Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications

Geert Jan Biessels[1] * *and Florin Despa*[2]

Abstract | Cognitive dysfunction is increasingly recognized as an important comorbidity of diabetes mellitus. Different stages of diabetes-associated cognitive dysfunction exist, each with different cognitive features, affected age groups and prognoses and probably with different underlying mechanisms. Relatively subtle, slowly progressive cognitive decrements occur in all age groups. More severe stages, particularly mild cognitive impairment and dementia, with progressive deficits, occur primarily in older individuals (>65 years of age). Patients in the latter group are the most relevant for patient management and are the focus of this Review. Here, we review the evolving insights from studies on risk factors, brain imaging and neuropathology, which provide important clues on mechanisms of both the subtle cognitive decrements and the more severe stages of cognitive dysfunction. In the majority of patients, the cognitive phenotype is probably defined by multiple aetiologies. Although both the risk of clinically diagnosed Alzheimer disease and that of vascular dementia is increased in association with diabetes, the cerebral burden of the prototypical pathologies of Alzheimer disease (such as neurofibrillary tangles and neuritic plaques) is not. A major challenge for researchers is to pinpoint from the spectrum of diabetes-related disease processes those that affect the brain and contribute to development of dementia beyond the pathologies of Alzheimer disease. Observations from experimental models can help to meet that challenge, but this requires further improving the synergy between experimental and clinical scientists. The development of targeted treatment and preventive strategies will therefore depend on these translational efforts.

Cognitive dysfunction
Any change from normal cognitive functioning. May range from subtle to severe.

Cognitive decrements
Subtle cognitive dysfunction not severe enough to meet formal neuropsychological criteria for cognitive impairment.

[1]*Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands.*

[2]*Department of Pharmacology and Nutritional Sciences and Department of Neurology, University of Kentucky, Lexington, KY, USA.*

**e-mail: G.J.Biessels@umcutrecht.nl*

https://doi.org/10.1038/s41574-018-0048-7

The global prevalence of diabetes mellitus is increasing in both absolute and relative numbers[1]. For type 2 diabetes mellitus (T2DM) in particular, this increase in prevalence is attributed to changing lifestyle factors, such as diet, overweight and physical inactivity[2]. Another key factor that adds to the prevalence of T2DM is the increased longevity and ageing of populations around the world. The latter is particularly evident in low-income and middle-income countries[1], and these trends are expected to continue for the foreseeable future.

The population trends for dementia are very similar to those observed in diabetes mellitus[3]. As a consequence, there is an increased co-occurrence of diabetes mellitus and dementia. We are now aware, however, that diabetes mellitus and dementia co-occur more frequently than is expected by chance alone. Epidemiological studies have established an increased risk of dementia among individuals with diabetes mellitus[4]. Diabetes mellitus is also linked to forms of cognitive dysfunction that are not as severe as dementia, such as mild cognitive impairment (MCI), but also to even more subtle cognitive changes, which are referred to as diabetes-associated cognitive decrements[5]. The increased co-occurrence of diabetes mellitus with different types of cognitive dysfunction has important implications for patient management, particularly in older (over ~65 years of age) individuals in whom dementia and pre-dementia stages of cognitive impairment most commonly occur.

In this Review, we address the different manifestations of diabetes-mellitus-associated cognitive dysfunction. We put an emphasis on dementia and pre-dementia stages of cognitive impairment in T2DM, but we also address the more subtle diabetes-associated cognitive decrements. Throughout the manuscript, we use the term 'diabetes' when referring to diabetes mellitus in general and 'T1DM' or 'T2DM' when referring to these specific subtypes. We show that studies on risk factors and on neuroimaging and neuropathology correlates of cognitive dysfunction provide important clues on the underlying pathophysiological mechanisms; however, many questions remain.

Key points

- Cognitive dysfunction in diabetes mellitus can manifest itself as diabetes-associated cognitive decrements, mild cognitive impairment (MCI) and dementia.
- Owing to the marked differences in affected age groups and trajectories of cognitive decline, diabetes-mellitus-associated cognitive decrements and dementia should be regarded as different entities that probably have different underlying mechanisms.
- Mechanisms of MCI and dementia in diabetes have mainly been studied in patients with type 2 diabetes mellitus (T2DM) and involve mixed vascular and neurodegenerative pathologies, often on a background of Alzheimer disease pathology; however, T2DM does not increase the burden of the latter.
- Key causative pathways in diabetes-associated cognitive dysfunction need to be identified in order to develop course-modifying therapies.
- Experimental models can single out individual causative pathways in ways and at a level of detail that are impossible in humans.
- Any potential mechanisms of brain dysfunction that are identified in experimental models of diabetes mellitus must also be evaluated in the complex setting of other morbidities with which they may co-occur in patients.

We also discuss the role of experimental models in improving our understanding of the pathophysiological mechanisms underlying diabetes-associated cognitive dysfunction and how these models could help us to further unravel the aetiology and identify treatment targets. A key strength of experimental models is that they can be used to single out individual causative pathways in ways and at a level of detail that is impossible in humans. Technical progress with regards to experimental techniques has enabled the development of tools that can boost studies of these pathways, from the level of specific molecular interactions to systems biology. However, we must ensure that we evaluate any potential mechanisms we identify in experimental models in the context of other morbidities with which they can co-occur in patients. In this Review, we make the point that by further improving the synergy between clinical and experimental scientists, we can foster innovation in designing animal models that accurately replicate the complexities of the interaction between diabetes and dementia in humans.

While awaiting these further research developments, cognitive dysfunction in diabetes already affects daily clinical care. In the final section of this Review, we address the clinical implications of the latest data on diabetic brain injury and future perspectives.

Cognitive dysfunction and diabetes

Substantial epidemiological evidence supports an association between diabetes and cognitive dysfunction[5–7]. Of note, however, we must not regard cognitive dysfunction in relation to diabetes as a unitary construct. Manifestations and prognosis of diabetes-associated cognitive dysfunction vary depending on the type of diabetes a patient has and the age of the patient[8].

For example, children with T1DM can display subtle changes in cognitive development, particularly if the onset of diabetes occurs before 7 years of age[9]. Adults with T1DM also present subtle decrements in cognitive performance relative to age-matched controls, particularly affecting the cognitive domains of intelligence, psychomotor efficiency and cognitive flexibility (Cohen's *d* effect sizes of 0.7, 0.6 and 0.5, respectively)[10]. These decrements generally remain stable over time, with little change relative to people without diabetes[11], although there can be subgroups of patients, particularly those with advanced microvascular complications, in whom the severity of cognitive dysfunction can worsen substantially over time[9,12].

In adults with T2DM, we can divide deficits in cognitive functioning into three approximate stages according to severity: diabetes-associated cognitive decrements, MCI and dementia[5]. The term 'diabetes-associated cognitive decrements' refers to subtle changes in cognitive function that might give rise to cognitive complaints (usually expressed only by the patient) but should not affect activities of daily life or diabetes self-management[5]. The subtle cognitive changes might concern one or several domains, including processing speed, executive function and memory, with a typical Cohen's *d* effect size of 0.2–0.5 relative to people without diabetes at the group level[13,14]. These decrements probably develop during the prediabetic stages[15] and evolve very slowly over the course of many years at a rate that is up to 50% faster than that of normal cognitive ageing[13,15–18].

MCI and dementia

Diagnostic constructs for MCI[19,20] and dementia[21] and their aetiologies in people with diabetes are the same as in people without diabetes (BOX 1). Of note, these diagnostic constructs do not refer to a particular aetiology. In clinical practice, as well as in most epidemiological studies, assumptions on the probable aetiology are primarily based on the nature of the symptoms (for example, acquired deficit in episodic memory is suggestive of Alzheimer disease) while excluding other causes (such as a brain tumour). However, this diagnostic approach is clearly not specific or sensitive enough to determine the actual aetiology[22]. Therefore, particularly in the research setting, clinicians use biomarkers reflecting the actual pathologies associated with Alzheimer disease, such as the concentration of amyloid-β and tau in the cerebrospinal fluid or the presence of amyloid on PET scans of the brain, to define the aetiology of MCI and dementia[23].

Two prospective population-based studies have reported similar findings on the risk of MCI in patients with diabetes. In one of the studies, the researchers observed an HR of 1.5 (95% CI 1.0–2.2) for amnesic MCI and an HR of 1.2 (95% CI 0.9–1.8) for nonamnesic MCI[24]. In the other study, the investigators reported an HR of 1.6 (95% CI 1.2–2.2) for amnesic MCI and an HR of 1.4 (95% CI 0.8–2.2) for nonamnesic MCI[25]. In addition, the prognosis of MCI is worse in patients with diabetes than in patients without diabetes. Two meta-analyses, each containing seven — not completely overlapping — studies, reported a relative risk (RR) of conversion to dementia of 1.7 (95% CI 1.1–2.4)[26] and an RR of 1.7 (95% CI 1.1–2.6)[27] for patients with MCI and diabetes compared with patients with MCI without diabetes.

A number of studies have investigated the risk of dementia in relation to diabetes. Systematic reviews and meta-analyses[4,6,7,28], including >25 original studies with >2 million participants, estimate the RR for all types of dementia at 1.73 (95% CI 1.65–1.82)[6], the RR for Alzheimer disease at 1.53 (95% CI 1.42–1.63)[7] and

Cognitive impairment
Cognitive dysfunction severe enough to be classified as 'abnormal' or 'impaired' on the basis of neuropsychological test results (mostly 1.5–2 s.d. below normative mean). Entails both mild cognitive impairment and dementia.

Cognitive domains
Distinct types of cognitive function supporting different aspects of behaviour. Domains include intelligence, attention, language, memory, executive functions (including cognitive flexibility), visual–spatial skills and psychomotor efficiency and may be differentially affected by disease.

Cohen's *d* effect sizes
Cohen's *d* is defined as the difference between two group means divided by the pooled standard deviation.

Amnesic MCI
Mild cognitive impairment (MCI) with the domain memory being affected. Regarded as the prototypical form of MCI preceding Alzheimer dementia.

Nonamnesic MCI
MCI with the domain memory being intact.

Box 1 | **Diagnostic constructs for MCI and dementia**

Mild cognitive impairment (MCI) refers to acquired objective cognitive impairment (mostly defined as a performance below ~1.5 s.d. of normative values) affecting one or more cognitive domains with largely preserved activities of daily life[19,20]. This construct captures a stage between normal cognition and dementia that identifies individuals who are at high risk of transition to dementia. Dementia is defined as acquired objective cognitive impairment affecting multiple cognitive domains that is severe enough to affect activities of daily life[21].

the RR for vascular dementia at 2.27 (95% CI 1.94–2.66)[6] for people with diabetes compared with people without diabetes. Interestingly, in 2015, a large cohort study from Canada indicated that the risk of dementia is already increased in patients with newly diagnosed diabetes (HR 1.16 (95% CI 1.15–1.18))[29]. Moreover, elevated plasma concentrations of glucose in individuals without diabetes have also been linked to an increased risk of dementia[30].

When stratified by ethnicity, the RR of Alzheimer disease in Western populations and Eastern populations was 1.36 (95% CI 1.18–1.53) and 1.62 (95% CI 1.49–1.75), respectively[7]. When stratified by sex, the RR of all types of dementia in women with diabetes was 1.62 (95% CI 1.45–1.80) and the RR of all types of dementia in men was 1.58 (95% CI 1.38–1.81)[28]. For vascular dementia, the RR was 2.34 (95% CI 1.86–2.94) in women and 1.73 (95% CI 1.61–1.85) in men, which translates into a 19% greater risk of the development of vascular dementia in women with diabetes than in men with diabetes[28]. Of note, to date, only a few studies have addressed the potential modifying effects of sex and ethnicity on the risk of dementia in patients with diabetes[7,28,31]; therefore, these topics need further exploration.

Stages of cognitive dysfunction

On the basis of current evidence, we argue that the different stages of cognitive dysfunction in patients with diabetes should not be regarded as a continuum[15]. Diabetes-associated decrements (the mildest stage of cognitive dysfunction in patients with diabetes) can occur in all age groups — from young adults and adolescents with T2DM[32,33] to the oldest old (that is, >85 years of age)[34]. These subtle cognitive changes generally occur slowly over the course of many years[15]. Owing to the subtle nature of the cognitive changes involved in diabetes-associated decrements, these cognitive changes do not qualify as abnormal on formal neuropsychological testing. Consequently, at an individual level, it can be difficult for clinicians to establish whether a patient's cognition is actually affected.

These aspects are all very different for dementia. Dementia is a diagnosis that applies to individual patients, in whom cognitive function clearly deviates from what is considered normal, in terms of both impact on daily life and objective deficits on neuropsychological testing. Regarding affected age groups, in contrast to diabetes-associated cognitive decrements, dementia is primarily a condition of old age[3]. Although diabetes might also increase the risk of young-onset dementia (that is, before 65 years of age)[35,36], the majority of individuals with diabetes who develop dementia are well over 65 years of age, just like people without diabetes[3]. Regarding cognitive trajectories, dementia typically is characterized by relentless, year-by-year cognitive decline.

Hence, considering these different features, diabetes-associated cognitive decrements and dementia should be regarded as different entities that probably have different underlying mechanisms.

Mechanisms of cognitive dysfunction

In light of the increasing global prevalence of diabetes, changes in population trends in ageing and the effect of cognitive dysfunction on affected individuals and society as a whole, we need a preventive treatment for cognitive dysfunction in diabetes, particularly for the more severe stages. However, our understanding of potential therapeutic targets and the mechanisms underlying cognitive dysfunction in diabetes is incomplete. Nevertheless, the scientific literature does provide important clues.

A key trend in the literature is that studies from the past 5 to 10 years not only provide data on risk factors and brain imaging correlates for diabetes-associated cognitive decrements but also increasingly do the same for dementia in relation to diabetes. Although dementia is clearly the most impactful cognitive outcome, it is also much more challenging to address with epidemiological studies, as to conduct such studies researchers require large cohorts to acquire a sufficient number of cases of patients with T2DM and incident dementia. Fortunately, such studies are becoming available[31]. Moreover, large collaborative autopsy studies[37] and novel in vivo biomarkers of dementia aetiology, such as amyloid and tau[22,23], have also stimulated progress in this field. In this section, we summarize this literature, focusing on T2DM.

Risk factors for cognitive dysfunction

Numerous risk factors for cognitive dysfunction in diabetes have been reported in the literature, but each appears to have small effects[15,38]. Of these risk factors, glycaemic control has received much attention among researchers in the field. Converging evidence shows that increased HbA_{1C} levels are linked with diabetes-associated cognitive decrements, but the strength of the relationship is weak[39]. Increased HbA_{1C} levels — or repeated glucose measurements over the course of years — in the non-diabetic range have also been linked to elevated dementia risk in people without diabetes[30]. However, whether a similar link also exists among people with diabetes is less clear. Only a few studies have investigated the link between HbA_{1C} levels and dementia risk in people with diabetes[39], and the results of these studies have demonstrated indications of nonlinearity, whereby both low and high HbA_{1C} levels are related to increased dementia risk[30]. Emerging literature also indicates that apart from chronically elevated glucose levels, fluctuations or peaks in glucose levels might be linked to cognitive decrements as well as an increased risk of dementia[39,40].

Observational studies have reported that glucose-lowering compounds might have beneficial effects on cognition and that some compounds might have greater beneficial effects on cognition than others[41]. These findings suggest that the benefit of some therapeutics for improving cognition in patients with diabetes go beyond glucose-lowering effects alone, and therefore other compounds (possibly those with direct effects on the brain) might also need to be considered. For example, a large registry study in veterans with T2DM who were <75 years of age[42] found that metformin use was associated with a lower risk of subsequent dementia than sulfonylurea use while adjusting for glycaemia and other known confounders. However, randomized controlled intervention studies thus far do not support that intensive glycaemic control, or any glucose-lowering agent for that matter, is associated with better cognitive functioning[39,43] or dementia[44]. On the other hand, occurrence of repeated hypoglycaemic episodes is clearly linked to cognitive decline and increased dementia risk[29,31,38,39].

Vascular risk factors, in particular hypertension and dyslipidaemia, might be associated with cognitive decrements in people with T2DM, although the evidence is inconsistent despite a substantial number of studies[38]. Few studies have addressed how vascular risk factors affect dementia risk among patients with T2DM[29,38]. However, because many studies in the general population have demonstrated the importance of vascular risk factors (especially during midlife) for dementia risk[45,46], and because prediabetes and T2DM are associated with an adverse vascular risk factor profile[1], it is reasonable to assume that these factors contribute to dementia risk among patients with T2DM and are a possible target for preventive therapies. Evidence also shows that patients with manifestations of microvascular (such as diabetic retinopathy) or macrovascular disease (such as myocardial infarction or stroke) have worse cognitive performance[15,38] and are at increased risk of dementia[29,31] compared with people who do not have these manifestations. Other studies have identified insulin resistance, inflammation and depression as potential risk factors for cognitive dysfunction in people with diabetes[38,39].

In sum, it is clear that multiple risk factors are involved in diabetes-associated cognitive decrements as well as in dementia in relation to diabetes[38]. On the basis of our assessment of the literature, it is also clear that there are still substantial knowledge gaps on how the risk factors interconnect, how the risk factors translate to potentially modifiable mechanisms and which genetic factors are involved.

Patterns of brain injury

The number of brain imaging studies in patients with diabetes has steadily increased over the past 20 years[47,48], although of the currently available studies, very few focused on patients who were affected by MCI or dementia.

As a framework for the interpretation of the findings, it is important to distinguish between imaging markers that primarily reflect brain injury, markers that reflect specific aetiological processes and markers that reflect both. Markers of injury include, for example, measures of atrophy and microstructural white matter integrity. Although patterns of injury might be suggestive of a particular aetiology, they are by no means aetiologically specific (for example, medial temporal lobe atrophy cannot be taken as proof for Alzheimer disease as a primary aetiology). Imaging markers of aetiological processes include amyloid PET scans of the brain, which are used to detect the processes underlying Alzheimer disease. Another example are measures of cerebral blood flow on MRI, PET or single-photon emission CT (SPECT), as disturbed cerebral blood flow can contribute to cerebral injury. However, the interpretation of cerebral blood flow as an aetiological imaging marker has its limitations, as perfusion can also change as a consequence of brain injury.

The literature clearly shows that T2DM is associated with brain atrophy (FIG. 1), but the regional pattern of brain volume changes varies between studies[47,48]. The magnitude of the volume reduction is modest, with effect sizes of 0.2–0.6 s.d., which is similar to the decrease seen with 3–5 years of normal ageing[47]. Another emerging marker of brain injury in T2DM is diffusion tensor imaging (DTI). This technique allows researchers to explore microstructural integrity of the white matter and related changes in brain networks. DTI studies show widespread changes in white matter microstructure and connectivity in relation to T2DM, which are clearly related to cognitive dysfunction[47,48].

Given the links between diabetes and vascular disease, manifestations of so-called cerebral small vessel disease on MRI are clearly of interest to researchers in the field. These manifestations include lacunes, white matter hyperintensities, visible perivascular spaces, cerebral microbleeds and microinfarcts[49]. Although widely accepted as markers of vascular injury, these MRI-visible lesions have limited specificity for underlying aetiological processes[49]. For example, white matter hyperintensities can develop as a consequence of different underlying vascular pathologies and processes, such as lipohyalinosis, arteriosclerosis, cerebral amyloid angiopathy and hypoperfusion, but also as a consequence of non-vascular processes such as inflammation[50]. The current literature suggests that T2DM is associated with an increased occurrence of lacunes and a modest increase in the volume of white matter hyperintensities[47] (FIG. 1). There might be an increased occurrence of cerebral microbleeds in patients with T2DM, but evidence is not consistent[47,51,52]. Very few imaging studies have investigated the relationship between T2DM and perivascular spaces[53,54] and microinfarcts[55] thus far.

Aetiological markers and neuropathology

As also indicated in the preceding section, diabetes is associated with vascular brain injury, which can be observed by MRI. Indeed, neuropathological studies also report an increased burden of cerebrovascular lesions, especially lacunes, in people with diabetes[37,56]. By contrast, these same studies did not observe a clear increase in the burden of large artery infarcts or microinfarcts in patients with diabetes[37,56]. The increased occurrence of lacunes might be attributable to abnormalities in the small cerebral perforating arterioles, such as arteriolosclerosis, lipohyalinosis or fibrinoid necrosis[57].

Lacunes
Round or ovoid, subcortical, fluid-filled cavities (signal on MRI similar to cerebrospinal fluid) between 3 mm and ~15 mm in diameter that are consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole.

White matter hyperintensities
Signal abnormality of variable size in the white matter that is hyperintense on T2-weighted MRI images such as fluid-attenuated inversion recovery, without cavitation (signal different from cerebrospinal fluid), often due to vascular injury but may have other causes.

Perivascular spaces
Fluid-filled spaces that follow the typical course of a vessel as it goes through grey or white matter. The spaces have a signal intensity similar to that of cerebrospinal fluid on all MRI sequences[49].

Cerebral microbleeds
Small (generally 2–5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects, mostly representing a haemosiderin remnant after a small previous haemorrhage.

Microinfarcts
Small lesions of presumed ischaemic origin, detectable with microscopic examination of brain autopsy material but also detectable in vivo with dedicated MRI protocols.

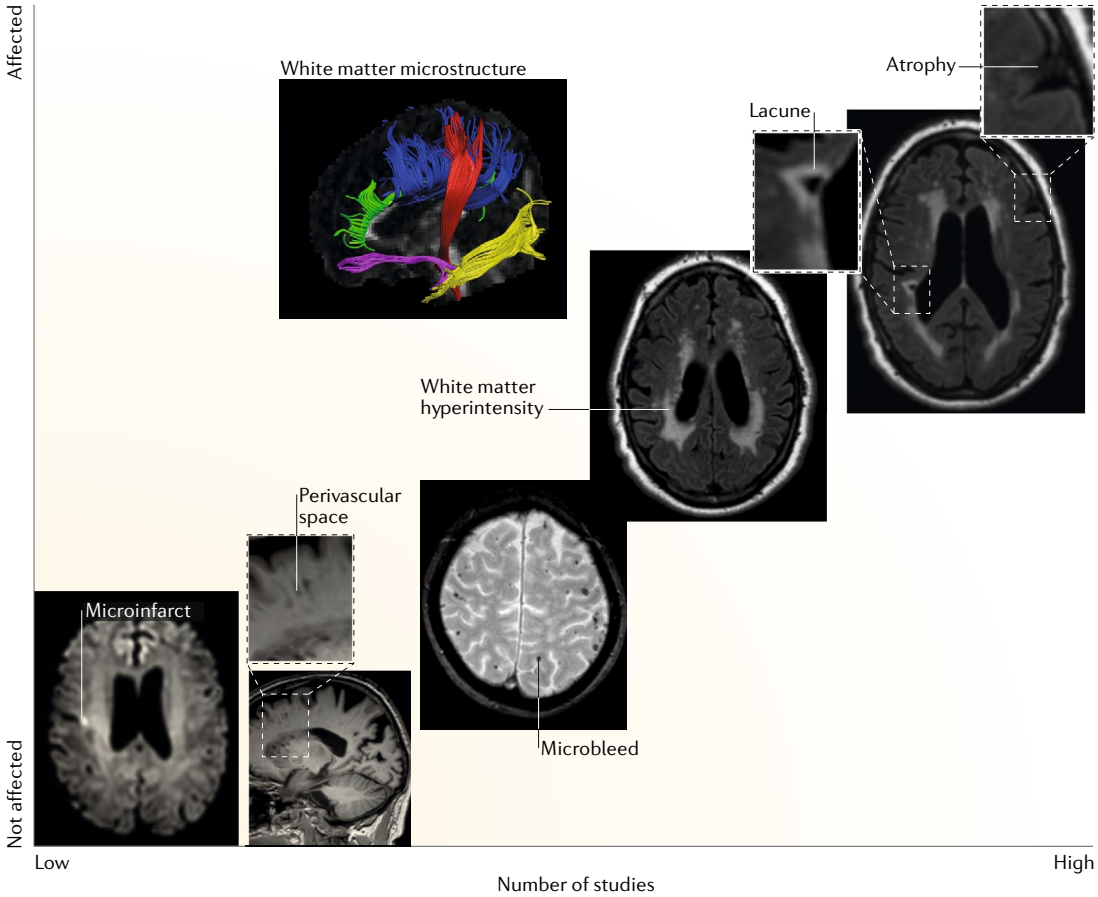

Fig. 1 | **Brain imaging findings in patients with type 2 diabetes mellitus.** The figure summarizes findings on structural brain changes from MRI studies in type 2 diabetes mellitus (T2DM). Different imaging markers that have been studied in relation to T2DM are depicted, including microinfarcts and microbleeds, perivascular spaces, white matter hyperintensities, white matter microstructure (as assessed with diffusion MRI), lacunes and atrophy[47,48,51–55]. The position of each imaging marker on the *x*-axis reflects how intensively it has been studied in relation to T2DM. The position on the *y*-axis reflects the extent to which a marker is affected in individuals with T2DM relative to controls on the basis of the evidence from available studies. Image of white matter microstructure courtesy of Y. Reijmer, UMC Utrecht.

Indeed, there are studies in human brain autopsy material that show cerebral arteriolar abnormalities in patients with diabetes[58,59], but it should be noted that to date the effect of diabetes on different types of cerebral blood vessels has not been assessed systematically. In addition, uncertainties still exist with regard to cerebrovascular dysfunction in T2DM. Some reports show reduced cerebral perfusion and impaired cerebrovascular reactivity, but results of different studies have been conflicting[60], which is probably owing to differences in study populations, imaging techniques and variation in dealing with confounding factors, such as cerebral atrophy[60].

Evidently, Alzheimer disease is another key aetiology to consider. Converging evidence from brain autopsy studies from the past decade shows that the core neuropathological features of Alzheimer disease (such as, so-called 'plaques' (extracellular deposits of amyloid-β) and 'tangles' (intraneuronal aggregates of hyperphosphorylated tau)) are not more common in patients with T2DM than in those without T2DM[61]. Several studies of large autopsy cohorts report that the occurrence of neuritic amyloid plaques (OR 0.96 (95% CI 0.68–1.36)[37]; OR 1.08 (95% CI 0.84–1.38)[56]; and OR 0.97 (95% CI 0.68–1.38)[62]) and tau tangles (OR 0.82 (95% CI 0.61–1.11)[37]; OR 0.85 (95% CI 0.66–1.11)[56]; and OR 1.12 (95% CI 0.81–1.54)[62]) is not increased in T2DM. Studies on in vivo biomarkers of Alzheimer disease pathology are completely in line with these observations; T2DM is not associated with cerebrospinal fluid or PET biomarkers of increased deposition of cerebral amyloid-β or tau pathology[63–65]. However, despite these findings, T2DM is associated with an increase in MRI and PET biomarkers of neurodegeneration[65], suggesting that T2DM accelerates neurodegeneration via non-Alzheimer-disease mechanisms.

Another emerging concept in mechanistic studies is the potential role of cerebral insulin resistance[66,67]. Insulin signalling in the brain has important roles in brain physiology and cognition[66,67]. For example, insulin is involved in central control of the body's energy homeostasis, but it also directly appears to influence learning and memory[66,67]. Moreover, disturbances in insulin signalling have been noted in the brain tissue of people with Alzheimer disease, irrespective of T2DM[67]. These data give rise to the possibility that a core feature of T2DM, disturbed insulin signalling causing insulin resistance, not only affects systemic metabolism but also directly affects the brain

by disturbing cerebral insulin pathways. Other aetiological leads from studies in humans that warrant further investigation are accumulation of advanced glycation end products (AGEs)[68] (for which skin autofluorescence is a non-invasive proxy) and increased blood–brain barrier permeability[69], pointing to possible roles of inflammation and endothelial dysfunction.

Diverging observations or converging pathways?

The preceding sections on studies in humans clearly do not point to a single mechanism underlying diabetes-associated cognitive dysfunction. The different stages of cognitive dysfunction in T2DM differ in severity and prognosis and probably have different underlying aetiologies. Moreover, although diabetes is associated with several different manifestations of cerebral injury that can be observed using cerebral imaging techniques (MRI, for example), one patient might show one manifestation and the next patient another. Furthermore, how should we explain that diabetes increases the risk of a clinical diagnosis of Alzheimer disease when biomarker and neuropathological studies clearly indicate that the burden of Alzheimer disease pathologies is not increased in patients with diabetes? One probable explanation is that in the majority of individuals with diabetes, the clinical phenotype of cognitive dysfunction or dementia is due to multiple pathologies (FIG. 2).

Although Alzheimer disease pathologies are not increased in patients with T2DM, they are still considered to be the most common cause of dementia, and that is also true for people with T2DM: >40% of individuals with T2DM have intermediate to severe (that is, on a scale from no, low, intermediate or severe Alzheimer changes) Alzheimer disease pathology in their brain at the time of death[37,62]. The elevated risk of dementia in patients with T2DM should apparently be attributed to pathologies other than those associated with Alzheimer disease. Therefore, aetiological studies need to identify diabetes-related disease processes that are specific mechanisms affecting the brain beyond Alzheimer disease pathology, which is a major challenge. This processes clearly include vascular disease but also non-Alzheimer-disease mechanisms of neurodegeneration. In the next section, we summarize how animal models might contribute in meeting that challenge.

Experimental models

The diverse spectrum of findings identified in patients with diabetes with or without dementia is explored mechanistically using experimental models, such as cell lines, organoids and animal models that range from rodents to nonhuman primates. Investigators commonly use rodent models in both diabetes and dementia research owing to their genetic similarities to humans (similar genome size, similar number of genes (99% similarity) and similar synteny). Neither diabetes pathology nor Alzheimer-disease-like pathology develops spontaneously in rodents unless specific gene manipulations or pharmacological interventions are used. Depending on the intervention, conditions associated with diabetes, dementia or both can be induced in rodents (TABLE 1). For the most part, insights from these interventions have been restricted to cerebral effects of inducing diabetes in normal rodents[70–81] (TABLE 1; Non-Alzheimer-disease mouse and rat models) and in rodents genetically modified to accumulate amyloid-β in the brain[82–86] (TABLE 1; Mouse and rat models of Alzheimer disease).

Here, we review these rodent models with the objective of identifying pathophysiological processes that might contribute to an Alzheimer disease phenotype without entailing Alzheimer disease pathology (for example, increased deposition of amyloid-β in the brain or hyperphosphorylation of intraneuronal tau). We also suggest characteristics that need to be captured in novel animal models in order to optimize our chances of uncovering mechanisms that underlie the dementia risk in diabetes.

Crosstalk in diabetes and Alzheimer disease

In mice without pre-existing Alzheimer disease pathology (TABLE 1; Non-Alzheimer-disease mouse and rat models), induction of diabetes, genetically, pharmacologically (such as streptozotocin injection) or by diet, is associated with increased generation of amyloid-β[75–78] and hyperphosphorylation of tau protein[71–74]. Similarly, diabetic Alzheimer disease mice showed accelerated cerebral amyloid-β formation[84,85] and cerebrovascular pathologies[82,83], including aneurisms and small strokes (TABLE 1; Mouse and rat models of Alzheimer disease). In contrast to humans, however, the brains of diabetic Alzheimer disease mice had no brain atrophy[83]. An increased vascularization has been observed in the brains of diabetic Alzheimer disease mice, which are generated by crossing Alzheimer disease mice with *db*/*db* mice[83]. The increase in cerebral vascularization in these mice probably compensated for the leptin-deficiency-mediated vascular disruption. Thus, inducing diabetic states reduces the threshold for neurodegeneration in Alzheimer disease in mice via mechanisms that involve cerebrovascular pathologies[82–86].

Cerebral insulin resistance

As mentioned earlier in this Review, data from experimental models of Alzheimer disease and diabetes demonstrate commonalities with regards to abnormalities in signalling pathways between cerebral insulin resistance and systemic insulin resistance. These data provide evidence for potential pathways that can link metabolic changes with changes to the brain in T2DM[67]. Moreover, experimental models show that brain insulin resistance might contribute to Alzheimer disease by promoting amyloid-β generation and hyperphosphorylation of tau[71–78,84,85]. Increased levels of soluble amyloid-β in the brains of rats and mice correlate with altered insulin signal transduction and autophagy as well as an increase in the activities of two enzymes that are involved in the production of amyloid-β — β-secretase 1 (also known as β-site amyloid precursor protein cleaving enzyme 1 (BACE1)) and γ-secretase[77,78]. The results of these studies suggest that insulin resistance, and subsequent hyperinsulinaemia, is involved in the increased production of amyloid-β in the brain. Furthermore, data from mice show that treatment with streptozotocin, which causes insulin deficiency that is characteristic of an advanced diabetic state, seems to be linked to abnormal levels of hyperphosphorylated tau protein in the brain[71,72,74,79].

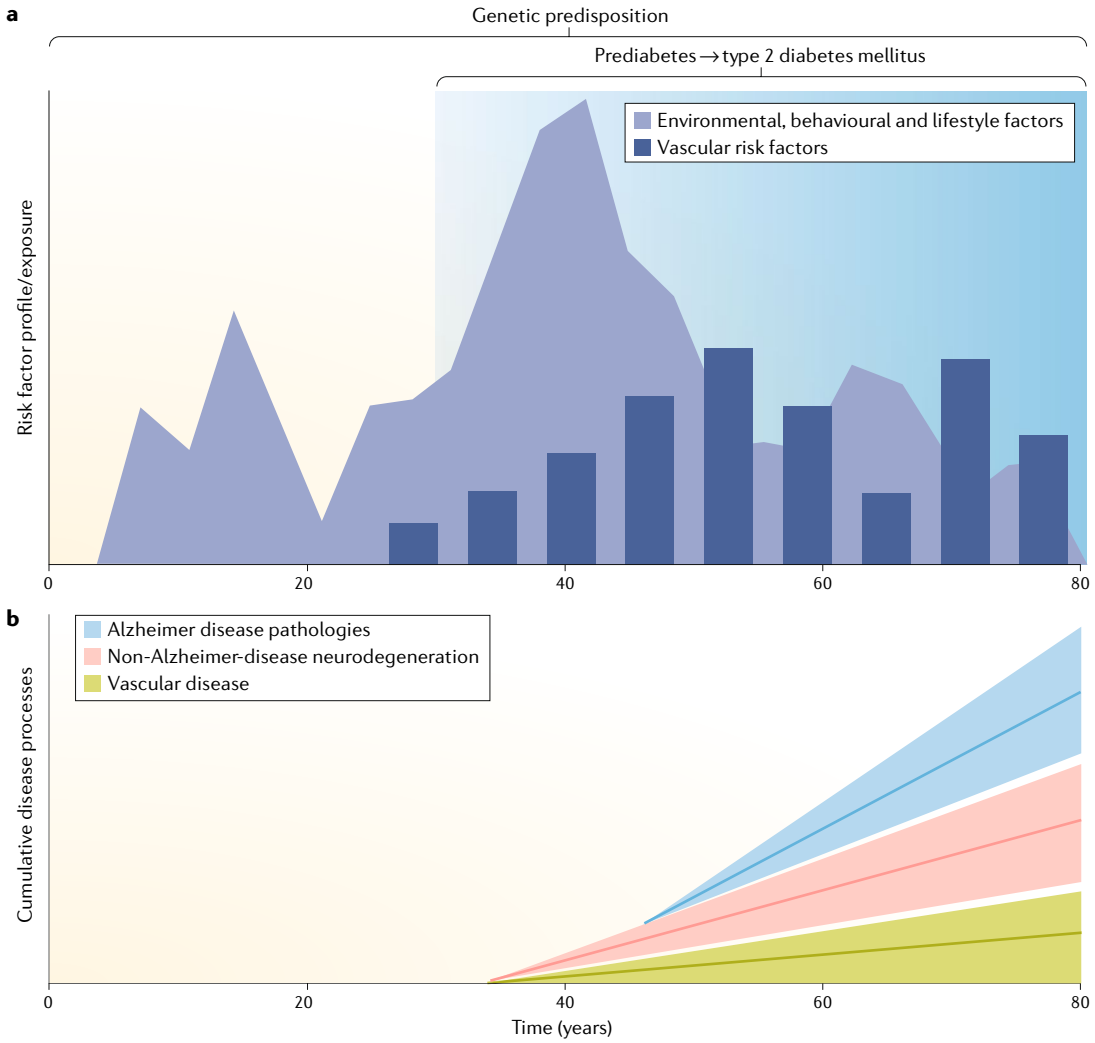

Fig. 2 | **Risk factors and underlying pathologies for dementia in type 2 diabetes mellitus.** The figure provides a life course perspective on risk factors and disease processes contributing to the development of type 2 diabetes mellitus (T2DM) and dementia. **a** | T2DM commonly develops in midlife or late life, in the context of environmental, behavioural and lifestyle factors that vary over the course of life, on a background of genetic risk[2]. People with T2DM frequently have an adverse vascular risk factor profile, including obesity, hypertension and dyslipidaemia, and are often already in prediabetic stages. Many of the factors that predispose an individual to T2DM and co-occur with T2DM, as well as factors that are related to having T2DM (such as elevated glucose and glucose-lowering treatment), can affect the brain[15,66,67]. Evidently, with so many factors involved there are marked interindividual differences in risk factor profiles and exposures. **b** | Brain pathologies contributing to the development of dementia accumulate over the course of decades in the context of an individual's risk profile. In the majority of cases, multiple pathologies co-occur, with variable proportions between individuals. Vascular pathologies are more common in individuals with T2DM than in those without diabetes[37,47,48,56]; therefore, they might contribute to the elevated dementia risk in T2DM. Of note, although Alzheimer disease pathologies are a key contributor to dementia in people with T2DM, the burden of these pathologies is not increased compared with that in people with T2DM[61,62]. The excess dementia risk in people with T2DM is therefore potentially also attributable to additional non-Alzheimer-disease neurodegenerative pathologies that are yet to be identified.

Other studies on brain insulin resistance have shown that stimulating hippocampal insulin receptors by direct administration of insulin into the hippocampus improved learning ability in normal mice[87,88]; however, a similar treatment had less effect in diabetic mice[88]. In addition, levels of amyloid-β and tau hyperphosphorylation in the brain were reduced in a mouse model of Alzheimer disease by treatments that improved insulin availability and/or sensitivity (experimental work reviewed in REF.[66]). In sum, brain insulin resistance has a complex role in promoting Alzheimer disease pathology and is a promising therapeutic target to slow the progression of cognitive decline in humans.

Non-Alzheimer-disease processes

The induction of diabetic states in non-Alzheimer-disease rodent models can cause memory and learning impairments[59,70,79–81,89]. In this section, we discuss possible non-Alzheimer-disease processes contributing to cognitive dysfunction in rodent models of diabetes (see BOX 2).

Table 1 | **Rodent models of diabetes and Alzheimer disease**

Intervention	Pathophysiology	Functional deficits	Refs
Non-Alzheimer-disease mouse[71–74,76,78,81,85,87] and rat[59,75,77,79,95,97] models			
Streptozotocin	•Increased tau generation and phosphorylation •Altered hippocampal synaptic plasticity	Impaired memory and learning	71-74
Hypothalamic leptin deficiency or action	Increased generation of amyloid-β	Impaired memory and learning	75-78
Diet	Mild alterations to the central nervous system	None	81
Amylin dyshomeostasis	•Vascular amylin deposits •Microhaemorrhages •Brain atrophy •Microglia activation •Cerebral amylin plaques •Impaired synthesis of neurotransmitters	•Impaired memory and learning •Abnormalities with gait •Difficulties with motor function and balance	59,87,95,97
Mouse[81–85] and rat[79,111] models of Alzheimer disease			
Streptozotocin	•Exacerbated cerebral amyloidosis •Neuroinflammation •Neurovascular injury	Exacerbated impairment of memory and learning compared with non-diabetic Alzheimer disease rodents	79,85
Hypothalamic leptin deficiency or action	•Cerebral plaques of amyloid-β •Aneurisms •Small strokes (no brain parenchymal loss)	Accelerated memory and learning compared with non-diabetic Alzheimer disease rodents	81-85
Diet	Aggravated amyloid-β pathology compared with chow-diet-fed Alzheimer disease rodents	Aggravated impairment of memory and learning compared with chow-diet-fed Alzheimer disease rodents	84
Amylin dyshomeostasis	Mixed amyloid-β and amylin cerebral plaque formation	Exacerbated impairment of memory and learning compared with Alzheimer disease rodents expressing rodent amylin	111

Cerebral effects of inducing diabetes or insulin resistance in normal rodents (that is, non-Alzheimer-disease rodent models) and in rodents genetically modified to accumulate amyloid-β in the brain (that is, rodent models of Alzheimer disease). Common interventions to induce diabetic conditions in rodents included recessive mutations in the leptin gene (*Lep*; also known as *Ob*), defects in the leptin receptor (LEPR; also known as OB-R), diet and administration of streptozotocin. Rodents with pancreatic overexpression of human amylin spontaneously develop both type 2 diabetes mellitus and dementia-like pathology.

Vascular endothelial dysfunction. In diabetes, endothelial dysfunction is linked to the accumulation of toxic lipids[90], AGEs[91] and/or aggregated proteins[59] in the vasculature. Proteinaceous deposition on blood vessel walls damages endothelial cells[59,91], increases the production of reactive oxygen species (ROS)[92,93] and impairs production of vasodilatory substances[92], which results in a reduced cerebral blood flow. Stalled blood flow can lead to neurovascular uncoupling and hypoxic neuronal injury[92–94]. Elevated ROS production can further damage cellular structures and activate matrix metalloproteinases, inducing cytoskeletal reorganization and vascular remodelling[93]. Cytoskeletal reorganization affects the stability of tight junction proteins, resulting in increased capillary permeability, depletion of energy resources and altered neural viability[92,93].

Inflammation and blood–brain barrier injury. Vascular endothelial dysfunction upregulates inflammatory mediators, which can disrupt the blood–brain barrier[59,89,93,94]. Blood–brain barrier disruption exposes the brain parenchyma to potentially neurotoxic blood proteins, thrombin, fibrin, plasmin and haemoglobin and the iron from lysed red blood cells. A leaky blood–brain barrier induces abnormal neuronal activity[93].

White matter disease of vascular origin. White matter disease, which is also known as small vessel disease, has been clinically associated with vascular contributions to cognitive impairment and dementia[93,94]. This pathology might be the result of long-term endothelial dysfunction, capillary loss and subsequent ischaemia[93,94]. Indeed, a study from 2017 (REF.[59]) in a rat model of T2DM demonstrated the association of white matter rarefaction and axon demyelination with chronic vascular endothelial dysfunction, microhaemorrhages and reduced brain perfusion.

Demyelination and axonal loss. Compared with normal rats, brains of diabetic rats are smaller in volume and have myelin loss and abundant white matter vacuoles[59]. Demyelination and loss of axons can alter synthesis and/or release of neurotransmitters in the brain, which can further accentuate white matter disease and brain atrophy. Brain phenylalanine and tyrosine (which are precursors of catecholamine) were reduced by >50% in diabetic rats compared with normal rats[95]. Thus, experimental diabetes can cause impairments of protein synthesis in the brain.

Peroxidative membrane injury, mitochondrial dysfunction and neurodegeneration. Exposure of unsaturated fatty acids to cytosolic ROS generates reactive aldehydes, such as 4-hydroxynonenal and malondialdehyde[96]. Elevated reactive aldehyde levels cause peroxidative

Neurovascular uncoupling
Neurovascular coupling is the mechanism that links local changes in neural activity and cerebral blood flow involving the so-called neurovascular unit. Neurovascular uncoupling is a disturbance of this mechanism.

Box 2 | **Mechanisms contributing to an Alzheimer disease phenotype in diabetes**

Here, we provide a breakdown of the non-Alzheimer-disease processes that contribute to an Alzheimer disease phenotype in diabetes, as suggested from experimental studies in rodents.

Non-Alzheimer disease processes contributing to an Alzheimer disease phenotype in diabetes

- Proteotoxicity
- Increase in reactive oxygen species
- Peroxidative membrane damage
- Release of cytokines and/or chemokines
- Altered ion fluxes across cellular membranes
- Post-translational modifications of calcium cycling proteins
- Altered protein synthesis

Affected cell types and structures

- Vascular endothelium
- Astrocytes
- Microglia
- Axon myelin sheath
- Neurons

Consequences of Alzheimer disease phenotypes

- Increased blood–brain barrier permeability
- Microhaemorrhages
- Loss of tight junction proteins
- Astrocyte activation and swollen end feet
- Disrupted cerebrovascular basement membrane
- Transporter dysfunction
- Impaired synthesis and/or release of neurotransmitters
- Altered neural circuit function

membrane injury and have been used as biomarkers for neuronal oxidative damage[96]. Indeed, one study reported that brain tissues from diabetic rats and from patients with diabetes and Alzheimer disease as comorbidities had intraneural accumulation of 4-hydroxynonenal-based adducts[97], which suggests that the peroxidative cell damage contributes to neurodegeneration in diabetes.

Accumulating evidence from experimental models of insulin resistance and T2DM indicates systemic mitochondrial dysfunction as a pathological mechanism contributing to health deterioration and cognitive decline. Specific mechanisms linking mitochondrial and metabolic dysfunction with neurodegeneration and Alzheimer disease are discussed elsewhere[98].

Post-translational modification of calcium-dependent protein kinases. In diabetic rats, altered calcium (Ca^{2+}) signalling contributes to neuron dysfunction via multiple mechanisms[99]. A 2013 study in brains (and hearts) of humans with diabetes and Alzheimer disease as comorbidities and in brains of diabetic rats identified post-translational modification of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)[100]. The authors reported that diabetes induces *O*-GlcNAcylation (which is the covalent binding of *O*-linked *N*-acetylglucosamine) of CaMKII, which activates the CaMKII[100]. Overactivity of CaMKII can cause neuronal excitotoxicity and dysfunction of ion channels that are involved in gene transcription and viability[101].

Amylin dyshomeostasis

Amylin (also known as islet amyloid polypeptide) is a pancreatic β-cell hormone co-secreted with insulin that is involved in normal glucose homeostasis[102]. Amylin from humans (but not rodents[102]) is amyloidogenic and aggregates quickly when overexpressed. The majority of individuals with T2DM have large deposits of aggregated amylin in the pancreatic islets[102], kidneys[103] and heart[104]. Aggregated amylin induces cell dysfunction and apoptosis[102]. Accumulating data from several laboratories have confirmed that the brains of patients with T2DM and Alzheimer disease contain an abnormally increased level of aggregated amylin and mixed amylin–amyloid-β plaques[105–108] (FIG. 3). In addition, an epidemiological study from 2017 indicated a genetic risk of developing mixed amylin–amyloid-β plaques in the brain[109]. The results indicate that amylin dyshomeostasis is a possible new link between T2DM and an increased risk of Alzheimer disease[105–109].

Amylin is oversecreted in individuals with prediabetic insulin resistance (that is, hyperinsulinaemia always coincides with hyperamylinaemia)[102]. Overexpression (a threefold increase) of human amylin in the pancreatic β-cells of human islet amyloid polypeptide (HIP) rats and HIP mice results in amylin–amyloid deposition in pancreatic islets, β-cell apoptosis and overt hyperglycaemia[110]. In addition to the development of late-onset T2DM, HIP rats showed vestibulomotor dysfunction, altered balance and impaired memory and learning[59,89]. Brain dysfunction in HIP rats correlated with amylin deposition within the walls of the blood vessels of the brain[59,89] and in the brain parenchyma[59]. In contrast to diabetic Alzheimer disease mice generated by crossing Alzheimer disease mice with *db*/*db* mice[83], which showed brain microhaemorrhages without parenchymal loss, HIP rats have brain microhaemorrhages associated with white matter rarefaction and brain atrophy[59] (TABLE 1). A 2017 study[111] demonstrated that HIP mice expressing a mutated form of the amyloid precursor protein in neurons develop cross-seeding of amylin–amyloid-β pathology, leading to accelerated brain dysfunction compared with transgenic mice expressing only amylin or the amyloid-β protein. These results suggest that systemic amylin dyshomeostasis is a trigger of mixed vascular amylin–amyloid-β pathologies. Interaction of amylin with amyloid-β pathology was also documented in the brains of patients with diabetes and Alzheimer disease as comorbidities[105,106]. These results suggest that an increased amyloid-β burden does not develop in the brains of patients who have both diabetes and Alzheimer disease, but amyloid with a different composition might develop.

Next steps and challenges

Each animal model (TABLE 1) has certain limitations, and no experimental model exists that accurately phenocopies the human brain condition in diabetes and Alzheimer disease. For example, transgenic mouse models of Alzheimer disease overexpressing the amyloid precursor protein show not only exacerbated amyloid-β but also elevated full-length amyloid precursor protein and other fragments of amyloid-β processing[112,113]. These data

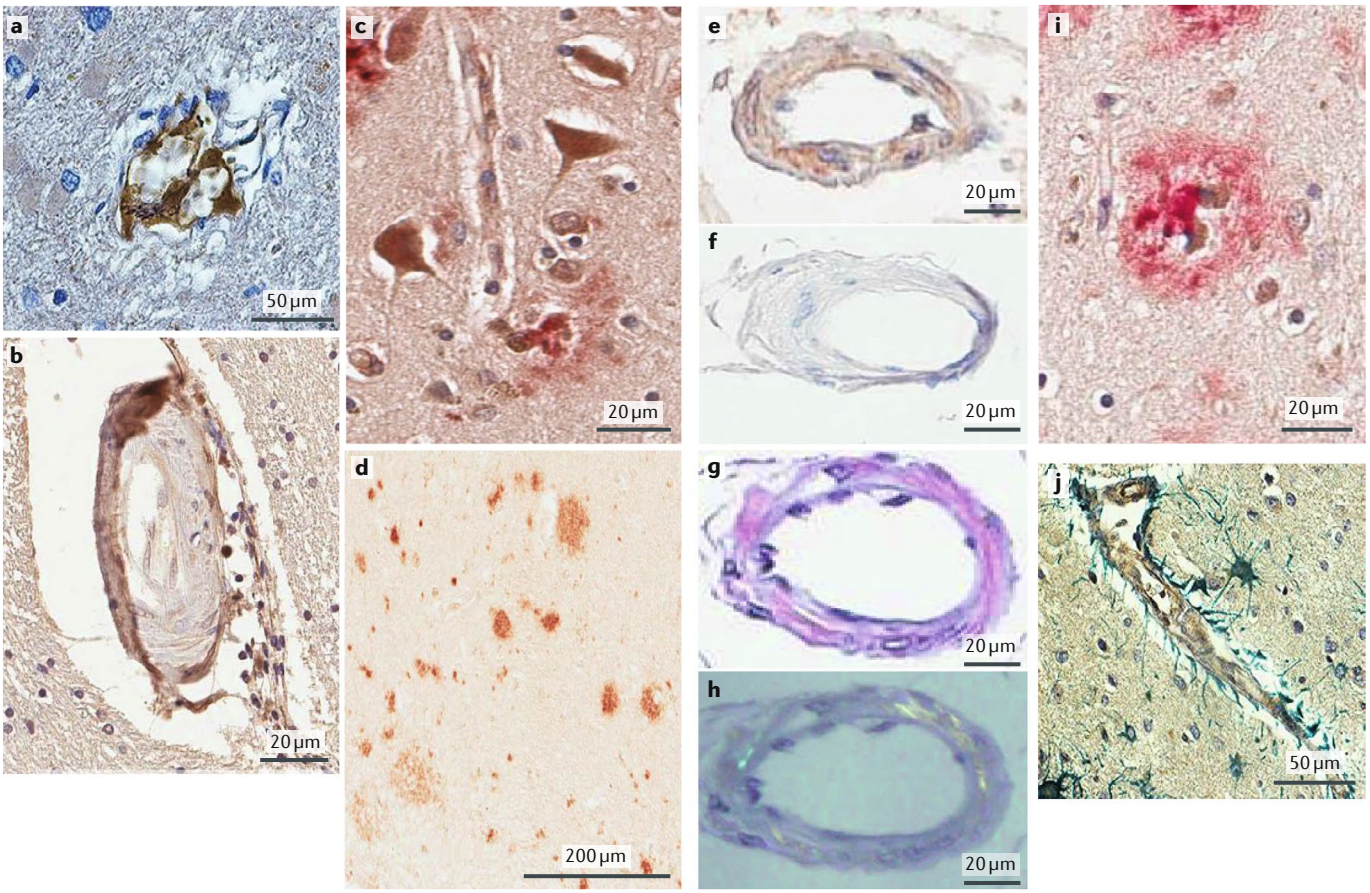

Fig. 3 | **Pancreatic amylin forms amyloid and interacts with amyloid-β in the brains of patients with type 2 diabetes mellitus.** Sections through the brains of patients with type 2 diabetes mellitus (T2DM) and Alzheimer disease showing amylin-positive vascular wall contours (brown) in capillaries (part **a**), small arterioles (parts **b**, **e**), neurons (part **c**) and plaques (part **d**). When congo red stain (purple; part **g**) is viewed under a under the polarized light microscope, vascular amylin deposits that appear brown in part **e**, appear apple-green birefringence (part **h**). The same blood vessel shown in parts **g**, **h** has no amyloid-β immunoreactivity (part **f**). In parts **c** and **i**, amylin (brown) interacts with amyloid-β (red), forming cerebral mixed amylin–amyloid-β deposits. In part **j**, vascular deposition of amylin (brown) and astroglial reaction (green stain for glial fibrillary acidic protein (GFAP)) are shown. Parts **a** and **j** are adapted with permission from REF.[59], John Wiley and Sons. Parts **b**, **e**, **f**, **g**, **h** and **i** are adapted with permission from REF.[105], John Wiley and Sons. Parts **c** and **d** are reprinted from *J. Alzheimers Dis.* **53**, Verma, D. et al. Intraneuronal amylin deposition, peroxidative membrane injury and increased IL-1beta synthesis in brains of Alzheimer's disease patients with type-2 diabetes and in diabetic HIP rats. 259–272, ©2016, with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-160047 (REF.[97]).

might explain why the amyloid burden is increased in diabetic Alzheimer disease mice but not in patients who have T2DM and Alzheimer disease as comorbidities.

The pathophysiology of T2DM encompasses a complex interplay of multiple deficiencies involving insulin resistance, relative insulin deficiency and pancreatic β-cell dysfunction that ultimately result in multiorgan impairments. Although Alzheimer disease is primarily a neurodegenerative process, it often occurs in the context of vascular risk factors, cardiovascular disease and cerebral vascular pathology in humans[45,46,114]. Mice that accumulate amyloid-β in the brain do not demonstrate these comorbidities (that is, mouse models of Alzheimer disease do not develop cardiovascular disease and/or diabetes spontaneously; however, induction of heart failure increases the amyloid-β production in the brain). Thus, to achieve progress in investigating and validating causative mechanisms of increased risk of cognitive decline in patients with T2DM, we think a vital tool will be animal models carrying considerable heterogeneity of diabetes pathology along with a broad spectrum of phenotypes seen in patients with dementia. Novel lines of transgenic mice that are engineered to achieve inducible and reversible expression of human proteins involved with diabetic brain injury could be an important step to identify a cerebral pathological substrate of diabetes-associated cognitive decline (BOX 3).

Implications for patient management

Manifestations of cognitive dysfunction in diabetes, as reviewed herein, receive increasing attention in research and in clinical care. Clinical diabetes guidelines from the past 5 years have started to provide suggestions on how clinicians should detect cognitive impairment and how the presence of cognitive impairment in patients with diabetes should affect diabetes management[115–117].

Box 3 | **Translational potential**

Enhancing crosstalk between clinical and experimental studies

- Key features of cognitive dysfunction and dementia in humans with type 2 diabetes mellitus (T2DM) to be addressed:
  - Cognitive dysfunction and dementia in T2DM are due to mixed aetiologies, which typically occur in the context of brain ageing.
  - Molecular or cellular processes involved in multiple aetiologies (that is, converging pathways) would be key targets for therapy.
  - T2DM does not accelerate the occurrence of Alzheimer disease pathologies. However, because Alzheimer disease pathologies are still very common in patients with T2DM, other aetiologies will often occur on a background of Alzheimer disease pathology.
  - In addition to vascular pathologies, non-Alzheimer disease mechanisms of neurodegeneration should be a key focus of aetiological research.
- Insights from experimental studies:
  - The intervention used to induce diabetes can affect the cerebral phenotype in rodent models (TABLE 1). Animal models that adequately capture the heterogeneity of diabetes seen in humans are essential to uncover a pathological substrate for cognitive dysfunction and dementia in T2DM.
  - A number of non-Alzheimer disease processes seem to induce an Alzheimer disease-like phenotype in diabetic rat[59,89] and mouse[111] models. For example, vascular lesions and mixed amylin–amyloid-β plaque formation occur both in rodent models of amylin dyshomeostasis and in humans with dementia and T2DM. Understanding how these various pathways translate to cognitive dysfunction in humans with T2DM needs further investigation.

The detection and management of cognitive dysfunction in T2DM is not a 'one size fits all' approach. The different stages of cognitive dysfunction have different features and affect patients in different ways; therefore, each stage requires a unique clinical approach. Diabetes-associated cognitive decrements are by definition subtle and do not clearly affect social or occupational functioning or diabetes self-management[5]. Therefore, it suffices to act on cognitive complaints rather than to strive for active detection strategies, such as screening programmes.

Approaches to diagnose and manage diabetes-associated cognitive decrements and to differentiate these subtle cognitive deficits from more severe stages of cognitive dysfunction, in particular MCI and dementia, have been proposed before[5]. First, the age of the patient provides important context, as cognitive decrements occur in all age groups, whereas MCI and dementia rarely occur before 60–65 years of age[20]. Second, the nature of the complaints should be compatible with decrements. For example, patients might express worries about their cognitive abilities, often in terms of forgetfulness, but there should be no examples in which the cognitive complaints consistently had major consequences (for example, repeatedly forgetting important appointments or not remembering recent major life events occurring in close relatives). Finally, the complaints should have developed insidiously, with limited progression over time, and there should be no alternative explanations. In such cases, it can often be sufficient to explain to the patient that the complaints could be due to diabetes-associated cognitive decrements and that although the complaints can be annoying, further marked decline is not expected to occur (particularly true if a patient is younger than 60–65 years of age). However, it should be acknowledged that a diagnostic label of diabetes-associated cognitive decrements always remains a probable diagnosis based purely on the symptoms as there are no definite signs on which a diagnosis can be based[5]. Hence, re-evaluation of the patient after 6–12 months is generally warranted so that a clinician can verify whether the course of the complaints, which should not reflect evident further cognitive decline, is indeed compatible with the diagnosis.

MCI and dementia warrant another approach. These stages of cognitive dysfunction are associated with a reduced ability to self-manage diabetes and maintain glycaemic control, with an increased frequency of hospital admissions and occurrence of severe hypoglycaemic episodes and with an increased occurrence of major cardiovascular events and death in patients with diabetes[44,118,119]. In order to try to avoid these adverse disease outcomes, screening for cognitive impairment in older adults with diabetes is being advocated[117]. Nevertheless, it should be acknowledged that there are still open questions regarding the actual target group and frequency for screening, the appropriate screening instrument and, importantly, whether early identification of cognitive impairment can indeed avert these adverse outcomes.

With regard to the diagnostic approach to patients with diabetes who are suspected to have cognitive impairment, the clinical approach is the same as for patients with suspected MCI without diabetes[5]. As there are no diabetes-specific features to MCI and dementia, the same diagnostic tests are indicated in patients without diabetes. Particularly in patients with MCI, there should be serial assessments over time to monitor for changes in cognitive status[20], as some patients can progress to dementia whereas others might remain stable or even improve.

At present, there are no established treatments that can halt or delay the processes that underlie cognitive impairment except for adequate cardiovascular risk factor management. Importantly, these vascular prevention strategies apply to patients of all age groups. Although we have argued that there might be little benefit to actively screening for cognitive deficits in young adults or in adults during midlife, vascular risk factor management and lifestyle modifications, according to available vascular risk management guidelines, probably have the highest effect (also on cognitive outcomes) if started early and maintained throughout life. Of note, in patients who never experienced cardiovascular events, guidelines for primary vascular risk prevention apply. However, if an MRI is performed and manifestations of small vessel disease are detected, cardiovascular risk factor treatment can be modified according to the 2017 recommendations for vascular risk management in relation to these lesions[120].

Finally, it has been proposed that the presence of cognitive impairment in patients with diabetes should be a reason to use less strict glycaemic targets (for details, see 2017 guidelines[116,121]). The argument for these recommendations is that in patients with cognitive impairment, particularly if there are additional comorbidities, the risk:benefit ratio of intensive glycaemic control shifts to higher risk and lower gain.

Conclusions

In conclusion, clinicians now accept cognitive dysfunction as an important and common comorbidity — or even complication — of diabetes mellitus. Research over the past decades has delineated the clinical features and brain imaging correlates of diabetes-associated cognitive dysfunction in different age groups across the lifespan[5,8]. Insights derived from clinical research are increasingly being translated to daily clinical care for individual patients with diabetes, but there are still gaps in our knowledge. Current challenges include improving the delineation of the diagnostic construct of diabetes-associated cognitive decrements and development of effective strategies to detect undiagnosed frank cognitive impairment in vulnerable individuals.

Course-modifying treatment and prevention strategies for diabetes-associated cognitive dysfunction, in particular MCI and dementia, remain the highest unmet needs. Therapies should target diabetes-specific mechanisms of cognitive dysfunction; however, the disease processes that are not unique to diabetes but also contribute to cognitive decline also need to be elucidated further. For example, processes that contribute to the typical pathologies of Alzheimer disease — although apparently not accelerated by diabetes — are probably still important contributors to cognitive dysfunction in people with diabetes, just like they are in people without diabetes. Thus, developments in the aetiological treatment of patients with Alzheimer disease and other dementia aetiologies outside the field of diabetes are also highly relevant[122]. From a prevention perspective, individuals with T2DM who are at an elevated risk of developing dementia can already be identified at an early stage with established risk scores[31]. These individuals might constitute a target group in dementia prevention trials. In the meantime, it is important that randomized controlled trials on prevention of diabetic complications consider cognitive outcomes, if not as a primary outcome then at least as a secondary outcome.

Published online: 18 July 2018

1. International Diabetes Federation. *IDF Diabetes Atlas, Eighth edition, 2017*, http://www.diabetesatlas.org/resources/2017-atlas.html (2017).
2. Kahn, S. E., Cooper, M. E. & Del Prato, S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* **383**, 1068–1083 (2014).
3. Prince, M. et al. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement **9**, 63–75 (2013).
4. Biessels, G. J., Staekenborg, S., Brunner, E., Brayne, C. & Scheltens, P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* **5**, 64–74 (2006).
5. Koekkoek, P. S., Kappelle, L. J., van den Berg, E., Rutten, G. E. & Biessels, G. J. Cognitive function in patients with diabetes mellitus: guidance for daily care. *Lancet Neurol.* **14**, 329–340 (2015).
6. Gudala, K., Bansal, D., Schifano, F. & Bhansali, A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. *J. Diabetes Investig.* **4**, 640–650 (2013).
7. Zhang, J. et al. An updated meta-analysis of cohort studies: diabetes and risk of Alzheimer's disease. *Diabetes Res. Clin. Pract.* **124**, 41–47 (2017).
8. Biessels, G. J., Deary, I. J. & Ryan, C. M. Cognition and diabetes: a lifespan perspective. *Lancet Neurol.* **7**, 184–190 (2008).
9. Ryan, C. M., van Duinkerken, E. & Rosano, C. Neurocognitive consequences of diabetes. *Am. Psychol.* **71**, 563–576 (2016).
10. Brands, A. M., Biessels, G. J., de Haan, E. H., Kappelle, L. J. & Kessels, R. P. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care* **28**, 726–735 (2005).
11. The Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. *N. Engl. J. Med.* **356**, 1842–1852 (2007).
12. Nunley, K. A. et al. Clinically relevant cognitive impairment in middle-aged adults with childhood-onset type 1 diabetes. *Diabetes Care* **38**, 1768–1776 (2015).
13. Monette, M. C., Baird, A. & Jackson, D. L. A meta-analysis of cognitive functioning in nondemented adults with type 2 diabetes mellitus. *Can. J. Diabetes* **38**, 401–408 (2014).
14. Palta, P., Schneider, A. L., Biessels, G. J., Touradji, P. & Hill-Briggs, F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. *J. Int. Neuropsychol. Soc.* **20**, 278–291 (2014).
15. Biessels, G. J., Strachan, M. W., Visseren, F. L., Kappelle, L. J. & Whitmer, R. A. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. *Lancet Diabetes Endocrinol.* **2**, 246–255 (2014).
16. Bangen, K. J. et al. Relationship between type 2 diabetes mellitus and cognitive change in a multi9ethnic elderly cohort. *J. Am. Geriatr. Soc.* **63**, 1075–1083 (2015).
17. Pappas, C., Andel, R., Infurna, F. J. & Seetharaman, S. Glycated haemoglobin (HbA1c), diabetes and trajectories of change in episodic memory performance. *J. Epidemiol. Commun. Health* **71**, 115–120 (2017).
18. Yaffe, K. et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch. Neurol.* **69**, 1170–1175 (2012).
19. Petersen, R. C. MCI as a diagnostic entity. *J. Intern. Med.* **256**, 183–194 (2004).
20. Petersen, R. C. et al. Practice guideline update summary: MCI: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* **90**, 126–135 (2018).
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV)* (American Psychiatric Association, Washington DC, 1994).
22. Scheltens, P. et al. Alzheimer's disease. *Lancet* **388**, 505–517 (2016).
23. Dubois, B. et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* **9**, 1118–1127 (2010).
24. Luchsinger, J. A. et al. Relation of diabetes to MCI. *Arch. Neurol.* **64**, 570–575 (2007).
25. Roberts, R. O. et al. Association of diabetes with amnestic and nonamnestic MCI. *Alzheimers Dement.* **10**, 18–26 (2014).
26. Cooper, C., Sommerlad, A., Lyketsos, C. G. & Livingston, G. Modifiable predictors of dementia in MCI: a systematic review and meta-analysis. *Am. J. Psychiatry* **172**, 323–334 (2015).
27. Li, J. Q. et al. Risk factors for predicting progression from MCI to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *J. Neurol. Neurosurg. Psychiatry* **87**, 476–484 (2016).
28. Chatterjee, S. et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care* **39**, 300–307 (2016).
29. Haroon, N. N. et al. Risk of dementia in seniors with newly diagnosed diabetes: a population-based study. *Diabetes Care* **38**, 1868–1875 (2015).
30. Crane, P. K. et al. Glucose levels and risk of dementia. *N. Engl. J. Med.* **369**, 540–548 (2013).
31. Exalto, L. G. et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. *Lancet Diabetes Endocrinol.* **1**, 183–190 (2013).
32. Brady, C. C. et al. Obese adolescents with type 2 diabetes perform worse than controls on cognitive and behavioral assessments. *Pediatr. Diabetes* **18**, 297–303 (2017).
33. Yates, K. F., Sweat, V., Yau, P. L., Turchiano, M. M. & Convit, A. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. *Arterioscler. Thromb. Vasc. Biol.* **32**, 2060–2067 (2012).
34. van den Berg, E., de Craen, A. J., Biessels, G. J., Gussekloo, J. & Westendorp, R. G. The impact of diabetes mellitus on cognitive decline in the oldest of the old: a prospective population-based study. *Diabetologia* **49**, 2015–2023 (2006).
35. Kadohara, K., Sato, I. & Kawakami, K. Diabetes mellitus and risk of early-onset Alzheimer's disease: a population-based case-control study. *Eur. J. Neurol.* **24**, 944–949 (2017).
36. Heath, C. A., Mercer, S. W. & Guthrie, B. Vascular comorbidities in younger people with dementia: a cross-sectional population-based study of 616 245 middle-aged people in Scotland. *J. Neurol. Neurosurg. Psychiatry* **86**, 959–964 (2015).
37. Abner, E. L. et al. Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. *Alzheimers Dement.* **12**, 882–889 (2016).
38. Feinkohl, I., Price, J. F., Strachan, M. W. & Frier, B. M. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. *Alzheimers Res. Ther.* **7**, 46 (2015).
39. Geijselaers, S. L. C., Sep, S. J. S., Stehouwer, C. D. A. & Biessels, G. J. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. *Lancet Diabetes Endocrinol.* **3**, 75–89 (2015).
40. Rawlings, A. M. et al. Glucose peaks and the risk of dementia and 20-year cognitive decline. *Diabetes Care* **40**, 879–886 (2017).
41. Patrone, C., Eriksson, O. & Lindholm, D. Diabetes drugs and neurological disorders: new views and therapeutic possibilities. *Lancet Diabetes Endocrinol.* **2**, 256–262 (2014).
42. Orkaby, A. R., Cho, K., Cormack, J., Gagnon, D. R. & Driver, J. A. Metformin versus sulfonylurea use and risk of dementia in US veterans aged ≥65 years with diabetes. *Neurology* **89**, 1877–1885 (2017).
43. Areosa Sastre, A., Vernooij, R. W., Gonzalez-Colaco Harmand, M. & Martinez, G. Effect of the treatment of type 2 diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst. Rev.* **6**, CD003804 (2017).
44. de Galan, B. E. 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* **52**, 2328–2336 (2009).
45. Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K. & Brayne, C. Potential for primary prevention of

Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* **13**, 788–794 (2014).
46. de Bruijn, R. F. et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC. Med.* **13**, 132 (2015).
47. Biessels, G. J. & Reijmer, Y. D. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes* **63**, 2244–2252 (2014).
48. Moran, C. et al. Neuroimaging and its relevance to understanding pathways linking diabetes and cognitive dysfunction. *J. Alzheimers Dis.* **59**, 405–419 (2017).
49. Wardlaw, J. M. et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* **12**, 822–838 (2013).
50. Wardlaw, J. M., Valdes Hernandez, M. C. & Munoz-Maniega, S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *J. Am. Heart Assoc.* **4**, 001140 (2015).
51. Qiu, C. et al. Diabetes, markers of brain pathology and cognitive function: the Age, Gene/Environment Susceptibility-Reykjavik Study. *Ann. Neurol.* **75**, 138–146 (2014).
52. Caunca, M. R. et al. Cerebral microbleeds, vascular risk factors, and magnetic resonance imaging markers: the Northern Manhattan Study. *J. Am. Heart Assoc.* **5**, e003477 (2016).
53. Gutierrez, J., Rundek, T., Ekind, M. S., Sacco, R. L. & Wright, C. B. Perivascular spaces are associated with atherosclerosis: an insight from the Northern Manhattan Study. *AJNR Am. J. Neuroradiol* **34**, 1711–1716 A3498 (2013).
54. Bouvy, W. H. et al. Perivascular spaces on 7 Tesla brain MRI are related to markers of small vessel disease but not to age or cardiovascular risk factors. *J. Cereb. Blood Flow Metab.* **36**, 1708–1717 (2016).
55. van Veluw, S. J. et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol.* **16**, 730–740 (2017).
56. Pruzin, J. J. et al. Diabetes, hemoglobin A1C, and regional Alzheimer disease and infarct pathology. *Alzheimer Dis. Assoc. Disord.* **31**, 41–47 (2017).
57. Wardlaw, J. M., Smith, C. & Dichgans, M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol.* **12**, 483–497 (2013).
58. Nelson, P. T. et al. Human cerebral neuropathology of type 2 diabetes mellitus. *Biochim. Biophys. Acta* **1792**, 454–469 (2009).
59. Ly, H. et al. Brain microvascular injury and white matter disease provoked by diabetes-associated hyperamylinemia. *Ann. Neurol.* **82**, 208–222 (2017).
60. Brundel, M., Kappelle, L. J. & Biessels, G. J. Brain imaging in type 2 diabetes. *Eur. Neuropsychopharmacol.* **24**, 1967–1981 (2014).
61. Arvanitakis, Z. et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. *Neurology* **67**, 1960–1965 (2006).
62. Dos Santos Matioli, M. N. P. et al. Diabetes is not associated with Alzheimer's disease neuropathology. *J. Alzheimers Dis.* **60**, 1035–1043 (2017).
63. Gottesman, R. F. et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA* **317**, 1443–1450 (2017).
64. Moran, C. et al. Type 2 diabetes mellitus and biomarkers of neurodegeneration. *Neurology* **85**, 1123–1130 (2015).
65. Vemuri, P. et al. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Ann. Neurol.* **82**, 706–718 (2017).
66. Biessels, G. J. & Reagan, L. P. Hippocampal insulin resistance and cognitive dysfunction. *Nat. Rev. Neurosci.* **16**, 660–671 (2015).
67. Arnold, S. E. et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat. Rev. Neurol.* **14**, 168–181 (2018).
68. Moran, C. et al. Type 2 diabetes, skin autofluorescence, and brain atrophy. *Diabetes* **64**, 279–283 (2015).
69. Janelidze, S. et al. Increased blood-brain barrier permeability is associated with dementia and diabetes but not amyloid pathology or APOE genotype. *Neurobiol. Aging* **51**, 104–112 (2017).
70. Biessels, G. J. & Gispen, W. H. The impact of diabetes on cognition: What can be learned from rodent models? *Neurobiol. Aging* **26** (Suppl. 1), 36–41 (2005).
71. Clodfelder-Miller, B. J., Zmijewska, A. A., Johnson, G. V. & Jope, R. S. Tau is hyperphosphorylated at multiple sites in mouse brain in vivo after streptozotocin-induced insulin deficiency. *Diabetes* **55**, 3320–3325 (2006).
72. de la Monte, S. M., Tong, M., Lester-Coll, N., Plater, M. Jr & Wands, J. R. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. *J. Alzheimers Dis.* **10**, 89–109 (2006).
73. Planel, E. et al. Insulin dysfunction induces in vivo tau hyperphosphorylation through distinct mechanisms. *J. Neurosci.* **27**, 13635–13648 (2007).
74. Kim, B., Backus, C., Oh, S., Hayes, J. M. & Feldman, E. L. Increased tau phosphorylation and cleavage in mouse models of type 1 and type 2 diabetes. *Endocrinology* **150**, 5294–5301 (2009).
75. Li, Z. G., Zhang, W. & Sima, A. A. Alzheimer-like changes in rat models of spontaneous diabetes. *Diabetes* **56**, 1817–1824 (2007).
76. Puig, K. L., Floden, A. M., Adhikari, R., Golovko, M. Y. & Combs, C. K. Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. *PLOS ONE* **7**, e30378 (2012).
77. Liu, Y. et al. Impaired amyloid beta-degrading enzymes in brain of streptozotocin-induced diabetic rats. *J. Endocrinol. Invest.* **34**, 26–31 (2011).
78. Son, S. M. et al. Accumulation of autophagosomes contributes to enhanced amyloidogenic APP processing under insulin-resistant conditions. *Autophagy* **8**, 1842–1844 (2012).
79. Wang, J. Q. et al. Brain aging and AD-like pathology in streptozotocin-induced diabetic rats. *J. Diabetes Res.* **2014**, 796840 (2014).
80. Heyward, F. D. et al. Adult mice maintained on a high-fat diet exhibit object location memory deficits and reduced hippocampal SIRT1 gene expression. *Neurobiol. Learn. Mem.* **98**, 25–32 (2012).
81. Ramos-Rodriguez, J. J. et al. Differential central pathology and cognitive impairment in pre-diabetic and diabetic mice. *Psychoneuroendocrinology* **38**, 2462–2475 (2013).
82. Takeda, S. et al. Diabetes-accelerated memory dysfunction via cerebrovascular inflammation and Abeta deposition in an Alzheimer mouse model with diabetes. *Proc. Natl Acad. Sci. USA* **107**, 7036–7041 (2010).
83. Niedowicz, D. M. et al. Obesity and diabetes cause cognitive dysfunction in the absence of accelerated beta-amyloid deposition in a novel murine model of mixed or vascular dementia. *Acta Neuropathol. Commun.* **2**, 64 (2014).
84. Ramos-Rodriguez, J. J. et al. Prediabetes-induced vascular alterations exacerbate central pathology in APPswe/PS1dE9 mice. *Psychoneuroendocrinology* **48**, 123–135 (2014).
85. Devi, L., Alldred, M. J., Ginsberg, S. D. & Ohno, M. Mechanisms underlying insulin deficiency-induced acceleration of beta-amyloidosis in a mouse model of Alzheimer's disease. *PLOS ONE* **7**, e32792 (2012).
86. Gao, C., Liu, Y., Li, L. & Holscher, C. New animal models of Alzheimer's disease that display insulin desensitization in the brain. *Rev. Neurosci.* **24**, 607–615 (2013).
87. Bell, G. A. & Fadool, D. A. Awake, long-term intranasal insulin treatment does not affect object memory, odor discrimination, or reversal learning in mice. *Physiol. Behav.* **174**, 104–113 (2017).
88. Marks, D. R., Tucker, K., Cavallin, M. A., Mast, T. G. & Fadool, D. A. Awake intranasal insulin delivery modifies protein complexes and alters memory, anxiety, and olfactory behaviors. *J. Neurosci.* **29**, 6734–6751 (2009).
89. Srodulski, S. et al. Neuroinflammation and neurologic deficits in diabetes linked to brain accumulation of amylin. *Mol. Neurodegener.* **9**, 30 (2014).
90. Beckman, J. A. & Creager, M. A. Vascular complications of diabetes. *Circ. Res.* **118**, 1771–1785 (2016).
91. Basta, G., Schmidt, A. M. & De Caterina, R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. *Cardiovasc. Res.* **63**, 582–592 (2004).
92. Quaegebeur, A., Lange, C. & Carmeliet, P. The neurovascular link in health and disease: molecular mechanisms and therapeutic implications. *Neuron* **71**, 406–424 (2011).
93. Iadecola, C. The pathobiology of vascular dementia. *Neuron* **80**, 844–866 (2013).
94. Viswanathan, A., Rocca, W. A. & Tzourio, C. Vascular risk factors and dementia: how to move forward? *Neurology* **72**, 368–374 (2009).
95. Ilaiwy, A. et al. Human amylin proteotoxicity impairs protein biosynthesis, and alters major cellular signaling pathways in the heart, brain and liver of humanized diabetic rat model in vivo. *Metabolomics* **12**, https://doi.org/10.1007/s11306-016-1022-9 (2016).
96. Mattson, M. P. & Rydel, R. E. Alzheimer's disease. Amyloid ox-tox transducers. *Nature* **382**, 674–675 (1996).
97. Verma, N. et al. Intraneuronal amylin deposition, peroxidative membrane injury and increased IL-1beta synthesis in brains of Alzheimer's disease patients with type-2 diabetes and in diabetic HIP rats. *J. Alzheimers Dis.* **53**, 259–272 (2016).
98. Neth, B. J. & Craft, S. Insulin resistance and Alzheimer's disease: bioenergetic linkages. *Front. Aging Neurosci.* **9**, 345 (2017).
99. Thibault, O. et al. Hippocampal calcium dysregulation at the nexus of diabetes and brain aging. *Eur. J. Pharmacol.* **719**, 34–43 (2013).
100. Erickson, J. R. et al. Diabetic hyperglycaemia activates CaMKII and arrhythmias by O-linked glycosylation. *Nature* **502**, 372–376 (2013).
101. Ashpole, N. M. & Hudmon, A. Excitotoxic neuroprotection and vulnerability with CaMKII inhibition. *Mol. Cell Neurosci.* **46**, 720–730 (2011).
102. Westermark, P., Andersson, A. & Westermark, G. T. Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. *Physiol. Rev.* **91**, 795–826 (2011).
103. Gong, W. et al. Amylin deposition in the kidney of patients with diabetic nephropathy. *Kidney Int.* **72**, 213–218 (2007).
104. Despa, S. et al. Hyperamylinemia contributes to cardiac dysfunction in obesity and diabetes: a study in humans and rats. *Circ. Res.* **110**, 598–608 (2012).
105. Jackson, K. et al. Amylin deposition in the brain: a second amyloid in Alzheimer's disease? *Ann. Neurol.* **74**, 517–526 (2013).
106. Oskarsson, M. E. et al. In vivo seeding and cross-seeding of localized amyloidosis: a molecular link between type 2 diabetes and Alzheimer disease. *Am. J. Pathol.* **185**, 834–846 (2015).
107. Schultz, N., Byman, E., Fex, M. & Wennstrom, M. Amylin alters human brain pericyte viability and NG2 expression. *J. Cereb. Blood Flow Metab.* **37**, 1470–1482 (2017).
108. Fawver, J. N. et al. Islet amyloid polypeptide (IAPP): a second amyloid in Alzheimer's disease. *Curr. Alzheimer Res.* **11**, 928–940 (2014).
109. Roostaei, T. et al. Genome-wide interaction study of brain beta-amyloid burden and cognitive impairment in Alzheimer's disease. *Mol. Psychiatry* **22**, 287–295 (2017).
110. Matveyenko, A. V. & Butler, P. C. Islet amyloid polypeptide (IAPP) transgenic rodents as models for type 2 diabetes. *ILAR J.* **47**, 225–233 (2006).
111. Moreno-Gonzalez, I. et al. Molecular interaction between type 2 diabetes and Alzheimer's disease through cross-seeding of protein misfolding. *Mol. Psychiatry* **22**, 1327–1334 (2017).
112. Wang, Z. et al. Presynaptic and postsynaptic interaction of the amyloid precursor protein promotes peripheral and central synaptogenesis. *J. Neurosci.* **29**, 10788–10801 (2009).
113. Young-Pearse, T. L., Chen, A. C., Chang, R., Marquez, C. & Selkoe, D. J. Secreted APP regulates the function of full-length APP in neurite outgrowth through interaction with integrin beta1. *Neural Dev.* **3**, 15 (2008).
114. Arvanitakis, Z., Capuano, A. W., Leurgans, S. E., Bennett, D. A. & Schneider, J. A. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. *Lancet Neurol.* **15**, 934–943 (2016).
115. International Diabetes Federation. *Global Guideline for Managing Older People with Type 2 Diabetes* https://www.idf.org/e-library/guidelines/78-global-guideline-for-managing-older-people-with-type-2-diabetes.html (2013).
116. Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee on Improving Care for Elderly Patients with Diabetes. Committee Report: Glycemic targets for elderly patients with diabetes. *J. Diabetes Investig.* **8**, 126–128 (2017).
117. American Diabetes Association. Standards of Medical Care in Diabetes-2017. *Diabetes Care* **40**, S1–S142 (2017).
118. Munshi, M. N. Cognitive dysfunction in older adults with diabetes: what a clinician needs to know. *Diabetes Care* **40**, 461–467 (2017).
119. Feil, D. G. et al. Risk of hypoglycemia in older veterans with dementia and cognitive impairment: implications for practice and policy. *J. Am. Geriatr. Soc.* **59**, 2263–2272 (2011).
120. Smith, E. E. et al. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement

for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* **48**, e44–e71 (2017).
121. American Diabetes Association. Standards of Medical Care in Diabetes-2017: Section 11. Older Adults. *Diabetes Care* **40**, S99–S104 (2017).
122. Sevigny, J. et al. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. *Nature* **537**, 50–56 (2016).

Acknowledgements
The research of G.J.B. is supported by Vici Grant 918.16.616 from the Netherlands Organisation for Scientific Research (NWO). F.D. acknowledges funding from NIH (R01AG053999 and R01AG057290), the Alzheimer's Association (VMF-15-363458) and the American Stroke Association (16GRNT310200).

Author contributions
G.J.B. provided a substantial contribution to the discussion of content, wrote the article and reviewed and edited the manuscript before submission. F.D. provided a substantial contribution to the discussion of content and wrote the article.

Competing interests statement
G.J.B. consults for and receives research support from Boehringer Ingelheim. All financial compensation for these services is transferred to his employer, the University Medical Center Utrecht. F.D. has no potential conflict of interest to disclose.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Review criteria
Owing to the wide scope of this Review, the references we cite represent a selection of the available literature. Where possible, we refer to published (systematic) reviews that provide a complete overview of available original studies. When we cite original studies on a particular topic and multiple studies were available, we cite the first landmark studies and/or the most recent comprehensive studies that, in our view, represent a major advance to the field. For further background on specific topics, the reader is encouraged to read the cited papers and to explore the additional references provided in those papers.

Reviewer information
Nature Reviews Endocrinology thanks J. Morley, H. Umegaki and S. Seshadri for their contribution to the peer review of this work.