressive symptoms, problems with self-care and problems with usual activities were more common in those with cognitive impairment compared to the screen negatives (Table 1). Table 3 shows that both people with and without cognitive impairment but with the above mentioned problems have an increased risk of using acute health care services. This is not an unexpected finding, because these factors are interrelated with cognitive impairment. A study among 683 elderly home care recipients in Canada found significant associations between poor self-rated health, greater functional dependency and acute health care use.[15] Cognitive impairment can cause depressive symptoms and problems in self-care and usual activities, which could lead to impaired (diabetes) self-management skills and to an increased need for acute health care. Depressive symptoms, problems with

self-care and problems with usual activities are therefore possible mediating factors in the association between cognitive impairment and use of acute health care services.

Low educational level is a known risk factor for cognitive impairment.[16] In addition, Table 3 shows that people with a low educational level in our study population tend to use acute health care services more often. It is therefore possible that educational level accounts for part of the differences between people with and without screen detected cognitive impairment in the utilization of acute health care services. This conclusion does not decrease the relevance of our findings, because in any case detection of cognitive impairment will identify a vulnerable patient group that may need extra attention and tailored care.

The use of acute health care services and falls are important health outcomes with a considerable impact on health expenditures, morbidity and patients' well-being.[17-19] Therefore, our results are also relevant in light of recent American Diabetes Association (ADA) guidelines which recommend to screen elderly patients with type 2 diabetes for cognitive impairment.[9] Taken together these findings confirm the vulnerability of patients with type 2 diabetes and cognitive impairment and emphasize the importance of an individualized treatment strategy for these people.

Of note, most GPs did not adjust the diabetes treatment in patients with cognitive impairment, despite our written advice. It should be acknowledged, however, that formal guidance from organizations of health care professionals on how to manage diabetes in people with cognitive impairment was largely published after our study was performed[9]. A more active intervention is probably warranted to ensure that these guidelines are put to practice. Important points are avoiding overly intensive diabetes management and using therapies with a low risk of hypoglycaemia, as recommended by both the ADA and the Dutch College of General Practitioners.[9,20] In clinical practice, de-intensifying glucose lowering treatment is not yet successfully implemented.[21,22]

A strength of this study is the use of a comprehensive neuropsychological assessment at the memory clinic to diagnose cognitive impairment. The response rate for the follow-up questionnaires was high; 93% of the general practitioners completed the questionnaire about acute health care visits of their patient and 83% of the participants reported about their falls after 24 months. Some limitations should also be mentioned. As shown in Figure 1, the COG-ID participation rate was low (18%). The results of this study can therefore not be generalized to all older people with type 2 diabetes, only to those willing to participate in a screening program for cognitive impairment. In addition, we may have missed more differences between the two groups since the screening tests used in the COG-ID study do not have a sensitivity of 100%. We may assume that the group of screen negative patients included about 16% of patients with cognitive impairment.[23]

However, we opted to use all screen negatives as a comparison group because a screening program for cognitive impairment in primary care will also result in false negative outcomes. Furthermore, it is possible that missing data was related to worse health status and subsequently more use of acute health services (e.g. medical records were inaccessible when the patient moved to a nursing home). This might have caused a slight underestimation of the use of acute health care in the group with most missing data, i.e. those with cognitive impairment. We could not assess the effect of the screening program and a subsequent diagnosis of cognitive impairment on acute health care use and falls, because it was not possible to compare the patients diagnosed with cognitive impairment to patients with cognitive impairment but without a diagnosis. At last, it would have been interesting to compare the number of hypoglycaemic events between the groups, however this data was not available.

Conclusions

This study shows that elderly patients with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often than patients who screened negative. These findings confirm that screening for cognitive impairment can identify a vulnerable group of patients that might benefit from more tailored care.

References

1. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J Diabetes Investig 2013;4:640-650.
2. Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. Arch Neurol 2007;64:570-575.
3. Feil DG, Zhu CW, Sultzer DL. The relationship between cognitive impairment and diabetes self-management in a population-based community sample of older adults with Type 2 diabetes. J Behav Med 2012;35:190-199.
4. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. Diabetes Res Clin Pract 2000;50:203-212.
5. Bruce DG, Davis WA, Casey GP et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. Diabetologia 2009;52:1808-1815.
6. Cukierman-Yaffe T, Gerstein HC, Miller ME et al. The Relationship Between the Score on a Simple Measure of Cognitive Function and Incident CVD in People With Diabetes: A Post Hoc Epidemiological Analysis From the ACCORD-MIND Study. J Clin Endocrinol Metab 2017;102:3218-3225.
7. Punthakee Z, Miller ME, Launer LJ et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787-793.
8. Koekkoek PS, Biessels GJ, Kooistra M, Janssen J, Kappelle LJ, Rutten GE. Undiagnosed cognitive impairment, health status and depressive symptoms in patients with type 2 diabetes. J Diabetes Complications 2015;29:1217-1222.
9. American Diabetes Association. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. Clin Diabetes 2017;35:5-26.
10. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Dis Assoc Disord 2009;23:306-314.
11. Kaduszkiewicz H, Zimmermann T, Van den BH et al. Do general practitioners recognize mild cognitive impairment in their patients? J Nutr Health Aging 2010;14:697-702.
12. van den Dungen P, Moll van Charante EP, van de Ven PM et al. Dutch family physicians' awareness of cognitive impairment among the elderly. BMC Geriatr 2015;15:105.
13. Koekkoek PS, Janssen J, Kooistra M et al. Cognitive Impairment in Diabetes: Rationale and Design Protocol of the Cog-ID Study. JMIR Res Protoc 2015;4:e69.
14. Dreyer K, Steventon A, Fisher R, Deeny SR. The association between living alone and health care utilisation in older adults: a retrospective cohort study of electronic health records from a London general practice. BMC Geriatr. 2018; 18: 269.
15. Paddock K, Hirdes JP. Acute health care service use among elderly home care clients. Home Health Care Serv Q. 2003;22(1):75-85.
16. Exalto LG, Biessels GJ, Karter AJ, at al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. Lancet Diabetes Endocrinol. 2013 Nov; 1(3): 183–190.
17. Heinrich S, Rapp K, Rissmann U, Becker C, Konig HH. Cost of falls in old age: a systematic review. Osteoporos Int 2010;21:891-902.
18. Paddock K, Hirdes JP. Acute health care service use among elderly home care clients. Home Health Care Serv Q 2003;22:75-85.
19. Vinik AI, Vinik EJ, Colberg SR, Morrison S. Falls risk in older adults with type 2 diabetes. Clin Geriatr Med 2015;31:89-99, viii.
20. Barents ESE Bilo HJG. The Dutch College of General Practitioners Standard on type 2 diabetes mellitus. 2018.
21. Doucet JA, Bauduceau B, Le Floch JP, Verny C. Medical treatments of elderly, French patients with type 2 diabetes: results at inclusion in the GERODIAB Cohort. Fundam Clin Pharmacol 2016;30:76-81.
22. Hart HE, Rutten GE, Bontje KN, Vos RC. Overtreatment of older patients with type 2 diabetes mellitus in primary care. Diabetes Obes Metab 2018;20:1066-1069.
23. Koekkoek PS, Janssen J, Kooistra M et al. Case-finding for cognitive impairment among people with Type 2 diabetes in primary care using the Test Your Memory and Self-Administered Gerocognitive Examination questionnaires: the Cog-ID study. Diabet Med 2016;33:812-819.
24. Verhage F. Intelligentie en leeftijd. Groningen:Rijksuniversiteit. Proefschrift.1964.

Additional file 1

Table – Advice provided to the general practitioners of people diagnosed with MCI or dementia

Subject	Advice
HbA1c target	Strict glycaemic control is associated with hypoglycaemic events and associated falls. This risk is even higher in people with cognitive impairment. A beneficial effect of strict glycaemic control HbA1c < 8% (64 mmol/mol) in older people and those with a long duration of diabetes is not proven. An HbA1c target around 8% (64 mmol/mol) is probably best.
Prevention of hypoglycaemic events	The risk of hypoglycaemic events is higher when insulin is used, adequate use of insulin is more difficult than taking oral medication, perhaps you can replace insulin by an oral drug.
Medication adherence	The use of blister packing makes it easier for people with diabetes to use multiple drugs safely, in people with cognitive impairment this might be even more important.
Hyperglycaemia	If HbA1c is >10.4% (90 mmol/mol) and the patient experiences symptoms which could be due to hyperglycaemia you can explore how to support the patient with his or her treatment or to simplify the treatment.
Cardiovascular risk factors	Treat other cardiovascular risk factors according to corresponding guidelines, but take into account that patient's compliance can be affected.
Reminders	Patients may forget instructions and appointments; it might help to provide notes or written instructions.

Additional file 2

Table – Classification of unplanned and other hospitalizations

Unplanned hospitalizations	N	Other hospitalizations	N
Asthma/COPD/pneumonia/dyspnoe	**13**	Surgery/procedure because of malignancy	**12**
Abdominal pain/obstipation/diarrhoea/ileus	**9**	Cataract surgery	**10**
ACS	**5**	Arthrosis (joint replacement or arthrodesis)	**10**
Atypical thoracic pain	**4**	Insertion or replacement of ICD	**8**
Arrhythmia	**4**	Cholecystectomy	**3**
Observation/social indication after a fall	**4**	PTA for intermittent claudication	**2**
Diverticulitis	**3**	Aortic valve replacement	**2**
Fracture of hip or vertebra	**3**	Hand surgery (Dupuytren, trigger finger)	**2**
Urinary tract infection	**3**	CT abdomen	**2**
Cholecystitis	**3**	HNP surgery	**2**
Decompensatio cardis	**3**	Vitrectomy	**1**
Electrocardioversion for AF	**3**	Meniscus surgery	**1**
Less responsive	**2**	Maxillary surgery	**1**
CVA/SAB	**2**	Sinus surgery	**1**
Hypo/hyper kalium	**2**	Circumcision	**1**
Allergic reaction	**2**	Implementation ECG log	**1**
Gastrointestinal bleeding	**2**	Coronary Angiography	**1**
Infection abdominal wall	**2**	Surgery cyst dig I	**1**
Dysregulation DM	**1**		
Pain hip/leg	**1**		
Head trauma	**1**		
Haematuria due to high INR	**1**		
Infected kidney cyst	**1**		
Analysis of falls, fatigue and weight loss	**1**		
Leaking ileostomy	**1**		
Altitude Sickness	**1**		
Suspected arthritis	**1**		
Infection eci	**1**		
Surgery biceps rupture	**1**		
PCI	**1**		

PART 2

Etiology and prevention of cognitive impairment in type 2 diabetes

CHAPTER 5

Rationale and design of the CAROLINA®-cognition substudy: a randomised controlled trial on cognitive outcomes of linagliptin versus glimepiride in patients with type 2 diabetes mellitus

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Abstract

Background
Type 2 diabetes mellitus is associated with cognitive dysfunction and an increased risk of dementia. Linagliptin is a glucose-lowering agent of the dipeptidyl peptidase-IV (DPP-IV) inhibitor class that is of particular interest for the prevention of accelerated cognitive decline, because it may potentially benefit the brain through pleiotropic effects, beyond glucose lowering. This paper presents the design of a study that aims to establish if linagliptin is superior to the sulfonylurea glimepiride in the prevention of accelerated cognitive decline in patients with type 2 diabetes mellitus.

Methods
The cognition substudy is an integral part of the ongoing event-driven, randomised, double blind CARdiOvascular safety of LINAgliptin (CAROLINA®) trial, which evaluates the effect of treatment with linagliptin versus glimepiride on cardiovascular outcomes. CAROLINA® includes patients with type 2 diabetes mellitus with sub-optimal glycaemic control at elevated cardiovascular risk. The substudy will evaluate patients randomised and treated who have a baseline Mini Mental State Examination (MMSE) score ≥ 24, documented years of formal education with at least one valid cognitive assessment at baseline and during follow-up. The primary cognitive outcome is the occurrence of accelerated cognitive decline at the end of follow-up. The two treatment groups will be compared by using a logistic regression. Accelerated cognitive decline is defined as a rate of cognitive decline that falls at or below the 16th percentile of decline for the whole cohort on either the MMSE or a combined score of the trail making and verbal fluency test. Potential confounders are taken into account at an individual patient level, using a regression based index.

Discussion
Between December 2010 and December 2012, 6042 patients were randomised and treated with either linagliptin (5mg) or glimepiride (1-4mg) once daily in the CAROLINA® study. Cognitive tests were conducted in nearly 4500 participants at baseline and are scheduled for two subsequent assessments, after 160 weeks of follow-up and the end of follow-up. This substudy of the ongoing CAROLINA® trial will establish if linagliptin is superior to glimepiride in the prevention of accelerated cognitive decline in patients with type 2 diabetes mellitus. Final results are expected in 2020.

Background

Type 2 diabetes mellitus (T2DM) is a rising public health concern with over 400 million cases worldwide in 2015 and an estimated number of over 600 million cases by 2040.[1] Prevention of long-term complications is a major focus of diabetes treatment. In this respect, cognitive dysfunction and dementia are diabetes-associated complications that receive increasing attention.[2,3] It is well recognised that the risk of dementia is increased in people with T2DM.[4] A recent meta-analysis evaluated 20 studies reporting on the risk of any type of dementia, 20 on Alzheimer's disease and 13 on vascular dementia (VaD), including a total of 1,148,041 participants, of whom 89,708 had diabetes. The pooled relative risk (95% CI) for dementia in people with diabetes was 1.73 (1.65–1.82), for Alzheimer's disease 1.56 (1.41–1.73) and for VaD 2.27 (1.94–2.66)[5] as compared to people without. In addition, diabetes is associated with more subtle cognitive changes, that are referred to as diabetes-associated cognitive decrements.[2,3]

Accelerated cognitive decline is a cause for concern in patients with T2DM, yet no preventive treatment has been established. Lifestyle, vascular, and diabetes-specific risk factors present many promising targets for prevention and treatment.[2,6,7] These include management of glycaemic control and avoidance of severe hypoglycaemic events.[8] Previous observational studies that examined the effect of glucose-lowering treatments (including metformin, sulfonylureas, thiazolidinedione, insulin or a combination of these) on the risk of cognitive decline have not demonstrated consistent findings.[2] Because observational studies have a substantial risk of bias, randomised controlled trials (RCTs) are needed; unfortunately few have been performed. A recent meta-analysis summarised the results of five well conducted RCTs on the effect of intensive versus standard glycaemic control on cognitive decline in patients with T2DM, involving over 24,000 participants.[9] This pooled analysis showed that intensive glycaemic control was not associated with a slower rate of cognitive decline, compared with standard glycaemic control, although there was some heterogeneity among studies.[9] These previous RCTs have in common that they used mean cognitive performance as their primary outcome, which may include many participants with little or no cognitive decline. Although duration of follow-up of the studies ranged from 3-6 years,[9] the actual average decline in mean cognitive performance was limited.[10-13] Over the past years it has become clear, also from observational studies, that the average decline in cognition over time associated with diabetes[2] is relatively slow, limiting the sensitivity of follow up studies to detect meaningful differences. Importantly however, among patients with T2DM there is heterogeneity in the rate of cognitive decline, where some have accelerated decline which in some cases progresses to dementia. For example, in a large cohort of patients with T2DM over the age of 60 years, an annual incidence of dementia of 2.6% was reported.[14] It might therefore be more appropriate - and clinically meaningful with regards to establishing interventions - to focus on occurrence of accelerated cognitive decline in individual patients. Such an approach

is chosen in the CAROLINA®-cognition substudy. Interestingly, the ORIGIN study (which studied effects on outcomes of intensive glucose lowering with insulin glargine) did a post-hoc analysis using this approach in the ORIGIN MIND substudy and observed a modest, albeit statistically non-significant, benefit of intensive glycaemic control[10] versus standard care.

Dipeptidyl peptidase-IV (DPP-IV) inhibitors improve glycaemic control by inhibiting the enzyme DPP-IV thereby enhancing the incretin effects, i.e., increasing the availability of active glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), which are secreted from the intestine after a meal. In the presence of hyperglycaemia, these hormones promote glucose-dependent insulin secretion and reduce glucagon secretion.[15] Beyond their effects on DPP-IV activity and glucose, several preclinical studies suggest anti-inflammatory, anti-atherosclerotic and neuroprotective effects that might be relevant in the context of preventing accelerated cognitive decline.[15-19] Experimental studies also show promising results of incretin-based therapies in models of Alzheimer's disease and stroke.[17] These potential pleiotropic modes of action make DPP-IV inhibitors attractive candidate drugs to prevent accelerated cognitive decline in T2DM. Recently, an observational study found that increased plasma DPP-IV activity was associated with a high risk of mild cognitive impairment in elderly patients with T2DM,[20] providing further support to test a strategy of modulating DPP-IV activity in T2DM to prevent cognitive impairment. The international, randomised, double blinded CARdiOvascular safety of LINAgliptin (CAROLINA®) trial is designed to provide a long-term evaluation of treatment durability and cardiovascular safety of treatment with the DPP-IV inhibitor linagliptin compared to the currently widely used sulfonylurea (SU) glimepiride.[21,22] Linagliptin is a once-daily, DPP-IV inhibitor with a xanthine-based structure that is characterised by a pharmacological profile distinct from other drugs in this class[23] largely due to its non-renal route of elimination (80% hepatic versus 5% renal).[24] The cognition substudy is an integrated part of CAROLINA®.

Objectives

The primary objective of the CAROLINA®-cognition substudy is to investigate if the proportion of participants with accelerated cognitive decline is lower in the group randomised to treatment with linagliptin compared to the group randomised to glimepiride after 160 weeks, or at end of follow-up.

Secondary objectives:

Unravelling the processes that underlie cognitive decline in T2DM is important to support future prevention strategies. Secondary objectives are therefore:

1) At baseline: to explore associations between characteristic features of T2DM (i.e., glycaemic and anthropometric parameters), cardiovascular risk factors (i.e., blood pressure and lipid levels) and cognitive performance
2) Longitudinal: to explore associations between baseline characteristic features of T2DM, cardiovascular risk factors – and changes in these factors over time – and cognitive decline during follow-up
3) Longitudinal: to explore the associations between baseline mood – and changes in mood over time - and cognitive decline during follow-up

Methods

Design and sample

The CAROLINA® trial is a randomised, active comparator, double blind study to evaluate the cardiovascular safety of linagliptin versus glimepiride in patients with T2DM at elevated cardiovascular risk. Patients were randomised between 2010 and 2012 from approximately 600 trial centres in 43 different countries. Key inclusion criteria are shown in Table 1.

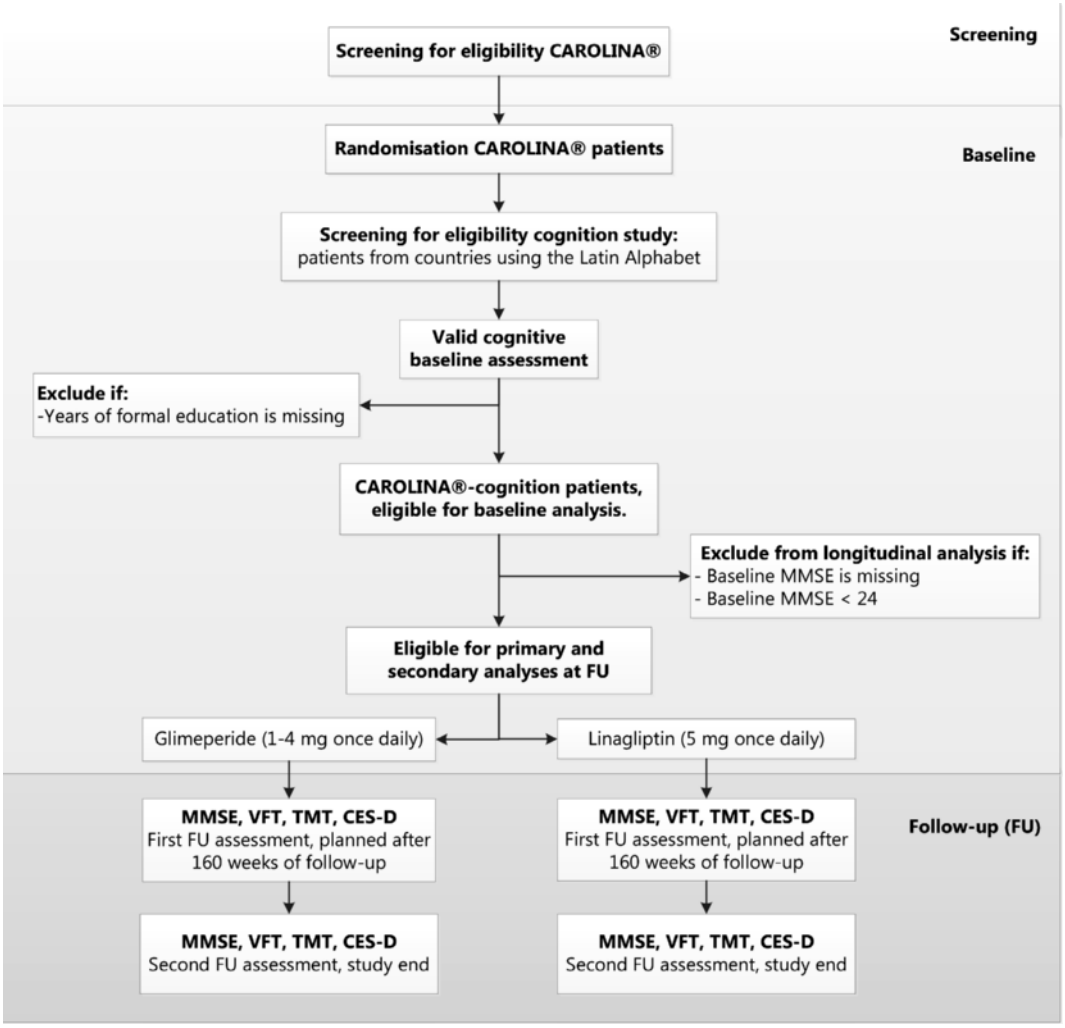
CAROLINA® is an event driven study. It is planned to run until a minimum of 631 confirmed Major Adverse Cardiovascular Events (MACE) have been accrued. MACE include cardiovascular death (including fatal stroke and fatal myocardial infarction (MI)), non-fatal MI (excluding silent MI) and non-fatal stroke. The estimated study duration is about 432 weeks. For more detailed information about the CAROLINA® main study see the Boehringer Ingelheim trial protocol (1218.74, Clintrial.gov id NCT01243424) and the previously published paper on the design and baseline characteristics.[21]

Table 1 Key inclusion criteria CAROLINA®

Insufficient glycaemic control defined as one of the criteria (A or B)	**AND**	**Elevated risk of cardiovascular events defined as any (one or more) of the criteria (A, B, C or D)**
(A) HbA1c 6.5 - 8.5% (48 - 69 mmol/mol) while patient is treatment naïve or treated with: **(1)** Metformin monotherapy **(2)** α-Glucosidase inhibitor monotherapy (e.g. acarbose, voglibose) **(3)** Metformin plus α-glucosidase inhibitor (e.g. acarbose, voglibose)		**(A) Previous vascular disease:** **(1)** MI (>6 weeks prior to informed consent IC) **(2)** Documented coronary artery disease ≥ 50% luminal diameter narrowing of left main coronary artery or in at least two major coronary arteries in angiogram) **(3)** Percutaneous coronary intervention (>6 weeks prior to IC) **(4)** Coronary artery bypass grafting (>4 years prior to IC) or with recurrent angina following surgery **(5)** Ischaemic or haemorrhagic stroke (>3 months prior to IC) **(6)** Peripheral occlusive arterial disease
(B) HbA1c 6.5 - 7.5% (48 - 58 mmol/mol) while patient is treated with: **(1)** SU monotherapy **(2)** Glinide monotherapy (e.g. repaglinide, nateglinide) **(3)** Metformin plus SU (for a maximum of 5 years) **(4)** Metformin plus glinide (for a maximum of 5 years) **(5)** α-Glucosidase inhibitor plus SU (for a maximum of 5 years) **(6)** α-Glucosidase inhibitor plus glinide (for a maximum of 5 years)		**(B) Evidence of vascular-related end-organ damage:** **(1)** Moderately impaired renal function (as defined by MDRD formula) with eGFR 30-59 ml/min/1.73 m2 **(2)** Random spot urinary albumin:creatinine ratio ≥ 30 µg/mg in two of three unrelated specimens in the previous 12 months. **(3)** Proliferative retinopathy defined as retinal neovascularization or previous retinal laser coagulation therapy
		(C) Age ≥70 years **(D) At least two of the following cardiovascular risk factors:** **(1)** T2DM duration >10 years **(2)** Systolic BP > 140 mmHg (or on at least 1 BP-lowering treatment) <6 months prior to IC **(3)** Current daily cigarette smoking **(4)** LDL-cholesterol ≥ 135 mg/dL (3.5 mmol/L) (or specific current treatment for this lipid abnormality) <6 months prior to IC

Table adapted from Marx et al. 2015.[21] *CAROLINA: CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes; IC: informed consent; T2DM: type 2 diabetes mellitus; BP: blood pressure; SU: sulphonylurea; MI: myocardial infarction; MDRD: modified diet in renal disease; eGFR: estimated glomerular filtration rate.*

Figure 1 – overview design CAROLINA®-cognition substudy.



Abbreviations: FU: follow-up, A&E score: Attention and Executive functioning score, MMSE: Mini Mental State Examination, VFT: Verbal Fluency Test, TMT: Trail Making Test, CES-D: Centre for Epidemiologic Studies Depression Scale.

CAROLINA® cognition substudy

Cognitive tests are conducted at baseline, after 160 weeks and at planned end of follow-up (or at permanent treatment-discontinuation). To be eligible for cognitive testing in this substudy, participants need to live in a country that have a native language built on the Latin alphabet, due to psychometric test-battery validation. Participants are included in the analysis data-set of the CAROLINA®-cognition substudy of baseline data if they are randomised and treated with at least one dose of study drug and have at least one valid cognitive assessment at baseline and documented years of formal education. For the analyses of follow-up data in addition at least one valid cognitive assessment during follow-up and baseline Mini Mental State Examination (MMSE) score ≥ 24 is required as illustrated in Figure 1.

Cognitive assessment and psychometric tests

This cognitive assessment included a cognitive paper based test battery that is brief and easy to administer in a standardised way. The tests are sensitive to relatively mild cognitive changes in T2DM, well standardised and validated, and available in multiple languages (using the modern Latin alphabet). The specific tests selected were:

1. Mini Mental State Examination (MMSE). The MMSE is a screening instrument that was developed to determine whether older adults have cognitive impairments.[25] It consists of a range of items assessing orientation, memory for words, drawing, backward counting and semantic knowledge, with a maximum score of 30. The MMSE takes approximately five minutes to administer and participating centres use country-specific validated questionnaires of the MMSE. A cut-off of <24 is widely used, and has been accepted, as indicating the presence of cognitive impairment.[26] A limitation of the MMSE is that it is insensitive to cognitive decrements in domains affected by vascular-related cognitive impairment, in particular attention, executive functioning and information processing speed.[27] Therefore two additional tests that tap into these domains were included - the Trail Making Test (TMT) and the verbal fluency test (VFT). Although the TMT and the VFT measure different cognitive processes, there is a clear consensus in cognitive theory and clinical practice that both tests assess important aspects of speed, attention and executive functioning.[28]

2. TMT. The TMT is a test of scanning, visuomotor tracking, divided attention and cognitive flexibility.[29] The test requires a subject to 'connect-the-dots' of 25 consecutive targets on a sheet of paper. Two versions are available: A, in which the targets are all numbers (1,2,3, etc.), and B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.). The goal is to finish the test as quickly as possible, and the time taken to complete the test is recorded. The maximum score (i.e. 300 seconds) is assigned to patients who are unable to complete the test within five minutes. The TMT is highly sensitive to the presence of cognitive impairment.[30] The TMT B is sensitive to T2DM-associated cognitive decrements,

and in older individuals test performance clearly decreases over time.[31-33] The English versions of the TMT test instructions were translated into the local languages. Potential effects of translation of the test instructions on test difficulty, although unlikely, cannot be ruled out a priori and therefore will be tested (see sensitivity analyses, Table 2).

3. VFT. The VFT requires a subject to generate as many words as possible in 60 seconds. The category version (semantic fluency) requires generation of words from a certain category (e.g. animals), the letter version (phonemic fluency) requires generation of words starting with a specific letter. The tests are sensitive to the effects of ageing and performance is clearly affected in T2DM.[27,32,33] It is viewed as a sensitive indicator of (even mild) cognitive dysfunction. In CAROLINA®, the category animals and the letters F, A and S are used for all languages. The number of words/animals after 15 seconds and after 60 seconds are recorded. The test takes approximately five minutes to complete. The English versions of the test instructions were translated into the local languages. Because of word-frequency differences between different Latin-based languages the letters FAS will not yield identical performance in different languages. However, FAS-equivalent letter combinations were available in a minority of languages only. Therefore, we chose to calculate a language-specific correction score (see below).

For the purpose of assessing effects on Attention and Executive functioning, the TMT and the VFT are combined to one composite score for Attention and Executive functioning (the A&E score). The A&E score is calculated as follows:

1) The VFT scores for the letters F, A and S in 60 seconds are averaged to one VFT letter fluency score.
2) The VFT is corrected for language influences by calculating least square (LS) means in an analysis of covariance (ANCOVA) model including age, gender, years of formal education, race and language as independent variables. The LS means for language are derived and then compared to one reference language (English), i.e. correction factors are calculated for each language separately (LSmean language/ LSmean English). Correction factors will be calculated for the three letters F, A and S taken together, and for the category fluency (i.e. animals) separately. The VFT scores of each participant are then corrected by multiplying the score with the corresponding correction factor. After correction, the scores are converted into z-scores. Z-scores are used to standardise raw test scores and make them directly comparable, z-scores are calculated as follows: (individual raw test score – mean baseline test score study population)/ baseline standard deviation.
3) The corrected VFT letter fluency and the VFT category fluency z-scores (both after 60 seconds) are averaged to one VFT overall score, where the letter fluency and the category fluency each account for 50%.
4) The TMT ratio is calculated, providing an index for executive functioning:

(TMT B –TMTA) / TMT A.

5) The TMT ratio and VFT overall score are converted into z-scores.
6) The mean of the TMT ratio and VFT overall z-scores is used to generate one composite score for attention and executive functioning. In secondary analyses the TMT and VFT will be analysed separately to control for potential test-specific effects.

As depression is a confounder to cognitive performance, participants also complete a depression questionnaire. In the CAROLINA® cognition substudy, we use the Centre for Epidemiologic Studies Depression Scale (CES-D), a widely used and validated 20-item questionnaire on depressive symptoms over the past week.[34] A score of ≥ 16 is indicative of a depression.[35] Whenever available in a county, the validated version of the CES-D was used. For languages were no validated version was available, a back translation was created and verified.

As both too high or too low blood glucose values can affect cognitive performance, self-monitoring of blood glucose (SMBG) values levels are to be measured (finger prick) prior to each cognitive assessment. Whenever the SMBG is not within 4 – 13 mmol/L the cognitive assessment is postponed. If values >3 or <18 mmol/L the finger prick could be repeated after at least one hour provided that the SMBG is within the 4-13 mmol/L range. In case glucose values ≤3 or ≥18 mmol/L glycemic management should be reviewed and the assessment postponed 1-7 days.

To optimise the quality of the cognitive outcomes, face-to-face meetings including training for examiners were organised in conjunction with the study start-up meetings. In addition, written step-by-step instructions for the (preparation of the) test assessment were provided. All tests were administered by the investigator or designated site-personnel who were all fluent in the language of test administration. The language in which the tests are performed is captured in the case report form (CRF). It is also recorded whether this language is the native language of the patient. If the tests are not performed in patient's native language the VFT scores are considered to be invalid and are set to 'missing'.

The investigator or designated site-personnel can add a comment to the test score if they doubt the validity of the test. All those comments are independently reviewed by two members of the analysis team and categorised into whether those have an impact on the test score results ("valid" or "not valid" test score results). Discrepancies are resolved by means of discussion and before unblinding of the study. All test scores considered as not valid are set to 'missing'. If the comments indicate that all tests of the patient are invalid (e.g. patient is illiterate) the patient is excluded from CAROLINA®-cognition analysis. Furthermore impossible scores (e.g. VFT score after 60 seconds which is less than after 15 seconds) are also set to 'missing'.

When baseline VFT and TMT scores are very low, deterioration over time cannot be reliably assessed due to floor effects. Therefore, patients with a baseline VFT score below 3 will not be considered for longitudinal analysis on the VFT and patients with a TMT ratio z-score of 2 or higher at baseline not for the longitudinal analyses on the TMT. In this case the composite score for attention and executive funtioning is just based on the valid data.

Cognitive outcomes

The primary outcome of CAROLINA®-cognition is the occurrence of accelerated cognitive decline at the end of follow-up (a dichotomous outcome measure; presence or absence of accelerated cognitive decline).

Secondary cognitive outcomes are assessed as follows:

- The actual change in cognitive performance at end of follow-up (i.e. a continuous outcome measure; change in performance from baseline).
- The proportion of participants with accelerated cognitive decline after 160 weeks of follow-up.
- The actual change in cognitive performance after 160 weeks of follow-up (i.e. a continuous outcome measure; change in performance from baseline).

Primary outcome considerations

Conceptually, there are different ways to define accelerated cognitive decline. A fixed cut-off (e.g. occurrence of MMSE < 24 at time point of assessment) or a minimal amount of decline (e.g. occurrence of > 4 points of decline from baseline) can be used. However, a fixed cut-off does not take baseline performance into account and an absolute decline does not account for important individual factors influencing cognitive decline, such as education. We therefore choose to use a regression based index score (RBI score) of cognitive change over time. This RBI score adjusts for potential confounders as age, language, education, baseline performance, and regression to the mean on an individual participant basis.[36] In addition, the RBI also reduces the impact of learning effects: repeated neuropsychological assessment can cause practice effects; both material-specific effects and the fact that a person is no longer “test-naïve” after the first neuropsychological assessment. While the latter cannot be prevented, the former is countered by the use of RBI. Accelerated cognitive decline in the CAROLINA® cognition substudy is defined as a score at or below the 16th percentile (the equivalent of approximately one standard deviation below the mean) on the MMSE RBI z-score or the A&E RBI z-score.

To convert MMSE and A&E z-scores into RBI scores, predicted follow-up scores (FUpredict) are calculated for each individual by means of an ANCOVA model. This model includes the following covariates: the individual's baseline test performance, age, years of formal education, gender, race, and test–retest interval. Subsequently the RBI scores are calculated for each individual by comparing his/her actual observed cognitive (FUobserved) score to his/her predicted cognitive score (RBI-score = (FUobserved – FUpredict)/standard deviation (SD) of residuals). Hence, a negative RBI-score reflects a decline in cognitive function (relative to the other study participants) faster than expected (based on the adjusted covariates).

Clearly, dichotomizing the cognitive test results for the primary outcome measure does have implications for the analyses. It is also different from the approach of previous studies in the field.[10-13] Of note, our rationale for the dichotomy is that it has become apparent that cognitive decline in older individuals with T2DM is clearly not a unitary construct.[2] On average – at the group level - cognition declines only very slowly over time.[10-13] Yet, there is a subset of individuals with accelerated decline.[2] While ideally this accelerated cognitive decline would be defined in terms of incident dementia or mild cognitive impairment, this was not deemed to be feasible in the present multinational, multicenter study, because of variability in diagnostic approaches. We therefore choose the pragmatic approach as described above, which is likely to capture the patients with the worst cognitive outcome, although not in terms of a fixed diagnostic construct. Dichotomizing the cognitive test results based on the RBI could result in an underestimation of the standard error of the primary estimate of group difference in rate of cognitive decline. It also comes at the expense of information loss and power. Yet, it was decided to sacrifice some statistical power in order to enable the possibility of having a more powerful statement at the end of the trial. Moreover, the actual change in cognitive performance at end of follow-up (i.e. change in performance from baseline as a continuous measure) is an additional predefined outcome measure to confirm the results of the primary analysis.

Time windows

The time from baseline to end of follow-up cognitive assessment will vary between participants as patients were recruited over a period of two years. Furthermore, as visits may be rescheduled and each patient is followed up for a different time interval, as per study design, time windows were defined to assign each cognitive assessment to either baseline, week 160 or end of follow-up.

Baseline cognitive assessments were planned to be conducted at the day of randomisation, prior to intake of the first dose of study drug. The first follow-up assessment is scheduled after 160 weeks of follow-up (a time window up to 166 weeks is accepted) and the final cognitive assessment is scheduled within seven days after the last intake of study medication.

In practice the baseline test was conducted between Dec 2010 – Dec 2012 and the planned week 160 test was conducted between Dec 2013 – Jan 2016. The formal end of the trial will be determined in time, by reaching the predefined number of patients with primary endpoint events in the mother-trial, estimated to occur in Q1 2019. All patients that are still on treatment by then have their end of follow-up assessment at that time point. Patients that stop their treatment before the end of the trial will have their end of follow-up assessment at that moment. For all participants with a cognitive assessment after week 166, this assessment will be assigned to the second time interval (end of follow-up).

Other study parameters

Demographics at baseline (full definitions are listed in additional file*)*

Demographic information is collected at baseline and includes age, gender, years of formal education, race (Black/African American, White, Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander), ethnicity (Latino/Hispanic, non-Latino/Hispanic), medication use, medical history, and alcohol use.

Diabetes-related variables

Blood samples are drawn at baseline and at the day of the first and second cognitive follow-up assessments and includes HbA1c, FBG, and C-peptide. Samples are always taken after an overnight fast (at least 10 hours after the last meal) and all blood samples are analysed at a central laboratory using validated assays. Medical history is recorded in the case report form (CRF) and includes duration of diabetes and presence of diabetic complications (diabetic neuropathy, diabetic foot and proliferative retinopathy; full definitions listed in *additional file*). Previous medication use, including SU or glinide is recorded. Episodes of hypoglycaemia, including severe hypoglycaemic episodes, are recorded prospectively.

Cardiovascular risk profile (full definitions listed in additional file*)*

Cardiovascular risk factors are assessed at baseline and at the day of the first and second cognitive follow-up assessments. They include: smoking habits, systolic and diastolic blood pressure, body mass index (BMI), waist circumference, a lipid panel (total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides), and assessment of renal function/albuminuria. Blood pressure is measured using either a standard mercury sphygmomanometer or an electronic device after five minutes of rest. Weight measurements are standardised and similar scales are used at each visit. Waist circumference is measured in the midpoint between the lowest rib and the iliac crest using a non-elastic tape, after the patient exhaled. Estimated glomerular filtration rate is calculated using the Modification of Diet in Renal Disease (MDRD) formula.

History of macrovascular disease includes: ischemic heart disease, cerebrovascular disease and peripheral arterial occlusive disease. Cardiovascular events are recorded prospectively.

Statistical analysis

Sample size considerations

Accelerated decline is defined as an RBI score within the lowest 16 percent for the MMSE and/or the A&E RBI score. It is expected that an estimated 20-22% will meet this criterion for the primary cognitive outcome measure of CAROLINA®. There were no formal power calculations performed for this substudy. However with 4500 participants, approximately 900-1000 participants will thus meet this primary cognitive outcome measure, which will allow, at a reasonable power, a detection of a hypothesised relative risk reduction with linagliptin for accelerated cognitive decline of approximately 20% (power 0.8; alpha 0.05, two-sided testing).

Primary analysis

The primary analysis will be performed in all patients randomised and treated with at least one dose of study drug, who have a baseline assessment and at least one follow-up cognitive assessment available (of which at least one of the two RBI scores can be calculated). In this modified intention to treat analysis the proportion of participants with accelerated cognitive decline will be compared between the two treatment groups at end of follow-up using a logistic regression analysis with factor for treatment. The odds ratio (OR) along with the 95% Wald confidence interval (CI) and the two-sided p-value for treatment comparison will be presented.

Predefined subgroup analyses

The primary outcome will be analysed in the following subgroups to explore the consistency of the treatment effect: gender (male, female), age (<70, ≥70 years), race (black, white), ethnicity (Latino/Hispanic, non-Latino/Hispanic), CES-D (score <16, ≥ 16 and median split), cardiovascular risk groups (based on inclusion criterion groups A, B, C, D; see Table 1) and duration of diabetes (<=1 year, >1 to <=5 years, >5 to <=10 years, >10 years).

Handling of missing cognitive data

Missing baseline cognitive data will not be imputed. For missing data due to incomplete testing, the remaining test scores will be used to judge if accelerated cognitive decline is present. If one of the VFT subscores is missing, the remaining scores will be used to calculate the overall score. If either the TMT A or the TMT B is missing no TMT ratio will be calculated. If either the VFT overall z-score or the TMT ratio is missing the remaining score will be used to calculate the A&E score at baseline and follow-up.

If a patients follow-up assessment is completely missing it will be replaced by her/his last observed post-randomization measurement or linearly intrapolated in case of a missing assessment in between assessments. If a cognitive test is not done or not completed, the investigator or research assistant should indicate whether this was due to the inability of the patient to understand the instructions. If this is the case at a follow-up visit and neither the MMSE nor the A&E RBI-score can be calculated due to missing values, the patient is classified as having accelerated cognitive decline.

Sensitivity analyses for the primary outcome
To test the robustness of the results, sensitivity analyses will be performed for the primary outcome (for the second FU assessment), as shown in table 2.

Secondary analyses
To investigate potential early treatment effect, we will also look into the occurrence of accelerated cognitive decline at week 160, i.e., the first cognitive assessment post baseline.

In addition, to determine whether the definition we used for accelerated cognitive decline influenced the results, we will investigate the following alternative definitions for accelerated cognitive decline at week 160 and at the end of follow-up:

- having a score at or below the 16th percentile on the MMSE z-score or the A&E z-score (i.e. without using RBI scores).
- having a score at or below the 10^{th} (instead of the 16^{th}) percentile on the MMSE RBI-score or the A&E RBI-score
- having a follow-up MMSE score of <24 or a decline of >4 points in MMSE relative to baseline

Table 2 Sensitivity analyses for the primary outcome

Reason sensitivity analysis	How is the sensitivity analysis performed?
Check the influence of inappropriate inclusion, potentially confounding co-morbid conditions and trial medication use	Participants will be excluded from the analysis if: • major inclusion or exclusion criteria are violated • incorrect trial medication is taken • major neurological or psychiatric disease was present at baseline
Check the influence of classifying participants who did not understand the instructions at follow-up as having accelerated cognitive decline	The last observation carried forward method will be used for patients with missing MMSE and A&E RBI-scores at follow-up if the reason for missing is the inability of the patient to understand the instructions (instead of classifying them as having accelerated cognitive decline)
Check for bias by differential lost to follow-up (worst case scenario)	All patients with missing MMSE and A&E RBI-scores at follow-up will be considered to have accelerated cognitive decline
Investigate the impact of further baseline variables on the RBI score result, Check for confounding by depression symptoms	Age, gender, years of formal education, race, ethnicity and language and CES-D (score <16, ≥16) are included as covariates in the logistic regression analysis

To investigate the actual change in cognitive performance over time, the change in z-scores for all individual test scores (from baseline to first and second follow-up assessment) will be analysed. This will be done using a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM) approach. The primary comparison will be the difference in adjusted least squares means between the two treatment groups.

Finally, to investigate the effect of treatment on the occurrence of depression, the occurrence of a CES-D score of ≥16 will be analysed for the first and second follow-up assessments. This will be done using a logistic regression analyses, as for the primary outcome.

Exploratory analyses of risk factors for cognitive dysfunction
Additional analyses are planned to investigate the association between mood, diabetes-related factors, and cardiovascular factors and cognitive dysfunction. Cross-sectional baseline analyses will be conducted aimed at answering etiologic questions. Longitudinal analyses will be performed exploring both etiologic and prognostic questions in relation to cognitive decline.

Linear regression analyses will be used for the baseline analysis including the MMSE score and the A&E z-score as the cognitive outcome measures. These analyses will be adjusted for age, gender, years of formal education and race. If a significant association is found for a certain variable (e.g. HbA1c levels) other covariates may be added stepwise to the model

to investigate this relation further. Non-linear associations will also be considered. We will perform subgroup analyses stratified by age (<70, ≥70 years) and gender (male, female). Similar approaches will be taken for etiologic longitudinal analyses, using a restricted maximum likelihood based mixed model repeated measures approach.

Since all of these secondary analyses are considered of exploratory nature, no correction for multiple testing will be made.

Discussion

The CAROLINA® trial provides a unique opportunity to investigate the effect of treatment with linagliptin compared to the SU glimepiride on the occurrence of accelerated cognitive decline in patients with T2DM. The large sample size, the long follow-up period and the study population of middle aged and older (mean age 64.7± 9.4 years) individuals at elevated cardiovascular risk, offer an excellent cohort to study cognitive outcomes. With the primary outcome measure occurrence of accelerated cognitive decline the cognition study focuses on those individuals who suffer from cognitive problems; a novel and very clinically meaningful approach.

CAROLINA®-cognition, a substudy of the CAROLINA® trial, is the first large RCT that will yield important information regarding DPP-IV inhibitor versus SU treatment in the reduction of accelerated cognitive decline in patients with T2DM. A positive result in CAROLINA®-cognition could provide important leads towards a new prevention strategy for dementia in T2DM and as such have major clinical T2DM treatment ramifications.

References

1. International Diabetes Federation. IDF diabetes atlas - 7th edition. http://www.diabetesatlas.org. 2015. Accessed 3 octobre 2016.
2. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol. 2014;2:246-255.
3. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol. 2015;14:329-340.
4. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5:64-74.
5. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J Diabetes Investig. 2013;4:640-650.
6. Feinkohl I, Price JF, Strachan MW, Frier BM. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimers Res Ther. 2015;7:46.
7. Feinkohl I, Keller M, Robertson CM, Morling JR, McLachlan S, Frier BM et al. Cardiovascular risk factors and cognitive decline in older people with type 2 diabetes. Diabetologia. 2015;58:1637-1645.
8. Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol. 2015;3:75-89.
9. Tuligenga RH. Intensive glycaemic control and cognitive decline in patients with type 2 diabetes: a meta-analysis. Endocr Connect. 2015;4:R16-R24.
10. Cukierman-Yaffe T, Bosch J, Diaz R, Dyal L, Hancu N, Hildebrandt P et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. Lancet Diabetes Endocrinol. 2014;2:562-572.
11. Koekkoek PS, Ruis C, van den DM, Biessels GJ, Gorter KJ, Kappelle LJ et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes--the ADDITION-Netherlands study: a cluster-randomized trial. J Neurol Sci. 2012;314:71-77.
12. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol. 2011;10:969-977.
13. Luchsinger JA, Palmas W, Teresi JA, Silver S, Kong J, Eimicke JP et al. Improved diabetes control in the elderly delays global cognitive decline. J Nutr Health Aging. 2011;15:445-449.
14. Exalto LG, Biessels GJ, Karter AJ, Huang ES, Katon WJ, Minkoff JR et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. Lancet Diabetes Endocrinol. 2013;1:183-190.
15. Phillips LK, Prins JB. Update on incretin hormones. Ann N Y Acad Sci. 2011;1243:E55-E74.
16. Chen S, Liu AR, An FM, Yao WB, Gao XD. Amelioration of neurodegenerative changes in cellular and rat models of diabetes-related Alzheimer's disease by exendin-4. Age (Dordr). 2012;34:1211-1224.
17. Groeneveld ON, Kappelle LJ, Biessels GJ. Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus. J Diabetes Investig. 2016;7:5-16.
18. Porter DW, Irwin N, Flatt PR, Holscher C, Gault VA. Prolonged GIP receptor activation improves cognitive function, hippocampal synaptic plasticity and glucose homeostasis in high-fat fed mice. Eur J Pharmacol. 2011;650:688-693.
19. Satoh-Asahara N, Sasaki Y, Wada H, Tochiya M, Iguchi A, Nakagawachi R et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism. 2013;62:347-51.
20. Zheng T, Qin L, Chen B, Hu X, Zhang X, Liu Y et al. Association of Plasma DPP4 Activity With Mild Cognitive Impairment in Elderly Patients With Type 2 Diabetes: Results From the GDMD Study in China. Diabetes Care. 2016;39:1594-1601.
21. Marx N, Rosenstock J, Kahn SE, Zinman B, Kastelein JJ, Lachin JM et al. Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA(R)). Diab Vasc Dis Res. 2015;12:164-174.
22. Rosenstock J. Rationale and Design of the CAROLINA Trial. An Active Comparator CARdiOvascular Outcome Study of the DPP-4 inhibitor LINAgliptin in Patients with Type 2 Diabetes at High Cardiovascular Risk. Diabetes. 2011;60:A303.
23. Deacon CF, Holst JJ. Linagliptin, a xanthine-based dipeptidyl peptidase-4 inhibitor with an unusual profile for the treatment of type 2 diabetes. Expert Opin Investig Drugs. 2010;19:133-140.
24. Blech S, Ludwig-Schwellinger E, Grafe-Mody EU, Withopf B, Wagner K. The metabolism and disposition of the oral dipeptidyl peptidase-4 inhibitor, linagliptin, in humans. Drug Metab Dispos. 2010;38:667-678.
25. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J.Psychiatr Res.

1975;12:189-198.
26. Tombaugh TN, McIntyre N. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40:922-935.
27. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006;37:2220-2241.
28. Lezak MD, Howieson BD, Bigler ED, Tranel D. Neuropsychological Assessment. 5th ed. Oxford: Oxford University Press Inc; 2012.
29. Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the Trail Making Test. J Clin Psychol. 1987;43:402-409.
30. Reitan RM, Wolfson. A selective and critical review of neuropsychological deficits and the frontal lobes. Neuropsychol Rev. 1994;4:161-198.
31. Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. Arch Intern Med. 2000;160:174-180.
32. Kanaya AM, Barrett-Connor E, Gildengorin G, Yaffe K. Change in cognitive function by glucose tolerance status in older adults: a 4-year prospective study of the Rancho Bernardo study cohort. Arch Intern Med. 2004;164:1327-1333.
33. van den Berg E, Reijmer YD, de BJ, Kessels RP, Kappelle LJ, Biessels GJ. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia. 2010;53:58-65.
34. Radloff LS. The CES-D Scale. A Self-Report Depression Scale for Research in the General Population. Appl Psychol Measurem. 1977;385-401.
35. Smarr KL, Keefer AL: Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S454-S466.
36. Temkin NR, Heaton RK, Grant I, Dikmen SS: Detecting significant change in neuropsychological test performance: a comparison of four models. J Int Neuropsychol Soc. 1999;5:357-369.

Additional file - definitions of terms

Baseline:

Term	Definition
Hypertension	Systolic blood pressure >140 mmHg (or on at least one blood pressure lowering treatment)
Hypercholesterolemia	Current LDL cholesterol ≥135 mg/dL (3.5 mmol/l) (or specific current treatment for this lipid abnormality)
Smoking	Current daily cigarette smoking
Myocardial infarction	Myocardial infarction (>6 weeks prior to informed consent)
Coronary artery disease	Documented coronary artery disease (≥ 50% luminal diameter narrowing of left main coronary artery or ≥50% in at least two major coronary arteries in angiogram)
Previous PCI **OR** **Previous CABG**	Percutaneous Coronary Intervention (PCI) >6 weeks prior informed consent OR Coronary Artery By-pass Grafting (CABG) >4 years prior to informed consent or with recurrent angina following surgery
Ischemic heart disease	Includes myocardial infarction, coronary artery disease and previous PCI or CABG
Macrovascular disease	Includes ischemic heart disease, cerebrovascular disease and peripheral occlusive arterial disease
Cerebrovascular disease	Ischemic or hemorrhagic stroke (> 3 months prior to informed consent)
Peripheral occlusive arterial disease	Includes: previous limb bypass surgery, stenting or percutaneous transluminal angioplasty; previous limb or foot amputation due to circulatory insufficiency, angiographic or ultrasound detected significant vessel stenosis (≥50%) of major limb arteries (common iliac, internal iliac, external iliac, femoral and/or popliteal artery), history of intermittent claudication with uni- or bilateral ankle: arm blood pressure ratio <0.90)
Proliferative retinopathy	Retinal neovascularisation or previous retinal laser coagulation therapy
Renal impairment	Includes moderate and severe renal function impairment: • Moderate renal function impairment: eGFR 30-59 mL/min/1.73m2 • Severe renal function impairment: eGFR <30 mL/min/1.73m2; The modified diet of renal disease (MDRD) formula is used to estimate the glomerular filtration rate (eGFR)
Diabetic neuropathy	Based on patient's medical history. Not further defined.
Microvascular complications	Includes proliferative retinopathy, renal impairment and diabetic neuropathy
Diabetic foot	Based on patients medical history. Not further defined
Depression	A score of 16 or more on the Center for Epidemiologic Studies Depression (CES-D) scale

On treatment:

Term	Definition
Hypoglyceamic episodes	Includes e.g.: • Documented hypoglycaemia with glucose concentration ≤70 mg/dl (≥3.0 mmol/l and ≤3.9 mmol/l) • Severe hypoglycaemic episode: event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions
Cardiovascular events	Includes adjudicated events of: • Non-fatal MI (excluding silent MI) • Hospitalisation for coronary revascularization procedures (CABG, PCI) • Non-fatal stroke • Hospitalisation for unstable angina pectoris • Transient ischemic attack • Hospitalisation for heart failure

CHAPTER 6

HbA1c, Insulin Resistance, and β-Cell Function in Relation to Cognitive Function in Type 2 Diabetes: The CAROLINA® Cognition Substudy

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Cognitive dysfunction is increasingly recognized as a complication of type 2 diabetes. There is a growing evidence for etiologic roles of glycemia and insulin resistance, although important questions remain.[1,2] Elevated levels of glycosylated hemoglobin (HbA1c) appear to be related to worse cognition, but there are indications that the same holds true for lower HbA1c levels, possibly because intensive glycemic control increases the risk of hypoglycemia.[1] Previous studies relating HbA1c to cognition did not sufficiently address this possible nonlinear relationship. Regarding insulin resistance, it has been postulated that disturbances in cerebral insulin signaling might negatively affect cognition.[2] Indeed, in individuals without type 2 diabetes, both hyperinsulinemia and insulin resistance have been related to poorer cognitive performance and dementia.[2] However, a comprehensive understanding of the interrelationship between markers of insulin homeostasis and cognition in type 2 diabetes is still lacking.[1] Finally, there may be interindividual differences in susceptibility for developing cognitive dysfunction, where factors such as age and sex could modify the relations between glycemia, insulin resistance, and cognition. We therefore investigated, in a large cohort of patients with type 2 diabetes, how HbA1c and indices of insulin resistance and β-cell function relate to cognitive function, specifically addressing potential nonlinear associations and the influence of age and sex.

We studied participants of the cognition substudy of the CAROLINA® (CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes) trial (NCT01243424). CAROLINA® is a randomized, active comparator, doubleblind study of 6,041 patients with relatively early type 2 diabetes, where the primary purpose is to evaluate the cardiovascular safety and efficacy of the dipeptidyl peptidase 4 inhibitor linagliptin versus the sulfonylurea glimepiride. The CAROLINA® Cognition substudy investigates if linagliptin is superior to glimepiride in the prevention of accelerated cognitive decline.[3] In brief, the Mini-Mental State Examination (MMSE), a test of global cognitive function, and the Trail Making Test and Verbal Fluency Test combined into one composite score for an attention and executive functioning score were conducted at baseline, after 160 weeks of treatment, and at study end.[3] Baseline scores were used for the present analyses. Insulin resistance was assessed with the HOMA2 of insulin resistance (HOMA2-IR). Indices of β-cell function were proinsulin, C-peptide, the proinsulin-to-C-peptide ratio, and the HOMA2 of β-cell function (HOMA2-β). The relationships between HbA1c and indices of insulin resistance and β-cell function and the cognitive measures, adjusted for confounders (age, sex, education, and race, and for HbA1c, use of glinide or sulfonylurea), were assessed with ANCOVA; we also examined analyses stratified by HbA1c (by median value), age (≥70 years, <70 years), and sex (women, men). Nonlinear associations were addressed by adding a quadratic term of the mean-centered variable to the ANCOVA model. Potential confounding and mediating factors were added stepwise to the model to investigate any relationship further. Relationships between indices of insulin resistance and β-cell function and the cognitive measures were only examined in patients not using sulfonylurea or glinide.

This analysis involves 4,335 patients with type 2 diabetes (60.7% male; mean [SD] age 64.7 [9.4] years, diabetes duration 7.8 [6.2] years, HbA1c 7.1 [0.6]% [55 (6) mmol/mol], MMSE score 28.0 [2.5]). The association between HbA1c and MMSE was nonlinear (P < 0.001) and proved to be bell shaped. An analysis by median split (HbA1c <7.1, ≥7.1% [<54, ≥54 mmol/mol]) revealed that both low and high HbA1c levels were associated with worse performance (Table 1), independent of use of sulfonylurea or glinide, estimated glomerular filtration rate, duration of diabetes, depression, cardiovascular risk factors, macrovascular disease, microvascular complications, and diabetic foot. A significant age–HbA1c interaction (P = 0.01) was observed, where data suggested that associations between both high and low HbA1c levels and worse MMSE scores were most prominent in patients ≥70 years. A significant sex–HbA1c interaction (P = 0.04) was also found in patients with HbA1c levels ≥7.1% (54 mmol/mol), where data suggested a more prominent relationship between high HbA1c and poor performance in women (Table 1). Negative linear associations were found between both proinsulin and the proinsulin–to–C-peptide ratio and the MMSE, independent of HbA1c, HOMA2-IR, estimated glomerular filtration rate, duration of diabetes, depression, cardiovascular risk factors, macrovascular disease, microvascular complications, and diabetic foot. For the proinsulin–to–C-peptide ratio, a significant interaction with sex (P = 0.01) was observed. For other insulin related measures (Table 1) and for the attention and executive functioning score (data on file), no significant (linear or nonlinear) associations were observed.

This large cross-sectional study in patients with type 2 diabetes shows a bellshaped association between HbA1c and cognitive function, with modifying effects of age and sex, with those over the age of 70 years and women being more vulnerable. Although a causal relationship between HbA1c and cognitive function cannot be inferred by these cross-sectional observations, they add to an emerging literature indicating that in older individuals, particularly, both tight and loose glycemic control may adversely affect cognition.[1] This issue clearly needs further investigation. The lack of association between cognitive performance and C-peptide and the HOMA2 indices are congruent with recent studies in patients with type 2 diabetes.[4] The negative linear association between elevated proinsulin and cognitive function could involve a direct effect of proinsulin on cardiovascular risk.[5] Another explanation for this finding could be that proinsulin and the proinsulin–to–C-peptide ratio are more suitable markers of β-cell function in people with type 2 diabetes, particularly because proinsulin secreted by the β-cells increases further as diabetes progresses, whereas C-peptide and insulin levels decrease when β-cells get exhausted.

Table – Beta coefficients (95% CIs) for the relationship between HbA1c (%), indices of insulin-resistance and beta-cell function and the MMSE.

	N	All	† Age < 70	† Age ≥ 70	Interaction	‡ Men	‡ Women	Interaction
(%) HbA1c	4335	(-0.14,0.10) -0.02	(-0.13,0.14) 0.00	(-0.30,0.19) -0.05	p = 0.73	(-0.12,0.17) 0.02	(-0.28,0.15) -0.07	p = 0.31
Median split								
HbA1c <7.1% (%) HbA1c	2148	*(0.09,0.90) 0.50	(-0.25,0.66) 0.21	*(0.29,1.83) 1.06	p = 0.06	(-0.12,0.83) 0.36	(-0.06,1.37) 0.65	p = 0.36
HbA1c ≥7.1% (%) HbA1c	2187	*(-0.04,-0.49) -0.27	(-0.32,0.19) -0.07	*(-0.25,-1.15) -0.70	*p = 0.01	(-0.37,0.15) -0.11	*(-0.11,-0.91) -0.51	*p = 0.04
Only patients without use of SU or glinide Beta-cell function								
C-peptide ((nmol/L	2027	(-0.20,0.32) 0.06	(-0.25,0.35) 0.05	(-0.51,0.53) 0.01	p = 0.87	(-0.36,0.21) -0.08	(-0.16,0.93) 0.39	p = 0.19
Proinsulin ((qmol/L	2232	-,-0.006) -0.003 *(0.000	(-0.005,0.001) -0.002	(-0.015,0.001) -0.007	p = 0.30	(-0.005,0.001) -0.002	(-0.012,0.001) -0.006	p = 0.31
Proinsu-lin-to-C-peptide ratio	2011	-,-0.082) -0.051 *(0.021	-,-0.077) -0.045 *(0.012	(-0.126,0.018) -0.054	p = 0.96	(-0.053,0.012) -0.021	*(-0.052,-0.176) -0.114	*p = 0.01
HOMA2-β	2026	0.0006 (-0.0037,0.0024)	-0.0010 (-0.0043,0.0024)	-0.0008 (-0.0074,0.0057)	p = 0.98	-0.0011 (-0.0044,0.0021)	0.0004 (-0.0058,0.0067)	p = 0.54
Insulin resistance								
HOMA2-IR	2026	0.0119 (-0.0859,0.1096)	0.0101 (-0.1011,0.1212)	-0.0085 (-0.2085,0.1915)	p = 0.84	-0.0407 (-0.1444,0.0630)	0.1432 (-0.0626,0.3491)	p = 0.18

*p–value < 0.05. Estimates for all patients are obtained from an ANCOVA with factors sex, race (for HbA1c also use of sulfonylurea (SU) or glinide) and covariates age, years of formal education and baseline value of interest. Estimates within subgroup HbA1c (<7.1%/>=7.1%) are obtained from an ANCOVA using the same model within the HbA_{1c} subgroup. † For the subgroup age (<70/>=70yrs) the same models without covariate age were run. ‡ For the subgroup sex the same models without factor sex were run. Interaction p–values are taken from models as above with additional subgroup term (subgroup age or sex respectively) and interaction term (subgroup age*baseline value of interest or sex*baseline variable of interest respectively). MMSE, Mini-Mental State Examination. CI, confidence interval. HbA1c, glycosylated Hemoglobin. † = not adjusted for age, ‡ not adjusted for sex*

References

1. Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose regulation, cognition, and brain MRIin type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol 2015;3:75–89
2. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol 2018;14:168–181
3. Biessels GJ, Janssen J, van den Berg E, et al.; CAROLINA Investigators. Rationale and design of the CAROLINA - cognition substudy: a randomised controlled trial on cognitive outcomes of linagliptin versus glimepiride in patients with type 2 diabetes mellitus. BMC Neurol 2018;18:7
4. Geijselaers SLC, Sep SJS, Schram MT, et al. Insulin resistance and cognitive performance in type 2 diabetes - The Maastricht study. J Diabetes Complications 2017;31:824–830
5. Zethelius B, Byberg L, Hales CN, Lithell H, Berne C. Proinsulin is an independent predictor of coronary heart disease: report from a 27-year follow-up study. Circulation 2002;105:2153–2158

PART 3

Diagnosing cognitive impairment

CHAPTER 7

How to choose the most appropriate cognitive test to evaluate cognitive complaints in primary care

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Abstract

Background
Despite the wealth of research devoted to the performance of individual cognitive tests for diagnosing cognitive impairment (including mild cognitive impairment and dementia), it can be difficult for general practitioners to choose the most appropriate test for a patient with cognitive complaints in daily practice.

In this paper we present a diagnostic algorithm for the evaluation of cognitive complaints in primary care. The rationale behind this algorithm is that the likelihood of cognitive impairment -which can be determined after history taking and an informant interview- should determine which cognitive test is most suitable.

Methods
We distinguished three likelihoods of cognitive impairment: not likely, possible or likely. We selected cognitive tests based on pre-defined required test features for each of these three situations and a review of the literature. We incorporated the cognitive tests in a practical diagnostic algorithm.

Results
Based on the available literature, in patients with complaints but where cognitive impairment is considered to be unlikely the clock-drawing test can be used to rule out cognitive impairment. When cognitive impairment is possible the Montreal cognitive assessment can be used to rule out cognitive impairment or to make cognitive impairment more likely. When cognitive impairment is likely the mini-mental state examination can be used to confirm the presence of cognitive impairment.

Conclusions
We propose a diagnostic algorithm to increase the efficiency of ruling out or diagnosing cognitive impairment in primary care. Further study is needed to validate and evaluate this stepwise diagnostic algorithm.

Background

In case of cognitive complaints expressed by the patient or a relative, or suspicion of cognitive impairment by the general practitioner (GP), it is important to evaluate cognitive symptoms with a reliable and efficient diagnostic procedure. Differentiating between subjective cognitive complaints and cognitive impairment, i.e. mild cognitive impairment (MCI) or early dementia, can be difficult.[1] Yet, history taking and the informant interview provide crucial information for the diagnostic procedure. The GP can complement this information with additional cognitive tests to reach more certainty about the presence or absence of cognitive impairment.[2]

A wealth of research is devoted to the performance of individual cognitive tests. However, the literature gives limited consideration of and guidance on which and how cognitive tests should be used in the context of the sequential and probabilistic nature of the diagnostic procedure. Since the true value of a test is determined by the extent to which it provides information on top of the information that has already been gathered,[3] the choice of the most appropriate cognitive test should be based on the estimated likelihood that the patient has cognitive impairment.

In this paper we propose a stepwise diagnostic algorithm for the evaluation of cognitive complaints in primary care, taking into account both the GP's assessment of the likelihood of cognitive impairment and properties of the test.

Methods

To optimise the selection of cognitive tests we distinguished three likelihoods of objective cognitive impairment in patients with cognitive complaints, namely 1: cognitive impairment is not likely; 2: cognitive impairment is possible, but activities of daily living (ADL) appear to be preserved (i.e. MCI); and 3: cognitive impairment likely and ADL is affected (i.e. dementia).

First, the authors (including both neurologists and GPs experienced in diagnosing cognitive impairment) discussed the required test features for each of these situations. Secondly, we performed a literature search on cognitive tests used in primary care. We searched for English language articles listed on PubMed from January 2000 to January 2017. We used the search terms 'dementia' and 'cognitive' combined with 'screening', 'assessment', 'instrument', 'tool' and 'measure' combined with 'primary care'. Due to the large and heterogeneous body of literature we limited our selection to systematic reviews and meta-analyses. Third, we selected the most appropriate cognitive tests in relation to the GP's assessment of the likelihood of cognitive impairment. At last, we incorporated the

cognitive tests in a practical diagnostic algorithm and completed this algorithm using current guidelines and consensus documents to determine the key points that should be addressed in the first steps of the diagnostic procedure.

Required test features

For all three likelihoods of cognitive impairment, we identified the cognitive tests of which appropriate cut-off scores had been reported in at least two independent studies.

Cognitive impairment not likely

When a patient complains but the GP considers cognitive impairment to be not likely, the prior probability that this patient has cognitive impairment is low and the chance this patient has dementia will be even lower.[4] The main objective of a cognitive test in this situation is to rule out cognitive impairment, in particular MCI. A test should have a high negative predictive value (NPV) and should preferably be brief. A high positive predictive value (PPV) is less relevant if one aims to rule out a condition, as a low PPV can be amended by performing an additional test in case of a positive test result. For this situation we only considered tests that have been studied for MCI.

Cognitive impairment possible

This is the most challenging diagnostic situation, the "grey zone". When the GP considers cognitive impairment to be possible, but ADL appears to be preserved, the prior probability that the patient has MCI, or possibly even dementia is substantial.[4] The main objective of a cognitive test in this situation is to distinguish between presence or absence of cognitive impairment. A cognitive test in this situation should therefore be able to detect MCI and dementia in a population with a moderately high prevalence of cognitive impairment. We may assume that a test validated for MCI with an adequate NPV, will also detect dementia. Therefore, we considered tests that have been studied for MCI only, or MCI and dementia. We prioritised a high NPV above a high PPV to avoid false reassurance.

Cognitive impairment likely

When the GP considers the likelihood of cognitive impairment to be high and ADL appears to be affected and, the prior probability that this patient has dementia is high.[4] A cognitive test in this situation should therefore be able to detect dementia in a population with a high prevalence of cognitive impairment. For this situation we only considered tests that have been studied for dementia. The main objective of a test in this situation is to confirm that the patient has dementia, a test with a high PPV for dementia is therefore preferred.

Results

We critically appraised ten systematic reviews and two meta-analyses.[5-16] Only one review, which is based on the comprehensive research report produced by Kaiser Permanente Research Affiliates Evidence-based Practice Center, provided sufficient details to assess the value of cognitive tests for our algorithm.[17] It includes a dual independent review of studies on brief (i.e. administered within 10 minutes or self-administered within 20 minutes) cognitive tests conducted in a primary care setting.

Selecting cognitive tests

Cognitive impairment not likely

As shown in Table 1, both the clock-drawing test[18] and the Montreal cognitive assessment (MoCA)[19] have a high (≥89%) NPV and a moderate PPV (≤50%) in populations with relatively low prevalence rates of MCI (14-24%). Taking into account their comparable diagnostic accuracy, the short administration time of the clock-drawing test (1-3 minutes) relatively to the MoCA (10 minutes), we selected the clock-drawing test for our algorithm. The clock-drawing test assesses multiple aspects of cognitive functioning, in particular visuospatial and praxis abilities. In contrast, the MoCA contains multiple subtests that tap into different cognitive domains and can thus provide some more information on the actual nature of the cognitive impairment.

Table 1: Evidence summary[17] of cognitive tests for MCI (MCI versus normal cognition, dementia not included)

Test	Studies (n)	Test time (min)	Cut-off score	Study population, % MCI	Number of participants analysed	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
CDT	3	1-3	≤ 9	48	465	41 (34, 47)	83 (78, 88)	69 (60, 77)	60 (55, 65)
			≤ 9	15	3198	58 (54, 63)	57 (55, 59)	19 (17, 22)	89 (87, 90)
			≤ 9	14	428	69 (56, 81)	63 (58, 68)	23 (17, 30)	93 (89, 96)
MMSE	2	7-10	< 28	84	91	47 (36, 59)	73 (45, 92)	90 (76, 97)	22 (11, 35)
			< 28	44	524	45 (39, 52)	80 (75, 84)	64 (56, 71)	66 (60,70)
MoCA	2	10	< 26	24	152	100 (91, 100)	50 (41,59)	39 (29, 50)	100 (94, 100)
			< 26	20	99	80 (56, 94)	76 (65, 85)	46 (29, 63)	94 (85, 98)

Only the studies reporting a cut-off score that was studied more than once are depicted in the table. 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=ClockDrawing Test; MMSE=Mini Mental State Examination; MoCA = Montreal Cognitive Assessment.

Table 2: Evidence summary[17] of cognitive tests for cognitive impairment (dementia and MCI versus normal cognition)

Test	Studies (n)	Test time (min)	Cut-off score	Study population, % dementia / % MCI	Number of participants analysed	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
MoCA	1	10	< 26	8/19	107	86 (67, 96)	76 (65, 85)	56 (40, 71)	94 (85, 98)
Mini-Cog	2	3-4	2/3	40/12	371	84 (79, 89)	88 (81, 93)	92 (87, 95)	77 (70, 83)
			2/3	3/39	630	39 (34, 45)	78 (73, 82)	57 (49, 64)	63 (59, 68)
MMSE	3	7-10	23/24	4/26	269	53 (43, 64)	92 (88, 95)	71 (59, 81)	85 (78, 89)
			23/24	9/47	160	77 (67, 85)	70 (58, 80)	77 (67, 85)	70 (56, 80)
			23/24	4/5	1115	72 (62, 81)	89 (65, 99)	39 (32, 47)	97 (96, 98)

Only the studies reporting a cut-off score that was studied more than once are depicted in the table. 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: MoCA = Montreal Cognitive Assessment; MMSE=Mini Mental State Examination.

Table 3: Evidence summary[17] of cognitive tests for dementia (dementia versus no dementia)

Test	Studies (n)	Test time (min)	Cut-off score	Study population, % dementia	Number of participants analysed	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
AMT	2		7/8	29	269	42 (31, 53)	93 (89, 96)	71 (56, 83)	80 (74, 85)
			7/8	4	358	92 (64, 100)	95 (93, 97)	43 (25, 63)	100 (98, 100)
Mini-Cog	2	3-4	2/3	40	371	97 (93, 99)	71 (65, 77)	71 (64, 77)	97 (93, 99)
			2/3	3	630	76 (54, 90)	73 (69, 76)	9 (5, 14)	99 (97,100)
MIS	3	4	4	10	483	80 (66, 90)	96 (94, 98)	70 (57, 82)	98 (96, 99)
			4	18	318	76 (42, 100)	73 (56, 96)	38 (29, 47)	94 (89, 97)
			4	12	240	86 (67, 96)	97 (94, 99)	80 (61, 92)	98 (95, 100)
MMSE	5	7-10	23/24	4	1115	91 (78, 98)	87 (85, 89)	23 (17, 29)	100 (99, 100)
			23/24	1	709	87 (78, 95)	89 (86, 92)	52 (44, 60)	98 (96, 99)
			23/24	4	358	77 (46, 95)	97 (94,98)	46 (24, 68)	99 (97, 100)
			23/24	6	648	88 (74, 96)	88 (85, 90)	32 (24, 42)	99 (98, 100)
			23/24	28	360	84 (75, 90)	88 (84, 92)	73 (64, 81)	94 (90, 96)
MMSE	4	7-10	24/25	29	283	81 (70, 88)	76 (70, 82)	57 (48, 67)	90 (85, 95)
			24/25	4	269	98 (78, 100)	84 (79, 87)	21 (13, 33)	100 (99, 100)
			24/25	14	274	85 (70, 94)	81 (75, 86)	42 (31, 54)	97 (94, 99)
			24/25	19	449	84 (75, 91)	83 (79, 87)	55 (46, 63)	96 (93, 98)
MSQ	2	4	7/8	16	164	100 (87, 100)	84 (76, 89)	54 (39, 69)	100 (97, 100)
			7/8	4	358	92 (64, 100)	98 (96, 99)	67 (41, 87)	100 (98, 100)
SPMSQ	2	3-4	7/8	3	119	100 (29, 100)	100 (97, 100)	100 (29, 100)	100 (97, 100)
			7/8	4	358	100 (75, 100)	97 (94, 98)	54 (33, 75)	100 (99, 100)

Only the studies reporting a cut-off score that was studied more than once are depicted in the table. Abbreviations: CI=Confidence Interval; Sens=Sensitivity; Spec=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value.

Abbreviations cognitive tests: *AMT=Abbreviated Mental Test; MIS=Memory Impairment Screen; MMSE=Mini Mental State Examination; MSQ=Mental Status Questionnaire; SPMSQ=Short Portable Mental Status Questionnaire*

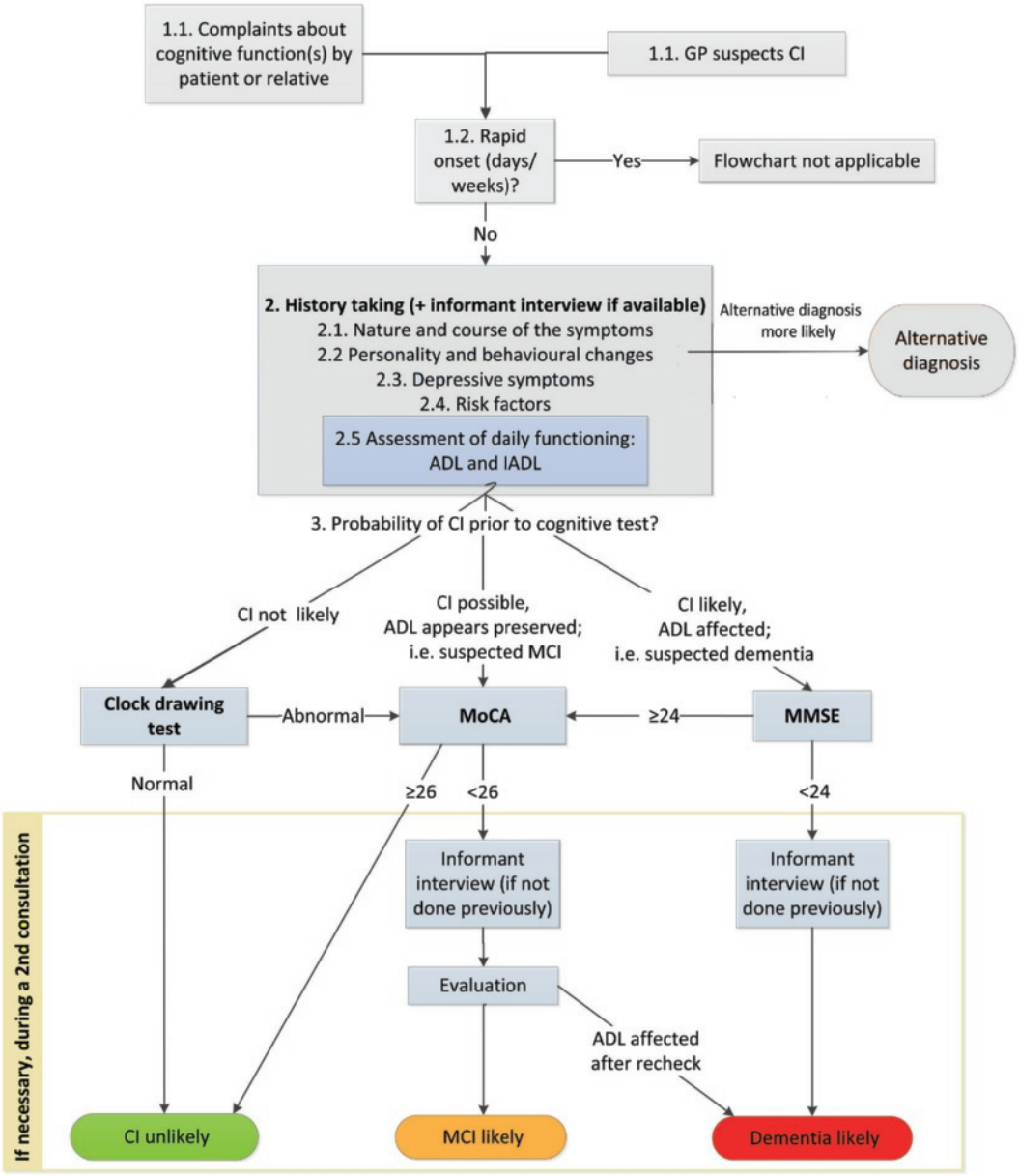
Cognitive impairment possible

As shown in tables 1 and 2, all tests that have been studied for MCI only, or cognitive impairment, have limited PPVs (≤71%), with the exception of study populations in which MCI or cognitive impairment is highly prevalent (≥50%). The MoCA has the most favorable NPV (≥ 94%) for both MCI and cognitive impairment overall and was therefore selected for our algorithm.

Cognitive impairment likely

Table 3 demonstrates that the Mental Status Questionnaire, the Short Portable Mental Status Questionnaire and the Memory Impairment Screen were only investigated in study populations with a prevalence of dementia ≤18% and it is therefore unclear if they are suitable in a situation with a high prior probability of dementia. The Abbreviated Mental Test and the Mini-Cog were both studied twice, once in a population with a very low prevalence of dementia (3% and 4% respectively) and once in a population with a high prevalence of dementia (29% and 40% respectively). In populations with a high prevalence of dementia the PPV of both tests was 71%. The MMSE (cut-off <24) has a comparable PPV (73%) in a population with a dementia prevalence of 28%. The NPV of all tests - with the exception of the Abbreviated Mental Test - was above 90%. In conclusion, both the Mini-cog and the MMSE with a cut-off <24 have favourable test features for this situation. Since the MMSE[20] is most frequently studied and well known we selected this test as most suitable for our algorithm.

Figure1: Proposed algorithm for a cognitive evaluation



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; MoCA = Montreal cognitive assessment; MMSE=mini mental state examination.

Proposed algorithm for a cognitive evaluation

1. Cognitive complaints

The starting point of the algorithm (1.1) is cognitive complaints expressed by the patient or a relative, or suspicion of cognitive impairment by the GP. In the evaluation of the complaints the mode of onset (1.2) provides essential guidance. In MCI and dementia, which is mostly caused by neurodegenerative or vascular pathologies, cognitive impairment is acquired and has a slowly progressive onset. This 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. History taking and informant interview

History taking and an informant interview are fundamental in a cognitive evaluation.[2] Concerns expressed by a close informant are generally even more predictive of cognitive impairment than self-reported symptoms.[2] 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 symptoms started and how these developed over time. Memory problems are typically one of the first symptoms of cognitive impairment, but other cognitive domains may also be affected (Table 4).[21]

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 relatives. The Neuropsychiatric Inventory Questionnaire is frequently recommended to assess severity and impact of behavioural changes.[22,23] The score of this 12-item informant questionnaire ranges from 0 to 36 with higher scores indicating more behavioural disturbance.[24]

2.3. Depressive symptoms.

GPs should be alert for depressive symptoms in patients with suspected cognitive impairment.[25] Depression can be a prodromal symptom of dementia but depressive symptoms can also follow cognitive decline. In addition, depressive symptoms 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, can be used.[26] Cognitive symptoms should always be re-evaluated after the depression is treated.

Table 4: Signs and symptoms to discuss during history taking and to help signalling cognitive impairment [21]

Memory impairment • Repeating 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

2.4. Risk factors.

Age is the most important predisposing risk factor for cognitive impairment with estimated prevalence rates around 1% at the age of 60 and 30-60% in individuals of ≥90 years.[27] Lower intelligence, education and occupational attainment are associated with a higher risk of developing cognitive impairment.[28] Additional risk factors are a positive family history (especially early-onset cases) and head trauma.[29] Diabetes and cardiovascular risk factors, such as smoking and hypertension are other predisposing factors.[30]

2.5. Daily functioning.

Daily functioning comprises ADL and instrumental ADL (IADL). 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, housekeeping, laundry, transportation, responsibility for medication and handling finances.

In patients with MCI, ADLs are preserved while there can be minimal impairment in IADLs.[31] In patients with dementia (I)ADLs are affected by definition.[32] It should be noticed that the boundaries between "normal" and "impaired" daily functioning are not always evident and are influenced by pre-existent activity levels. The Katz ADL [33] and the Lawton IADL [34] scales are frequently recommended to assess (I)ADL. Both scales can be completed by the patient or an informant.

3. Is cognitive impairment not likely, possible or likely?
Based on the previous steps the GP can estimate the likelihood that the patient has cognitive impairment and choose the most suitable cognitive test (Figure 1). If according to the GP the likelihood that the patient has cognitive impairment is very low or very high, it may well be that none of the cognitive tests are of added value. Not using any cognitive test could then be a good option.

What if the cognitive test result does not match the GPs expectations?
The steps in the proposed algorithm will guide the GP towards the most probable diagnosis (Figure 1). However, if there is a mismatch between the findings of history taking and the test, the results need to be reconsidered. It is important to perform an informant interview if not done previously and to consider alternative diagnoses. If uncertainty persists the GP may decide to re-evaluate the patient in 6-12 months or to refer to a specialist for a more comprehensive cognitive assessment.

Discussion

Current guidelines and guidance articles about which, when and how to use cognitive test during a cognitive evaluation in primary care are diverse. Most often the same cognitive test(s) are recommended for *all* patients who consult the GP with cognitive complaints regardless of the prior probability of cognitive impairment.[21-23,35-41] The MMSE is most frequently recommended, followed by the MoCA, the clock-drawing test and the Mini-Cog. The choices of the cognitive tests in our algorithm are therefore consistent with current recommendations. However, we recommend the use of three different tests in three different situations to make the diagnostic procedure more efficient and tailored to the individual patient.

To our knowledge this is the first time that a diagnostic algorithm is presented where the choice of cognitive tests is guided by the prior probability that the patient has cognitive impairment. This allows the GP to take into account the true value of a test, in addition to information that has already been gathered. For example, the short and sensitive clock-drawing test will have no added value in patients who visit the GP with typical signs and symptoms of dementia and the added value of a normal MMSE score is limited in patients with only mild symptoms of cognitive impairment. It can therefore be expected that our algorithm is more efficient, although its true value should still be established.

Several limitations of our approach in constructing the algorithm should be considered. The information on test characteristics of many tests was limited. Only a few tests have been studied in more than one fair or good quality study that included specific cut-off values. Hence at present the available evidence to select suitable cognitive tests for the diagnostic algorithm was limited. Prioritising test characteristics is to a certain extent subjective, we tried to avoid subjectivity as much as possible by means of pre-defined criteria based on expert opinion and consensus; however, other opinions are possible and could lead to the selection of other cognitive tests. In addition, we had to make assumptions about the pre-test probability in each of the three situations we distinguished. Further study is needed to validate and evaluate this diagnostic algorithm.

In conclusion, the ‘one-size-fits-all’ approach for patients with cognitive complaints appears obsolete. The prior probability that the patient has cognitive impairment should be taken into account when choosing a cognitive test. The algorithm reflected in Figure 1 may guide GPs during this diagnostic procedure.

References

1. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Dis Assoc Disord. 2009;23:306-314.
2. Olazarán J, Torrero P, Cruz I, Aparicio E, Sanz A, Mula N, et al. Mild cognitive impairment and dementia in primary care: the value of medical history. Fam Pract. 2011;28:385-392.
3. Grobbee D, Hoes A. Clinical Epidemiology: Principles, Methods, and Applications for Clinical Research. London: Jones and Bartlett, 2014.
4. van den Dungen P, Moll van Charante EP, van de Ven PM et al. Dutch family physicians' awareness of cognitive impairment among the elderly. BMC Geriatr. 2015;15:105.
5. Brodaty H, Low LF, Gibson L, Burns K. What is the best dementia screening instrument for general practitioners to use? Am J Geriatr Psychiatry. 2006;14:391-400.
6. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry. 2007;78:790-799.
7. Harvan JR, Cotter V. An evaluation of dementia screening in the primary care setting. J Am Acad Nurse Pract. 2006;18:351-360.
8. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. Int J Geriatr Psychiatry. 2010;25:111-120.
9. Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013; doi:10.7326/0003-4819-159-9-201311050-00730.
10. Lorentz WJ, Scanlan JM, Borson S. Brief screening tests for dementia. Can J Psychiatry. 2002; doi:10.1177/070674370204700803.
11. Kansagara D, Freeman M. A systematic Evidence Review of the Signs and Symptoms of Dementia and Brief Cognitive Tests Available in VA. 2010 Apr. Available from: https://www.ncbi.nlm.nih.gov/books/NBK49021/
12. Milne A, Culverwell A, Guss R, Tuppen J, Whelton R. Screening for dementia in primary care: a review of the use, efficacy and quality of measures. Int Psychogeriatr. 2008;20:911-926.
13. Mitchell AJ, Malladi S. Screening and case finding tools for the detection of dementia. Part I: evidence-based meta-analysis of multidomain tests. Am J Geriatr Psychiatry. 2010;18:759-782.
14. Mitchell AJ, Malladi S. Screening and case-finding tools for the detection of dementia. Part II: evidence-based meta-analysis of single-domain tests. Am J Geriatr Psychiatry. 2010;18:783-800.
15. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. QJM. 2007;100:469-484.
16. Yokomizo JE, Simon SS, Bottino CM. Cognitive screening for dementia in primary care: a systematic review. Int Psychogeriatr. 2014; doi: 10.1017/S1041610214001082.
17. Lin J, O'Connor E, Rossom R, Perdue L, Burda B, Thompson M, et al. Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Nov. (Evidence Syntheses, No. 107.) https://www.ncbi.nlm.nih.gov/books/NBK174643/. Accessed 10 August 2017.
18. Shulman KI. Clock-drawing: is it the ideal cognitive screening test? Int J Geriatr Psychiatry. 2000;15:548-561.
19. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695-699.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J.Psychiatr Res. 12, 189-198. 1975.
21. Moll van Charante EP. Dementia guideline of the Dutch College of General Practitioners. Huisarts Wet. 2012; 55:306-317.
22. Cummings JL, Frank JC, Cherry D et al. Guidelines for managing Alzheimer's disease: part I. Assessment. Am Fam Physician. 2002; 65(11):2263-72.
23. Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. J Am Board Fam Med. 2012;25:367-382.
24. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12:233-239.
25. Thorpe L. Depression vs Dementia: How Do We Assess? The Canadian Review of Alzheimer's Disease and Other Dementias. 2009; 17-21. http://www.alzheimer.ca/~/media/Files/national/Articles-lit-review/article_Depression_vs_Dementia_2009_e.pdf. Accessed 24 November 2016.
26. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17:37-49.
27. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013;9:63-75.
28. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative

analyses. PLoS One. 2012;7:e38268.
29. Stephan BC, Brayne C. Risk factors and screening methods for detecting dementia: a narrative review. J Alzheimers Dis. 2014; doi:10.3233/JAD-141413.
30. Exalto LG, Quesenberry CP, Barnes D, Kivipelto M, Biessels GJ, Whitmer RA. Midlife risk score for the prediction of dementia four decades later. Alzheimers Dement. 2014;10:562-570.
31. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256:240-246.
32. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.
33. Katz S, Akpom CA. 12. Index of ADL. Med Care. 1976;14:116-118.
34. Graf C. The Lawton instrumental activities of daily living scale. Am J Nurs. 2008;108:52-62.
35. Adelman AM, Daly MP. Initial evaluation of the patient with suspected dementia. Am Fam Physician. 2005;71(9):1745-1750.
36. Feldman HH, Jacova C, Robillard A, Garcia A, Chow T, Borrie M, et al. Diagnosis and treatment of dementia: 2. Diagnosis. CMAJ. 2008;178:825-836.
37. Geldmacher DS, Kerwin DR. Practical Diagnosis and Management of Dementia Due to Alzheimer's Disease in the Primary Care Setting: An Evidence-Based Approach. Prim Care Companion CNS Disord. 2013;15.
38. Lee L, Weston WW, Heckman G, Gagnon M, Lee FJ, Sloka S. Structured approach to patients with memory difficulties in family practice. Canadian Family Physician. 2013;59(3):249-254.
39. Fairbairn A, Gould N, Kendall T, Ashley P, Bainbridge I, Bower, L, et al. National Institute for Health and Clinical Excellence. Dementia: Supporting people with dementia and their carers in health and social care. Published 2006, Last updated September 2016. https://www.nice.org.uk/guidance/cg42/resources/dementia-supporting-people-with-dementia-and-their-carers-in-health-and-social-care-pdf-975443665093. Accessed 17 November 2016.
40. Dyer SM, Laver K, Pond CD, Cumming RG, Whitehead C, Crotty M. Clinical practice guidelines and principles of care for people with dementia in Australia. Aust Fam Physician. 2016;45(12):884-889.
41. Connelly P, Archibald C, Backett S, Brockie J, Carnon A, Cooper G, et al. Scottish Intercollegiate Guidelines Network. Managment of patients with dementia: A national clinical guideline. 2006. http://umh1946.edu.umh.es/wp-content/uploads/sites/172/2015/04/Management-of-patients-with-dementia-NHS.pdf. Accessed 17 November 2016.

CHAPTER 8

Cognitive Impairment in Diabetes: Rationale and Design Protocol of the 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
The aim of this study is to develop a stepped diagnostic procedure, consisting of a screening test complemented by an evaluation by a general practitioner (GP), 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 GP will be assessed. A diagnosis of mild cognitive impairment (MCI) or dementia at a memory clinic will serve as reference standard. This cognitive impairment in diabetes (Cog-ID) study will include 513 people from primary care facilities aged ≥70 with type 2 diabetes. The participants will first fill out the TYM and SAGE tests, followed by a standardized GP evaluation for cognitive impairment, including a mini mental state examination (MMSE). Subsequently, participants suspected of cognitive impairment (on either test or the GP assessment) and a random sample of 14.9% (65/435) of participants without suspected cognitive impairment will be referred to the memory clinic. At the memory clinic, a medical examination, neuropsychological examination, and magnetic resonance imaging (MRI) of the brain will be performed. Participants will also fill out questionnaires assessing health status and depressive symptoms at baseline and after 6 and 24 months.

Results
This research obtained funding and ethical approval. Enrolment started in August, 2012, and all study-related activities will be completed in September, 2016.

Conclusion
With the results from this study, physicians will be able to detect cognitive impairment affecting type 2 diabetes patients through case-finding, and can use tailored care to reduce associated complications. Additionally, the results may stimulate discussions about cognitive impairment and whether early recognition is desirable.

Introduction

Background

Patients with type 2 diabetes have an increased risk of cognitive impairment and a doubled risk of dementia compared to 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] Early recognition of cognitive impairment could assist the general practitioner (GP) in taking 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. While screening algorithms have been established for microvascular complications, such as retinopathy or nephropathy, there is no established method to detect undiagnosed cognitive impairment. The ideal procedure for the 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, evaluations by the GP 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 (TYM)[11] and the Self-Administered Gerocognitive Examination (SAGE)[12] tests. 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).[11-13] 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. However, before the effect of a diagnostic procedure can be evaluated, which specific tests to include must be determined. The latter

is examined in this cognitive impairment in diabetes (Cog-ID) study. We aim to establish a reliable, valid, and efficient stepped diagnostic procedure to detect cognitive impairment in patients ≥70 years of age with type 2 diabetes, starting with the TYM and the SAGE tests. It is unknown which of these two tests is best suited for application in a primary care setting; therefore we will assess the accuracy and feasibility of both. 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 the main study. Together, the results will help shape future studies with the goal of answering the unresolved, but increasingly relevant and heavily debated question,[14] whether early recognition of cognitive impairment in patients with type 2 diabetes will help the GP to take appropriate measures in disease management, and ultimately prevent treatment-related complications. Future studies are needed to assess the effect of the established diagnostic procedure on clinical outcomes in a randomized controlled trial.

Objectives

Our overall aim is to establish a reliable, valid, and efficient stepped diagnostic procedure to detect undiagnosed cognitive impairment in patients ≥70 years of age with type 2 diabetes. The procedure will consist of a self-administered cognitive test and an evaluation by a GP. Additionally, we will describe how early detection of cognitive impairment affects treatment and quality of life in participating patients in a parallel observational study. The specific objectives of the study are (1) to assess the validity of two self-administered cognitive tests (TYM and SAGE) in detecting 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 GP in detecting undiagnosed cognitive impairment in patients with type 2 diabetes, (3) to estimate the accuracy and efficiency of the best cognitive test(s) combined with the evaluation by the GP, and (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 (GPs) in the surroundings of Utrecht, the Netherlands, will be asked to select patients with type 2 diabetes mellitus ≥70 years of age. Exclusion criteria include a diagnosis of dementia, 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 GP 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 the 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 tasks.[11] It is a self-administered test and takes a patient around 5 minutes to complete. 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); because of our study design all patients will receive these 5 points. The maximum score is 50 points. A score of ≤39 is suggestive of dementia.[11] The TYM was translated into Dutch and then translated back to English by a bilingual native English speaker, which resulted in a version almost identical to the original.

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 is suggestive of dementia.[12] Like the TYM, the SAGE was translated into Dutch and then back into English, which resulted in a version almost identical to the original.

The Diagnostic Strategy

Part 1: Home Visit

Participants will be visited at home by a research physician (a trainee GP). The home visit will take about 1 hour. The participant will be asked to fill out the TYM, SAGE, and a questionnaire assessing health status and depressive symptoms, including the Short

Form Health Survey (SF-36),[15] EuroQol (EQ)-5D and EQ-VAS,[16] and the Center for Epidemiologic Studies Depression Scale (CES-D).[17] The research physician will be blinded for the scores on the TYM and the SAGE, and will not provide any assistance in filling out the questionnaires. Following the questionnaires, the research physician will administer a standardized diagnostic interview based on the Dutch guideline for case finding of dementia by GPs to both the participant and (if possible) a close informant,[18] representing the evaluation by the GP. The interview will include 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 11 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 is suggestive of dementia.

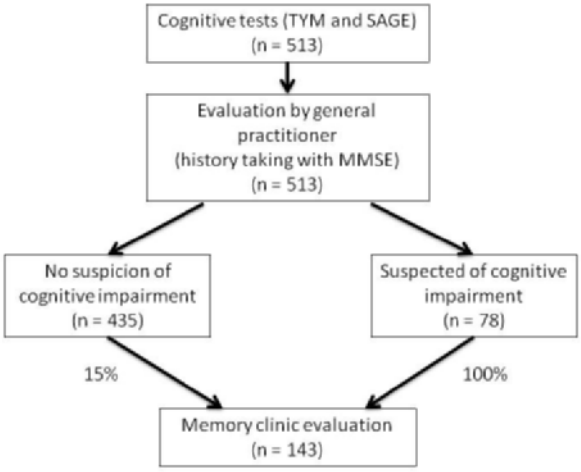
Based on the history taken, the research physician will decide whether the participant should be classified as "suspected of cognitive impairment" or "no cognitive impairment" according to the criteria for MCI and dementia.[19,20] If the MMSE score is ≤24, the participant will always be classified as "suspected of cognitive impairment".

Part 2: Selection Criteria for Memory Clinic Visit
After the home visit, an independent physician, not 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 visited the participant at home will not be informed about the results of the memory clinic. The following 3 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 criteria, the participant will be invited to the memory clinic. In addition, a random sample of 15% (65/435) of participants with negative scores on all 3 criteria will be invited to the memory clinic (see section sample size calculation and Figure 1).

Table 1. List of questions about acquired cognitive symptoms for the participant and informant.

Questions
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 depressed?
Do you still have pleasure in things?
Do you have problems with hearing or vision?
The following 3 questions to be completed by the informant
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
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



Part 3: Memory Clinic Visit
All professionals involved in the memory clinic will be blinded to the results of the TYM and 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 will perform a diagnostic interview and a neurological examination, administer the Cambridge Cognitive Examination (CAMCOG)[21], and measure body weight, height, and blood pressure. Body mass index (BMI) will also be calculated. In addition, the Disability Assessment for Dementia (DAD)[22] and the Neuropsychiatric Inventory (NPI)[23] 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 90-minute standardized neuropsychological assessment examining memory, information processing speed, attention and executive functioning, and visuoconstruction. The division in cognitive domains will be made a priori, according to standard neuropsychological practice and cognitive theory.[24] 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 (RAVL), and the delayed recall of the Rey-Osterrieth Complex Figure Test (ROCF). The domain "information processing speed" will be assessed by the trail-making test (part A), the Stroop Color-Word Test (parts 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 ROCF, the Judgement of Line Orientation (JLO), and the Visual Object and Space Perception Battery (VOSP). Furthermore, the premorbid level of intelligence (intelligence quotient (IQ)) will be estimated by the Dutch version of the National Adult Reading Test (NART). 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 consisting 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.

Cognitive Impairment Diagnosis

Within two weeks of 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 will be used.[19] In short, dementia will be defined as memory impairment and impairment in at least one other cognitive domain, including aphasia, apraxia, agnosia, and 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.[20] In addition, the presumed etiology of dementia will be specified (e.g., Alzheimer’s disease).

Guided by the diagnosis, tailored treatment advice will be given to the participants’ GP regarding management of the diabetes treatment and cognitive impairment. Advice for the diabetes treatment will consist of re-evaluation of the proper glycemic target and the risk of insulin treatment. As well, advice evaluating the need for extra support for participants unable to meet treatment goals or in need of tools, for example a memory aid for appointments or medication, will be provided.

After the Diagnosis

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

Follow-Up

Following the home visit (6 months), participants will receive a follow-up questionnaire, 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. A second follow-up questionnaire with the same questions will be sent after 24 months.

After the home visit (6 months), the medical records of the participants will be examined to obtain information on the medical history, values of recent diabetes controls (HbA1c, lipids, creatinine, weight, height, blood pressure), 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, GPs of participants that attended the memory clinic will receive a questionnaire 6 months after the evaluation at the memory clinic to assess whether the study led to new insights and whether it changed their treatment plan (Textbox 1).

Textbox 1. Follow-up questions for the general practitioner (GP).

Questions

1. **Did the result come 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 your 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?**

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, false positive, false negative, or true negative separately for the evaluation by the GP, TYM, and SAGE.

Not all of the patients in our study will receive the reference standard, which could lead to partial verification bias.[25] However, if only patients with the reference standard were 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.[25] A reliable method to reduce this bias is to impute the reference standard.[25] A cognitive impairment diagnosis (yes or no) in the memory clinic will, therefore, be imputed for patients who did not attend the memory clinic. Imputed databases (N=10) will be generated with the predictors TYM, SAGE, MMSE, GP evaluation, as well as age, gender, educational level, living situation, and score on the domain mobility of the EQ-5D. The latter two are chosen because they can influence why some patients did 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 GP discriminate between participants with and without cognitive impairment will be determined by the area under the receiver operating characteristic (ROC) curve. Next, the optimal cutoff values of the tests for this population will be determined 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 cutoff point.[26] 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 results of the best cognitive test and the evaluation by the GP will be combined. This should reflect the future implementation of the stepped diagnostic procedure, in which a GP 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 GP are positive. This combination will likely have a higher positive predictive value (PPV) than the cognitive test or the evaluation by the GP alone, leading to a more efficient diagnostic procedure. The added value of the GP’s evaluation will be assessed by calculating the adjusted ROC curve and the net reclassification index.[27]

The fourth objective of this study 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 at the 6- and 24-month 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 (i.e., 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%. Since little quantitative information is available on the prevalence of undiagnosed cognitive impairment, we based this assumption on four considerations. The first assumption is the prevalence of dementia in the Dutch population >65 years of age is around 16%.[28] The prevalence of cognitive impairment will be even higher if MCI is also considered. The second is that around half of all patients with cognitive impairment are undiagnosed. The third is the prevalence of cognitive impairment is higher in people with diabetes. And the fourth is the oldest old, in whom dementia prevalence is highest, are least likely to participate in research projects.

In previous research in adults aged ≥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 have a PPV comparable with that of the most commonly used instrument, the MMSE, which has a PPV of 53.6% for the diagnosis of dementia in primary care.[29] 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 and an alpha of 5% and one-sided testing (we are only interested in the lowest 5% of cognitive scores), 52 participants with a positive test result ($0.11= 1.65*\sqrt{(0.64*(1-0.64)/n)}$) are needed to have reliable, interpretable results. To achieve this number of test positive participants, given an assumed prevalence of 8% and a sensitivity of 79%, 513 participants are required. 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 3 tests (TYM, SAGE, and evaluation by the GP), 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 the 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 in order to establish the true and false positive rates of each of the tests. In addition, a sample (14.9%, 65/435) of the participants in which all 3 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 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.

Results

Participant enrolment started in August, 2012. All study-related activities were completed in September, 2016. The results are described in the chapters 2, 3, 4 and 9 of this thesis.

Discussion

This cognitive impairment in diabetes (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 (i.e., combining a cognitive test with history taking by a GP) to detect cognitive impairment in primary care. In addition, we will collect observational data on the impact of such diagnostic procedures on several aspects of patients' lives (health status, depressive symptoms, complications, and diabetes treatment) after 6 and 24 months. Physicians often assume that informing the patient about a diagnosis of cognitive impairment will negatively influence their health status, quality of life, and depressive symptoms.[30] However, one could also argue that undiagnosed cognitive impairment might cause a reduced quality of life and depressive symptoms, because it is likely to impact patients. If these aspects of patients' lives are affected by undiagnosed cognitive impairment, and could be ameliorated by informing the patient, then the tailoring and possibly the adjustment of treatment and/or organizing support could be another argument as to the importance of detecting cognitive impairment at an early stage.

A potential bias in diagnostic studies in which not all patients receive the reference standard is partial verification bias.[25] However, we tried to reduce this verification bias by imputing the reference standard in participants that do not visit the memory clinic. This method has been shown to give reliable estimates of missing reference data.[25]

With the information from this study, we can advise GPs on 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 future discussions on whether the early recognition of cognitive impairment in patients with type 2 diabetes with a case-finding strategy is desirable.

References

1. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006 Jan;5(1):64-74.
2. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 2012 May;42(5):484-491.
3. Bamford C, Eccles M, Steen N, Robinson L. Can primary care record review facilitate earlier diagnosis of dementia? Fam Pract 2007 Apr;24(2):108-116
4. Boustani M, Callahan CM, Unverzagt FW, Austrom MG, Perkins AJ, Fultz BA, et al. Implementing a screening and diagnosis program for dementia in primary care. J Gen Intern Med 2005 Jul;20(7):572-577
5. Bruce DG, Davis WA, Casey GP, Clarnette RM, Brown SGA, Jacobs IG, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. Diabetologia 2009 Sep;52(9):1808-1815.
6. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, ACCORD Group of Investigators, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012 Apr;35(4):787-793
7. Okura T, Heisler M, Langa KM. Association between cognitive function and social support with glycemic control in adults with diabetes mellitus. J Am Geriatr Soc 2009 Oct;57(10):1816-1824
8. Sinclair AJ, Hillson R, Bayer AJ, National Expert Working Group. Diabetes and dementia in older people: a Best Clinical Practice Statement by a multidisciplinary National Expert Working Group. Diabet Med 2014 Sep;31(9):1024-1031.
9. American Diabetes Association. Standards of medical care in diabetes--2013. Diabetes Care 2013 Jan;36 Suppl 1:S11-S66
10. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006 Sep;37(9):2220-2241
11. Brown J, Pengas G, Dawson K, Brown LA, Clatworthy P. Self administered cognitive screening test (TYM) for detection of Alzheimer's disease: cross sectional study. BMJ 2009;338:b2030
12. Scharre DW, Chang SI, Murden RA, Lamb J, Beversdorf DQ, Kataki M, et al. Self-administered Gerocognitive Examination (SAGE): a brief cognitive assessment Instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord 2010;24(1):64-71.
13. Koekkoek PS, Rutten GEHM, van den Berg E, van Sonsbeek S, Gorter KJ, Kappelle LJ, et al. The "Test Your Memory" test performs better than the MMSE in a population without known cognitive dysfunction. J Neurol Sci 2013 May 15;328(1-2):92-97
14. Brunet MD, McCartney M, Heath I, Tomlinson J, Gordon P, Cosgrove J, et al. There is no evidence base for proposed dementia screening. BMJ 2012;345:e8588
15. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998 Nov;51(11):1055-1068.
16. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001 Jul;33(5):337-343.
17. Bouma J, Ranchor AV, Sanderman R, van Sonderen E. Measuring symptoms of despression with the CES-D; instructions. Groningen, the Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken; 1995.
18. Luning-Koster M, Perry M, Moll van Charante EP, Vernooij-Dassen M, Wiersma T, Burgers JS. [Summary of Dutch College of General Practitioners' (NHG) practice guideline 'Dementia']. Ned Tijdschr Geneeskd 2012;156(49):A5323.
19. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychiatric Association; 2000.
20. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004 Sep;256(3):240-246.
21. Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S, et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986 Dec;149:698-709.
22. Gélinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. Am J Occup Ther 1999;53(5):471-481.
23. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994 Dec;44(12):2308-2314.
24. Lezak M, Loring DW, Howieson DB. Neuropsychological assessment. Oxford: Oxford University Press; 2004.
25. de Groot JAH, Janssen KJM, Zwinderman AH, Bossuyt PMM, Reitsma JB, Moons KGM. Correcting for partial verification bias: a comparison of methods. Ann Epidemiol 2011 Feb;21(2):139-148.

26. Youden WJ. Index for rating diagnostic tests. Cancer 1950 Jan;3(1):32-35.
27. Pencina MJ, D'Agostino RBS, D'Agostino RBJ, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008 Jan 30;27(2):157-72; discussion 207.
28. Poos M, Meijer S. Nationaal Kompas. Bilthoven; 2014 Jun 23. What is the prevalence of dementia and how many people die of it? URL: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/psychische-stoornissen/dementie/omvang/ [accessed 2015-05-27]
29. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 2009 Jan;43(4):411-431.
30. Iliffe S, Manthorpe J, Eden A. Sooner or later? Issues in the early diagnosis of dementia in general practice: a qualitative study. Fam Pract 2003 Aug;20(4):376-381

CHAPTER 9

Case-finding for cognitive impairment among people with Type 2 diabetes in primary care using the Test Your Memory and Self-Administered Gerocognitive Examination questionnaires: the Cog-ID study

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Abstract

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

Methods
Of 1243 invited patients with type 2 diabetes, aged ≥70 years, 228 participated in a prospective cohort study. Exclusion criteria were: 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 and Self-Administered Gerocognitive Examination). Secondly, a general practitioner, blinded to Test Your Memory and Self-Administered Gerocognitive Examination scores, performed a structured evaluation using the Mini-Mental State Examination. Subsequently, patients suspected of cognitive impairment (on either the cognitive tests or general practitioner evaluation) and a random sample of 30% of patients not suspected of cognitive impairment were evaluated at a memory clinic. Diagnostic accuracy and area under the curve were determined for the Test Your Memory, Self-Administered Gerocognitive Examination and general practitioner evaluation compared with a memory clinic evaluation to detect cognitive impairment (mild cognitive impairment or dementia).

Results
A total of 44 participants were diagnosed with cognitive impairment. The Test Your Memory and Self- Administered Gerocognitive Examination questionnaires had negative predictive values of 81 and 85%, respectively. Positive predictive values were 39 and 40%, respectively. The general practitioner evaluation had a negative predictive value of 83% and positive predictive value of 64%. The area under the curve was ~0.70 for all tests.

Conclusions
Both the tests evaluated in the present study can easily be used in case-finding strategies for cognitive impairment in patients with type 2 diabetes in primary care. The Self-Administered Gerocognitive Examination had the best diagnostic accuracy and therefore we would have a slight preference for this test. Applying the Self-Administered Gerocognitive Examination would considerably reduce the number of patients in whom the general practitioner needs to evaluate cognitive functioning to tailor diabetes treatment.

Introduction

The American Diabetes Association advices physicians to individualize diabetes treatment to the cognitive capacities of a patient.[1] In patients with type 2 diabetes the incidence of dementia is twice as high as in those without diabetes.[2] When cognitive function is deteriorating, self-management capacities diminish, resulting in problems with diabetes self-management, treatment adherence and monitoring.[3]

Usually the general practitioner (GP) evaluates cognitive functioning when a patient visits the surgery with memory complaints. If necessary the GP administers a cognitive test, most often the Mini-Mental State Examination (MMSE); however, many cases of cognitive impairment remain undiagnosed in this way.[4,5] Case-finding for cognitive impairment in elderly patients with type 2 diabetes has therefore been advocated.[6] Examining all people with diabetes, however, is time-consuming. A cognitive test that easily, quickly and reliably identifies people who require a GP-evaluation could make case-finding feasible by minimizing the number of people the GP needs to examine. Self-administered paper-and-pencil tests, like the Test Your Memory test (TYM)[7] and the Self-Administered Gerocognitive Examination (SAGE),[8] seem appropriate for this purpose. At the memory clinic, both tests can differentiate people with dementia and mild cognitive impairment (MCI) from those with normal cognition.[7,8] Their usefulness in a primary care setting is not yet assessed. The Cognitive Impairment in Diabetes (Cog-ID) study examined a stepped diagnostic procedure, to detect undiagnosed cognitive impairment in patients ≥70 years with type 2 diabetes.[9] In the present study, we report the diagnostic accuracy of the TYM and SAGE in that procedure.

Patients and Methods

Study design

The design of the Cog-ID study has been reported previously.[9] Briefly, people aged ≥70 years with type 2 diabetes were recruited from primary care. Exclusion criteria were a dementia diagnosis, previous memory clinic evaluation and inability to write or read Dutch. People with a disorder that might influence cognitive functioning, such as 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 SAGE were translated into Dutch and back-translated, resulting 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 5 minutes.[7] The tasks include orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visuospatial abilities and recall of a copied sentence. The ability to complete the test without help represents an 11th task. The maximum score is 50 points. A score <40 is suggestive of dementia.[7]

Self-Administered Gerocognitive Examination

The SAGE is a self-administered test, filled out in 10-15 minutes, that examines orientation, language, memory, executive function, calculations, abstraction and visuospatial abilities.[8] It includes questions on demographic information, medical and family history and current status. The maximum score is 22 points. A score <15 is suggestive of dementia.[8]

Diagnostic strategy

Part 1: home-visit

During a home-visit by a research physician (a trainee GP) that took one hour, participants were first asked to fill out the TYM, SAGE and questionnaires assessing health status and depressive symptoms. The physician remained blinded for the TYM- and SAGE-scores and did not help with filling out these questionnaires. Next, the physician administered a standardized interview on cognitive impairment, representing a GP-evaluation. Afterwards the MMSE was administered. It consists of eleven tasks including the domains orientation in time and space, registration of three words, concentration and calculation, word recall, language, and visuospatial abilities.[10] The maximum score is 30 points. A score <25 is suggestive of dementia.

Based on history taking and MMSE, the research physician classified the participant as "suspected of cognitive impairment" or "no suspicion of cognitive impairment" according to criteria for MCI and dementia.[11,12] In case of a MMSE-score <25 the participant 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 participant should be selected for a memory clinic evaluation. Three criteria were used: 1. "suspected of cognitive impairment" by the research physician; 2. a TYM-score <40; and 3. a SAGE-score <15. If a participant scored positive on one of these three criteria the participant was invited to the memory clinic. In addition a random sample of 30% of participants with three negative scores 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 SAGE. The visit took half a day and consisted of a standardized evaluation. Participants were examined by a (resident) neurologist and a neuropsychologist, magnetic resonance imaging 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. Additionally, intelligence level, educational level and activities of daily living were assessed. More details of the memory clinic evaluation have been described previously.[9]

Cognitive impairment (MCI or dementia) was our primary outcome and established by a multidisciplinary team. Dementia (using the diagnostic and statistical manual of mental disorders-IV[11]) was defined as memory impairment and impairment in at least one other cognitive domain that significantly affected social or occupational functioning compared with the previous level of functioning and was not caused by delirium. MCI (using the Winblad criteria) 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.[12] During the study, a category "cognition otherwise disturbed" appeared necessary for participants that did not fulfill MCI-criteria.

Statistical analyses
The diagnosis of cognitive impairment at the memory clinic was the reference standard. In our primary analyses the participants with 'cognition otherwise disturbed' were categorized in the group of 'normal cognition'. The outcomes MCI and dementia were combined. Participants were classified as true positive, false positive, false negative or true negative with regard to the GP-evaluation, the TYM and SAGE separately.

Not all participants visited the memory clinic (i.e. the reference standard) and selection of participants with the reference standard was not random. Performing a complete case analysis could lead to partial verification bias[13] and could lead to incorrect conclusions of diagnostic accuracy. Partial verification bias can be considered as a missing data problem and can be reduced with multiple imputation.[13] Patients with similar characteristics (age, gender, education) and comparable test scores (TYM, SAGE, GP-evaluation) would be likely to receive the same outcome (cognitive impairment yes/no). This principle is used in multiple imputation to estimate the missing data based on available information in the dataset; therefore to reduce this bias in the current study, a diagnosis of the memory clinic (cognitive impairment yes/no) was imputed for participants who did not attend the memory clinic.[13] Ten imputed databases were generated with the predictors TYM, SAGE, MMSE, GP-evaluation, age, gender, educational level, living situation and score on the EuroQol five-dimensions questionnaire mobility domain. The latter two were chosen because they could be associated with attending 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 participants with and without cognitive impairment was determined by the area under the receiver operating characteristic curve (AUC). Next, the optimal score tresholds were assessed using the Youden index.[14] Rubin's rule was used to calculate the 95%-confidence intervals for the combined AUCs and Youden indices.[15]

Because of the study design all participants scored five points for the last task of the TYM, performing the test without help. A sensitivity analysis giving all patients zero points for this task was performed. Another sensitivity analysis excluded patients with the diagnosis "cognition otherwise disturbed".

Categorical variables are reported as numbers and percentages, continuous variables as means with standard deviation (SD) values and not normally distributed variables as median with interquartile ranges (IQRs). 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 continuous variables without normal distribution. All statistical analyses were performed with IBM SPSS Statistics V.21.

Sample size calculation

The sample size calculation was described previously.[9] Because of uncertainty on the actual prevalence of undiagnosed cognitive impairment in our cohort, an interim analysis was performed after including 80 participants, in which only the proportion of participants classified as 'suspected of cognitive impairment' was checked, without unblinding the test

scores or the memory clinic findings . Because this proportion (45%) deviated significantly from the assumed proportion (15%), fewer participants were needed to achieve reliable results. We therefore reduced our study population from 513 to 228 participants. Subsequently we increased the sampling of screen-negatives (i.e., patients with a negative TYM, SAGE and GP-evaluation) from 15% to 30% to maintain a sufficient number of screen-negatives receiving the memory clinic evaluation.

Results

Study population

Between August 2012 and September 2014, 1243 patients from 22 general practices were invited to take part in the study. A total of 959 participants (77%) responded of which 228 participated (18%). Six participants 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 attending the memory clinic. After inclusion three participants were excluded because of a previous memory clinic evaluation (n=2) or inability to write (n=1)(Figure 1). The mean age of the remaining 225 participants was 76.8 years (70–92 years), 60% was men and median (IQR) educational level was 5 (4-6), defined as 10-11 years of education. In all, 40% of the participants lived alone and 61% had walking problems. Table 1 provides an overview of participants characteristics and median test values per test.

Figure 1. Flowchart

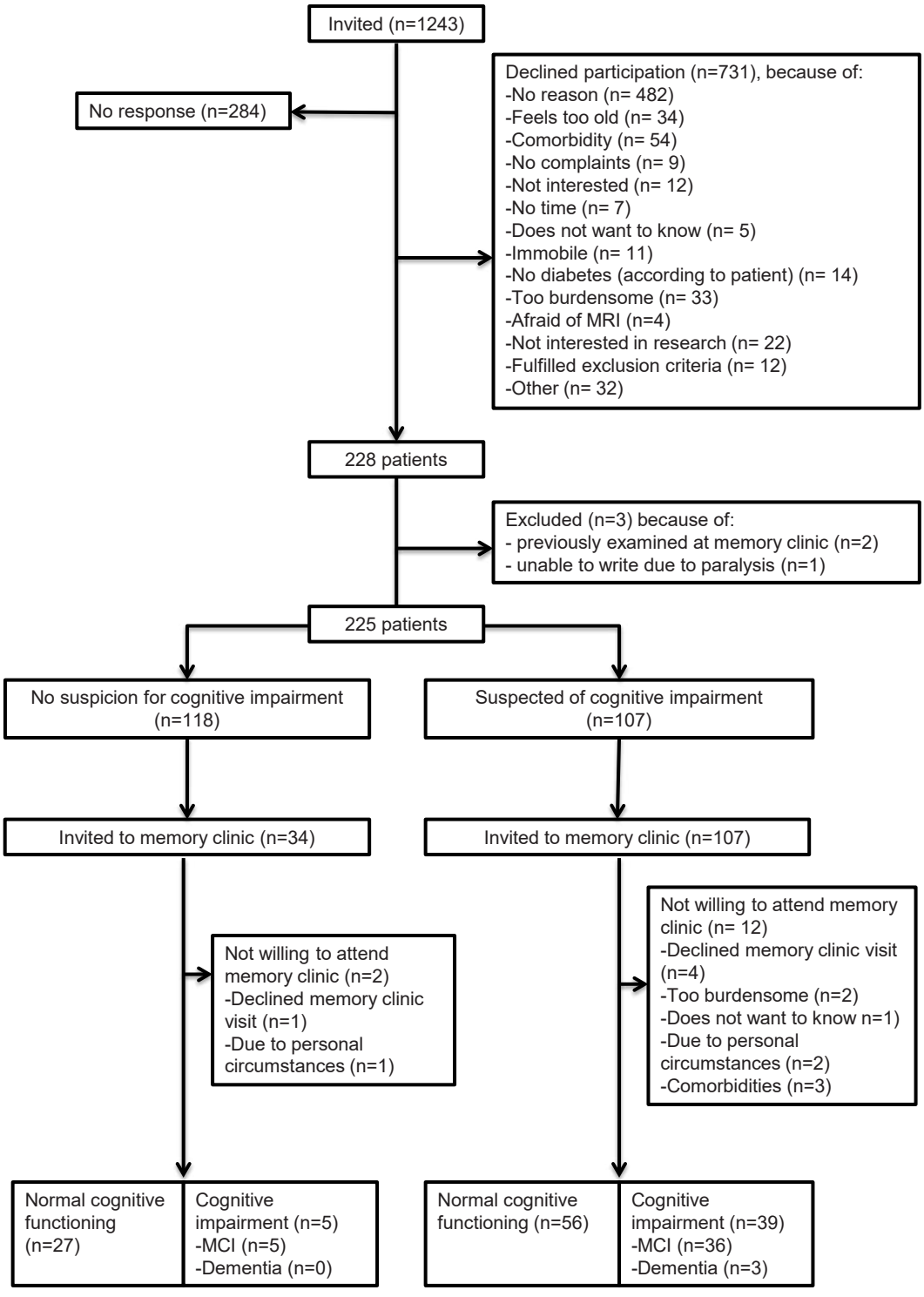


Table 1. Patient characteristics stratified per test

	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, MMSE: Mini Mental State Examination.

Cognitive tests results and memory clinic evaluation
Four participants missed values on the TYM questionnaire and seven did not complete the full SAGE; these participants were excluded from the respective analyses.

The median TYM-score was 43 (IQR 39-46; range 14–49), with 64 patients (29%) scoring <40. The median SAGE-score was 16 (IQR 13-19; range 2–22), with 77 patients (35%) scoring <15. In total 107 patients were selected for a memory clinic evaluation because of suspected cognitive impairment (Figure 1). Suspicion of cognitive impairment was based on both the tests and the GP-evaluation in 31 participants, on only the GP-evaluation in 8 participants, and on only the tests in 68 participants (16 on TYM; 26 on SAGE; 26 on both TYM and SAGE). The 34 participants selected as part of the random sample of screen-negatives were comparable to the whole group of screen-negatives with respect to age, gender and education (data not shown).

At the memory clinic three participants were diagnosed with dementia and 41 participants with MCI. Seventeen participants received the diagnosis “cognition otherwise disturbed”; 15 of them had an abnormal score on the cognitive tests (three on on the TYM test; four on the SAGE test; eight on both TYM and SAGE tests), four were also suspected by the GP (in addition to the tests) and two were part of the sample of screen-negatives.

Table 2 summarizes the test results with the memory clinic evaluation, after imputation, as reference standard. Because of the imputation the numbers of participants with cognitive impairment and normal cognition differ from those in Figure 1.

Table 2. Results of Test Your Memory, Self-Administered Gerocognitive Examination, Mini-Mental State Examination and general practitioner evaluations, 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)**
GP-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, General practitioner (GP) 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.

Diagnostic accuracies

Table 3 shows the diagnostic accuracy of each test. The TYM and SAGE tests have NPVs of 81% and 85% respectively; their PPVs were low. The GP evaluation had a similar NPV and a higher PPV. The MMSE had a PPV of 100% and a NPV of 77%.

Giving all patients zero points for the 11th task of the TYM, did not significantly change its predictive values, but the sensitivity increased to 85% and the specificity decreased from 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 tests by 5%.

Table 3. Diagnostic accuracy (95% CI) of the Test Your Memory, Self-Administered Gerocognitive Examination, Mini-Mental State Examination and general practitioner evaluations for cognitive impairment

	Sensitivity	Specificity	PPV	NPV	AUC†	Youden index†
TYM (threshold <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 (threshold <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 (threshold <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)
GP-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; GP: general practitioner

Receiver-operating characteristics 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 mean AUCs and Youden indices for the score tresholds used are presented in Table 3. Youden indices were calculated for all possible tresholds in each imputed database, leading to ten 'highest' indices. The highest index for the TYM ranged between 0.23 and 0.34 with corresponding cut-off scores between 40–44; 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 27–29.

Discussion

This study shows that the TYM and SAGE questionnaires both have sufficient diagnostic accuracy to support a case-finding strategy for cognitive impairment in patients with type 2 diabetes in primary care. With a negative test result, the chances that the patient has no cognitive impairment are 81% and 85% for the TYM test and SAGE respectively. If a patient scores positive on the test there will be cognitive impairment in 40% of patients. A GP-evaluation should then exclude or establish cognitive impairment. The MMSE has contrasting results. If the MMSE is positive cognitive impairment is almost certainly present, but the MMSE misses seven out of eight cases of cognitive impairment. Furthermore, a professional needs to administer the MMSE. Although the GP-evaluation alone might do just as well as the tests, the use of these tests would considerably reduce the number of patients that the GP needs to evaluate. The SAGE might be most suitable because of its highest predictive values and the availability of four different test versions.

Strenghts of the present study include its use of the memory clinic evaluation as reference standard and the population included. The cognitive tests were evaluated in patients with diabetes in primary care at risk of cognitive impairment and not unwilling to know their cognitive functioning. The response rate was 74%, and 24% of those responding agreed to participate. Selection bias cannot be excluded, as people with complaints about their cognitive performance might have been more willing to participate. Conversely, people with complaints could also be more reluctant to participate because they are afraid of a diagnosis of cognitive impairment. Because the PPV and NPV are dependent on the disease prevalence, the diagnostic properties 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 aged >65 years is around 16%.[16]

The GP-evaluation was performed without knowledge of the test results, as is current practice. The SAGE questionnaire, however, can be used for a first selection of patients that need further examination. The GP would then only evaluate patients with a positive result. Doing so, the prevalence of cognitive impairment in the group that receives a GP-evaluation will be higher than the prior probability in our study population. Consequently, the diagnostic accuracy of such stepped procedure is likely to increase. The design of the present study did not allow us to test this added value.

Partial verification bias was reduced by imputing the reference standard in participants without a memory clinic evaluation. This method provides reliable estimates of missing reference data.[13]

As a result of the study protocol, a modification of the TYM was needed to maintain blinding of the GP, which meant that executive functioning was examined less thoroughly.

Although the sensitivity analysis showed no difference in both PPV and NPV, our strategy could have reduced the diagnostic accuracy of the TYM. Additionally we chose to dichotomize our outcome in participants with and without cognitive impairment. As a results, participants with cognitive disorders not fulfilling the MCI-criteria (the group 'cognition otherwise disturbed') are labeled 'normal'. A number of these participants were detected by the tests and it is debatable whether it is justified to consider these results false-positives. This is, however, inherent to our study design and also applies to other diagnostic studies. It underlines the importance of a stepped procedure complementing tests with a GP-evaluation.

The diagnostic accuracy of the TYM was previously examined at several memory clinics,[7,17-23] but not in a primary care population. The SAGE was examined in a geriatric and memory clinic setting and as a screening tool in a community setting.[8,24] In the latter the diagnosis of cognitive impairment was based on the SAGE questionnaire 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.[17] The Youden indices in our study showed that our score treshold of <15 for the SAGE was close to the optimum tresholds (<15/<16), but the optimal cut-off scores for the TYM and MMSE were higher than our cut-off scores (<43 versus <40; <27 versus <25 respectively). Changing these tresholds would reduce the number of false-negatives, but would increase the number of false-positives, thereby increasing the number of people that need a GP-evaluation. These cognitive tests are not perfect, 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 major impact on long-term patient outcomes. Cognitive impairment was present in 25% of the people who accepted our invitation. We think it could be worthwhile to routinely offer patients aged ≥70 with type 2 diabetes a simple self-administered cognitive test. In case of a positive score, the GP could then start a conversation to discuss possible signs and symptoms of cognitive impairment and evaluate diabetes treatment.

To conclude, case-finding identifies a substantial number of people with cognitive impairment among patients aged ≥70 years with type 2 diabetes who are not unwilling to know their cognitive performance. In our strategy, the TYM and SAGE adequately identified people that need further examination, limiting the number of people needing a GP-evaluation. Further research should examine whether our suggested procedure results in an improvement in diabetes management and a reduction in treatment-related complications.

References

1. American Diabetes Association. Clinical practice recommendations. Diabetes Care 2013; 36 Suppl 1: S3.
2. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006; 5: 64-74.
3. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. Diabetes Res Clin Pract 2000; 50: 203-212.
4. Bamford C, Eccles M, Steen N, Robinson L. Can primary care record review facilitate earlier diagnosis of dementia? Fam Pract 2007; 24: 108-116.
5. Boustani M, Callahan CM, Unverzagt FW, Austrom MG, Perkins AJ, Fultz BA et al. Implementing a screening and diagnosis program for dementia in primary care. J Gen Intern Med 2005; 20: 572-577.
6. Sinclair AJ, Hillson R, Bayer AJ. Diabetes and dementia in older people: a Best Clinical Practice Statement by a multidisciplinary National Expert Working Group. Diabet Med 2014; 31: 1024-1031.
7. Brown J, Pengas G, Dawson K, Brown LA, Clatworthy P. Self administered cognitive screening test (TYM) for detection of Alzheimer's disease: cross sectional study. BMJ 2009; 338: b2030.
8. Scharre DW, Chang SI, Murden RA, Lamb J, Beversdorf DQ, Kataki M et al. Self-administered Gerocognitive Examination (SAGE): a brief cognitive assessment Instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord 2010; 24: 64-71.
9. Koekkoek P, Janssen J, Kooistra M, van den Berg E, Kappelle L, Biessels G et al. Rationale and design of the Cognitive Impairment in Diabetes (Cog-ID) study. JMIR Research Protocols, 2015; in press. doi:10.2196/resprot.4224
10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 2000.
12. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004; 256: 240-246.
13. de Groot JA, Janssen KJ, Zwinderman AH, Bossuyt PM, Reitsma JB, Moons KG. Correcting for partial verification bias: a comparison of methods. Ann Epidemiol 2011; 21: 139-148.
14. Youden WJ. Index for rating diagnostic tests. Cancer 1950; 3: 32-35.
15. Rubin DB. Multiple Imputations for Nonresponse in Surveys. 1987.
16. Poos M, Meijer S. [What is the prevalence of dementia and how many people die of it?] Bilthoven 2014 .
17. Hancock P, Larner AJ. Test Your Memory test: diagnostic utility in a memory clinic population. International journal of geriatric psychiatry 2011; 26: 976-980.
18. Hanyu H, Maezono M, Sakurai H, Kume K, Kanetaka H, Iwamoto T. Japanese version of the Test Your Memory as a screening test in a Japanese memory clinic. Psychiatry Research 2011; 190: 145-148.
19. Iatraki E, Simos PG, Lionis C, Zaganas I, Symvoulakis EK, Papastefanakis E et al. Cultural adaptation, standardization and clinical validity of the test your memory dementia screening instrument in greek. Dement Geriatr Cogn Disord 2014; 37: 163-180.
20. Munoz-Neira C, Henriquez CF, Delgado C, Brown J, Slachevsky A. Test Your Memory-Spanish version (TYM-S): a validation study of a self-administered cognitive screening test. Int J Geriatr Psychiatry 2014; 29: 730-740.
21. Sato T, Hanyu H, Kume K, Takada Y, Onuma T, Iwamoto T. Differentiation of dementia with Lewy bodies from Alzheimer's disease using the Japanese version of the Test Your Memory. J Am Geriatr Soc 2012; 60: 594-596.
22. Szczesniak D, Wojtynska R, Rymaszewska J. Test Your Memory (TYM) as a screening instrument in clinical practice - the Polish validation study. Aging Ment Health 2013; 17: 863-868.
23. Postel-Vinay N, Hanon O, Clerson P, Brown JM, Menard J, Paillaud E et al. Validation of the Test Your Memory (F-TYM Test) in a French memory clinic population. Clin Neuropsychol 2014; 28: 994-1007.
24. Scharre DW, Chang SI, Nagaraja HN, Yager-Schweller J, Murden RA. Community Cognitive Screening Using the Self-Administered Gerocognitive Examination (SAGE). J Neuropsychiatry Clin Neurosci 2014; doi: 10.1176/appi.neuropsych.13060145.

CHAPTER 10

General discussion

This thesis searched for answers to the following questions:

I. What is the impact of cognitive impairment on people with type 2 diabetes?
II. Are there ways to prevent cognitive impairment in patients with type 2 diabetes?
III. How can we identify patients with type 2 diabetes and cognitive impairment who may benefit from a more tailored treatment and support?

Concerning the first question I will discuss the findings of chapters 2, 3 and 4, where we investigated the impact of cognitive impairment on health status, depressive symptoms and the use of acute health care services. With respect to the second question, I will discuss the etiologic role of dysglycaemia, insulin resistance and beta-cell function in relation to cognitive dysfunction in diabetes, as possible starting points for preventive strategies (chapter 6). Different ways to identify cognitive impairment are described and discussed in chapters 7, 8 and 9. The clinical implications of these studies and ideas for future research will be discussed at the end of this section.

As discussed in the introduction of this thesis, different stages of cognitive dysfunction can be distinguished: subtle diabetes-related cognitive decrements and the more severe stages MCI and dementia. The differences in trajectories and affected age groups suggest that these stages of cognitive dysfunction are not necessarily one continuum, but should be regarded as different entities with possibly different underlying mechanisms.[1] This has implications for diagnosis, prevention and management. The diabetes-related cognitive decrements are by definition subtle, do not affect daily functioning or diabetes self-management and their impact on people with type 2 diabetes will therefore not be discussed. There is also no need to identify these subtle decrements or to adjust the patient's treatment. I will therefore focus on cognitive impairment, including mild cognitive impairment and dementia.

Impact of cognitive impairment on people with type 2 diabetes

People with both type 2 diabetes and cognitive impairment have an increased risk of cardiovascular events, severe hypoglycaemic events and death.[2-4] **Chapter 2** additionally shows that people with type 2 diabetes and (mostly mild) cognitive impairment, but without being diagnosed with the latter, already have a reduced health status and more depressive symptoms compared to people without cognitive impairment. The prevalence of depressive symptoms was about doubled in those with cognitive impairment compared to those with normal cognition, a result that is in line with other studies.[5] Apart from having impact on many aspects of life, depression also has a negative effect on the patient's and the family's caregiver ability to effectively manage diabetes, it decreases the adherence to treatment and it increases the risk of hypoglycaemic events.[6-8] Since symptoms of depression and cognitive impairment are partially overlapping, differentiating the two can be challenging.[9] If depression is likely it should be treated. Cognitive

symptoms can be re-assessed after treatment of the depressive symptoms.

We also found that the same group of patients uses acute health care services, including visits to the GP out of hours service, emergency room visits and unplanned hospitalizations more often (**Chapter 4**). This difference in acute health care utilisation might (partly) be caused by their increased risk of hypoglycaemic events.[10,11] Our observations are in line with the results of a recent study among 787 elderly patients in the USA -not restricted to those with type 2 diabetes- who were screened for cognitive impairment.[12] Those who screened positive for cognitive impairment had higher rates of acute health care utilisation. Similar to our findings, also this study in the USA observed hardly any change in provider action; and health care utilisation did not decrease after screening. Screening for and a subsequent diagnosis of cognitive impairment alone is probably not sufficient to change the care provided by physicians or to reduce patient's healthcare utilisation. A more active approach and clear guidance on how to provide tailored care to these vulnerable patients are probably needed. Particularly adjustments to patient treatment to prevent hypoglycaemia seems to be a key factor to reduce the use of acute health care services in those with diabetes and cognitive impairment.[2]

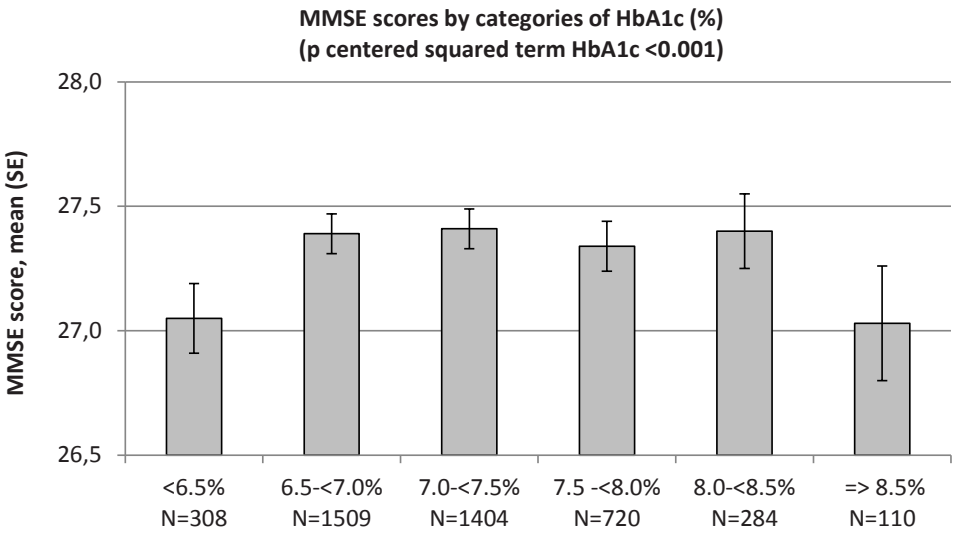
To conclude, these results confirm that patients with both type 2 diabetes and cognitive impairment are a vulnerable group of individuals. We may assume that these patients benefit from more tailored diabetes care aimed at improving compliance and preventing treatment-related complications. In my view, finding ways to prevent cognitive impairment and timely identifying cognitive impairment in elderly people with diabetes are therefore important issues.

Possible treatment targets for prevention of cognitive impairment in diabetes

1. Dysglycaemia

In **chapter 6**, we investigated the association between HbA1c and cognitive function in 4335 patients with type 2 diabetes at elevated cardiovascular risk. We found a bell-shaped association between HbA1c and the Mini-Mental State Examination (MMSE; as a measure for global cognitive function), as shown in the Figure 1 below. Both the highest and the lowest HbA1c levels were associated with worse cognitive dysfunction, the increased risk of hypoglycaemic events with lower HbA1c values possibly explaining the latter finding.

Figure 1. The association between HbA1c (%) and the MMSE. Adjusted for age, sex, years of formal education, race and prior use of sulfonylurea or glinide.



**HbA1c categories are used for display purposes only, the p-value corresponds to the centered squared term in the linear model*

Most studies investigating the relation between HbA1c and cognitive function in patients with type 2 diabetes used linear regression analyses and found a negative association or no association at all.[13] The largest cross-sectional study thus far on the subject, the ACCORD-MIND study (n=2977) found a negative association between HbA1c and cognitive function.[14] It was performed in a population with on average a high HbA1c level, namely 8.3% (67 mmol/mol). We may assume that in such a population the number of people with low HbA1c levels is relatively low. Together with our results, these findings indicate that in populations with high mean HbA1c levels there will be a negative association with cognition. Yet, when study populations include more patients with low HbA1c levels, non-linearity can be an issue. If both high and low HbA1c levels are associated with worse cognitive performance (as in Figure 1), this effect will be levelled out in a linear regression analysis. The results of previous cross-sectional studies are therefore not contradictory to our findings of a bell-shaped association between HbA1c levels and cognition. Moreover, our findings are in line with the result of a large longitudinal study in which the risk of developing dementia within 10 years was higher in patients with diabetes with low (<5% [31 mmol/mol]) or high (>10% [86 mmol/mol]) HbA1c levels compared to those within the range of 5-10% (31-86 mmol/mol).[15] Nonlinearity should therefore be taken in consideration in the analytic approach of future studies.

Clinical trials that investigated the effect of intensified treatment with stricter HbA1c targets on cognitive function could not demonstrate that lowering blood glucose levels is effective in the prevention of cognitive decline (*Table* below).[14,16-18] Two out of three clinical trials investigating the effect of a multifactorial treatment, including stricter control of both HbA1c, blood pressure and lipids, could not demonstrate a positive effect on cognitive functioning either.[19,20] HbA1c, blood pressure and lipid levels decreased significantly during the J-EDIT and ADDITION trials, however, this reduction was also observed in the usual care groups. Besides, ADDITION included relatively young (mean age 59 years) people with screen-detected diabetes and therefore a relatively low risk of cognitive decline.[20] The IDEATel trial compared telemedicine case management to usual diabetes care and demonstrated a significant slower rate of cognitive decline in the intensive treatment group, mediated by Hba1c levels and not by LDL or blood pressure.[21] An important difference between this trial and all other trials is that the target value for HbA1c was adjusted from 7% to 8% for participants with significantly reduced life expectancy and/or severe hypoglycemic unawareness. The bell-shaped association between HbA1c and cognitive function, as in the figure above, could have played a role here. Stricter glycaemic control in people with intermediate HbA1c levels, as in most trials in the table below, might not be very beneficial when only the extremes are associated with worse cognitive functioning, as is suggested by our findings. Besides, stricter glycaemic control in all participants may result in (too) low values in some participants, as three different trials showed that severe hypoglycaemia was significantly more likely in participants in the intensive glycaemic control arm.[14,18,22] The negative effect of the increased number of hypoglycaemic events could have outweighed positive effects of stricter glycaemic control. Glycaemic targets tailored to each individual might be more beneficial.

Next to the nonlinearity of the association between HbA1c and cognition, we found modifying effects of age and sex. In our analyses of the CAROLINA dataset, as presented in **chapter 6**, the association between HbA1c and the MMSE differed significantly between those <70 years and those ≥70 years old, where associations between both high and low HbA1c levels and worse MMSE scores were most prominent in patients over 70 years. Previous studies already observed this interaction between age and hyperglycaemia in relation to cognition, but as far as we know this has not yet been reported for low HbA1c levels.[23] Since older individuals are more vulnerable for cognitive decline, this may explain why harmful effects of both high and low HbA1c levels are most evident in this subgroup. The other way around, poorer self-management skills and treatment adherence in older people with worse cognitive functioning, could also cause the (very) low and high HbA1c values. Either way, these findings highlight the importance of tailored HbA1c targets and extra support in the treatment of diabetes in older people. Besides these age differences, we also observed sex influences. The associations between HbA1c and cognition were strongest in women. In line with these findings, higher historical HbA1c was associated with accelerated cognitive decline in women and not in men in the Edinburgh Type

2 Diabetes Study.[24] Both sex-specific risk factors (e.g. lifestyle, metabolic factors and neuroanatomical differences) and sex hormones might play a role in this respect.[25,26]

To conclude, current evidence suggests that both high and low HbA1c levels are associated with worse cognitive performance and that stricter glycaemic targets for all patients with type 2 diabetes are not the best way to reduce the risk of cognitive impairment. Nonlinearity and modifying effects of age and sex seem to play an important role and may provide important insights for individualised prevention strategies.

Randomised controlled trials investigating the effect of stricter HbA1c targets on cognitive functioning, dementia, brain MRI, all-cause mortality and hypoglycaemic events

Trial name (author) year	N	Inclusion criteria	Mean HbA1c at inclusion	Mean age	Intervention	Comparison	Follow-up period	Primary outcome(s)	Results
ADVANCE (de Galan) 2009	11140	T2D and substantial cardiovascular risk	7.5%	66 years	HbA1c target <6.5% , including Gliclazide (HbA1c 6.5 % at study end)	Usual care, without Gliclazide (HbA1c 7.3 % at study end)	60 mo.	Decline of ≥3 on MMSE Dementia (DSM-IV) Hypoglycaemic events. All cause mortality	No significant difference in cognitive decline or all cause mortality. Higher incidence of hypoglycaemic events for intensive glycaemic control.
ACCORD-MIND (Launer) 2011	2794	T2D and High cardiovascular risk + HbA1c > 7.5%	8.3%	62 years	HbA1c target ≤ 6.0 % (HbA1c at follow-up 6·6%)	Usual care, HbA1c target 7.0 %-7.9% (HbA1c at follow-up 7.5%)	40 mo.	Mean DSST score MMSE, RAVLT, Stroop test Brain MRI Hypoglycaemic events All cause mortality	No significant difference in cognitive decline Higher incidence of hypoglycaemic events and an increased mortality risk for intensive glycaemic control.
VADT (Zimering) 2016	1791	Military veterans with T2D and non-responsive to max dose oral agents or daily insulin, or both	9.4%	60 years	1.5% reduction in mean HbA1c (HbA1c 6.9% at study end)	Usual care (HbA1c 8.4% at study end)	60 mo.	TMT-B, Digit Span, DSST, Hypoglycaemic events All cause mortality	No significant difference in cognitive decline or all cause mortality Significantly higher incidence of hypoglycaemic events for intensive glycaemic control.
ACCORDION-MIND (Murray) 2017	1328	T2D and High cardiovascular risk + HbA1c (> 7.5%)	8.3%	62 years	HbA1c target < 6.0 % (HbA1c 7.6 % at study end)	Usual care , HbA1c target 7.0 %-7.9% (HbA1c 7.6% at study end)	80 mo.	Mean DSST score, brain MRI	No significant difference in cognitive decline or brain MRI outcomes on the long-term

Randomised controlled trials investigating the effect of stricter HbA1c, blood pressure and lipid targets on cognitive functioning

Trial name (author) year	N	Inclusion criteria	Mean HbA1c at inclusion	Mean age	Intervention	Comparison	Follow-up period	Primary outcome(s)	Results
IDEATEL (Luchsinger) 2011	2169	T2D and Living in a medically underserved area of New York	7.4%	71 years	HbA1c target ≤ 7%, or ≤ 8% for severe hypoglycaemic unawareness (HbA1c 7.06% at study end)	Usual care (HbA1c 7.38% at study end)	42 mo.	Comprehensive Assessment and Referral Evaluation (CARE) Scale (14items)	Intensive therapy was associated with a slower rate of cognitive decline, mediated by Hba1c and not by BP or LDL
ADDITION (Koekkoek) 2012	135	Screen-detected T2D	7.3%	59 years	HbA1c target ≤ 7%. (HbA1c 6.2% at end of study)	Usual care (HbA1c 6.5% at study end)	64 mo.	Composite score for memory, information-processing speed, attention, executive Function	No significant difference in cognitive decline
J-EDIT (Araki) 2012	1173	T2D, HbA1c ≥ 7.9% or HbA1c ≥ 7.4 and cardiovascular risk factors	8.5%	72 years	HbA1c target <6.9% (HbA1c 7.8% at study end)	Usual care (HbA1c 7.8% at study end)	72 mo.	Mean MMSE score	No significant difference in cognitive decline

ADVANCE; Action in Diabetes and Vascular Disease, ACCORD-MIND; Action to Control Cardiovascular Risk in Diabetes- Memory in Diabetes, ACCORDION-MIND; observational extension of the ACCORD-MIND trial, VADT; Veterans Affairs Diabetes Trial, IDEATEL; Informatics in Diabetes Education and Telemedicine Study, ADDITION; Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care, J-EDIT; Japanese Elderly Diabetes Intervention Trial, T2D; type 2 diabetes, MMSE; Mini-Mental State Examination, DSST; Digit Symbol Substitution Test, TMT: trail making test, BP; blood pressure, LDL; low density lipoprotein.

2. Insulin resistance and beta-cell dysfunction
Both proinsulin levels and the proinsulin-to-C-peptide ratio (as a measure of the efficiency of proinsulin processing) are increased in people with type 2 diabetes and can be used as surrogate markers of beta-cell dysfunction.[27] In **chapter *6*** we found that proinsulin and the proinsulin-to-C-peptide ratio are negatively associated with MMSE scores, predominantly in women. On the other hand, we did not observe an association between C-peptide (as a marker of insulin secretion by beta-cells) or HOMA-2 indexes (markers of beta cell function and insulin resistance) and cognitive functioning. A systematic review investigating the association between fasting insulin, insulin resistance (assessed with HOMA-ir) and cognitive impairment, including both cross-sectional and longitudinal studies, found conflicting results.[13] Some studies reported a moderate negative association, while most studies reported no relation at all.[13] To the best of our knowledge, there are no other studies that investigated the association between proinsulin, or the proinsulin-to-c-peptide ratio and cognitive functioning.

To conclude, our findings demonstrate that the etiologic role of beta-cell functioning and insulin resistance in cognitive impairment in patients with type 2 diabetes needs further elucidation.

3. Other etiologic factors that could be targeted
There are several other factors associated with cognitive impairment in diabetes including vascular risk factors such as hypertension, obesity and dyslipidemia.[28,29] The literature, however, is inconsistent about the etiologic role of these factors, modifying effects of age and sex might be important in this respect.[25,28] For example, hypertension and obesity seem to be risk factors for cognitive impairment in mid-life, while studies in late-life suggest a reversed association where obesity and hypertension are related to a lower risk of cognitive impairment.[28] It is clear that people with microvascular disease (such as diabetic retinopathy) or macrovascular disease (such as myocardial infarction or stroke) have an increased risk for dementia compared with people without.[15] Depression is also reported as a possible risk factor for cognitive impairment in type 2 diabetes.[9,30]

Interestingly, a large longitudinal study, using a community-dwelling sample including 1091 initially healthy individuals from the UK, showed that early life cognitive function (at the age of 11 years) is associated with both cognitive functioning and glucose levels in later life (at age 70).[31] Individuals with type 2 diabetes had lower cognitive function levels at the age of 11 years and scored worse on cognitive tests in later life than those without diabetes. The question therefore arises whether metabolic changes seen in young people result in subtle cognitive decrements, or that it is the other way around: because poor cognitive function in early life may relate to poor health management skills leading to e.g. inactivity and an unhealthy diet, causing metabolic changes.

To conclude, it is clear that multiple factors are associated with cognitive impairment in type 2 diabetes, each individual factor appears to have small effects. It is yet unclear how these factors are interrelated and to what extent they are in the causal pathway between diabetes and cognitive impairment, or that they are shared etiologic factors for both diabetes and cognitive impairment.

4. Incretin based therapies
Incretin based therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors, have been postulated to modulate the risk of cognitive impairment in patients with type 2 diabetes.[32] Incretins, of which GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are most important, are excreted from the gut in response to a meal (in particular carbohydrates). As a results, the glucose-lowering actions of incretins are only activated when it is needed (after eating) and the risk of (severe) hypoglycaemic events is generally low.[33] Next to their effect on glucose levels, incretin-based therapies might have direct and indirect beneficial effects on the brain.[32] A recent systematic review investigated the association between incretin-based therapies and cognitive function and concluded that incretin therapy might improve cognitive function, but that the evidence is limited.[34] Randomised controlled trials, such as the CAROLINA-cognition study (as described in **chapter 5**), will provide important information in this respect. The CARMELINA-cognition study is a randomised controlled trial with a design similar to CAROLINA-cognition. CARMELINA-cognition (n=1545), however, compared the DPP-IV inhibitor linagliptin to placebo instead of to glimepiride and included participants with cardiovascular and/or kidney disease. After a mean follow-up of 2.5 years linagliptin did not modulate cognitive decline. An important limitation of the CARMELINA-cognition study is the relatively short observation period. The longer running CAROLINA trial (mean follow-up expected to be 6 years) can address this limitation. Final results are expected at the end of 2019.

To conclude, if the DPP-IV inhibitor linagliptin would modulate cognitive impairment in people with type 2 diabetes at high cardiovascular risk, its use might be a treatment option to prevent cognitive decline in people with type 2 diabetes.

Identifying patients with cognitive impairment
Two different situations should be distinguished in the diagnostic evaluation of cognitive impairment:

1. A patient visits the general practice with cognitive complaints
2. Patients, without concerns about their cognition, are pro-actively approached to assess their cognitive functioning

People who visit the general practice with cognitive complaints
General practitioners (GPs) are generally the first health care providers to be consulted

when a patient or a relative has concerns about cognitive functioning. Patients will consult the GP to check whether their concerns are justified or not. The GP will always start with history taking, and ask the patients and/or relative about their concerns. In our diagnostic algorithm, as proposed in **chapter 7,** the information gathered during the patient and informant interview is used to estimate the probability that the patient has cognitive impairment and to guide GPs in choosing the most suitable cognitive test for the individual patient.

Recent reviews and meta-analyses that assessed the diagnostic value of the many different cognitive tests used in primary care conclude that all tests have their own pros and cons.[35-44] Most recommend GPs to get familiar with a few tests and to choose the most suitable test based on the patient in front of him or her.[35-44] This is basically what we propose in our algorithm. However, we made it more practical by focusing on the added value of the tests in the context of a diagnostic process instead of the diagnostic value of the test itself, in isolation.

Current guidelines most frequently recommend the use of the same cognitive test(s) for all patients, irrespective of the prior probability of cognitive impairment.[45-50] The MMSE is most frequently recommended, followed by the Montreal Cognitive Assessment (MoCA), the clock-drawing test and the Mini-Cog, which is in line with our diagnostic algorithm. However, we propose to use history taking and the interview with a relative to guide the choice of the cognitive test, instead of using the same test for all patients.

Current Dutch primary care guidelines recommend the use of cognitive tests in case the GP suspects dementia after the interview with the patient and relative.[50] Cognitive tests are not recommended when mild cognitive impairment is suspected. However, general practitioners do often not recognize dementia and we may assume that identifying mild cognitive impairment without helpful tests will be even more difficult.[51-53] As a result, the guideline can lead to false reassurance of people who visit the GP with cognitive complaints. In my view, it would be better to use cognitive tests in all patients who visit the GP with cognitive complaints and to use tests that are suitable to identify mild cognitive impairment as well as dementia. This will help the GP to take their patient's concerns seriously and to provide realistic and well-informed answers.

To conclude, a diagnostic procedure, such as proposed in **chapter 7,** could help to personalise diagnosing cognitive impairment in primary care, reduce the number of people that are falsely reassured and answer the questions of concerned patients more accurately. Further study is needed to validate and evaluate this diagnostic algorithm.

People without concerns about their cognition

If neither the patient nor a relative has any concern about cognitive functioning, they

will obviously not consult a health care provider with related questions. In that case, GPs will not always initiate diagnostic steps, even if they suspect cognitive impairment. A diagnosis of cognitive impairment is thus likely to be missed or delayed. A more active approach, such as screening, can help to identify patients with cognitive impairment who might benefit from a personalised intervention. In the general population, screening is not (yet) recommended because the evidence of the benefits of earlier diagnosing cognitive impairment is limited.[40] However, as mentioned before, cognitive impairment, even mild cognitive impairment, can affect patients' self-management skills and can result in increased risks of negative health outcomes. This especially concerns patients with chronic diseases, where self-management skills are important, such as people with type 2 diabetes.[54-56]

When the Cog-ID trial, as described in **chapter 8**, started, there was an ongoing discussion about the need for screening for cognitive impairment in elderly with type 2 diabetes.[57,58] Diabetes guidelines at that time did not include recommendations about what to do with cognitive impairment in diabetes management. In last years the medical view has changed significantly. The recently updated Dutch diabetes guidelines for primary care recommend to check whether there are signs or symptoms of cognitive impairment during the annual diabetes visit.[59] The guidelines of the American Diabetes Association (ADA) go a step further and recommend annual screening for cognitive impairment.[60] However, neither the Dutch nor the American guidelines are specific in how that should be implemented.

The Cog-ID trial shows that both the Test Your Memory (TYM) and the Self-administered Gerocognitive examination (SAGE) can be used as the first test of a case-finding strategy in elderly patients with type 2 diabetes, as described in **chapter 9**. A negative result on the SAGE indicates that the likelihood that the patient has no cognitive impairment is 85%, while a positive result indicates a likelihood of cognitive impairment of 40%. Besides, **chapter 3** demonstrates that the health status and the level of depressive symptoms remained quite stable in the two years after people were diagnosed with cognitive impairment. Thus, screening and a subsequent diagnosis of cognitive impairment do not seem to have a negative effect. However, case-finding will also result in false positive tests in people without cognitive impairment. When using the SAGE as a first test, 60 out of 100 people with a positive test do not have cognitive impairment and might be worried needlessly. Another drawback of a case-finding strategy for cognitive impairment might be that not all people may want an assessment of their cognition. The participation rate of the Cog-ID study was only 18%, however this study also included a visit to the memory clinic for most patients, including a brain MRI scan and completing multiple questionnaires. Most frequently mentioned reasons to decline participation were feeling too old, the presence of comorbidities and problems with attending the memory clinic. Fortunately, almost all (97%) of the highly selected group of Cog-ID participants did not regret that they participated and none of the patients indicated that they would not have wanted to know the diagnosis

of cognitive impairment.

To conclude, a case-finding strategy, including the TYM or SAGE, could be a good option to identify (mild) cognitive impairment in patients who are not dismissive to know that diagnosis.

Implications for practice and future research

In people with type 2 diabetes and cognitive impairment the prevalence of depressive symptoms is high, health related quality of life is relatively low and the use of acute health care services is increased. They also have an increased risk of cardiovascular events, severe hypoglycaemic events and death.[2-4] This indicates that these patients need extra attention. Early detection of both depression and cognitive impairment can facilitate tailored diabetes treatment that may help to reduce the risk of adverse outcomes. With the growing number of old and very old people with type 2 diabetes, this will be increasingly relevant.

Identifying cognitive impairment in people with type 2 diabetes
We now know that the TYM and SAGE are valid and practical tests to use in a stepwise case-finding strategy in primary care. The patient can complete the test without any help and the practice nurse could score it. It is, however, not yet clear how the other steps in such a case-finding strategy should look like. A patient and informant interview and an additional cognitive test in those who are screen positive could be a good option. If the effectiveness of such an approach on the prevention of complications and on patient's quality of life could be demonstrated, case-finding for cognitive impairment should be implemented in clinical practice. Until then, primary care providers could use the above mentioned tests with a low threshold in patients in whom cognitive impairment could have important implications for their diabetes treatment (e.g. patients living alone and using insulin). Furthermore, it is important to be alert for signs of cognitive impairment and to initiate a diagnostic evaluation when these are noticed. The diagnostic flowchart as proposed in **chapter 7** can be used for this purpose. Next to the "usual" signs of cognitive impairment,[50] signs of cognitive impairment that might be seen in people with type 2 diabetes include: unexplained weight loss, not completing usual diabetes self-care tasks or making mistakes in these tasks, deterioration in usual HbA1c levels and frequent episodes of hypoglycaemia or hyperglycaemia.[61]

We should realise that there are elderly people with type 2 diabetes who would not participate in a case-finding procedure. It is therefore important to search for other options to identify those who may benefit more tailored care. An option could be using the frailty concept to identify those at risk for negative health outcomes implicitly. Frailty is a clinical syndrome that indicates increased vulnerability to stressors and is increasingly used in

clinical research the last two decades.[62] There are numerous operational definitions and assessment tools for frailty, each of them tend to identify a specific population at risk of negative outcomes.[62] Most tools focus on physical frailty, but some also address 'cognitive frailty'.[63] Frailty is associated with hypoglycaemia, decreased quality of life, falls, disability, use of health-care services, and mortality in older people with type 2 diabetes.[64,65] Implementing the frailty concept on a larger scale, including cognitive frailty, could therefore be another way to improve care for those with cognitive impairment who do not want to know their cognitive functioning explicitly.

Clinical practice guidelines for treatment of older adults with type 2 diabetes recommend the use of several assessment tools, including one for functional status, one for depression, one for frailty, one for cognitive impairment, etcetera.[66,67] These conditions are all interrelated and often co-occurring. The key purpose of all these assessment tools is to identify one or more health care needs that can be addressed by providing tailored care. However, most research focuses on the diagnostic value of these tests for the specific diagnosis e.g. cognitive impairment. It is not feasible to use all these tools in all patients. In my opinion, it is therefore important that future research investigates which of these (combined) tools are most suitable to identify a person's health care needs that require treatment adjustments.

Tailored care for patients with type 2 diabetes and cognitive impairment

Tailored care should prevent hypoglycaemic events, falls or acute health care visits and it might improve quality of life and treatment adherence. However, evidence is lacking. A clear description of what tailored care means is warranted. To provide tailored diabetes care, the most recent ADA guidelines recommend deintensification (or simplification) of complex medication regimens, the use of adjusted (less stringent) glycaemic targets and choosing pharmacologic interventions with a low hypoglycaemia risk.[60] In this respect specifically the combination of sulfonylurea (SU) and insulin therapy should be avoided. Unfortunately, this is not yet current practice, even in frail patients.[68] Another important aspect of tailored diabetes care for those with cognitive impairment is involving and educating caregivers/family members in the patient's treatment.[69] Randomised controlled trials to demonstrate the beneficial effects of such tailored diabetes care are needed.

Prevention of cognitive impairment in patients with type 2 diabetes

We are currently facing a global epidemic of type 2 diabetes and cognitive impairment. In the Netherlands there are hundreds of thousands of people aged 70 years or older living with type 2 diabetes.[70] Due to increasing life expectancy the total number of patients with diabetes and cognitive impairment are expected to increase further. This highlights the importance of finding effective strategies to slow cognitive decline in people with type 2 diabetes.

In this thesis I focused on the diabetes-specific risk factors of cognitive impairment in people with type 2 diabetes. It is however important to keep in mind that other factors (e.g , vascular risk factors and lifestyle factors) also play an important role.[29] The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial demonstrated that intensive lifestyle based strategies (including diet, exercise, cognitive training, and vascular management) can prevent or delay cognitive impairment in people at high dementia risk in the general population.[71] Although the effect was small, these results demonstrate the potential of lifestyle modification to slow cognitive decline. In people with type 2 diabetes, trials investigating the effect of multifactorial interventions, could not (yet) demonstrate a beneficial effect. There are however no reasons to assume that such interventions would only work in the general population, and not in people with type 2 diabetes.

There are several factors that could have played a role in the negative results of prevention trials in people with type 2 diabetes. Because the effects of each individual risk factor seem to be small and preventive treatment already improved significantly in routine care, the chance that an intervention makes a big differences is limited. To detect small differences in cognitive decline, one will need a long follow-up period, sensitive cognitive tests and a study population at high risk for cognitive impairment. In my view, future prevention trials in people with type 2 diabetes should be long-lasting, multifactorial and tailored to the individual patient at high risk for cognitive impairment.

References

1. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol. 2015;14(3):329-340.
2. Bruce DG, Davis WA, Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. Diabetologia. 2009;52(9):1808-1815.
3. Cukierman-Yaffe T, Gerstein HC, Miller ME, et al. The Relationship Between the Score on a Simple Measure of Cognitive Function and Incident CVD in People With Diabetes: A Post Hoc Epidemiological Analysis From the ACCORD-MIND Study. J Clin Endocrinol Metab. 2017;102(9):3218-3225.
4. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care. 2012;35(4):787-793.
5. smail Z, Elbayoumi H, Fischer CE, et al. Prevalence of Depression in Patients With Mild Cognitive Impairment: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017;74(1):58-67.
6. Maneze D, Everett B, Astorga C, Yogendran D, Salamonson Y. The Influence of Health Literacy and Depression on Diabetes Self-Management: A Cross-Sectional Study. J Diabetes Res. 2016;2016:3458969.
7. Pouwer F, Nefs G, Nouwen A. Adverse effects of depression on glycemic control and health outcomes in people with diabetes: a review. Endocrinol Metab Clin North Am. 2013;42(3):529-544.
8. Schmitt A, Reimer A, Hermanns N, et al. Depression is linked to hyperglycaemia via suboptimal diabetes self-management: A cross-sectional mediation analysis. J Psychosom Res. 2017;94:17-23.
9. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas. 2014;79(2):184-190.
10. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab. 2012;14(7):634-643.
11. Signorovitch JE, Macaulay D, Diener M, et al. Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs. Diabetes Obes Metab. 2013;15(4):335-341.
12. Rosenbloom M, Barclay TR, Borson S, et al. Screening Positive for Cognitive Impairment: Impact on Healthcare Utilization and Provider Action in Primary and Specialty Care Practices. J Gen Intern Med. 2018;33(10):1746-1751.
13. Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol. 2015;3(1):75-89.
14. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol. 2011;10(11):969-977.
15. Exalto LG, Biessels GJ, Karter AJ, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. Lancet Diabetes Endocrinol. 2013;1(3):183-190.
16. de Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia. 2009;52(11):2328-2336.
17. Murray AM, Hsu FC, Williamson JD, et al. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. Diabetologia. 2017;60(1):69-80.
18. Zimering MB, Anderson RJ, Ge L, Moritz TE, Duckworth WC. Basic fibroblast growth factor predicts cardiovascular disease occurrence in participants from the veterans affairs diabetes trial. Front Endocrinol (Lausanne). 2013;4:183.
19. Araki A, Iimuro S, Sakurai T, et al. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial--study design, baseline characteristics and effects of intervention. Geriatr Gerontol Int. 2012;12 Suppl 1:7-17.
20. Koekkoek PS, Ruis C, van den Donk M, et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes--the ADDITION-Netherlands study: a cluster-randomized trial. J Neurol Sci. 2012;314(1-2):71-77.
21. Luchsinger JA, Palmas W, Teresi JA, et al. Improved diabetes control in the elderly delays global cognitive decline. J Nutr Health Aging. 2011;15(6):445-449.
22. Patel A, Macmahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-2572.
23. Feinkohl I, Price JF, Strachan MW, Frier BM. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimers Res Ther. 2015;7(1):46.
24. Feinkohl I, Keller M, Robertson CM, et al. Cardiovascular risk factors and cognitive decline in older people with type 2 diabetes. Diabetologia. 2015;58(7):1637-1645.
25. Maric-Bilkan C. Sex differences in micro- and macro-vascular complications of diabetes mellitus. Clin Sci

(Lond). 2017;131(9):833-846.
26. Mauvais-Jarvis F. Sex differences in metabolic homeostasis, diabetes, and obesity. Biol Sex Differ. 2015;6:14.
27. Bergman RN, Finegood DT, Kahn SE. The evolution of beta-cell dysfunction and insulin resistance in type 2 diabetes. Eur J Clin Invest. 2002;32 Suppl 3:35-45.
28. Bello-Chavolla OY, Antonio-Villa NE, Vargas-Vazquez A, Avila-Funes JA, Aguilar-Salinas CA. Pathophysiological mechanisms linking type 2 diabetes and dementia: Review of evidence from clinical, translational and epidemiological research. Curr Diabetes Rev. 2019.
29. Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol. 2014;2(3):246-255.
30. Katon WJ, Lin EH, Williams LH, et al. Comorbid depression is associated with an increased risk of dementia diagnosis in patients with diabetes: a prospective cohort study. J Gen Intern Med. 2010;25(5):423-429.
31. Altschul DM, Starr JM, Deary IJ. Cognitive function in early and later life is associated with blood glucose in older individuals: analysis of the Lothian Birth Cohort of 1936. Diabetologia. 2018;61(9):1946-1955.
32. Groeneveld ON, Kappelle LJ, Biessels GJ. Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus. J Diabetes Investig. 2016;7(1):5-16.
33. Gault VA. RD Lawrence Lecture 2017 Incretins: the intelligent hormones in diabetes. Diabet Med. 2018;35(1):33-40.
34. Dumbrill JL, Moulton CD. Effects of incretin-based therapies on neurocognitive function in humans: A systematic review of the literature. Prim Care Diabetes. 2018;12(1):51-58.
35. Brodaty H, Low LF, Gibson L, Burns K. What is the best dementia screening instrument for general practitioners to use? Am J Geriatr Psychiatry. 2006;14(5):391-400.
36. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry. 2007;78(8):790-799.
37. Harvan JR, Cotter V. An evaluation of dementia screening in the primary care setting. J Am Acad Nurse Pract. 2006;18(8):351-360.
38. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. Int J Geriatr Psychiatry. 2010;25(2):111-120.
39. Larner AJ. Comparing diagnostic accuracy of cognitive screening instruments: a weighted comparison approach. Dement Geriatr Cogn Dis Extra. 2013;3(1):60-65.
40. Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;159(9):601-612.
41. Milne A, Culverwell A, Guss R, Tuppen J, Whelton R. Screening for dementia in primary care: a review of the use, efficacy and quality of measures. Int Psychogeriatr. 2008;20(5):911-926.
42. Mitchell AJ, Malladi S. Screening and case finding tools for the detection of dementia. Part I: evidence-based meta-analysis of multidomain tests. Am J Geriatr Psychiatry. 2010;18(9):759-782.
43. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. QJM. 2007;100(8):469-484.
44. Yokomizo JE, Simon SS, de Campos Bottino CM. Cognitive screening for dementia in primary care: a systematic review. Int Psychogeriatr. 2014:1-22.
45. Adelman AM, Daly MP. Initial evaluation of the patient with suspected dementia. Am Fam Physician. 2005;71(9):1745-1750.
46. Cummings JL, Frank JC, Cherry D, et al. Guidelines for managing Alzheimer's disease: part I. Assessment. Am Fam Physician. 2002;65(11):2263-2272.
47. Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. J Am Board Fam Med. 2012;25(3):367-382.
48. Geldmacher DS, Kerwin DR. Practical Diagnosis and Management of Dementia Due to Alzheimer's Disease in the Primary Care Setting: An Evidence-Based Approach. Prim Care Companion CNS Disord. 2013;15(4).
49. Lee L, Weston WW, Heckman G, Gagnon M, Lee FJ, Sloka S. Structured approach to patients with memory difficulties in family practice. Can Fam Physician. 2013;59(3):249-254.
50. Luning-Koster M, Perry M, Moll van Charante EP, Vernooij-Dassen M, Wiersma T, Burgers JS. Dutch College of General Practitioners' (NHG) practice guideline 'Dementia'. Ned Tijdschr Geneeskd. 2012;156(49):A5323.
51. Mitchell AJ, Meader N, Pentzek M. Clinical recognition of dementia and cognitive impairment in primary care: a meta-analysis of physician accuracy. Acta Psychiatr Scand. 2011;124(3):165-183.
52. van den Dungen P, Moll van Charante EP, van de Ven PM, et al. Dutch family physicians' awareness of cognitive impairment among the elderly. BMC Geriatr. 2015;15:105.
53. van den DP, van Marwijk HW, van der Horst HE, et al. The accuracy of family physicians' dementia diagnoses at different stages of dementia: a systematic review. Int J Geriatr Psychiatry. 2012;27(4):342-354.
54. Feil DG, Zhu CW, Sultzer DL. The relationship between cognitive impairment and diabetes self-management in a population-based community sample of older adults with Type 2 diabetes. J Behav Med. 2012;35(2):190-199.

55. Harkness K, Heckman GA, khtar-Danesh N, Demers C, Gunn E, McKelvie RS. Cognitive function and self-care management in older patients with heart failure. Eur J Cardiovasc Nurs. 2013.
56. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. Diabetes Res Clin Pract. 2000;50(3):203-212.
57. Brunet MD, McCartney M, Heath I, et al. There is no evidence base for proposed dementia screening. BMJ. 2012;345:e8588.
58. McCartney M. "Case finding" in dementia is simply screening with no evidence of benefit. BMJ. 2014;349:g4791.
59. Barents ESE Bilo HJG BM, Van den Brink-Muinen A, Dankers M, Van den Donk M, Hart HE, Houweling ST, IJzerman RG, Janssen PGH, Kerssen A, Palmen J, Verburg-Oorthuizen AFE, Wiersma Tj. The Dutch College of General Practitioners Standard on type 2 diabetes mellitus. In:2018.
60. Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers. Clin Diabetes. 2019;37(1):11-34.
61. Alzheimer Australia. Dementia and diabetes toolkit. 2014
62. Cesari M, Calvani R, Marzetti E. Frailty in Older Persons. Clin Geriatr Med. 2017;33(3):293-303.
63. De Roeck EE, Dury S, De WN, et al. CFAI-Plus: Adding cognitive frailty as a new domain to the comprehensive frailty assessment instrument. Int J Geriatr Psychiatry. 2018;33(7):941-947.
64. Cobo A, Vazquez LA, Reviriego J, Rodriguez-Manas L. Impact of frailty in older patients with diabetes mellitus: An overview. Endocrinol Nutr. 2016;63(6):291-303.
65. Sinclair AJ, Abdelhafiz AH, Rodriguez-Manas L. Frailty and sarcopenia - newly emerging and high impact complications of diabetes. J Diabetes Complications. 2017;31(9):1465-1473.
66. LeRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline. J Clin Endocrinol Metab. 2019;104(5):1520-1574.
67. Dunning T, Sinclair A, Colagiuri S. New IDF Guideline for managing type 2 diabetes in older people. Diabetes Res Clin Pract. 2014;103(3):538-540.
68. Hart HE, Rutten GE, Bontje KN, Vos RC. Overtreatment of older patients with type 2 diabetes mellitus in primary care. Diabetes Obes Metab. 2018;20(4):1066-1069.
69. El-Saifi N, Moyle W, Jones C, Tuffaha H. Medication Adherence in Older Patients With Dementia: A Systematic Literature Review. J Pharm Pract. 2018;31(3):322-334.
70. RIVM. 2017. Available at: https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/cijfers-context/huidige-situatie#node-prevalentie-diabetes-naar-leeftijd-en-geslacht (accessed 13-05-2019)
71. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385(9984):2255-2263.

SUMMARY

In the Netherlands, hundreds of thousands of people aged 70 years or older are currently living with type 2 diabetes. Due to ageing of the population these numbers are expected to increase further over the next decades. Cognitive dysfunction is increasingly recognised as an important complication of type 2 diabetes. People with diabetes -predominantly those over the age of 65 years- are at risk for cognitive impairment, including both mild cognitive impairment and dementia. Indeed, the risk to develop dementia is doubled in those with type 2 diabetes. Such cognitive deficits are already posing a tremendous economic, social, and public health burden. Yet, the number of people affected is expected to increase further.

It is well known that physicians often fail to recognize and diagnose cognitive impairment. As a result, the prevalence of missed and delayed diagnoses of cognitive impairment is high. However, cognitive impairment, even mild cognitive impairment, can affect the self-management skills of patients with type 2 diabetes and can result in an increased risk of negative health outcomes.

In the first part of this thesis we studied the impact of cognitive impairment on people with type 2 diabetes. In the second part we investigated possible starting points for the prevention of cognitive impairment in patients with type 2 diabetes. In the third part we investigated how to identify cognitive impairment.

Part I: Consequences of cognitive impairment in type 2 diabetes

In **chapter 2** we examined whether undiagnosed cognitive impairment in patients with type 2 diabetes is associated with a reduced health status and depressive symptoms. This study was part of the Cognitive Impairment in Diabetes (Cog-ID) study (textbox). Patients were visited at their homes and completed questionnaires assessing health status (SF-36, EQ-5D, EQ-VAS) and depressive symptoms (CES-D) and were screened for cognitive impairment. Health status and depressive symptoms were compared between patients with and without cognitive impairment. Patients with cognitive impairment (n=57)

Cognitive Impairment in Diabetes (Cog-ID) study

- Aim: to develop a stepped diagnostic procedure to detect cognitive impairment
- 225 patients with type 2 diabetes aged ≥70 years from 22 general practices

Home-visit (all participants):

- Cognitive tests: Test Your Memory (TYM) and Self-Administered Gerocognitive Examination (SAGE)
- Evaluation by a trainee GP including history taking and MMSE

Memory clinic evaluation at the UMC Utrecht:

- Those suspected of cognitive impairment (TYM <40, SAGE <15, or based on the GP assessment)
- Random sample of 30% of those not suspected of cognitive impairment

showed significantly lower scores on all health status domains. Depression (CES-D≥16) occurred almost twice as often in patients with cognitive impairment (RR 1.8; 95%-CI: 1.1-3.0). In conclusion, undiagnosed cognitive impairment in patients with type 2 diabetes is associated with a reduced health status and more depressive symptoms.

Physicians often assume that informing patients about a diagnosis of cognitive impairment will influence them negatively. The lack of cure and the risk of stigmatization are important arguments in this respect. Some physicians fear that the diagnosis might evoke depressive symptoms or even suicidal thoughts. In **chapter 3** we therefore assessed changes in depressive symptoms and health status after participating a screening program for cognitive impairment in people with type 2 diabetes. 179 out of the 225 Cog-ID participants (textbox) were included; 39 screen positives with cognitive impairment, 56 screen positives without cognitive impairment and 84 participants not suspected of cognitive impairment during screening (screen negatives). Questionnaires assessing health status (SF-36, EQ-5D, EQ-VAS) and depressive symptoms (CES-D) were completed before screening, and 6 and 24 months after screening. At screening, participants diagnosed with cognitive impairment had significantly more depressive symptoms and a worse health status than screen negatives. Depression and health status scores of both groups remained stable over time. Screen positives without cognitive impairment scored between the other two groups at screening, but their depressive symptoms decreased significantly during follow-up (mean CES-D: -3.1 after 6 and -2.1 after 24 months); their health status also tended to improve. To conclude, depressive symptoms are common in older people with type 2 diabetes. Screening for and a subsequent diagnosis of cognitive impairment will not increase depressive symptoms.

In **chapter 4** we investigated whether people with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often than patients not suspected of cognitive impairment. Information about acute health care use of Cog-ID participants (see textbox at page 178) was collected for two years prior to and two years after screening and compared to data from 'screen negatives'. 154 participants were included, 37 patients with cognitive impairment and 117 screen negatives. A higher percentage of participants with cognitive impairment compared to screen negative patients used acute health care services; this difference was significant for general practitioner's out of hours services (56% versus 34% used this service over four years, p=0.02). The mean number of acute health care visits was also higher in those with cognitive impairment than in screen negatives (2.2±2.8 versus 1.4±2.2 visits in 4 years, $p<0.05$; 1.4±2.2 versus 0.7±1.5 visits in 2 years after screening, p=0.03). To conclude, people with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often.

Part II: Etiology and prevention of cognitive impairment in type 2 diabetes
Linagliptin is a glucose-lowering agent of the dipeptidyl peptidase-IV (DPP-IV) inhibitor class that may be of particular interest for the prevention of accelerated cognitive decline, because it has pleiotropic effects, beyond glucose lowering. In **chapter 5** we present the design of a study that aims to establish if linagliptin is superior to the sulfonylurea glimepiride in the prevention of accelerated cognitive decline in patients with type 2 diabetes. The cognition substudy is an integral part of the randomised, double blind CARdiOvascular safety of LINAgliptin (CAROLINA®) trial, which evaluates the effect of treatment with linagliptin versus glimepiride on cardiovascular outcomes. CAROLINA® includes patients with type 2 diabetes with sub-optimal glycaemic control at elevated cardiovascular risk. The cognition substudy only includes patients with a baseline MMSE score ≥24. The primary cognitive outcome is the occurrence of accelerated cognitive decline at the end of follow-up. Accelerated cognitive decline is defined as a rate of cognitive decline that falls at or below the 16th percentile of decline for the whole cohort on either the MMSE or a combined score of the trail making test (TMT) and the verbal fluency test (VFT). Between December 2010 and December 2012, 6042 patients were randomised and treated in CAROLINA®. Cognitive tests were conducted in nearly 4500 participants at baseline and during two subsequent assessments, after 160 weeks of follow-up and after 6 years. The final results of this cognition substudy, expected soon, will provide more insight in the role of linagliptin in the prevention of cognitive decline in patients with type 2 diabetes.

There is a growing evidence for etiologic roles of dysglycemia and insulin resistance in the increased risk of cognitive impairment in patients with type 2 diabetes. However, important questions remain. Elevated levels of glycosylated haemoglobin (HbA1c) appear to be related to worse cognition, but there are indications that the same holds true for lower HbA1c levels, possibly because intensive glycaemic control increases the risk of hypoglycaemia. Previous studies relating HbA1c to cognition did not sufficiently address this possible nonlinear relationship. In **chapter 6** we investigated HbA1c, indices of insulin-resistance, and beta-cell function in relation to cognitive function in individuals with type 2 diabetes addressing possible nonlinear associations and the influence of age and sex. Baseline data of 4361 patients with type 2 diabetes at elevated cardiovascular risk from the CAROLINA® trial was analysed cross-sectionally. Cognitive measures included the MMSE and a composite score for attention and executive functioning (A&E) based on the trail making test and the verbal fluency test. The association between HbA1c and MMSE proved to be non-linear ($p<0.001$). Both high and low HbA1c levels were associated with worse performance in MMSE, predominantly in women ≥70 years. Negative linear associations were found between proinsulin, the proinsulin-to-C-peptide ratio, and the MMSE score, predominantly in women. To conclude, these results demonstrated an inverted u-shaped association between HbA1c and cognitive function, with modifying effects of age and sex. These findings support recent recommendations to use a patient-

centered approach when choosing HbA1c goals and pharmacologic agents. The negative linear association between (disproportional) hyperproinsulinemia and cognitive function requires further elucidation.

Part III: diagnosing cognitive impairment

Despite the wealth of research devoted to the performance of individual cognitive tests for diagnosing cognitive impairment (including mild cognitive impairment and dementia), it can be difficult for general practitioners to choose the most appropriate test for a patient with cognitive complaints in daily practice. In **chapter 7** we present a diagnostic algorithm for the evaluation of cognitive complaints in primary care. The rationale behind this algorithm is that the likelihood of cognitive impairment - which can be determined after history taking and an informant interview - can determine which cognitive test is most suitable. We distinguished three likelihoods of cognitive impairment: not likely, possible or likely. We selected cognitive tests based on pre-defined required test features for each of these three situations and a review of the literature. We incorporated the cognitive tests in a practical diagnostic algorithm. In patients with complaints but where cognitive impairment is considered to be unlikely the clock-drawing test can be used to rule out cognitive impairment. When cognitive impairment is possible the Montreal Cognitive Assessment (MoCA) can be used to rule out cognitive impairment or to make cognitive impairment more likely. When dementia is likely the MMSE can be used to confirm the presence of cognitive impairment. To conclude, we think our diagnostic algorithm may increase the efficiency of ruling out or diagnosing cognitive impairment in primary care. Further study is needed to validate and evaluate this stepwise diagnostic algorithm.

Current Dutch diabetes guidelines for primary care recommend to check whether there are signs or symptoms of cognitive impairment during the annual diabetes visit. The guidelines of the American Diabetes Association (ADA) go a step further and recommend annual screening for cognitive impairment in older people with diabetes. However, neither the Dutch nor the American guidelines are specific in how that should be implemented. In **chapter 8** we present the design of the Cog-ID study (see textbox at page 178). The aim of this study was to develop a stepped diagnostic procedure to detect undiagnosed cognitive impairment in older people with type 2 diabetes. People were included from primary care practices and were screened for cognitive impairment. All participants were examined by a trainee GP and completed two cognitive tests: the Test Your Memory (TYM) and Self-Administered Gerocognitive Examination (SAGE). Part of the study population was referred to the memory clinic of the University Medical Centre Utrecht. At the memory clinic, a medical examination, neuropsychological examination, and magnetic resonance imaging (MRI) of the brain were performed. The results of the Cog-ID study are reported in **chapter 9.** From 22 general practices, 1243 patients were invited and 225 participated in the study. Cognitive impairment was diagnosed in 44 participants. The TYM and SAGE questionnaires had negative predictive values of 81 and 85%, respectively. Positive predictive values were

39 and 40%, respectively. A positive test thus requires further examination. We concluded that both tests can be used in screening strategies for cognitive impairment in patients with type 2 diabetes in primary care.

In **chapter 10**, we discuss our findings and their clinical implications in the light of the existing literature. In part 1 we investigated the consequences of cognitive impairment in type 2 diabetes. We found that these patients have more depressive symptoms and that they use acute health care services more often. Other studies found that people with type 2 diabetes and cognitive impairment have an increased risk of hypoglycaemia, cardiovascular events and even death. Taken together these results confirm that detection of cognitive impairment in patients with type 2 diabetes identifies a vulnerable patient group that could benefit from tailored treatment and care to prevent complications. Tailored diabetes care can include deintensification (or simplification) of complex medication regimens, the use of adjusted (less stringent) glycaemic targets and choosing pharmacologic interventions with a low hypoglycaemia risk. This reinforces the need to timely identify cognitive impairment in older people with type 2 diabetes.

In part II of this thesis we investigated possible starting points for the prevention of cognitive impairment in patients with type 2 diabetes. We found that both low and high HbA1c levels are associated with worse cognitive performance. Next to HbA1c, there are several other factors that have been related to cognitive impairment in type 2 diabetes. For example vascular risk factors such as obesity, hypertension and hyperlipidaemia. Lifestyle factors such as diet and physical activity might also play a role. It is noteworthy that, as we found for HbA1c, other associations are often influenced by age and sex. To conclude, the increased risk of cognitive impairment in people with type 2 diabetes seems to be multifactorial. It is still unclear if cognitive decline in people with type 2 can be delayed or prevented. A multifactorial approached that is tailored to the individual patient and takes age, sex and patient's preferences and abilities into account might have the most chance of success.

In part III we investigated how cognitive impairment can be identified in primary care. It is important to avoid false reassurance in people, with or without diabetes, who visit their general practitioner with cognitive complaints. Choosing the most suitable cognitive test, based on the likelihood of cognitive impairment after history taking and an informant interview (chapter 7), can be helpful. Timely identifying cognitive impairment is particularly important in older people with type 2 diabetes. Screening for cognitive impairment using the TYM or SAGE questionnaire could be a good option for the future. Yet, the benefits of screening for cognitive impairment in people with type 2 diabetes and subsequent modifications of treatment will need further evaluation. Until then, primary care providers should be alert for signs and symptoms of cognitive impairment in older people with type 2 diabetes, particularly in patients in whom cognitive impairment might play a role in their

diabetes management. Apart from the usual signs of cognitive impairment that can occur in any individual, also unexplained weight loss, not completing usual diabetes self-care tasks or making mistakes in these tasks, deterioration in usual HbA1c levels and frequent episodes of hypoglycaemia or hyperglycaemia should alert the treating physician to possible cognitive impairment in people with type 2 diabetes.

NEDERLANDSE SAMENVATTING

Alleen al in Nederland leven op dit moment honderdduizenden 70-plussers met type-2-diabetes. Behalve een verhoogd risico op de meer bekende complicaties van diabetes, zoals schade aan ogen, nieren, hart- en bloedvaten, hebben mensen met type-2-diabetes een tweemaal verhoogd risico op dementie. Het aantal mensen met type-2-diabetes is de afgelopen decennia explosief gestegen en door de vergrijzing is de verwachting dat dit aantal de komende jaren nog verder zal stijgen. Doordat mensen daarnaast ook steeds ouder worden, zal het aantal mensen met type-2-diabetes en tevens dementie nog sterker toenemen. Het verband tussen type-2-diabetes en dementie is al langer bekend, maar de oorzaken en gevolgen hiervan zijn nog onderbelicht. Dementie en zeker de lichte cognitieve stoornissen (zie verderop) worden vaak niet of pas laat vastgesteld. Dat kan in het geval van mensen met type-2-diabetes van extra belang zijn, omdat zij dan het risico lopen dat zij niet de adviezen en zorg krijgen die ze nodig hebben. Onderzoek is nodig om te achterhalen hoe we cognitieve stoornissen het beste vast kunnen stellen en hoe we deze groep mensen meer passende zorg kunnen bieden.

Bij dementie is er een geheugenstoornis en zijn één of meerdere andere cognitieve functies aangedaan. Met cognitieve functies bedoelen we de functies van de hersenen die te maken hebben met het opnemen en verwerken van informatie zoals bijvoorbeeld aandacht en concentratie, herkennen en plannen maken. In geval van dementie leidt dit tot beperkingen in dagelijkse activiteiten. Ook lichte cognitieve stoornissen, in het Engels 'mild cognitive impairment (MCI)', kunnen al voor problemen zorgen. Met cognitieve stoornissen bedoelen we in dit proefschrift zowel dementie als MCI.

In het eerste deel van dit proefschrift hebben we gekeken naar de gevolgen van cognitieve stoornissen bij type-2-diabetes. In het tweede deel gingen we op zoek naar mogelijke aangrijpingspunten voor preventie van cognitieve stoornissen bij type-2-diabetes. In het derde deel hebben we onderzocht hoe een huisarts cognitieve stoornissen het beste kan vaststellen.

Cognitive Impairment in Diabetes (Cog-ID) study

- Doel: ontwikkelen van een diagnostische procedure voor het opsporen van cognitieve stoornissen
- 225 deelnemers met type-2-diabetes van 70 jaar of ouder

Huisbezoek (bij alle deelnemers):

- Cognitieve testen: 'Test Your Memory' (TYM) en de 'Self-Administered Gerocognitive Examination' (SAGE)
- Beoordeling door een arts-onderzoeker d.m.v (hetero)anamnese en de MMSE

Geheugenpoli UMC Utrecht:

- Alleen bij degene die verdacht worden van een cognitieve stoornis (TYM <40, SAGE <15, of o.b.v. het oordeel van de arts-onderzoeker)
- Willekeurige steekproef van 30% van degene zonder verdenking op cognitieve stoornissen

Deel 1: de gevolgen van cognitieve stoornissen bij type-2-diabetes
In **hoofdstuk 2** keken we naar depressieve symptomen en naar de gezondheidstoestand van mensen met type-2-diabetes en een nog niet vastgestelde, maar wel al aanwezige cognitieve stoornis. Wij onderzochten dit bij de 225 deelnemers aan de 'Cognitive Impairment in Diabetes' (Cog-ID) studie, zie kader links. Er werd een huisbezoek verricht waarbij mensen thuis eerst vragenlijsten over depressie en gezondheidstoestand invulden (CES-D, SF-36, EQ-5d en EQ-VAS) en daarna werden gescreend op cognitieve stoornissen. In totaal bleken 57 (25%) van de deelnemers aan het onderzoek een cognitieve stoornis te hebben (in de meeste gevallen ging dat om MCI). Maar liefst 30% van deze mensen had een score passend bij een depressie. Dit was bijna twee keer zoveel als bij de mensen zonder cognitieve stoornissen (RR 1.8; 95% BI 1.1-3.0). Mensen met cognitieve stoornissen scoorden ook slechter op de vragenlijsten over de gezondheidstoestand. Deze resultaten laten zien dat mensen met een cognitieve stoornis ook op andere vlakken dan cognitie kwetsbaar zijn, zelfs al wanneer de cognitieve stoornis nog niet bekend is bij de huisarts en als het gaat om MCI (en niet om dementie).

Artsen zijn soms bang dat het stellen van een diagnose MCI of dementie een negatief effect op de patiënt kan hebben. Er is momenteel (nog) geen geneesmiddel dat MCI of dementie kan genezen, waardoor artsen het gevoel kunnen hebben alleen maar slecht nieuws te brengen en de patiënt niks te kunnen bieden. In **hoofdstuk 3** keken we daarom in dezelfde studiepopulatie naar het beloop van de depressieve symptomen en de gezondheidstoestand in de twee jaar na screening. We vergeleken hierbij drie verschillende groepen. Ten eerste [1] de mensen die op basis van de screening verdacht werden van een cognitieve stoornis (screen positief op basis van de TYM, SAGE of het oordeel van de arts), bij wie op de geheugenpoli inderdaad een cognitieve stoornis werd vastgesteld (n=39). Ten tweede [2], screen positieve mensen die op de geheugenpoli geen cognitieve stoornis bleken te hebben (n=56). Ten derde [3], de mensen bij wie er op basis van de screening geen verdenking was op een cognitieve stoornis en die ook niet op de geheugenpoli werden onderzocht (screen negatieven; n=84). Bij de mensen met een cognitieve stoornis [1] bleven de scores op de depressie- en gezondheidstoestandsvragenlijsten behoorlijk stabiel over de twee jaar na de diagnose. Ook bij de screen negatieven [3] bleven de scores stabiel. Opvallend bij de screen positieven, die toch geen cognitieve stoornis bleken te hebben op de geheugenpoli [2], was dat deze groep in vergelijking met de screen negatieven [3] significant meer depressieve symptomen ervaarden in de periode vóór de screening, maar dat zes maanden na screening het aantal depressieve symptomen in deze groep [2] was afgenomen en vergelijkbaar was met de groep screen negatieven [3]. Door de opzet van de studie kunnen we niet met zekerheid zeggen wat hiervan de oorzaak is. Wel is duidelijk dat het stellen van de diagnose MCI of dementie en het bespreken daarvan met de patiënt in de twee jaar daarna niet tot verergering van depressieve klachten leidt.

Hoewel we weten dat mensen met type-2-diabetes en cognitieve stoornissen een verhoogd risico hebben op met diabetes samenhangende complicaties (zoals te lage bloedglucosewaarden (hypoglycaemie)), is het nog onduidelijk of deze mensen ook daadwerkelijk meer acute zorg nodig hebben. Door de behandeling van een patiënt aan te passen kan mogelijk een deel van de benodigde acute zorg, waaronder onverwachte ziekenhuisopnames, spoedeisende hulp bezoek en bezoek aan de huisartsenpost, voorkomen worden. In **hoofdstuk 4** hebben we het gebruik van acute zorg bij mensen met type-2-diabetes en een cognitieve stoornis in kaart gebracht. We verzamelden hiervoor de gegevens over het acute zorggebruik van de Cog-ID deelnemers (zie kader pagina 186) in de twee jaar vóór en de twee jaar na screening. We vergeleken hierbij de mensen met een positieve screening en een bevestigde cognitieve stoornis (n=37) met de mensen bij wie er op basis van de screening geen verdenking was op een cognitieve stoornis (screen negatieven; n=117). Over de totale onderzoeksperiode van vier jaar was 56% van de mensen met een cognitieve stoornis tenminste eenmaal op de huisartsenpost geweest, in vergelijking met 34% van de screen negatieven (p=0.02). Het gemiddelde aantal acute zorg bezoeken was ook hoger bij de mensen met een cognitieve stoornis in vergelijking met de screen negatieven (2.2±2.8 versus 1.4±2.2 bezoeken in vier jaar, p<0.05; 1.4±2.2 versus 0.7±1.5 bezoeken in de twee jaar na screening , p=0.03). Deze resultaten laten zien dat oudere mensen met type-2-diabetes en tevens een cognitieve stoornis inderdaad vaker acute zorg nodig hebben.

Deel 2: oorzaken en preventie van cognitieve stoornissen bij type-2-diabetes
In **hoofdstuk 5** beschrijven we de opzet van de 'CARdiOvascular safety of LINAgliptin' (CAROLINA®) cognitie studie. Linagliptine is een medicijn dat gebruikt wordt als glucoseverlagend middel bij mensen met diabetes-type-2. Dit middel werkt via remming van het enzym dipeptidyl peptidase-IV (DPP-IV). Naast het glucoseverlagende effect van DPP-IV remmers, hebben deze medicijnen diverse andere aangrijpingspunten en zijn er aanwijzingen voor een beschermend effect op de hersenen. Het doel van de CAROLINA®-cognitie studie is om te kijken of linagliptine versnelde cognitieve achteruitgang bij mensen met type-2-diabetes zou kunnen voorkomen. Linagliptine wordt hierbij vergeleken met glimeperide, een ander type glucoseverlagend middel dat op dit moment wereldwijd vaak in combinatie met metformine of als eerste middel voor de behandeling van type-2-diabetes wordt gebruikt. Deelnemers aan de studie hebben allemaal type-2-diabetes, een verhoogd risico op cardiovasculaire aandoeningen (zoals een hartinfarct of beroerte), en een score op de Mini Mental State Examination (MMSE) van 24 of hoger bij aanvang van de studie. Halverwege (na 3 jaar) en aan het einde van de studie (na ongeveer 6 jaar) wordt gekeken hoeveel mensen in beide studie-armen versneld cognitief achteruit zijn gegaan. Versnelde cognitieve achteruitgang is hierbij gedefinieerd als een MMSE score en/of de samengestelde score voor de 'trail making test (TMT)' en de 'verbal fluency test (VFT)' die harder achteruit is gegaan dan de scores van andere mensen in de studie (met als afkapwaarde het 16^{e} percentiel). Tussen december 2010 en december 2012 werden

de deelnemers gerandomiseerd, startte de behandeling en werden bij bijna 4500 mensen cognitieve testen afgenomen. De eindresultaten van de CAROLINA®-cognitie studie, die binnenkort verwacht kunnen worden, zullen ons meer inzicht geven in de mogelijkheden van linagliptine om versnelde cognitieve achteruitgang tegen te gaan.

Het was al bekend dat hoge bloedglucosewaarden bij mensen met type-2-diabetes gerelateerd zijn aan slechter cognitief functioneren. Verschillende grote studies waarbij bloedglucosewaarden bij mensen met type-2-diabetes werden verlaagd door intensievere diabetesbehandeling konden echter geen positief effect op cognitie aantonen. Wel nam het risico op hypoglycaemie toe. In **hoofdstuk 6** hebben we daarom onderzocht hoe het verband tussen HbA1c, dat gebruikt wordt als maat voor het gemiddelde bloedglucosewaarden over de afgelopen 2 tot 3 maanden, en cognitie er precies uitziet. We gebruikten hiervoor de gegevens van 4361 CAROLINA®-cognitie deelnemers. Als maten voor cognitie gebruikten we de MMSE score en een samengestelde score voor aandacht en uitvoerende functies (A&E score) op basis van de bovengenoemde TMT en VFT. Om het verband tussen HbA1c en cognitie te onderzoeken corrigeerden we voor mogelijk verstorende factoren (leeftijd, geslacht, opleidingsniveau en etniciteit), keken we ook of het verband niet-lineair was en onderzochten we de invloed van leeftijd en geslacht. Hier kwam uit dat het verband tussen HbA1c en de MMSE niet lineair was, maar meer een omgekeerde U-vorm had ($p<0.001$). Zowel mensen met een hoge (>8.5%, 58 mmol/mol) als mensen met een lage (<6.5%, 48 mmol/mol) HbA1c waarde scoorden slechter op de MMSE ten opzichte van mensen met HbA1c-waarden daartussenin, met name vrouwen van 70 jaar of ouder. Hierbij kan het verband tussen lage HbA1c-waarden en slechtere cognitie mogelijk verklaard worden door de schadelijke effecten van hypoglycaemie. Verder vonden we een lineair verband tussen de MMSE en twee markers voor de bètacelfunctie, namelijk pro-insuline en de pro-insuline-c-peptide-ratio. De betekenis hiervan is echter nog niet geheel duidelijk. Deze resultaten laten zien dat een erg strikte regulering van het glucosegehalte zeker niet bij alle patiënten de beste manier is om cognitieve stoornissen te voorkomen. Behandeling op maat waarbij rekening wordt gehouden met leeftijd, geslacht en het risico op hypoglycaemie is waarschijnlijk een betere manier.

Deel 3: Het vaststellen van cognitieve stoornissen

Als duidelijk is dat een patiënt met vragen over of klachten van zijn of haar cognitie op het spreekuur komt, dan begint een huisarts met de anamnese, het liefst aangevuld met een heteroanamnese, gericht op zijn of haar klachten en op het dagelijks functioneren. Dit levert vaak al veel informatie op en is het belangrijkste onderdeel van de diagnostiek. Als aanvulling kan de huisarts een cognitieve test gebruiken. De meeste richtlijnen, waaronder de NHG-Standaard voor de Nederlandse huisartsen, adviseren het gebruik van één of twee standaardtesten voor alle patiënten. In **hoofdstuk 7** stellen wij voor om dit anders aan te pakken en een cognitieve test te kiezen op basis van de informatie die de

huisarts al heeft ingewonnen. Onze gedachte was dat de voorafkans op een cognitieve stoornis – geschat na de (hetero)anamnese – zou moeten bepalen welke cognitieve test de meeste diagnostische winst oplevert. Op basis van tevoren vastgestelde criteria en de resultaten van de beschikbare literatuur kozen wij de meest geschikte cognitieve testen voor drie verschillende situaties. Wanneer de huisarts denkt dat een cognitieve stoornis niet heel waarschijnlijk is, kan de kloktekentest gebruikt worden. Dit is een test die in drie minuten kan worden afgenomen en een hoge negatief voorspellende waarde heeft. Met andere woorden: als de score op de test goed is, zal de huisarts de patiënt niet onterecht geruststellen. Wanneer de huisarts twijfelt over de aanwezigheid van een cognitieve stoornis (mogelijk MCI, maar dementie onwaarschijnlijk), dan is de 'Montreal Cognitive Assessment' (MoCA) test meer geschikt. In de derde situatie tenslotte, wanneer de huisarts denkt aan dementie, kan de MMSE met een hoge positief voorspellende waarde gebruikt worden om dit vermoeden te bevestigen. Deze drie situaties met de daarbij horende testen hebben we weergegeven in een eenvoudig te gebruiken stroomdiagram. We verwachten dat gebruik van dit stroomdiagram ervoor kan zorgen dat de cognitieve test die de huisarts gebruikt beter aansluit bij de individuele patiënt en dat er minder mensen onterecht gerustgesteld zullen worden.

Hoewel zowel Nederlandse, Europese als Amerikaanse diabetesrichtlijnen adviseren om te screenen op, of in ieder geval rekening te houden met, cognitieve stoornissen bij ouderen met type-2-diabetes, is het onduidelijk hoe dit screenen er precies uit moet zien. In **hoofdstuk 8** beschrijven we de opzet van de 'Cognitive Impairment in Diabetes' (Cog-ID) studie (zie ook kader pagina 186). Het doel van deze studie was het ontwikkelen van een diagnostische procedure voor het opsporen van ongediagnosticeerde cognitieve stoornissen bij mensen met type-2-diabetes van 70 jaar en ouder. Alle patiënten werden thuis bezocht door een arts-onderzoeker en vulden zelf de TYM en de SAGE in. Vervolgens werden een (hetero)anamnese en de MMSE afgenomen. Een deel van de patiënten werd ook uitgenodigd voor een bezoek aan de geheugenpoli van het UMC Utrecht. In **hoofdstuk 9** beschrijven we de resultaten van de Cog-ID studie. Van de 1243 patiënten uit 22 verschillende huisartsenpraktijken die werden uitgenodigd wilden er 228 (18%) deelnemen. Drie hiervan werden later alsnog van deelname uitgesloten omdat ze niet bleken te voldoen aan de inclusiecriteria. Bij 44 deelnemers werd een cognitieve stoornis vastgesteld. De resultaten laten zien dat als de score op de TYM ≥ 40 of op de SAGE ≥ 15 is, de kans groot is dat de patiënt ook geen cognitieve stoornis heeft (negatief voorspellende waarde 81 respectievelijk 85%). Als de TYM score <40 of de SAGE score <15 is, dan is de kans dat de patiënt daadwerkelijk een cognitieve stoornis heeft 39% voor de TYM en 40% voor de SAGE. Hieruit concluderen wij dat beide testen gebruikt kunnen worden voor het screenen op cognitieve stoornissen bij 70-plussers met type-2-diabetes in de huisartsenpraktijk. Bij een positieve test zal wel verder gekeken moeten worden of er daadwerkelijk sprake is van een cognitieve stoornis.

In het afsluitende **hoofdstuk 10** bekijken we onze resultaten in het licht van andere onderzoeken. In deel 1 onderzochten we de gevolgen van cognitieve stoornissen bij type 2 diabetes. Hieruit bleek dat deze mensen vaker een depressie hebben en ook vaker acute zorg nodig hebben. Andere studies toonden aan dat mensen met type 2 diabetes en een cognitieve stoornissen een verhoogd risico hebben op hypoglycaemie, hart- en vaatziekten en zelfs overlijden. Samen bevestigen deze resultaten dat ouderen met type-2-diabetes en cognitieve stoornissen kwetsbare mensen zijn, die waarschijnlijk baat hebben bij een aangepaste behandeling om complicaties te voorkomen, bijvoorbeeld door het vereenvoudigen, afbouwen of aanpassen van diabetesmedicatie. Medicatie die hypoglycaemie kan veroorzaken dient zoveel mogelijk te worden vermeden. Het is daarom van belang om de groep kwetsbare ouderen met type-2-diabetes en een hoog risico op complicaties tijdig in beeld te hebben.

In het tweede deel van het proefschrift zochten we naar mogelijke aangrijpingspunten voor de preventie van cognitieve stoornissen bij type 2 diabetes. Wij vonden dat zowel lage als hoge HbA1c-waarden zijn gerelateerd aan slechter cognitief functioneren. Naast het HbA1c zijn er vele andere factoren die verband houden met slechtere cognitie bij type-2-diabetes. Bijvoorbeeld risicofactoren voor hart- en vaatziekten, zoals overgewicht, te hoge bloeddruk en te hoog cholesterol. Mogelijk spelen ook factoren als voeding en beweging een rol. Opvallend is dat, net zoals wij vonden voor HbA1c, de verbanden vaak verschillen tussen mannen en vrouwen en per leeftijdscategorie. Het verhoogde risico op cognitieve stoornissen bij type-2-diabetes blijkt dus van veel factoren af te hangen. Het is nog niet duidelijk of cognitieve achteruitgang bij mensen met diabetes af te remmen of te voorkomen is. Een benadering waarbij rekening wordt gehouden met geslacht, leeftijd en wensen en mogelijkheden van de patiënt lijkt op dit moment het meest kansrijk.

In deel 3 keken we hoe huisartsen cognitieve stoornissen het beste vast kunnen stellen. Het is van belang dat mensen, met of zonder diabetes, die met klachten over het geheugen bij de huisarts komen niet onterecht gerustgesteld worden. Het kiezen van een cognitieve test op basis van de informatie die de huisarts al heeft (zie hoofdstuk 7) kan hierbij helpen. Voor ouderen met type-2-diabetes is het van extra belangrijk om cognitieve stoornissen tijdig op te sporen. Screenen op cognitieve stoornissen met behulp van de TYM of SAGE is voor deze groep zeker een optie voor in de toekomt. Uiteraard moeten patiënten daartoe bereid zijn. Het invullen en beoordelen hoeft niet veel tijd te kosten. Het is op dit moment echter nog niet precies duidelijk hoe de behandeling van de patiënt aangepast moet worden als er cognitieve stoornissen worden gevonden en of dit inderdaad complicaties kan voorkomen. Tot die tijd is het van belang dat huisartsen extra alert zijn op mogelijke signalen van een cognitieve stoornis bij ouderen met type-2-diabetes, zeker wanneer dit van invloed kan zijn op de behandeling. Denk hierbij aan onverklaard gewichtsverlies, fouten bij medicatie-inname of het spuiten van insuline , een snelle verslechtering van HbA1c waarden of frequente hypo- of hyperglykemieën.

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CURRICULUM VITAE & LIST OF PUBLICATIONS

Curriculum vitae

Jolien Janssen was born on February 13th 1988 in Arnhem, the Netherlands. After graduating from secondary school (Dorenweerd College in Doorwerth) in 2006, she moved to Utrecht to study Medicine at the Utrecht University. During her fourth year of medical school, she started her first research project on preoperative fasting plasma C-peptide as a predictor of diabetes outcome after gastric bypass surgery under supervision of dr. Edo Aarts and Ignace Janssen at the Rijnstate Hospital in Arnhem. During her research internship at the Julius Center for Health Sciences and Primary Care of the University Medical Centre Utrecht (UMCU), in the last year of medical school, she worked on a project investigating whether six-monthly diabetes monitoring of well-controlled patients could be an alternative for three-monthly diabetes monitoring, under supervision of dr. Paulien Wermeling and prof. dr. Guy Rutten. These two projects formed the basis of her interest in the scientific research on type 2 diabetes, and resulted in her first scientific publications. After graduating from medical school in 2012, she started her PhD project about cognitive impairment in type 2 diabetes, under supervision of prof. dr. Guy Rutten and prof. dr. Geert Jan Biessels. In 2013, she continued the project as so called AIOTHO, combining the clinical work as a general practice trainee with research projects. After her PhD defense, Jolien will continue her training to become general practitioner and she will stay involved in the CAROLINA and CARMELINA research projects in the role of co-promotor.

Jolien is a passionate cyclist and she is married to René van Seumeren. Together they have two daughters: Maud (2016) and Jonne (2017).

List of publications

Publications in this thesis

1. Janssen J, Koekkoek PS, Kappelle LJ, Biessels GJ, Rutten GEHM and the Cog-ID study group. People with type 2 diabetes and screen-detected cognitive impairment use acute health care services more often: observations from the COG-ID study. Diabetol Metab Syndr. 2019;11:21.
2. Janssen J, Koekkoek PS, Kappelle LJ, Biessels GJ, Rutten GEHM on behalf of the Cog-ID study group. Depressive symptoms and quality of life after screening for cognitive impairment: observations from the Cog-ID cohort study. BMJ Open 2019;9:e024696
3. Janssen J, van den Berg E, Zinman B, Espeland MA, Geijselaers SLC, Mattheus M, Johansen OE, Biessels GJ. HbA1c, Insulin Resistance, and β-Cell Function in Relation to Cognitive Function in Type 2 Diabetes: The CAROLINA Cognition Substudy. Diabetes Care Nov 2018, dc180914.
4. Biessels GJ, Janssen J, van den Berg E, Zinman B, Espeland MA, Mattheus M, Johansen OE. Rationale and design of the CAROLINA® - cognition substudy: a randomised controlled trial on cognitive outcomes of linagliptin versus glimepiride in patients with type 2 diabetes mellitus. BMC Neurol. 2018 Jan 15;18(1):7
5. Janssen J, Koekkoek PS, Moll van Charante EP, Kappelle LJ, Biessels GJ, Rutten GEHM. How to choose the most appropriate cognitive test to evaluate cognitive complaints in primary care. BMC Fam Pract. 2017 dec 16;18 (1):101
6. Koekkoek PS, Biessels GJ, Kooistra M, Janssen J, Kappelle LJ, Rutten GE; Cog-ID study group. Undiagnosed cognitive impairment, health status and depressive symptoms in patients with type 2 diabetes. J Diabetes Complications. 2015 Nov-Dec;29(8):1217-22
7. Koekkoek PS, Janssen J, Kooistra M, Biesbroek JM, Groeneveld O, van den Berg E, Kappelle LJ, Biessels GJ, Rutten GE. Case-finding for cognitive impairment among people with Type 2 diabetes in primary care using the Test Your Memory and Self-Administered Gerocognitive Examination questionnaires: the Cog-ID study. Diabet Med. 2016 Jun;33(6):812-9
8. Koekkoek PS, Janssen J, Kooistra M, van den Berg E, Kappelle LJ, Biessels GJ, Rutten GE. Cognitive Impairment in Diabetes: Rationale and Design Protocol of the Cog-ID Study. JMIR Res Protoc. 2015 Jun 9;4(2):e69

Other publications

9. Biessels GJ, Verhagen C, Janssen J, van den Berg E, Zinman B, Rosenstock J, George JT, Passera A, Schnaidt S, Johansen OE; on behalf of the CARMELINA® investigators. Effect of Linagliptin on Cognitive Performance in Patients with Type 2 Diabetes and Cardiorenal Comorbidities: the CARMELINA Randomized Trial. Diabetes care 2019 Aug dc190783.
10. Groeneveld O, Reijmer Y, Heinen R, Kuijf H, Koekkoek P, Janssen J, Rutten GEHM, Kappelle LJ, Biessels GJ; COG-ID study group. Brain imaging correlates of mild cognitive impairment and early dementia in patients with type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis. 2018 Dec;28(12):1253-1260.
11. Janssen J, Koekkoek PS, Moll van Charante EP, Kappelle LJ, Biessels GJ, Rutten GEHM. Hoe weet je of cognitieve stoornissen waarschijnlijk zijn? Huisarts en wetenschap. 2018 Jul
12. Janssen J, Wermeling PA, Gorter KJ, Beulens JWJ, Rutten GEHM. Six-monthly diabetes monitoring of well-controlled patients: Experiences of primary care providers. Prim Care Diabetes. 2013 Oct;7(3):187-91
13. Wermeling PA, Janssen J, Gorter KJ, Rutten GEHM. Satisfaction of well-controlled type 2 diabetes patients with three-monthly and six-monthly monitoring. BMC Fam Pract. 2013 Jul 30;14:107.
14. Aarts EO, Janssen J, Janssen IMC, Berends FJ, Telting D, de Boer H. Preoperative fasting plasma C-peptide level may help to predict Diabetes outcome after Gastric Bypass Surgery. Obes Surg. 2013 Jul;23(7):867-73

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