Cognitive function in patients with diabetes mellitus: guidance for daily care
Paula S Koekkoek, J Jaap Kappelle, Esther van den Berg, Guy E H M Rutten, Geert Jan Biessels

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

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

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

Type 1 diabetes mellitus
Cognitive function
Neuropsychological studies in patients with type 1 diabetes consistently report subtle changes in cognitive function compared with individuals without diabetes, particularly in general intelligence, psychomotor speed, and mental flexibility. In a systematic review, performance on these domains in adult patients was on average half an SD (0·3–0·7 SDs) below that of people without diabetes. Additionally, overall cognition and the visual perception domain were slightly affected (0·3–0·4 SDs less than in people without diabetes), but the domain of learning and memory was not affected. In cross-sectional studies, the effect sizes of the cognitive decrements (decrements of SD) seem to be consistent across age groups, from young adults to those aged up to 70 years (figure 1). In type 1 diabetes often has its onset in childhood or adolescence. Decreased cognitive performance in adults

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
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<tr>
<td>Pathophysiology</td>
<td>Autoimmune disorder with destruction of pancreatic cells leading to insulin deficiency</td>
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<tr>
<td>Age of onset</td>
<td>Childhood or early adulthood</td>
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<tr>
<td>Cognitive dysfunction</td>
<td>Subtle changes in all age groups, resulting in reduced intelligence, processing speed, and mental flexibility, usually with slow progression over time; link with dementia not established yet</td>
</tr>
<tr>
<td>MRI findings in patients without dementia</td>
<td>Reduced brain volume, as a result of altered brain development or atrophy; altered structural and functional connectivity</td>
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Table 1: Characteristics of type 1 and type 2 diabetes
might therefore be a result of changes in cognitive function that began in childhood. A meta-analysis of studies comparing cognitive function in children (aged ≥19 years) with type 1 diabetes with that of children without diabetes reported reduced performance of about 0–2 SDs in the same domains that are affected in adults with type 1 diabetes. Changes in cognitive function seem to develop soon after diabetes onset, with only slow progression thereafter. Results of longitudinal studies confirm these trajectories. In 1144 participants from the DCCT trial, no clear deterioration of average cognitive performance (in overall performance or in particular domains) was reported during the course of 18 years (mean age at study entry 27 years). However, small subgroups of patients with type 1 diabetes might show accelerated cognitive decline, particularly those with advanced diabetic microvascular disease.

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

Brain imaging
Changes in cognitive function in people with type 1 diabetes are accompanied by structural brain abnormalities on MRI. Compared with people without diabetes, middle-aged patients with type 1 diabetes had reduced grey matter volumes in the frontal lobe (6–19% smaller) and the adjacent supramarginal and postcentral gyri (8–13% smaller). In many patients, these volumetric changes might have their origin in childhood, since reductions in grey matter volume have been reported in children (roughly 4% reduction in volume) and in young adults with childhood diabetes onset (roughly 10% reduction in volume). In adult patients aged 20–40 years, diabetes onset before the age of 7 years was associated with larger ventricular volumes compared with patients with a later diabetes onset (aged 7–17 years). Reduced brain volume in people with type 1 diabetes has been linked to disturbed integrity of fibre tracts connecting the main cortical areas. Additionally, structural (diffusion tensor imaging [DTI]) and functional (fMRI) imaging studies show disturbed brain networks in patients with type 1 diabetes, which are associated with reduced cognitive performance. Connectivity measures therefore seem to be interesting brain imaging markers for type 1 diabetes. Thus far, few studies have addressed the relation between type 1 diabetes and cerebral small vessel disease, and results are inconclusive.

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

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

**Management**

The DCCT is the only randomised trial in patients with type 1 diabetes thus far with cognition as an outcome measure. In the DCCT, intensive therapy, with three or more daily insulin injections or continuous subcutaneous insulin infusion, was compared with conventional therapy with one or two daily insulin injections. Prevention and slowing of progression of microvascular complications was the primary endpoint. Additionally, cognition was monitored closely, because of an expected (and observed) increase in incidence of severe hyperglycaemic episodes with intensive therapy (around 40 severe hyperglycaemic episodes per 100 patient-years). Cognitive function was similar in the two treatment groups, showing that intensive therapy was safe with regard to cognitive performance, but also that the intensive therapy group had 2% lower concentrations of HbA1c (20 mmol/mol), maintained for an average of 6.5 years, which did not lead to improved cognitive outcomes in the intensively treated group.

**Type 2 diabetes mellitus**

**Cognitive function**

Compared with people without diabetes, patients with type 2 diabetes perform slightly worse on a range of cognitive tasks. For memory, processing speed, and executive function, cognitive performance is on average 0.3–0.4 SDs lower than that of people without diabetes. These subtle changes in cognitive performance have been reported from adolescence up to the age of 80 years (figure 1). Because several domains are affected in patients with type 2 diabetes, a diminished efficiency of processing resources, which is likewise seen in cognitive ageing.

Patients with newly identified type 2 diabetes detected by screening, people with impaired fasting glucose, and people with metabolic syndrome (but without type 2 diabetes) show cognitive decrements in the same domains as patients with manifest type 2 diabetes. The processes underlying cognitive dysfunction seem to start in the prediabetic stages and progress subtly over time (figure 1). Results of longitudinal studies show that the speed of cognitive decline in patients with type 2 diabetes is in the same range or up to two times faster than that of normal ageing. Results of prospective population-based studies link diabetes to an increased risk of mild cognitive impairment (MCI) compared with people without diabetes. This increased risk involves both amnestic and non-amnestic MCI (panel 1), although the relation with non-amnestic MCI is attenuated if other vascular risk factors are taken into account.

In people with amnestic or non-amnestic MCI, the proportion of patients who convert from MCI to dementia is 1.5–3 times higher for those with diabetes compared with those without. Results of epidemiological studies also link type 2 diabetes to an increased dementia risk. A meta-analysis including data from 11 studies of more than 30 000 people, of whom 16% had type 2 diabetes, showed that the relative risk (RR) for dementia was 1.51 (95% CI 1.31–1.74) in people with diabetes compared with those without. Therefore, the diabetes-attributable risk of dementia is 6–7% (ie, one in 15 cases of dementia is attributable to diabetes). This attributable risk might be even higher in populations in which diabetes is more common, and might increase with increasing diabetes

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**Panel 1: Proposed stages of diabetes-associated cognitive dysfunction**

**Diabetes-associated cognitive decrements**

- Subtle changes in cognitive function in one or several domains, typically 0.3–0.5 SDs lower than in people without diabetes
- Might result in cognitive complaints (usually expressed only by the patient), but activities of daily life are preserved; unlikely to affect diabetes self-management
- Occur in all age groups in people with type 1 and type 2 diabetes
- Slowly progress

**Mild cognitive impairment (MCI)**

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

**Dementia**

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

*For MCI and dementia, the same diagnostic criteria apply in people with diabetes as in those without.
The increased dementia risk in people with diabetes includes both vascular dementia, with an RR of 2.48 (2.08–2.96), and Alzheimer’s disease, with an RR of 1.46 (1.20–1.77). Nevertheless, because the absolute risk of Alzheimer’s disease is higher than that of vascular dementia, Alzheimer’s disease is the most common type of dementia in people with diabetes.18

Indications that the risk of dementia is increased in the prediabetic stages are clear, since prediabetes is associated with an increased incidence of dementia.4,44 This finding raises the question of whether diabetes (ie, factors implicated in glucose dysregulation) increases the risk of dementia, or whether this risk is attributable to other diabetes-associated factors, particularly an adverse vascular risk-factor profile. In population-based cohort studies of older individuals (average age >65 years), adjustment for vascular risk factors did not weaken the association between diabetes and dementia.45 Nevertheless, the role of an adverse vascular risk-factor profile—even before diabetes onset— in dementia risk in patients with diabetes will need further study.

Whether increased risk of Alzheimer’s disease in people with diabetes involves an interaction between glucose dysregulation and the core molecular processes—ie, aberrant amyloid-β processing, involving aggregation of small toxic amyloid-β oligomers, and generation of the microtubule-associated protein MAPT—that are thought to underlie Alzheimer’s pathological changes is debated.46 Despite the epidemiological link between diabetes and a clinical diagnosis of Alzheimer’s disease, and many studies with experimental models linking aberrant cerebral insulin homeostasis to disturbances in amyloid and MAPT processing,47 autopsy studies48,49 have reported a decreased burden of Alzheimer’s pathological changes in the brains of people with diabetes compared with people without diabetes, whereas the burden of vascular pathological changes is clearly increased.48,49 These post-mortem findings have been complemented by results of PET imaging studies showing that diabetes is associated with an Alzheimer’s-like pattern of glucose hypometabolism in the bilateral angular gyri, posterior cingulate and precuneus, and inferior temporal cortical regions in both hemispheres, but not with increased amyloid deposition.50

Brain imaging
Type 2 diabetes is associated with reduced brain volume.51–54 Grey matter loss is most prominent in the medial temporal, anterior cingulate, and medial frontal lobes, and white matter loss is most prominent in frontal and temporal regions (figure 2).55

Results from longitudinal studies51,56–57 show that reductions in brain volume occur slowly during the course of years, at a speed that only modestly exceeds normal age-related loss of brain volume. Smaller grey and white matter volumes have been associated with, and suggested to mediate, reduced executive function, processing speed, and memory,54,55 in patients with type 2 diabetes, but not in all studies.56 Progression of cerebral atrophy in patients with type 2 diabetes has been linked to accelerated cognitive decline.54

In view of the links between type 2 diabetes and cerebrovascular disease, particularly ischaemic stroke,59 many studies have investigated the association of diabetes with damage to the brain vasculature as a potential mediator of cognitive dysfunction. Lacunar infarcts on MRI occur about twice as often in people with type 2 diabetes than in those without diabetes.55,60 Although several studies report that the burden of white matter hyperintensities is not increased in patients with type 2 diabetes,55,56 other studies report a modest increase (about 20%) in the volume of white matter hyperintensities compared with people without diabetes.55,57,61

Alterations in structural and functional connectivity have been identified as possible brain imaging markers of type 2 diabetes (figure 3).62,63 Although abnormalities in these connectivity markers are not specifically associated with particular signs or symptoms, they are clearly linked to cognitive function in people with type 2 diabetes.64 Longitudinal studies should further investigate the prognostic usefulness of connectivity markers in prediction of accelerated cognitive decline.

Risk factors
The subtle cognitive changes reported in people with type 2 diabetes do not necessarily have the same risk factors as those for MCI and dementia.6 Risk factors for the subtle cognitive changes in patients with type 2 diabetes have mostly been investigated in cross-sectional studies with modest sample sizes. Identification of risk factors for dementia and MCI in people with type 2 diabetes is complex and needs large cohort studies with prolonged follow-up.
Studies that have addressed the relation between glycaemic control (as measured by HbA1c concentrations) and cognitive dysfunction in type 2 diabetes have reported mixed results. The largest studies thus far reported that the relation between HbA1c and performance on different cognitive domains or in tests of cognitive performance was either weak or absent. Only very high HbA1c concentrations (>10% or >86 mmol/mol) are associated with a moderately increased risk of dementia.

Peripheral microvascular complications of diabetes, which develop as a result of long-term exposure to hyperglycaemia, have also been linked to cognitive dysfunction in type 2 diabetes. Albuminuria, as a marker of nephropathy, is associated with accelerated cognitive decline, and the results of several studies have linked diabetic retinopathy to cognitive decline and to an increased risk of dementia in patients with type 2 diabetes.

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

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

Management of diabetes and vascular risk factors
Several weeks or months of intensive metabolic treatment, with either rosiglitazone or glyburide in addition to metformin, have been shown to improve memory and concentration in patients with type 2 diabetes and high HbA1c concentrations (a reduction in fasting glucose of 2–3 mmol/L was seen for both treatment groups). However, several large randomised trials did not report a longer-term benefit of intensive glycaemic control on cognitive function in people with type 2 diabetes compared with people without diabetes (table 2).

The ACCORD-MIND study is the only study thus far that has specifically assessed the potential effects of anti hypertensive or lipid-lowering treatment on cognitive decline in patients with type 2 diabetes. Intensive therapy for hypertension (<120 mm Hg vs <140 mm Hg) and combination therapy with a statin plus a fibrate for 40 months did not improve cognition, but intensive blood-pressure lowering was, unexpectedly, associated with accelerated brain atrophy. Results of observational studies in the general population indicate that cardiovascular risk management might reduce the risk of cognitive impairment. Thus far, however, the results of randomised
trials have been mixed, and many have reported no significant benefit of intensified cardiovascular risk management. In the ONTARGET and TRANSCEND studies, for example, blood pressure lowering in 25 271 patients—35% of whom had diabetes—treated with ramipril, telmisartan, or both did not change the incidence of Alzheimer’s disease. So-called subjective cognitive complaints as diabetes-associated cognitive decrements is usually slow. Implications, because progression of the underlying diabetes-associated cognitive decrements has prognostic implications, because progression of the underlying diabetes-associated cognitive decrements is usually slow. Diagnosis of cognitive dysfunction in diabetes Classification of stages of cognitive dysfunction The data discussed in the preceding sections show that diabetes is associated with changes in cognitive function, ranging from subtle cognitive changes to MCI and dementia. In our view, differentiation between these different stages of cognitive dysfunction in clinical practice is essential, because they are likely to have a different prognosis and might need different management (panel 1). The same diagnostic criteria apply to cognitive impairment—ie, MCI and dementia—in people with diabetes as in people without diabetes (panel 2). An overlooked issue is how the subtle cognitive changes that occur in association with diabetes should be classified and managed in clinical practice. Outside the specialty of diabetes, efforts have been made to create a lexicon defining the earliest stages of cognitive dysfunction that precede dementia, particularly Alzheimer’s disease. The concept of MCI originates from this effort, as do terms such as prodromal, preclinical, or presymptomatic Alzheimer’s disease. So-called subjective cognitive decline in preclinical Alzheimer’s disease has also received increasing attention, and international efforts are being made to develop criteria for the condition. These terms, however, are not well suited for classification of subtle diabetes-associated cognitive changes. These subtle changes occur in all age groups, change slowly over many years, and are, in most patients with diabetes, unlikely to indicate the earliest stage of a dementia process. We propose to classify these subtle changes as “diabetes-associated cognitive decrements”. This classification can be considered if a patient with diabetes expresses concerns about his or her cognitive function, typically involving increased mental effort, but with mostly preserved social or occupational function. For a classification of diabetes-associated cognitive decrements, there should be no alternative explanations for the complaints, and there should be no cognitive deficits severe enough to be classified as MCI. In our view, classification of cognitive complaints as diabetes-associated cognitive decrements is important in such cases because it acknowledges the subtle but real changes in cognitive function that people with diabetes might experience. Moreover, diagnosis of diabetes-associated cognitive decrements has prognostic implications, because progression of the underlying cognitive changes is usually slow. Diagnosis of cognitive dysfunction To differentiate between diabetes-associated cognitive decrements and cognitive impairment (MCI and dementia), detailed information is needed about the severity and type of cognitive complaints, their changes over time, and their effects on activities of daily life and occupational function. Confirmation by an informant is recommended. The severity of the complaints is a key distinguishing feature and should be proportional to the presumed underlying functional deficit. The magnitude of diabetes-associated cognitive decrements is on average

<table>
<thead>
<tr>
<th>Study population</th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
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<tbody>
<tr>
<td></td>
<td>DCCT/EDIC†</td>
<td>ACCORD-MIND§</td>
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<tr>
<td></td>
<td>1441 patients aged 35–59 years</td>
<td>2977 patients aged 50–75 years</td>
</tr>
<tr>
<td></td>
<td>Intensive control (HbA1c &lt;42 mmol/mol)</td>
<td>Intensive treatment (HbA1c &lt;42 mmol/mol)</td>
</tr>
<tr>
<td></td>
<td>Standard control of blood glucose</td>
<td>Standard treatment (HbA1c 53–65 mmol/mol)</td>
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<tr>
<td></td>
<td>Trial 6.5 years; total follow-up 18 years</td>
<td>2.8 years</td>
</tr>
<tr>
<td></td>
<td>No difference in cognitive decline</td>
<td>No difference in cognitive performance and cognitive decline: Reduced rate of brain atrophy</td>
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</table>

Table 2: Trials of the effect of glucose-lowering treatment on cognitive function in diabetes
0·3–0·5 SDs greater than those of people without diabetes, which is equivalent to a reduced cognitive performance of 10–15 percentile points relative to the mean for people without diabetes.3,4,30 The magnitude of cognitive deficits that meet the criteria for MCI (a performance deficit of >40–45 percentile points relative to the mean for people without diabetes) is much larger.3,4,30 Previous likelihood is another issue to consider. Diabetes-associated cognitive decrements can occur in all age groups, whereas MCI and dementia are quite rare in people younger than 65 years, even in those with diabetes, with a prevalence that doubles every 5 years after the age of 65 years.6

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

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

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

Management of patients with diabetes and cognitive dysfunction

Cognitive impairment

No specific treatments exist for people with diabetes and MCI or dementia, and clinicians should treat MCI or dementia according to the same principles as in people without diabetes. Nevertheless, cognitive dysfunction in patients with diabetes is associated with poor glycaemic control—especially in the case of impaired executive function—with an increased frequency of hospital admissions and with an increased occurrence of severe hypoglycaemic episodes.72 Therefore, diagnosis of cognitive impairment should be a reason for the diabetes care provider to reassess the patient’s capacities for self-management and treatment adherence, and to consider additional measures (panel 2).95–96 First, the increased risk of medication errors should be addressed by use of medication dispensers, or the involvement of caregivers can be considered. Second, the physician should assess whether perfect glycaemic control is still possible and desirable or whether more lenient glycaemic targets are better to prevent hypoglycaemia. Finally, appointments at the surgery should be made easier, for example with reminders of appointments.

Panel 2: Typical case histories

Patient A

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

Patient B

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

Because of the slow progression over time, the prognosis of diabetes-associated cognitive decrements is generally favourable, particularly for patients younger than 60–65 years.\textsuperscript{6} The patient should be informed of this usually benign course. In patients older than 65 years, however, the incidence of dementia is higher. Cognitive decrements might be the first signs of further cognitive decline, and the prognosis is therefore less certain. In all patients, irrespective of age, a follow-up assessment is recommended to verify that the symptoms develop as expected (panel 2).

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

Screening
Outside the specialty of diabetes, the advantages and disadvantages of screening for cognitive disorders are debated intensively. Individuals opposed to screening argue that the benefit of an early diagnosis of dementia does not outweigh potential harm, because no treatment for dementia is yet available.\textsuperscript{7} This view assumes that, as long as people do not complain, detection of cognitive impairment is not relevant. This assumption might not be correct, particularly in the context of diabetes, where unrecognised cognitive dysfunction can, apart from affecting many other aspects of life, affect diabetes self-management with potentially serious results.\textsuperscript{75,98} Moreover, health-care professionals often overlook or discard the early signs of dementia in patients with cognitive complaints. From the initial presentation of patients’ symptoms, voicing of family concerns, or both, confirmation of a diagnosis of dementia can take months to years.\textsuperscript{99} Reasons for this slow diagnosis might be that physicians do not deem disclosure of a diagnosis relevant or that a diagnosis of cognitive impairment has only negative effects.\textsuperscript{95} We propose that a case-finding strategy, combined with appropriate support for diabetes management, can lead to improved quality of life and quality of care for patients. Such case-finding strategies should focus on detection of MCI and dementia, since these disorders are most likely to have implications for daily function and diabetes self-management. Evidence for the benefits of this approach might guide the debate between those who advocate an early diagnosis of cognitive impairment and those who are sceptical of case-finding strategies. As a result of the increasing number of elderly patients with diabetes, the need for knowledge about the optimum approach for, and advantages and disadvantages of, case-finding for cognitive impairment is becoming increasingly urgent and relevant. For now, a case-finding strategy could be considered in diabetes-specific scenarios in which cognitive impairment could play a part; for example, in patients with frequent hypoglycaemic events or in patients who need to start a new treatment because treatment targets are insufficiently reached with standard treatment.

Identification of patients at risk
In addition to identification of patients with existing cognitive impairment, prediction of which patients are most likely to become impaired in the future is also relevant. As indicated in this Personal View, only a subgroup of patients with diabetes will develop accelerated cognitive decline, MCI, or dementia. Novel treatments to prevent these adverse cognitive outcomes

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

The risk score was developed for patients with type 2 diabetes aged 60 years or older. Reproduced from Exalto and colleagues.\textsuperscript{66} For details, see original paper.

<table>
<thead>
<tr>
<th>Points</th>
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<td>60–64 years</td>
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<td>Acute metabolic event</td>
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<tr>
<td>65–69 years</td>
<td>3</td>
<td>Microvascular disease</td>
</tr>
<tr>
<td>70–74 years</td>
<td>5</td>
<td>Diabetic foot</td>
</tr>
<tr>
<td>75–79 years</td>
<td>7</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>80–84 years</td>
<td>8</td>
<td>Cardiovascular disease</td>
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<tr>
<td>≥85 years</td>
<td>10</td>
<td>Depression</td>
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Add up points and look up predicted 10-year risk of dementia.

<table>
<thead>
<tr>
<th>Predicted 10-year risk of dementia (%)</th>
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<tbody>
<tr>
<td>-1</td>
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<tr>
<td>0</td>
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<td>1</td>
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might be most effective if they can be applied at an early stage of the process in high-risk individuals. A risk score has been introduced that predicts the 10-year dementia risk specifically for patients with type 2 diabetes mellitus of 60 years or older (figure 4). The risk score consists of several clinical and demographic variables that are readily available from every patient, and ranges from a 10-year dementia risk of 5% for those with the lowest score up to a risk of 73% for the highest scores (figure 4). An advantage of this risk score is that it can readily be implemented to select patients for prevention programmes. A limitation is that specific disease processes in dementia cannot be targeted. Biomarkers that not only predict risk of impairment, but are also indicative of a specific modifiable treatment target, are clearly needed. Such biomarkers could then be integrated into a prediction model combining risk estimates on the basis of a clinical profile, which identifies the individuals at risk, with a biomarker panel that identifies optimum individualised interventions.

**Treatments**

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

**Conclusions**

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

**Contributors**

PSK, LJK, and GJB searched for and selected references, created the structure of the report, and prepared the first draft and subsequent versions. EvdB and GEHMR helped to refine the idea and structure of the report, and commented on the drafts.

**Declaration of interests**

PSK and GEHMR declare no competing interests. LJK has received consulting and speaker’s fees from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. EvdB consults for, and receives research support from, Boehringer Ingelheim. GJB consults for, and receives research support from, Boehringer Ingelheim, consults for Takeda Pharmaceuticals, and has received speaker’s fees from Eli Lily.

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