

# **Cognitive Decline and Diabetes: A Systematic Review of the Neuropathological Correlates Accounting for Cognition at Death**

Gina Hadley<sup>1</sup>, Jiali Zhang<sup>1,2</sup>, Eva Harris-Skillman<sup>1</sup>, Zoi Alexopoulou<sup>1,2</sup>, Gabriele C DeLuca<sup>1,3</sup>, Sarah T Pendlebury<sup>1,3</sup>

<sup>1</sup> Wolfson Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.

<sup>2</sup> St Anne's College, University of Oxford, Oxford, UK

<sup>3</sup>NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford, UK

Corresponding author:

Professor ST Pendlebury

Nuffield Department of Clinical Neurosciences,

University of Oxford,

Oxford, UK.

email: sarah.pendlebury@ndcn.ox.ac.uk

Word count: 3411

Number of references: 48

**Abstract:**

**Objectives:** Determine the relative contributions of different neuropathologies to the excess risk of cognitive decline in diabetes (DM) through systematic review of the literature.

**Methods:** Electronic searches conducted using EMBASE (1974-present) and MEDLINE (1946-present). Included studies compared subjects with and without DM and reported neuropathological outcomes accounting for cognition at death.

**Results:** Data on Alzheimer's disease (AD) pathology, cerebrovascular disease and non-vascular, non-AD pathology were extracted from each study. Eleven studies (n=8 prospective cohorts, n=3 retrospective post-mortem series, total n=6330) met inclusion criteria. All 11 studies quantified AD changes and 10/11 measured cerebrovascular disease: macroscopic lesions (n=9), microinfarcts (n=8), CAA (n=7), lacunes (n=6), white matter disease (n=5), haemorrhages (n=4), microbleeds (n=1), hippocampal microvasculature (n=1). Other pathology was infrequently examined. No study reported increased AD pathology in DM, three studies showed a decrease (n=872) and four (n=4018) showed no difference, after adjustment for cognition at death. No study reported reduced cerebrovascular pathology in DM. Three studies (n=2345) reported an increase in large infarcts, lacunes and microinfarcts. One study found lower cognitive scores in DM compared to non-DM subjects despite similar cerebrovascular and AD-pathology load suggesting contributions from other neuropathological processes.

**Conclusion:** Lack of an association between DM and AD-related neuropathology was consistent across studies, irrespective of methodology. In contrast to AD, DM was associated with increased large and small vessel disease. Data on other pathologies such as non-AD neurodegeneration, and blood-brain-barrier breakdown were lacking. Further studies evaluating relative contributions of different neuropathologies to the excess risk of DM are needed.

**Key words:** Diabetes, cognition, Alzheimer's, vascular dementia, neuropathology

**Abbreviations:** Advanced glycation end-products (AGE); Alzheimer's disease (AD); apolipoprotein E (APOE); Atherosclerosis Risk in Communities (ARIC); Automated Geriatric examination for computer assisted taxonomy (AGECAT); cerebral amyloid angiopathy (CAA); Cambridge Cognition Examination (CAMCOG); Clinical Dementia Rating scale (CDR); Consortium to Establish A Registry for Alzheimer's Disease (CERAD); diabetes mellitus (DM); Informant Questionnaire on Cognitive Decline in the Elderly (IQCOD); mini-mental state examination (MMSE); Neuritic Plaques (NPs); neurofibrillary tangles (NFTs); post mortem (PM); small vessel disease (SVD); Statistical Modelling of Aging and Risk of Transition (SMART); type 2 diabetes mellitus (T2DM); white matter hyperintensities (WMH)

## **Introduction**

Diabetes mellitus (DM) and dementia cause substantial worldwide morbidity. DM affects 422 million adults worldwide, a four-fold increase since 1980, with numbers projected to reach 693 million by 2,045 [1]. The majority of diabetes (~90%) is type 2 with the rising incidence and prevalence, associated mortality and disability-adjusted life years occurring in all global regions irrespective of income and level of development [2]. Dementia affects approximately 50 million people globally, with 5-8 per 100 people over the age of 60 years living with the condition [3]. Although data suggest a fall in the age-specific prevalence and incidence of dementia over the last couple of decades, the rising DM prevalence is likely to reverse this downward trend [4, 5].

DM and high blood glucose levels in both mid- and late life increase dementia risk in contrast to other vascular risk factors (e.g. hypertension), which have less impact with increasing age [6]. DM causes systemic vascular disease, stroke [5] and white matter disease [7] thereby contributing to (vascular) dementia [8, 9, 10]. However, DM increases the risk of post-stroke dementia over and above the overall cerebrovascular burden (white matter disease and stroke number and severity), [10] suggesting that non-vascular phenomena may contribute to the excess risk of cognitive decline. DM may potentiate pathological processes underlying Alzheimer's disease [11] although epidemiologic data are conflicting and some studies report no association [12]. In addition, DM may also impact cognition through pathways involving glucose toxicity, oxidative stress, insulin resistance, and accumulation of advanced glycation end products (AGEs) to name a few. AGE accumulation naturally occurs with aging but is accelerated by high glucose levels/DM [13].

Although there have been extensive epidemiological studies on DM and cognitive decline (Supplementary Tables 1 and 2), and many studies on the neuropathological changes observed in DM, there are relatively few studies which report neuropathological findings in DM vs non-DM subjects in relation to the level of cognitive impairment at death. Such studies are necessary to understand the relative contributions of the different neuropathologic changes to the excess risk of dementia in DM. We therefore undertook a systematic review of neuropathological studies comparing DM versus non-DM subjects including only those studies accounting for cognition at death to i) determine the neuropathological correlates and ii) identify the knowledge gaps to inform the design of future studies.

## **Methods**

The systematic search for this review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard for reporting of findings [14].

### **Selection of Studies**

Studies were identified via electronic searches in EMBASE (1974-present) and MEDLINE (1946-present) databases. The search terms were: (diabet\* OR glucose OR "blood sugar" OR HbA1c) AND (dementia OR (cognitive\* AND (impair\* OR decline))) AND (neuropathol\* OR immunohisto\* OR MMSE OR "Mini mental status examination" OR "Mini-mental status examination" OR MOCA OR "Montreal Cognitive Assessment").

Studies in any language were considered. Included studies described the DM status of subjects (present versus absent), cognition status (diagnosed cognitive syndrome - dementia or mild cognitive impairment versus no impairment, or assessment with a validated cognitive test), and had neuropathological endpoints. Studies were excluded if they were reviews or if they included nonhuman subjects.

### **Data Extraction:**

Two reviewers (GH and JZ) independently screened titles and abstracts against the inclusion criteria. The full texts were obtained for eligible studies and screened independently and consensus was reached, following discussion.

Study characteristics were recorded, including study design (longitudinal study of ageing, retrospective hospital post mortem (PM) series), duration and period over which data were collected, age at autopsy, sex, number with DM, and APOE  $\epsilon$ 4 status. Methods to assess cognition, diagnose diabetes and obtain neuropathological end points were extracted, including the type and severity of AD pathology (e.g. CERAD, Braak stage, other) and cerebrovascular disease (infarcts, haemorrhages, small vessel disease, microinfarcts, cerebral amyloid angiopathy-CAA). Information was also collected on other non-vascular, non-AD pathology, where relevant, including AGEs. Data on adjustment for potential confounders (e.g. age, sex, severity of cognitive impairment at death, APOE  $\epsilon$ 4 status) were recorded where included in analyses examining neuropathological findings in DM versus no DM individuals. We also determined the amount of missing data for covariates and neuropathological outcomes of interest.

## **Results**

### **Included studies**

Eleven studies containing 25 to over 1300 subjects (n=6330 subjects in total) met the inclusion criteria from 3567 publications identified (Figure 1, Table 1). Eight studies comprised cohorts of ageing of which one, the Statistical Modelling of Aging and Risk of Transition (SMART) database study [15, 16] comprised consortium data from 11 individual ageing cohorts from which new data had been extracted (Table 1). The 11 individual studies contained within SMART were not therefore included separately in this review. The remaining three studies comprised hospital or nursing home PM series [17, 18, 19].

Six out of 11 included studies specifically aimed to determine the neuropathological correlates of cognitive decline in DM [9, 15, 17, 18, 20, 21] whereas the remainder had a variety of primary aims, including the effect of CAA on dementia risk in AD, [22] vascular factors in dementia, [23] microvascular change in AD hippocampus, [24] subtypes of dementia in older people [19] and the association of N-epsilon-carboxymethyl lysine (CML) in vascular dementia [25].

### **Cohorts of Ageing**

In the cohort studies of ageing, sample sizes ranged from very small (n=25 of whom only 5 had DM) [25] to large (n=1037) [21]. The mean age at death was 8<sup>th</sup> or 9<sup>th</sup> decades in all except the Vantaa study, which recruited only those aged 85+ in which the mean age was ~92 years. [20] APOE  $\epsilon$ 4 status was measured in three of these studies [15, 20, 23].

In the SMART study, 2,365 subjects were included overall of whom >1,300 subjects had cognitive data [15]. SMART included data from the Honolulu-Asia Aging Study (n=769), [26] the Oregon Brain Aging Study I and II (n=77 and 32), [27] the African American Dementia Project (n=1), [16] the Klamath Exceptional Aging Project (n=80), [28] the Religious Orders Study (n=555), [29] the Memory and Aging Project at Rush University Medical Center (n=454), [30] the Memory and Aging Project at Washington University (n=126), [31] and the Biologically Resilient Adults in Neurological Studies (n=271) [32].

### **Retrospective PM series**

The three PM series had sample sizes ranging from 385 [17] to 1110 [19] and mean age at death spanned the 7<sup>th</sup> to 9<sup>th</sup> decades (Table 1). In all of these studies, clinical data were obtained retrospectively from the patients' notes although in the Mount Sinai Jewish Home and Hospital study, [17] this was supplemented by detailed interviews of staff and family

caregivers regarding antemortem functional and cognitive status. In the Viennese hospital study, all included subjects had dementia [19]. Two reported on APOE  $\epsilon$ 4 status [17, 18].

### **Assessment of DM**

Diabetic status was determined from self-reports [15, 20, 23], (proxy reports or retrospective informant interviews, [21, 23] retrieved medical records of DM diagnosis or use of anti-diabetic medications [9, 15, 17, 18, 19, 20, 22, 25] and death certificates [23] (Table 1). One study did not describe the method of diagnosis [24]. Only one study reported findings according to treated vs untreated DM status [9]. The age demographic of the participants and historical nature of the cohorts would favour type 2 diabetes over type 1, but this was not explicitly stated. Duration of disease, given the heterogeneity of diagnostic method and poor reporting, could not reliably be used as a proxy for the diabetes subtype.

### **Assessment of Cognition**

Cognition was assessed using a variety of scales: Mini Mental State Examination (MMSE) (n=4), [15, 18, 19, 25] Cambridge Cognition Examination (CAMCOG) (n=1), [25] Category Fluency Test (Animals) (n=1), [15] Cognitive Abilities Screening Instrument (CASI) (n=1), [9] Clinical Dementia Rating (CDR) score (n=4), [17, 21, 22, 24] and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (n=1) [21] (Table 1). Dementia was confirmed using the revised Diagnostic and Statistical Manual of Mental Disorders, 3<sup>rd</sup> edition (DMS-III-R) [18, 20, 23] or 4<sup>th</sup> edition (DMS-IV) [9, 19].

### **Adjustment for confounders and missing data**

10/11 studies adjusted neuropathologic findings for demographic covariates when comparing findings in DM versus no DM subjects: age, n=10; sex n=7, education, n=2 (Table 1). Nine studies adjusted for other potential confounders, including study centre, [15] ApoE status, [15, 17, 18, 20] and vascular risk factors [15, 21]. Adjustment for cognition at the time of death was done in 7 studies: dementia vs no dementia [9, 20, 25] dementia severity [17, 22, 24] and cognitive function assessed using a validated cognitive test [15] (Table 1).

Few studies reported on missing data and subjects with incomplete data were often excluded [20, 21, 23] although one study, imputed missing data on neuropathological changes using mean values for the relevant group [9]. In the SMART study, [15] missing data were reported in detail: cortical microinfarct data were missing on 23% with DM and 12.2% without. Cognitive data (MMSE) were lacking in 26.6% of those with DM and 18% without and subjects without cognitive data were more likely to be older and less educated.

## **Assessment of Neuropathology**

Neuropathology was assessed using a variety of methods (Tables 2, 3). The majority of studies (8/11) documented blinding of neuropathologists [15, 17, 20, 21, 22, 23, 24, 25]. The interval between death and brain tissue collection and preparation varied between 7 and 81 hours, where recorded [9, 17, 21, 25].

Considerable heterogeneity was observed in the pathological classification of AD pathology (Table 2). All 11 studies examined AD pathology. Braak and CERAD scores were reported in 6 and 6 studies, respectively, although methods to define severity differed (Table 2). The SMART study also used the National Institute on Ageing-Alzheimer Association criteria for AD pathologic change (ABC score) to enable compatibility with consensus based diagnostic criteria [15]. Where Braak and CERAD scoring was not applied, the assessment of the extent and distribution of AD core features, such as NFT and amyloid plaques, varied e.g. “None, have to be sought, easily found, extensive” for NFT density [18]. Some studies used silver staining (modified Bielchowsky method for NPs and NFTs, [18, 20] and methenamine-silver for amyloid plaques together with Bodian staining for NFTs [20]) whereas others used immunohistochemistry [17, 19, 21].

The methods used to define the different types of cerebrovascular pathology were also heterogeneous (Table 3). 10/11 studies examined cerebrovascular changes: macroscopic lesions of any type (n=9), lacunes (n=6), microinfarcts (n=8), white matter disease (n=5), CAA (n=7), hippocampal microvasculature (n=1), haemorrhages (n=4, in which microbleeds were identified in 2). The methodology used to define the different types of vascular pathology was often unclear, for example, 3/6 studies reporting on lacunes did not state how these were distinguished from large vessel infarcts, and 2/5 studies reporting on white matter disease did not describe how white matter abnormality was defined.

Biochemical analyses for markers of pathogenic processes [9] and immunohistochemistry for the most abundant advanced glycation end-product (AGE), N<sup>ε</sup> –(carboxymethyl)-lysine (CML) [25] were measured in one study each. Other neuropathological markers, including phosphorylated TDP-43, ubiquitin, alpha-synuclein, hippocampal sclerosis were variably measured (Table 2).

## **Neuropathological correlates of cognitive decline in DM vs no DM**

### *AD-type pathology*

No study reported an increase in AD pathology in DM vs no DM individuals (Table 1). In fact, in three studies, n=872, DM was associated with less AD pathology after adjustment for age at death, cognitive impairment/dementia severity and APOE  $\epsilon$  4 allele [9, 17, 20]. A further four studies, n= 4018, saw no difference in AD pathology prevalence by DM status [15, 18, 21, 23]. Where reported, there was no evidence of any interaction between APOE status and DM[20] although one study reported increased NFTs in the neocortex in those in the late stages of AD with vs without DM.[18] In the remaining four studies, AD pathology was measured but was not specifically compared between those with and without DM.

#### *Cerebrovascular disease*

Overall three studies, n=2345 subjects [9, 15, 20] reported an increase in cerebrovascular pathology in DM versus non-DM subjects of which all three controlled for the severity of cognitive impairment at death (Table 1). All these studies specifically aimed to determine neuropathological changes in relation to DM. In the SMART study, DM increased the likelihood of cerebral infarction (OR=1.57,  $P<0.0001$ ) and lacunes (OR=1.71,  $p<0.0001$  [15]) and findings were similar in the Vantaa 85+ cohort (adjusted HR=1.88, 95% CI 1.06-3.34 for cerebral infarcts [20].) In the Adult Changes in Thought study, the number of microvascular infarcts was greater in deep cerebral structures in patients with dementia whose diabetes was treated whereas amyloid plaque load tended to be greater for untreated diabetic patients with dementia [9]. The authors stated that these apparently paradoxical findings might be explained by greater severity of DM in treated patients as indicated by higher random blood glucose levels and HbA1C readings.

The remaining seven studies that examined aspects of cerebrovascular disease were inconclusive but none reported less vascular pathology in DM subjects (Tables 1 and 3). In the majority of these studies (5/7), the primary aim was not to determine neuropathological changes specifically associated with DM. Relevant findings not reaching statistical significance included more severe deep white matter lesions, [23] more microscopic infarcts,[18] different frequency and distribution of neuropathologically defined dementia subtypes with a greater likelihood of vascular versus mixed dementia [21] and high rates (61%) of DM in neuropathologically defined “pure” VD [19]. No differences were observed in hippocampal microvasculature changes by DM status but dementia severity correlated with microvasculature change in those without but not with DM [24].

#### *Non-AD, non-vascular pathology*



In the SMART study, individuals with DM had lower cognitive scores at the end of life than those without DM with similar cerebrovascular and AD-pathology load [15] suggesting contributions from other unidentified neuropathology. However, data on non-vascular, non-AD pathology in the included studies were sparse (Table 2). Only one study (n=25) examined AGEs finding an increase with DM or worse cognition but the effect of AGEs on dementia risk in DM was not examined because of small numbers [25]. One study measured cortical interleukin-6 (IL-6) concentration (a measure of inflammation) and F2-IsoPs (a measure of free radical activity).[9]F2-IsoPs was increased in individuals with dementia without DM whereas cortical IL-6 levels were increased in dementia with DM. Although other neuropathological markers were measured in some studies (e.g. TDP-43 [21, 22] alpha synuclein, tau [18]) differences by DM status were either neutral or not reported (Table 2).

## **Discussion**

We found that studies were highly heterogeneous with wide variation in the clinical characteristics of the cohorts, ascertainment of DM, measures of cognitive function, and neuropathological techniques and pathologies examined. Despite this, the available data strongly suggest that the excess risk of dementia in DM is not mediated by AD-type pathology but at least, in part, by an increase in cerebrovascular disease, including large and small vessel disease and micro-infarcts. Further, despite emerging evidence that DM impairs cognition over and above the burden of cerebrovascular and AD pathology, there are few studies on cellular or metabolic changes to provide insights into the underlying pathophysiological mechanisms.

The lack of an association between DM and AD-related neuropathology was consistent across all studies, irrespective of methodology, with some studies even showing reduced neurodegeneration for a given level of cognitive impairment at the time of death [9, 17, 20]. Lack of an effect on AD is supported by PET imaging and biomarker studies of amyloid in DM [33]. However, it is in stark contrast to findings from some, but not all, epidemiological studies (see Supplementary Tables 1 and 2). Reported associations between DM and AD in epidemiologic studies may have resulted from the poor specificity of clinical dementia subtype classification criteria for the neuropathological Gold Standard with a bias towards AD [34, 35]. Therefore, it appears that the proposed mechanisms put forward to explain how DM might promote AD pathology may not apply in practice possibly because cerebrovascular disease typically manifests before the emergence of AD pathology.

In contrast to AD, DM appeared associated with increased large and small vessel disease, including lacunes and microinfarcts, for a given level of cognitive impairment or with dementia, [9, 15, 20] and no study showed a reduced risk. This is unsurprising given the extensive literature describing associations between DM and large and small vessel vascular disease across all organs including the brain [36]. In DM, endothelial dysfunction is linked to build up of lipids, AGEs, and aggregated proteins and release of reactive oxygen species resulting in neurovascular uncoupling and tissue hypoxia [37]. Small vessel disease aetiology may be linked to inflammation. Interestingly, the observation of increased inflammation in association with micro-infarcts in DM [9] suggests that DM might promote an inflammatory environment thereby contributing to small vessel disease progression. However, our review has shown a lack of studies with careful classification and quantification of small vessel disease with few data on microbleeds, CAA, and the microvasculature (the one included study was not focussed—specifically on DM [24]). Failure to capture the full extent of small vessel disease

may under-estimate its contribution to cognitive decline, including in DM. Further, although APOE genotype has been reported to enhance the effects of DM on white matter disease, [38] only one study included in this review examined interactions between DM and APOE, finding no effect [20].

Data on non-AD/non-vascular pathology in DM vs no-DM subjects were sparse. This is an important gap given that data from the SMART study [15] and from post-stroke dementia cohorts [10] suggests that DM impacts cognition over and above vascular (and AD) pathology. Despite reports of increased AGEs in older people and those with DM, [13, 39] only one included study examined AGEs. Although this study was underpowered to examine the contribution of AGE accumulation to cognitive decline in DM, the authors proposed that AGEs might contribute to vascular (and DM-related) dementia [25]. Only few studies reported on TDP-43, associated hippocampal sclerosis, or Lewy bodies despite reports that DM may accelerate neurodegeneration via non-AD mechanisms [40, 41, 42]. There is an important unmet need to assess the influence of DM on the full spectrum of AD and other neurodegenerative pathologies in a systematic way using well-characterised post-mortem material derived from cohorts with robust sample sizes.

In a general population with an increasing Body Mass Index, DM and its inherent related metabolic syndrome may also increase the risk of cognitive decline through its effects on the blood-brain-barrier (BBB). The vascular endothelial dysfunction in DM impacts the stability of tight junctions and increases capillary permeability and thereby BBB dysfunction [37]. Widespread damage to the BBB is seen in animal models of DM [43] and increased permeability has been shown in human studies [39, 44]. Damage to the BBB allows influx of neurotoxic substances including fibrinogen, inflammatory cells and their mediators, and infectious organisms which initiate and propagate inflammatory and immune responses. Notably, fibrinogen has been shown to be associated with early neurological deterioration after stroke in DM but not non-DM patients, [45] which may be mediated by its role in activating innate inflammatory mechanisms that lead to free radical generation and subsequent neuronal/axonal injury loss to culminate in clinically relevant neurodegeneration [46, 47]. This BBB disruption and subsequent reduction of cerebral blood flow can lead to an accumulation of neurotoxic molecules and hypoperfusion, which can both initiate neuronal injury and by extension, cognitive decline.

Our study highlights the complexities around neuropathological studies in DM. Subjects were not characterised according to DM profile despite the fact that neuropathological findings may differ by disease duration, fluctuations in glucose level, tight versus lenient control, type of

therapy, and undiagnosed DM in controls [4, 5, 37]. In addition, although the majority of studies adjusted for important covariates, residual confounding may nevertheless have occurred since DM is associated with lower socioeconomic status, obesity, and comorbidities including hypertension, metabolic syndrome and reduced life expectancy [5].

### **Conclusions and recommendations for future studies**

The increased risk of cognitive decline in DM is mediated by vascular and not Alzheimer's pathology with other, as yet unidentified, non-AD neurodegenerative and metabolic/cellular mechanisms. There is a lack of studies using careful description and quantification of the subtypes of cerebrovascular disease and AD pathology in a consistent way. Few studies examine the impact of DM on downstream pathological mechanisms using techniques beyond conventional histological endpoints. Further large prospective studies are required with standardized methods for assessing cerebrovascular and in particular small vessel disease [48] and BBB damage, together with AGEs, as well as non-AD neurodegeneration, TDP-43, and other cellular/biochemical changes including inflammation and free radical damage. DM measures should include glycaemic control and treatments with careful recording of the level of cognitive impairment and other covariates to enable robust adjustment for confounders. Future studies should therefore ideally be longitudinal incorporating regular clinical assessment, and should allow for updated evaluation of histopathological samples where possible to accommodate advances in neuropathological criteria and techniques.

### **Ethical approval**

Only ethically approved articles were included in our systematic review.

### **Author contributions**

GH searched the literature, examined available studies, extracted the data, and led the review process. JZ reviewed available studies, extracted the data, analysed the results, and co-wrote the paper. EHS extracted the data and analysed the results. ZA participated in the literature search, contributed to and reviewed the paper. GH and STP wrote the paper. GCD reviewed and made critical revisions of the paper. STP and GCD conceived the original idea for this study.

### **Conflict of interests**

None declared.

### **Funding**

GC De Luca and ST Pendlebury are supported by the National Institutes of Health Research Biomedical Research Centre (BRC), Oxford.

## **Figures and Tables**

Figure 1: PRISMA Flowchart

Table 1: Executive Summary Table showing study characteristics, number of subjects including the number with DM, method of diagnosis of DM, adjustment for confounders, cognitive assessment and key neuropathologic findings in DM versus no DM subjects.

Table 2: Pathology Assessment Methods and Classification of Pathological Severity by Study

Table 3: Type of cerebrovascular pathology quantified by study

Supplementary Table 1: Systematic Reviews of Diabetes and Cognitive Function

Supplementary Table 2: Studies of Diabetes and Cognitive Function Included in Previous Systematic Reviews of Epidemiologic Studies

## **References**

- 1 WHO. World Health Organisation: Global Report on Diabetes. 2016.
- 2 Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep*. 2020;10:14790.
- 3 WHO. 2017.
- 4 Ott A, Stolk RP, van Harskamp F, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999;53:1937-42.
- 5 Nelson PT, Smith CD, Abner EA, et al. Human cerebral neuropathology of Type 2 diabetes mellitus. *Biochim Biophys Acta* 2009;1792:454-69.
- 6 Satizabal CL, Beiser AS, Chouraki V, et al. Incidence of Dementia over Three Decades in the Framingham Heart Study. *N Engl J Med* 2016;374:523-32.
- 7 Gouw AA, van der Flier WM, Fazekas F, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. *Stroke* 2008;39:1414-20.
- 8 Peila R, Rodriguez BL, Launer LJ, et al. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes* 2002;51:1256-62.
- 9 Sonnen JA, Larson EB, Brickell K, et al. Different patterns of cerebral injury in dementia with or without diabetes. *Arch Neurol* 2009;66:315-22.
- 10 Pendlebury ST, Rothwell PM, Oxford Vascular S. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol* 2019;18:248-58.
- 11 Baglietto-Vargas D, Shi J, Yaeger DM, et al. Diabetes and Alzheimer's disease crosstalk. *Neurosci Biobehav Rev* 2016;64:272-87.
- 12 Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. *Neurology* 2006;67:1960-5.
- 13 Moran C, Munch G, Forbes JM, et al. Type 2 diabetes, skin autofluorescence, and brain atrophy. *Diabetes* 2015;64:279-83.
- 14 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-9, W64.
- 15 Abner EL, Nelson PT, Kryscio RJ, et al. Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. *Alzheimers Dement* 2016;12:882-9.
- 16 Abner EL, Schmitt FA, Nelson PT, et al. The Statistical Modeling of Aging and Risk of Transition Project: Data Collection and Harmonization Across 11 Longitudinal Cohort Studies of Aging, Cognition, and Dementia. *Obs Stud* 2015;1:56-73.
- 17 Beeri MS, Silverman JM, Davis KL, et al. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. *J Gerontol A Biol Sci Med Sci* 2005;60:471-5.
- 18 Alafuzoff I, Aho L, Helisalmi S, et al. Beta-amyloid deposition in brains of subjects with diabetes. *Neuropathol Appl Neurobiol* 2009;35:60-8.
- 19 Jellinger KA, Attems J. Prevalence of dementia disorders in the oldest-old: an autopsy study. *Acta Neuropathol* 2010;119:421-33.

- 20 Ahiluoto S, Polvikoski T, Peltonen M, et al. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology* 2010;**75**:1195-202.
- 21 Mantioli M, Suemoto CK, Rodriguez RD, et al. Association between diabetes and causes of dementia: Evidence from a clinicopathological study. *Dement Neuropsychol* 2017;**11**:406-12.
- 22 Hecht M, Kramer LM, von Arnim CAF, et al. Capillary cerebral amyloid angiopathy in Alzheimer's disease: association with allocortical/hippocampal microinfarcts and cognitive decline. *Acta Neuropathol* 2018;**135**:681-94.
- 23 Richardson K, Stephan BC, Ince PG, et al. The neuropathology of vascular disease in the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Curr Alzheimer Res* 2012;**9**:687-96.
- 24 Schwartz E, Wicinski B, Schmeidler J, et al. Cardiovascular Risk Factors Affect Hippocampal Microvasculature in Early Ad. *Transl Neurosci* 2010;**1**:292-9.
- 25 Southern L, Williams J, Esiri MM. Immunohistochemical study of N-epsilon-carboxymethyl lysine (CML) in human brain: relation to vascular dementia. *BMC Neurol* 2007;**7**:35.
- 26 Gelber RP, Launer LJ, White LR. The Honolulu-Asia Aging Study: epidemiologic and neuropathologic research on cognitive impairment. *Curr Alzheimer Res* 2012;**9**:664-72.
- 27 Green MS, Kaye JA, Ball MJ. The Oregon brain aging study: neuropathology accompanying healthy aging in the oldest old. *Neurology* 2000;**54**:105-13.
- 28 Kaye J, Michael Y, Calvert J, et al. Exceptional brain aging in a rural population-based cohort. *J Rural Health* 2009;**25**:320-5.
- 29 Bennett DA, Schneider JA, Buchman AS, et al. The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology* 2005;**25**:163-75.
- 30 Bennett DA, Schneider JA, Buchman AS, et al. Overview and findings from the rush Memory and Aging Project. *Curr Alzheimer Res* 2012;**9**:646-63.
- 31 Berg L, McKeel DW, Jr., Miller JP, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch Neurol* 1998;**55**:326-35.
- 32 Schmitt FA, Nelson PT, Abner E, et al. University of Kentucky Sanders-Brown healthy brain aging volunteers: donor characteristics, procedures and neuropathology. *Curr Alzheimer Res* 2012;**9**:724-33.
- 33 Roberts RO, Knopman DS, Cha RH, et al. Diabetes and elevated hemoglobin A1c levels are associated with brain hypometabolism but not amyloid accumulation. *J Nucl Med* 2014;**55**:759-64.
- 34 Neuropathology Group. Medical Research Council Cognitive F, Aging S. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet* 2001;**357**:169-75.
- 35 Schneider JA, Arvanitakis Z, Bang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007;**69**:2197-204.
- 36 Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev* 2013;**93**:137-88.
- 37 Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol* 2018;**14**:591-604.

- 38 Cox SR, Ritchie SJ, Dickie DA, et al. Interaction of APOE e4 and poor glycemic control predicts white matter hyperintensity growth from 73 to 76. *Neurobiol Aging* 2017;**54**:54-8.
- 39 Prasad S, Sajja RK, Naik P, et al. Diabetes Mellitus and Blood-Brain Barrier Dysfunction: An Overview. *J Pharmacovigil* 2014;**2**:125.
- 40 Vemuri P, Lesnick TG, Przybelski SA, et al. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Ann Neurol* 2017;**82**:706-18.
- 41 Crane PK, Walker RL, Sonnen J, et al. Glucose levels during life and neuropathologic findings at autopsy among people never treated for diabetes. *Neurobiol Aging* 2016;**48**:72-82.
- 42 Lima MM, Targa AD, Nosedá AC, et al. Does Parkinson's disease and type-2 diabetes mellitus present common pathophysiological mechanisms and treatments? *CNS Neurol Disord Drug Targets* 2014;**13**:418-28.
- 43 Qiao J, Lawson CM, Rentrup KFG, et al. Evaluating blood-brain barrier permeability in a rat model of type 2 diabetes. *J Transl Med* 2020;**18**:256.
- 44 Starr JM, Wardlaw J, Ferguson K, et al. Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 2003;**74**:70-6.
- 45 Lee SJ, Hong JM, Lee SE, et al. Association of fibrinogen level with early neurological deterioration among acute ischemic stroke patients with diabetes. *BMC Neurol* 2017;**17**:101.
- 46 Merlini M, Rafalski VA, Rios Coronado PE, et al. Fibrinogen Induces Microglia-Mediated Spine Elimination and Cognitive Impairment in an Alzheimer's Disease Model. *Neuron* 2019;**101**:1099-108 e6.
- 47 Petersen MA, Ryu JK, Akassoglou K. Fibrinogen in neurological diseases: mechanisms, imaging and therapeutics. *Nat Rev Neurosci* 2018;**19**:283-301.
- 48 Skrobot OA, Attems J, Esiri M, et al. Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment. *Brain* 2016;**139**:2957-69.