Epidemiological Approaches to Understanding the Link Between Type 2 Diabetes and Dementia

Greg T. Sutherlanda, Julia Lima, Velandai Srikanthb and David G. Brucec,∗

aDiscipline of Pathology, Sydney Medical School, University of Sydney, Sydney, NSW, Australia
bMedicine, Peninsular Clinical School, Central Clinical School, Frankston Hospital, Peninsula Health, Melbourne, VIC, Australia
cSchool of Medicine & Pharmacology, University of Western Australia, Crawley, WA, Australia

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Abstract. Diabetes and dementia are two diseases that increased dramatically in most societies in direct proportion to increases in average life expectancy. The two conditions are strongly associated and there is much hope that understanding this association will unlock the enigma that is the pathogenesis of dementia. Previous studies suggest that type 2 diabetes is a risk factor for all-cause dementia, vascular dementia and Alzheimer’s disease. However these estimates may not necessarily have taken into account the overlap in dementia pathologies or the competing risk of death. Although the link between diabetes and vascular disease is intuitive, it is now becoming clear that type 2 diabetes is also associated with reduced brain volumes and with progression of brain atrophy, apparently independent of its relation with cerebrovascular disease. This raises the possibility that type 2 diabetes may also contribute to neurodegeneration, and particularly tau pathology. Prospective studies that record extensive multimodal in-vivo biomarkers and conduct rigorous postmortem neuropathological examination are certainly required to tease apart these complex pathways. However monitoring cognitive outcomes from current observational studies and randomized clinical trials of new diabetes treatments could be equally valuable in reducing the dementia epidemic.

Keywords: Alzheimer’s disease, dementia, diabetes, epidemiology

INTRODUCTION

Type 2 diabetes mellitus (T2D) and dementia are archetypal diseases of modernity. Both conditions have increased in importance as humankind has conquered the twin scourges of famine and disease that carried away so many young lives. In many societies people can now expect to avoid early deaths from infection, cardiovascular disease and even cancer and many reach old age only to suffer from the devastating consequences of dementia. Dementia in late life has increased dramatically in most societies in direct proportion to increases in average life expectancy, now estimated to be nine decades in advanced societies. T2D also increases in old age, affecting more than 20% of people aged over 75 years, and is directly caused by advances in agriculture and technology that led to (almost) worldwide access to cheap calories, coupled with considerable reductions in physical exercise and energy expenditure. That the two conditions have been found to be strongly associated has led to much research hoping to unlock the enigma that is the pathogenesis of dementia. In this paper, we review several key aspects of the epidemiology of
diabetes and dementia and highlight several important areas where further studies are required to help understand the pathogenesis of dementia.

**DIABETES MELLITUS**

Diabetes mellitus literally means ‘a flowing through’ of ‘honey’ consistent with glycosuria or excessive output of sweet urine [1]. Diabetes is broadly divided into three main forms type 1 diabetes (T1D), T2D and secondary diabetes although newer subtypes are being delineated. T1D is characterized by absolute insulin deficiency due to immune-mediated pancreatic beta cell destruction. T2D reflects an imbalance between ‘insulin resistance’ (where insulin-sensitive tissues, largely the liver, muscle and adipose tissue respond inadequately to the hormone) and pancreatic beta cell dysfunction where insulin secretion fails to control circulating glucose levels within the normal range. As such T1D is characterized by hyperglycemia and substantial or complete insulin deficiency, whereas T2D features hyperglycemia and hyperinsulinemia (relative to normal) in the early stages, followed by gradually progressive loss of beta cell function and insulin deficiency. The known complications of T2D largely result from vascular injury, manifesting as macrovascular (coronary artery disease, peripheral arterial disease, stroke) and microvascular disease (nephropathy, retinopathy, neuropathy). These are caused by diabetes-associated hyperglycemia, dyslipidemia and cardiovascular risk factors (hypertension, hyperlipidemia) that commonly cluster with T2D, and are strongly influenced by lifestyle factors, especially tobacco use [2, 3]. In addition to T2D and its components, several of these associated disorders are also related to a higher risk of dementia, making T2D an ideal model to unravel the pathogenesis of dementia. In this article, we will focus on the relation between T2D and dementia, an area in which there has been much progress, although substantial uncertainty remains regarding the mechanisms underlying the association between the two disorders.

**EPIDEMIOLOGY TO ADVANCE UNDERSTANDING THE LINK BETWEEN T2D AND DEMENTIA**

A substantial number of cohort studies have demonstrated that T2D increases the risk of all-cause dementia [4–7]. The relative risk has been estimated at between 1.51 and 1.62 for all-cause dementia in two meta-analyses [5, 6, 8] including sex-specific risk ratios [8]. Largely based on clinical diagnoses, the risk appears to be increased for both Alzheimer’s disease (AD) and vascular dementia (VaD) (risk ratios in meta-analyses: 1.46 and 1.56 for AD and 2.48 and 2.27 for VaD respectively [5, 6]). Dementia in T2D appears to occur at an earlier age than in the nondiabetic population [9] and there is evidence of shorter survival times when dementia is associated with diabetes [9–11]. There are several reasons why epidemiological research on this topic should continue.

**Epidemiological transition**

The epidemiology of both conditions is changing. In several European countries, the number of people with dementia is stabilizing despite an aging population [12–14], possibly because of improvements in education, housing and cardiovascular health [15]. In diabetes, improvements in clinical care have been accompanied by reduced rates of complications and cardiovascular disease [16, 17]. Of overarching concern, however, is the increasing incidence of T2D especially with onset at younger ages. How these phenomena might affect the incidence of dementia in T2D is unknown. An increased dementia risk could occur if more type 2 patients survive into old age. Alternatively, improvements in diabetes care could potentially reduce the excess dementia risk attributable to diabetes.

**Bias in the estimation of risk**

Current risk estimates of dementia in T2D based on existing studies may have substantial biases, notwithstanding the apparent consistency in quoted results. Almost all observational studies are associated with response and survival bias. This is especially marked in studies of older populations, where the recruited participants are effectively survivors who avoided dying before they could develop the disorder of interest. Another issue that is especially important in studies of age-related conditions such as dementia is whether or not to account for the competing risk of death [18, 19]. An example is the relationship between smoking and AD. Failure to account for premature mortality explains earlier studies that appeared to demonstrate that smoking was protective against AD, when in fact the smokers were dying before they reached the age when AD was likely
to become manifest. This is germane in studies of T2D in which premature mortality is high [20]. In T2D, it is likely that the risk factors for late-onset dementia are also associated with conditions causing premature mortality. As an example, the APOE e4 allele, the strongest known genetic risk factor for dementia, is also known to be a risk factor for coronary artery disease in T2D [21]. Importantly, taking account of such competing risks tends to produce lower estimates of risk attributed to a specific condition, especially where duration of follow up is long [18, 19]. This is because the statistical method frequently used to assess competing risks keeps the competing event (in this case death) in the denominator, hence the lower risk estimate (for dementia). It is notable that none of the studies included in recent reviews or meta-analyses took account of the competing risk of death [5–7], suggesting that some studies may have overestimated the strength of association between T2D and dementia.

Diabetes associated cognitive decrements and their contribution to dementia

Many studies have demonstrated that T2D is associated with early decrements in cognitive function [22]. These decrements are generally mild, within the normal range, stable over time and appear to be demonstrable in adults and even adolescents with T2D. However, there are no studies indicating whether these findings are associated with overt symptoms or impaired functioning, a knowledge gap that needs to be filled. These decrements in cognitive functioning appear to be related to reduced volumes of cortical gray matter, another consistent finding in T2D also common to dementia [23]. However, it remains to be demonstrated whether these findings that appear early in T2D are relevant in the causation of later life dementia. It is also striking that adverse early life influences known to affect cognitive development are also known to increase the risk of developing T2D, suggesting that there could be a shared risk for adult-onset diabetes and late-life dementia [24, 25]. Childhood intelligence and educational attainment are major determinants of dementia risk, and low cognitive reserve from adverse influences in early life may partly explain the shared risk.

Lifetime risk and causal relationships between factors

A major challenge is the sheer number of potential factors directly and indirectly associated with T2D that could contribute to the risk of cognitive impairment. These include T2D-associated phenomena (hyperglycemia, changes in circulating insulin, diabetes-associated dyslipidemia), treatment-associated issues (exogenous insulin, hypoglycemia, oral agents with potential brain effects), conditions that cluster with T2D (hypertension, hyperlipidemia) and diabetic complications (both macro- and microvascular). There is a range of problems associated with this degree of complexity. Many variables are closely associated with each other and hence may confound reported causal associations. Glycemic control in T2D progressively worsens due to worsening pancreatic beta cell function and medication regimes generally need to be escalated over time to control hyperglycemia [26]. Consequently, the duration of T2D is directly associated with both the development of microvascular complications and with the degree of hyperglycemia and the use of multiple agents including exogenous insulin. In addition, the risk of severe hypoglycemia in T2D increases substantially with the duration of insulin therapy [21]. Therefore, epidemiological studies aimed at exploring associations with dementia risk need to assess all relevant variables to avoid confounding by association. To add to this complexity, there is evidence to suggest that different risk factors may be relevant in mid-life rather than in old age [27] and evidence from twin studies that genetic factors may better explain late-onset rather than early-onset dementia in T2D [28].

There is also growing interest in anti-diabetic agents as potential treatments or preventive agents for AD and several epidemiological studies have provided supportive evidence [29]. However, pharmacoepidemiological studies carry additional methodological limitations that need to be borne in mind [30]. Confounding by indication describes where a drug is prescribed for a disorder, hence appears to be associated with that disease in epidemiological studies. In addition, the context of any medication prescription is rarely known and yet this determines whether a prescriber chooses a particular agent for a particular patient. For example, a potentially hazardous drug such as insulin may be avoided in a patient considered to be at risk from hypoglycemia because of age or early signs of cognitive change. A recent example relates to the controversy surrounding metformin following a report indicating that the drug may increase the risk of dementia [31, 32]. Metformin is probably the most widely used antidiabetic agent worldwide, is recommended as first-line
monotherapy and is commonly continued when other agents are added. It is considered to be safe largely because of its low risk for hypoglycemia. Consequently, an association between metformin and cognitive impairment could well be expected either because of confounding by indication or because most prescribers may consider this to be the safest option in older patients.

An intriguing but unanswered question is the direction of causality and temporal relationships between T2D and dementia. Theoretically, it is possible that risk of brain disease may precede diabetes [33]. A recent report has shown that incident impairment in fasting glucose is associated with greater cognitive decline over 2 years compared with maintenance of normal glucose [34] in people aged ∼78 years on average. However, in people aged ∼60 years, prevalent diabetes, but not incident diabetes, was associated with greater cognitive decline over 14 years [35]. These contradictory findings may be explained by the interaction of age with duration of T2D, leading to a greater expression of effects in older individuals over a shorter duration of diabetes.

**Studying mediation and effect modification**

Although several studies have shown that people with T2D or impaired glucose metabolism exhibit greater cognitive decline over time compared with those with normal glucose metabolism [34, 36–38], there is a significant paucity of epidemiological data examining why this occurs, particularly in working out disease pathways. For example, analyses conducted in previous studies have commonly focused on the individual effects of such factors (e.g., age, ApoE4, blood pressure) in multivariable regression models. However, there is much to be gained by using analyses of mediation or effect modification to examine potential causal pathways involved in diabetes-related cognitive decline. For example, it may be useful to question whether the effect of T2D on cognitive decline (relative to those without diabetes) is modified by factors such as age, sex, genes, central adiposity, glucose control or medical therapy, physical activity, diet etc. Such analyses, because of the levels of stratification required, often require very large samples to detect small but clinically relevant interactions between variables. Ultimately, such analyses could direct therapeutic efforts or indeed lead to in-depth investigation of mechanisms in the laboratory.

**T2D AND THE PATHOLOGY OF DEMENTIA AND AD: WHERE IS THE OVERLAP?**

On gross pathology, AD is characterized by widespread atrophy affecting the temporal, frontal and parietal lobes. It is not uncommon to see patient brain weights at postmortem reduced to 50% of those from age- and gender matched controls. Histopathologically, AD is characterized by neuronal loss, gliosis and two pathognomonic entities: extracellular plaques and intracellular (neuronal) neurofibrillary tangles (NFTs). The main constituents of plaques are a group of peptides that are proteolytically derived from the amyloid precursor protein, and collectively called amyloid-β (Aβ). NFTs are largely made up of hyperphosphorylated and fibrillar forms of microtubule associated protein tau. The spread of NFTs is more closely associated with the progression and severity of AD than plaques [39].

The neuropathological diagnosis of AD remains problematic due largely to the fact that approximately 30–50% of non-demented aged individuals have moderate levels of Aβ at autopsy [40] while tau pathology, at least restricted to regions such as the locus coeruleus and entorhinal cortex, is seen in 100% of individuals [41, 42]. The other major issue is the presence and relative contribution of mixed pathology such as vascular brain injury [43], while the opposite is also true with less than 5% of VaD cases having no AD pathology [44].

Notwithstanding tau and mixed pathologies, the amyloid cascade hypothesis, places Aβ accumulation as the precipitating and central factor in AD pathogenesis [45]. Indeed the levels of Aβ detected in neuroimaging and pathological studies follow a reasonable continuum from preclinical AD to MCI to clinical AD [46]. The early detection of Aβ accumulation in non-demented patients is the basis for current trials of asymptomatic patients with Aβ-modifying drugs [47]. In order to explain the earlier deposition of tau in the aging human brain, the term PART (primary age-related tauopathy) has been proposed [48, 49]. PART is considered unrelated to AD, although this is not a universally accepted paradigm with prominent neuropathologists maintaining that early tau deposition is very much 'part' of AD [50]. Similarly the term SNAP (suspected non-Alzheimer’s pathophysiology) has been used to corral those patients who display the clinical signs of AD-like neurodegeneration on neuroimaging studies in the absence of Aβ build-up or β-amyloidosis [51]. SNAP refers to AD-like
Fig. 1. The etiology of sporadic Alzheimer’s disease (AD). The cause of the common form of AD is unknown. Here a cartoon demonstrates some of the known and proposed risk and protective factors for AD and how a predominance of risk factors in a certain individual, over time, ‘tips the scales’ toward dementia. As discussed here, type 2 diabetes is a risk factor for all-cause dementia but also increases the risk for AD by 50% [55]. Being female increases the risk of AD by about 20% while higher levels of education are increasing protective [55]. Other environmental risk factors for AD include physical inactivity, midlife obesity [74], and head injury [55]. The largest risk factor for AD is aging and over time monomeric forms of beta-amyloid and tau are transformed to oligomeric, and then fibrillar forms. The next largest risk factor is the possession of the common variant of the apolipoprotein E gene, apoE4. The E2, E3, and E4 variants are determined by two single nucleotide polymorphisms (rs429358 and rs7412) that result in either an arginine or cysteine at amino acids 112 and 158 in the APOE protein. A single copy of apoE4 increases the risk of AD by 3.5× (Alzgene; [75]) while apoE4 homozygotes have a 12 fold increased risk over the common E3/E3 genotype. A family history of dementia increases the risk of AD by 2-3 fold [55] and genome-wide association studies have identified approximately 20 other common variants with relatively small risk effects and these can be functionally grouped into immune function, cholesterol homeostasis and vesicle recycling [76]. Presumably there are common variants that have protective effects at a similar magnitude.

increases in cerebrospinal fluid total and phospho-tau and decreased fluorodeoxyglucose uptake and atrophy in medial temporal lobes that is seen in up to 25% of cognitively normal or mildly impaired people aged over 65 years [48]. The concepts of PART and SNAP, as tau-only pathologies, may be highly relevant to the effects of T2D on the brain.

Alternative hypotheses linking AD and T2D have also been posited. One of these suggests a role for the pancreatic islet peptide, amylin, that bears structural and behavioral similarities to Aβ. Misfolding of amylin leads to oligomerization and deposition in the pancreatic islets in T2D in a manner analogous to that seen with Aβ in AD. Amylin oligomers and aggregates are released from damaged islets in T2D and can be found in the brain parenchyma and cerebral blood vessels as amylin plaques and mixed amylin-Aβ deposits in some patients with T2D [52]. Intraneuronal amylin has recently been shown to be potentially injurious [53] and amylin in the brain may also exacerbate AD pathology by interacting with Aβ [54].

In the absence of deterministic mutations, the cause of Aβ accumulation in common sporadic forms of the disease remains unknown. Like many neurodegenerative diseases AD pathogenesis is regarded as a complex interaction between genetic and environmental risk factors on a background of aging (reviewed by [55]) (Fig. 1).

It is postulated that T2D may contribute to the pathogenesis of dementia by leading down the path of cerebrovascular disease, neurodegeneration, or (most likely) both. Certainly T2D is a major risk factor for cerebrovascular disease and is considered a form of “accelerated aging”. What is unclear is the timing of these disease contributions, the mechanisms involved and the interactions between these two dominant pathways. Data on these issues have been provided from postmortem studies, which are highly sensitive and specific in identifying cerebrovascular
or neurodegenerative pathology, and in-vivo studies, which are less likely to be selective in design but less sensitive in identifying neuropathology than autopsy studies. The data from these studies point towards apparent contradictions in evidence as discussed below. There have been several postmortem studies performed to elucidate the pathological link between T2D and dementia (Table 1). Some have confirmed the excess cerebrovascular pathology in diabetes [56, 57] but most have found no tangible excess in markers of neurodegenerative dementia. Results from these studies suggest that the cerebral load of tau-related neurofibrillary tangles or amyloid plaques are either similar [56–60] or even lower [61–63] in those with T2D than in those without. These different findings may largely be explained by factors related to study design, specifically relating to selection and/or survival bias or to exposure phenotyping, both of which are common limitations of postmortem studies. While age at death is generally controlled for in recent studies [56], no studies have been able to control for differences in age or survival with dementia in T2D [9] and most are in people with relatively short duration diabetes [56]. Some were single center studies [58, 62, 63] or with retrospectively ascertained diabetes, [58, 62, 63] in people whose mean age at death was >80 years [61–64] suggesting survivor-bias, possibly related to protection by high education [57, 65] and healthy lifestyles. However, there are some data suggesting that the effect of T2D or insulin resistance on AD pathology may be greater among those positive for the ApoE4 allele suggesting a synergistic effect of T2D and genetic predisposition to AD [66–68].

So how does the evidence from postmortem studies align with in-vivo evidence? Such in-vivo studies rely on the measurement of biomarkers using either imaging or biosamples (blood, cerebrospinal fluid). Relative to direct neuropathology, such biomarkers are at best indirect measures and are less sensitive. Nevertheless, their results offer insights into the effects of diabetes early in the course of disease that is impossible to achieve in autopsy. Such studies have shown largely cross-sectional associations of T2D with the presence of cerebral infarcts, but less consistently with other MRI cerebrovascular disease markers such as white matter hyperintensities [23, 69]. The few longitudinal MRI studies have indicated an increased risk of incident infarcts in T2D [69], but uncertainty remains with respect to progression of white matter hyperintensities. Although the link between diabetes and vascular disease is intuitive, it is now becoming clear that T2D is also associated with reduced brain volumes [23, 70] and with progression of brain atrophy, apparently independent of its relation with cerebrovascular disease [69]. Therefore, there may be metabolic or pro-inflammatory mechanisms related to T2D that may contribute to neurodegeneration. Additionally, other biomarker studies have indicated that T2D is associated with greater tau phosphorylation based on cerebrospinal fluid levels of tau [71], whereas no tangible links have yet been reported between diabetes and amyloid accumulation in the brain [59, 71, 72]. This raises several interesting possibilities that T2D-related neurodegeneration may be linked with amylin-related pathological changes and/or aligned with either the concepts of PART, SNAP or indeed both. A further unresolved issue is whether or not neurodegeneration precedes cerebrovascular lesions, or vice versa, in T2D. Recent studies using functional brain imaging in people with insulin resistance or prediabetes [73] have shown alterations in brain metabolism in people who are cognitively intact and without substantial cerebrovascular disease, raising the interesting possibility that direct neuronal effects of diabetes may well precede vascular disease. An ideal way to provide a complete picture of such complex and potentially interacting pathways would be to follow a carefully phenotyped cohort with extensive multimodal in-vivo biomarkers to death and conduct rigorous postmortem neuropathological examination.

RECOMMENDATIONS FOR FUTURE STUDIES

This review has emphasized that there are many gaps in current knowledge of the relationship between T2D and dementia but that the stakes are high as increased understanding of the relevant causal pathways may not only help reduce the impact of dementia in the population with diabetes but elucidate the cause of dementia in the general population. The number and complexity of potential causal pathways coupled with the considerable potential for bias, confounding and reverse causality means that future studies should include comprehensive assessments of all relevant variables. The ideal study would be large, life-long and would follow well-characterized birth cohorts until the development of T2D and continue until dementia or death. Such cohorts exist and some are reaching early adulthood but in the meantime
G.T. Sutherland et al. / Epidemiology of Type 2 Diabetes and Dementia

### Table 1

Summary of diabetes and neuropathology studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Samples</th>
<th>Endpoints</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heitner &amp; Dickson, 1997 [58]</td>
<td>37 T2D/52 ND</td>
<td>Amyloid, NFT</td>
<td>No differences</td>
<td>Small sample. T2D phenotyping unclear.</td>
</tr>
<tr>
<td>Peila, 2002 [66]</td>
<td>216 Japanese American men</td>
<td>Infarcts, NP, NFT, CAA</td>
<td>Strong interaction between ApoE4 and T2D for NP and NFT</td>
<td>Men only. 20% autopsy rate.</td>
</tr>
<tr>
<td>Janson, 2004 [33]</td>
<td>100 AD/138 Controls</td>
<td>Serial FPG; islet amyloid, NP</td>
<td>More diabetes in AD cases; increased islet amyloid; no difference in Aβ pathology</td>
<td>NFTs not determined. Supports reverse causation.</td>
</tr>
<tr>
<td>Schnaider Beeri, 2005 [77]</td>
<td>61 T2D/324 ND</td>
<td>CERAD categories, NP, NFT</td>
<td>More NP and NFT in ND</td>
<td>Possible survivor effect.</td>
</tr>
<tr>
<td>Arvanitakis, 2006 [57]</td>
<td>36 T2D/197 ND</td>
<td>Infarcts, NP, NFT</td>
<td>2-3-fold increase in infarction in T2D; no relation with NP, NFTs</td>
<td>Possible survivor effect. High education, low exposures to health risk behaviors, T2D by self-report.</td>
</tr>
<tr>
<td>Alafuzoff, 2009 [60]</td>
<td>134 T2D/567 ND</td>
<td>Amyloid, NP, NFT</td>
<td>No differences</td>
<td>T2D diagnosed based on medical records.</td>
</tr>
<tr>
<td>Sonnen, 2009 [78]</td>
<td>196 community-based Adult Changes in Thought Study</td>
<td>Infarcts, Amyloid</td>
<td>ND had greater amyloid load; T2D had greater microvascular infarcts</td>
<td>Possible survivor effect.</td>
</tr>
<tr>
<td>Ahtiluoto, 2010 [61]</td>
<td>70 T2D/221 ND</td>
<td>Infarcts, Amyloid, NP, NFT</td>
<td>Greater infarcts in T2D; More amyloid in ND</td>
<td>Phenotyping of T2D not based on biosamples.</td>
</tr>
<tr>
<td>Matsuzaki, 2010 [68]</td>
<td>135 Japanese men and women</td>
<td>NP, NFT</td>
<td>No differences overall; Greater NP in ApoE4 positive subjects with insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Thambisetty, 2013 [59]</td>
<td>30 T2D-30/167 ND</td>
<td>NP, NFT, Braak Score</td>
<td>No differences</td>
<td>Possible survivor effect. No immunostaining.</td>
</tr>
<tr>
<td>Malek-Ahmadi, 2013 [67]</td>
<td>40 T2D/ 322 ND</td>
<td>NP, NFT</td>
<td>No overall difference; Greater NP and NFT in ApoE4 positive people with T2D.</td>
<td></td>
</tr>
<tr>
<td>Abner, 2016 [56]</td>
<td>2365 community-dwelling</td>
<td>Infarcts, NP, NFT</td>
<td>No difference in NP and NFT; Greater infarcts in T2D; Interaction between T2D and neuropathology in explaining cognitive scores</td>
<td>Possible survivor effect.</td>
</tr>
</tbody>
</table>

T2D, type 2 diabetes; ND, no diabetes; NP, neuritic plaque; NFT, neurofibrillary tangles; CAA, cerebral amyloid angiopathy; FPG, fasting glucose concentration.

there are a number of key questions where progress can be made.

1. **The relationship between diabetes-associated cognitive decrements, cerebral atrophy and subsequent dementia.** This would require longitudinal studies that assess change in cognitive function and cerebral volumes with dementia as an end-point. An established relationship would open the field to risk factor studies for these surrogate end-points including the relevance of early life influences such as early metabolic abnormalities or levels of achieved cognitive abilities.

2. **Unraveling key risk factors.** This requires two kinds of studies: i) Large long-term
observational studies of well-characterized patients with T2D preferably from diagnosis or from middle age in order to narrow the list of meaningful risk factors. National and international collaborations are likely to be required given issues about sample size, cohort retention and feasibility. Such large studies would be ideal to support relevant genetic and epigenetic studies. ii) Smaller focused studies aimed at elucidating specific pathways but again such studies require comprehensive clinical assessments to supplement assessments of specific interest. Modern techniques are likely to be particularly useful, including in vivo measures of neuroinflammation and microvascular function. Several topics of concern for patients with T2D are urgently required including whether the use of specific anti-diabetic drugs in middle age and insulin-induced hypoglycemia are harmful.

3. Risk estimates for dementia. The changes in the epidemiology of both T2D and dementia that have been documented in advanced societies indicate that the risk of dementia is not immutable. Ongoing studies of risk need to be conducted in societies where the association has already been documented to monitor change (whether favorable or unfavorable) but these are urgently required in societies where the risk may be higher for social and economic reasons and where T2D is increasing rapidly. These studies should take account of the competing risk of early mortality given that this specific epidemiological issue has rarely been addressed. Re-analysis of existing observational cohorts taking account of this competing risk would also be informative.

4. Treatment trials. There is currently insufficient data to inform randomized trials to prevent dementia in T2D. However, millions of T2D patients are treated with antidiabetic, antihypertensive-lowering and lipid-lowering agents annually every year and there are recent and planned introduction of new medications, some of which theoretically may reduce the risk of AD [29]. Future trials of these and other agents in T2D should include dementia or an appropriate biomarker of cognitive risk as an end-point. Further pharmacoepidemiological studies of these agents are required provided they are appropriately powered and designed to detect or avoid confounding by indication.

5. Autopsy studies. Many considerations listed above are also relevant in autopsy studies. These include efforts to reduce the impact of survival bias, the possibility of reverse causation or the limited impact from short-duration T2D. Consequently comprehensive clinical data should be included where possible, including estimates of duration of diabetes and differences in onset and survival with dementia that may help interpret autopsy study findings. Furthermore extending these studies to include PART cases, assessments of cerebral amylin deposits and ensuring that a comprehensive evaluation of cerebrovascular changes is undertaken will be informative in prioritizing probable mechanisms by which T2D confers dementia risk.

**CONCLUSION**

Diabetes and T2D in particular is a risk factor for all cause dementia and AD. For AD this risk is likely conferred via both cerebrovascular disease and neurodegeneration yet the mechanisms remain poorly understood. Opportunities for providing greater clarity in this area include greater inclusion of dementia biomarkers and cognitive end-points in prospective studies of T2D patients and clinical trials of new T2D medications. There is a distinct possibility that the current T2D epidemic will translate into an equally debilitating dementia epidemic but there is also room for optimism that “optimal diabetes” management could mean “killing two (common disease) birds with the one stone” [1].

**DISCLOSURE STATEMENT**

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