

2020

## Cognitive Performance in Midlife Type 2 Diabetes: Results from the ENBIND Study

A. H. Dyer

*Tallaght University Hospital, Dublin*

L. McKenna

*Tallaght University Hospital, Dublin*

G. Gamage

*Tallaght University Hospital, Dublin*

*See next page for additional authors*

Follow this and additional works at: <https://arrow.tudublin.ie/engschmecart>

Part of the [Dietetics and Clinical Nutrition Commons](#), and the [Mechanical Engineering Commons](#)

### Network Recommended Citation

Dyer, A., McKenna, L. & Gamage, G. (2020). Cognitive performance in midlife type 2 diabetes: results from the ENBIND study. *Diabetic Medicine*, vol. 38, no. 6, : 14412 doi:10.1111/dme.14412

This Article is brought to you for free and open access by the School of Mechanical and Design Engineering at ARROW@TU Dublin. It has been accepted for inclusion in Articles by an authorized administrator of ARROW@TU Dublin. For more information, please contact [arrow.admin@tudublin.ie](mailto:arrow.admin@tudublin.ie), [aisling.coyne@tudublin.ie](mailto:aisling.coyne@tudublin.ie).



This work is licensed under a [Creative Commons Attribution-NonCommercial-Share Alike 4.0 License](#)

Funder: Meath Foundation

Footer logo

---

**Authors**

A. H. Dyer, L. McKenna, G. Gamage, N. M. Bourke, Isabelle Killane, M. Widdowson, C. P. Woods, J. Gibney, R. Reilly, D. O'Neill, and s. P. Kennelly

DR ADAM HENRY DYER (Orcid ID : 0000-0003-1356-510X)

Article type : Research Article

Title: Diabetic Medicine

Created by: Maria Davie

Email proofs to: dyera@tcd.ie

Article no.: DME-2020-0408

Article type: Research Article

Short title/*Authors running head*: Cognition in midlife type 2 diabetes • A. H. Dyer *et al.*

## **Cognitive performance in midlife type 2 diabetes: results from the ENBIND study**

A. H. Dyer<sup>1,3</sup>, L. McKenna<sup>1</sup>, G. Gamage<sup>1</sup>, N. M. Bourke<sup>3</sup>, I. Killane<sup>6</sup>, M.

Widdowson<sup>2</sup>, C. P. Woods<sup>2</sup>, J. Gibney<sup>2</sup>, R. Reilly<sup>3,4,5</sup>, D. O'Neill<sup>3,5</sup> and S. P.

Kennelly<sup>1,3,5</sup>

<sup>1</sup>Department of Age-Related Healthcare and <sup>2</sup>Robert Grave's Institute of Endocrinology,

Tallaght University Hospital, <sup>3</sup>Department of Medical Gerontology, School of Medicine,

<sup>4</sup>Department of Bioengineering and <sup>5</sup>Global Brain Health Institute, Trinity College Dublin,

and <sup>6</sup>Department of Engineering, Technological University Dublin, Dublin, Ireland

*Correspondence to:* Adam H. Dyer. E-mail: dyera@tcd.ie

## What's new?

- Type 2 diabetes in midlife (age 40–60 years) is associated with a greater risk of dementia in later life, although it is not clear at what age cognitive decrements begin to emerge.
- We found that type 2 diabetes in midlife (age  $52 \pm 8$  years) was associated with lower scores on tests of global and domain-specific cognition in comparison to healthy controls.
- Our findings show that, even in midlife, type 2 diabetes is associated with lower scores on tests of cognitive function, which has important implications for the development of preventative interventions targeting those with type 2 diabetes

## Abstract

**Aims** Midlife type 2 diabetes, particularly in those aged 40-60, is associated with the later development of cognitive impairment/dementia. However, it is currently unclear how early cognitive decrements can be first detected. Early identification of those most at-risk of later cognitive decline may have important implications for the development of potential preventative interventions.

**Methods** We performed a cross-sectional study of middle-aged adults with uncomplicated type 2 diabetes and a cohort of healthy control participants. General cognition was assessed using the Montreal Cognitive Assessment test and neuropsychological assessment was undertaken using a detailed neuropsychological assessment battery.

**Results** A total of 152 participants (102 with type 2 diabetes and 50 controls) were recruited (mean age  $52 \pm 8$  years, 51% women). Participants with midlife type 2 diabetes were more than twice as likely to make an error on the Montreal Cognitive Assessment test [incidence

rate ratio 2.44 (95% CI 1.54 to 3.87);  $P < 0.001$ ). Further, type 2 diabetes was also associated with significantly lower memory composite score [ $\beta$ :  $-0.20$  (95% CI  $-0.39$  to  $-0.01$ );  $P = 0.04$ ] and paired associates learning score [ $\beta$ :  $-1.97$  (95% CI  $-3.51$ ,  $-0.43$ );  $P = 0.01$ ] on the neuropsychological assessment battery following adjustment for age, sex, BMI, educational attainment and hypercholesterolaemia.

**Conclusions** Even in midlife, type 2 diabetes was associated with small but statistically significant cognitive decrements. These statistically significant decrements, whilst not clinically significant in terms of objective cognitive impairment, may have important implications in selecting out individuals most at risk of later cognitive decline for potential preventative interventions in midlife.

## Introduction

Midlife type 2 diabetes is one of the greatest risk factors for the later development of dementia [1]. Whilst the cognitive effects of diabetes were first reported nearly 100 years ago, it was not until the first longitudinal studies came of age (such as the Rotterdam and Rochester studies) that the evidence surrounding this association began to accumulate [2,3]. More recent reports have found that midlife type 2 diabetes contributes nearly as much risk for dementia as the APOE genotype, the strongest genetic risk factor for dementia [4].

Importantly, type 2 diabetes is only a strong risk factor for dementia when those affected by type 2 diabetes are middle-aged (in fact, after age 65 years, the type 2 diabetes–dementia association is much weaker) [5,6]. Whilst studies have shown the cognitive effects of midlife type 2 diabetes up to 20 years later, the particular age at which cognitive decrements begin to emerge in those with type 2 diabetes is less clear.

Only a handful of small studies have investigated the association between type 2 diabetes and cognitive function in midlife [7–13]. The few studies which have assessed cognition in midlife type 2 diabetes in those aged <60 years are limited by small sample sizes and between-study heterogeneity [7]. Thus, whilst it appears that type 2 diabetes may affect cognitive function across the lifespan, whether or not cognitive decrements are present in midlife type 2 diabetes remains to be fully elucidated. This may be particularly important in selecting out those at greatest risk of cognitive decline for multi-domain preventative interventions aimed at mitigating the later risk of cognitive decline [14,15]. Notably, there is a lack of potential preventative interventions aimed at those with midlife type 2 diabetes [16]. Knowledge of which individuals with midlife type 2 diabetes are most at risk is lacking, and understanding this may be crucial in the development and of such interventions.

The Exploring Novel Biomarkers of Brain Health in Diabetes (ENBIND) study is a longitudinal cohort study of individuals with midlife type 2 diabetes free from any objective cognitive impairment or diabetes-related complications. In the present study, we analysed baseline data from ENBIND to examine if type 2 diabetes in midlife was associated with demonstrable cognitive decrements, both on validated tests of global cognition and detailed neuropsychological assessment.

## **Methods**

### **Study design**

The ENBIND study is a longitudinal study of cognition in midlife type 2 diabetes. Middle-aged adults with type 2 diabetes and healthy controls similar in age, sex and socio-economic status were recruited from a type 2 diabetes clinic located in a tertiary referral hospital

(Tallaght University Hospital) and by local advertisement within the same hospital in a 2:1 ratio.

### **Inclusion and exclusion criteria**

Participants aged 35–65 years with a diagnosis of type 2 diabetes were invited to participate at the time of routine outpatient appointment (study assessment occurred during a separate appointment). Exclusion criteria included: established diagnosis of cognitive impairment/dementia, non-type 2 diabetes, known macrovascular (previous stroke, myocardial infarction, ischaemic heart disease, peripheral vascular disease) or microvascular (diabetic retinopathy, peripheral neuropathy, diabetic nephropathy) complications of type 2 diabetes as per self-report or medical notes, active depression (within the past 6 months), diagnosed Diagnostic and Statistical Manual of Mental Disorders (DSM) Axis I psychiatric disorder or neurological disorder. We excluded individuals with another medical condition known to impact on cognitive function in addition to those with a significant musculoskeletal, cardiac or respiratory comorbidity.

People with a score of  $<23$  on the Montreal Cognitive Assessment (MoCA) test consistent with cognitive impairment, in addition to those with a score of  $\geq 8$  on the Centre for Epidemiological Scale 8 (CESD-8) consistent with an elevated risk of current depression, were excluded from participation in the study [17,18].

### **Health and diabetes assessment**

Each participant underwent full assessment, including comprehensive medical and type 2 diabetes review by a research physician. Information collected included routine demographic information, medical history and daily medications. Hypertension was defined as history of known hypertension, being on anti-hypertensive medication, or seated clinic blood pressure

of  $\geq 140/90$  mmHg, measured using an automated sphygmomanometer on a single occasion after a 5-min rest. Hyperlipidaemia was defined as history of hyperlipidaemia, being prescribed a statin (or other agent for dyslipidaemia) or total or LDL cholesterol above the local reference range.

Additional information collected from those with type 2 diabetes included years since diagnosis, in addition to medications used for diabetes. Participants were assessed at the study visit for peripheral neuropathy by administration of the Diabetic Neuropathy Symptom Score (DNSS) [19] and standard neurological examination by the research physician.

Individuals with evidence of peripheral neuropathy (examination/DNSS $\geq 2$ ) were excluded from further participation.

### **Cognitive assessment**

All cognitive assessment was carried out in the same office under standardized assessment conditions. Participants with type 2 diabetes were asked to present to their research appointment following a standard meal and having checked their fingerprick blood glucose level, ensuring that readings were within the range 4.0–14.0 mmol/l prior to study participation. Assessment was performed by a trained research physician (fellow) with a clinical and research interest in early cognitive impairment and dementia.

#### *Montreal Cognitive Assessment test*

General cognitive function was assessed using the standardized MoCA test, which is a short assessment of cognitive function used both clinically and in population studies for the detection of cognitive impairment. MoCA subdomains include: visuospatial/executive function, naming, attention, language, abstraction, delayed memory and orientation. A one-



point adjustment is made for  $\leq 12$  years of formal education. Participants with a score of  $< 23$  were excluded from the present study at the screening stage [17]. We calculated a total MoCA score from a possible 30, in addition to calculating the number of errors on the MoCA (30 – total MoCA score) for each participant.

### *Neuropsychological assessment*

We used a custom study-specific battery created from the Cambridge Neuropsychological Assessment Battery (CANTAB) [20,21] consisting of the following six tests (60-min duration).

- (1) *Paired associates learning*. Participants memorize the locations of geometric patterns presented on screen, with levels of increasing difficulty. Performance assessed using 'first attempt memory score' (0–20), with lower scores indicating worse performance.
- (2) *Spatial working memory*: Participants memorize the location of 'tokens' on screen in order to find other hidden tokens. Performance is analysed using 'SWM Strategy' (2–12), with lower scores indicating worse performance.
- (3) *Delayed pattern recognition*. Participants memorize specific geometric patterns and are tested after a 20-min delay. Performance analysed as percentage correctly remembered, with lower scores indicating worse performance.
- (4) *One Touch Stockings of Cambridge*. Participants match patterns by moving coloured balls inside stockings in the minimum number of moves. Performance assessed using 'problems solved on first choice' (0–15), with lower scores indicating worse performance.
- (5) *Rapid visual processing*. Participants detect sequences of numbers amongst a rapidly changing series of digits. Performance measured as signal detection, ranging from 0.00 to 1.00. Lower scores indicate worse performance.

(6) *Reaction time task*. This test is carried out using five coloured circles, assessing participants reaction time, in milliseconds. A greater number of milliseconds, representing a slower reaction time, indicates worse performance.

We additionally created composite scores for the separate domains of neuropsychological function. For memory, we averaged the z-scores (computed for the cohort scores as a whole) for the paired associates learning, spatial working memory and delayed pattern recognition memory tests. For a composite score of executive function/attention, we averaged the z-scores from the One Touch Stockings of Cambridge and the rapid visual processing tasks. For both composite z-scores, decreasing z-scores indicate lower scores.

### **Statistical analysis**

All statistical analysis was performed using STATA v.15.0 (Stata Corp., College Station, TX, USA) with  $P$  values  $< 0.05$  taken to indicate statistical significance. Descriptive statistics are reported as means  $\pm$  SD, numbers (%) and medians with interquartile ranges (IQRs), as appropriate. Between-group differences were assessed using  $t$ -tests, chi-squared tests and Wilcoxon rank-sum tests, as appropriate. For regression models, age ( $<45$  years, 45–49.9 years, 50–54.9 years, 55–55.9 years,  $>60$  years) and BMI ( $< 25$  kg/m<sup>2</sup>, 25–29.9 kg/m<sup>2</sup>, 30–34.9 kg/m<sup>2</sup>, 35–39.9 kg/m<sup>2</sup>,  $\geq 40$  kg/m<sup>2</sup>) were divided into strata.

We assessed the impact of type 2 diabetes on general cognition using Poisson regression, with the total number of errors on the MoCA test as the dependent variable (due to the strong left skew of the data) and study group (type 2 diabetes vs controls) as the dependent variable. We first tested the association unadjusted (Model 1), then adjusted for age, sex, BMI and education as above (Model 2). This was followed by further adjustment for hypertension and

hyperlipidaemia (Model 3). Covariates were selected based on known association with the dependent variable (cognitive function), independent variable (type 2 diabetes), or both.

Results are reported as incidence rate ratios (IRRs), with corresponding 95% CIs and *P* values, which indicate the likelihood of error on the MoCA test in those with type 2 diabetes in comparison with controls. We further employed these models to assess for performance on the subdomains of the MoCA test (detailed above).

To assess the effect of midlife type 2 diabetes on neuropsychological test performance, we used linear regression, given that our data were continuous and normally distributed. Again, the independent variable was type 2 diabetes status (in comparison to healthy controls) and the dependent variable was neuropsychological test score. We tested associations unadjusted (Model 1), then adjusted for important covariates (Model 2/3 as above). We examined residual vs fit plots and variance inflation factors *post hoc* to examine for multi-collinearity.

Results are reported as effect size ( $\beta$  coefficient for type 2 diabetes) with appropriate 95% CI and *P* value. We also reported results of standardized  $\beta$  in order to enable wider comparison of our results.

We re-ran the regression models (as above) only in those with type 2 diabetes with the following predictors added: diabetes duration (years), HbA<sub>1c</sub> (mmol/mol), diabetes treatment (metformin, sulfonureas, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 analogues, insulin, either alone or in combination). In the first instance each predictor was examined unadjusted, with adjustment subsequently made for important covariates (Models 2/3 as above).

## **Ethics**

Ethical approval for the study was obtained from the Tallaght–St James’s Joint Research Ethics Committee [reference: 2018/09/02 /2018-10 List 34(4)].

## **Results**

### **Participant characteristics**

After exclusion of a single participant (MoCA score <23), 102 participants with midlife type 2 diabetes (age 53±8 years, 59% women) and 50 healthy controls (age 52±8 years, 47% women) were recruited (Table 1). BMI, prevalence of hypertension and prevalence of hyperlipidaemia significantly differed between those with type 2 diabetes and controls (all  $P < 0.001$ ; Table 1). The median (IQR) number of years since diagnosis in those with type 2 diabetes was 6 (2–11) and the mean HbA<sub>1c</sub> was 61 ± 19 mmol/mol (7.7 ± 1.8%; Table 1).

### **Midlife type 2 diabetes and general cognitive function**

All participants underwent a MoCA assessment and scored above the cut-off score of 23. As detailed above, given the skew of MoCA scores, the impact of type 2 diabetes on likelihood of error on the MoCA was analysed. Overall, type 2 diabetes was associated with a greater than twofold increased likelihood of error on the MoCA test under the unadjusted model [IRR 2.4 (95% CI 1.5–3.6);  $P < 0.001$ ]. This association persisted on robust covariate adjustment (Models 2 and 3; Table 2). On analysing MoCA subdomains, type 2 diabetes was associated with greater likelihood of error on visuospatial/executive function [IRR 3.7 (95% CI 1.6–9.0);  $P = 0.003$  adjusted, model 3], attention [IRR 6.6 (95% CI 1.5–28.8);  $P = 0.011$  adjusted, model 3] and delayed memory [IRR 1.6 (95% CI 1.0–2.3);  $P = 0.031$  adjusted, model 3] domains.

## Midlife type 2 diabetes and neuropsychological test performance

Overall, 149 participants underwent complete neuropsychological assessment. One participant with type 2 diabetes opted to terminate testing early and for two participants with type 2 diabetes the delayed pattern memory task did not complete because of technical difficulties (assessment was available for the other 5/6 tasks). Results are given with appropriate effect sizes, *P* values, and standardized  $\beta$  values for type 2 diabetes in Table 3.

Type 2 diabetes was associated with significantly lower scores in the 'memory' composite score under all three models [ $\beta$ : -0.21 (95% CI -0.42 to -0.01); *P* = 0.04; standardized  $\beta$ : -0.19]. On analysis of individual tasks, type 2 diabetes was associated with lower scores on the paired associates learning task after adjustment under Models 2 [ $\beta$ : -1.97 (95% CI -3.51 to -0.43); *P* = 0.01; standardized  $\beta$ : -0.21] and 3 [ $\beta$ : -2.21 (95% CI -3.86 to -0.55); *P* = 0.01; standardized  $\beta$ : -0.24].

## Type 2 diabetes-related variables and cognitive performance

On analysing the association between type 2 diabetes-related variables and likelihood of error on the MoCA test, neither HbA<sub>1c</sub>, type 2 diabetes diagnosis duration (years) or type 2 diabetes treatment were significantly associated with likelihood of error on the MoCA test or performance on the neuropsychological test battery.

## Discussion

In the present study, midlife type 2 diabetes was associated with greater likelihood of error on an assessment of overall cognitive function in addition to lower scores on the memory domain of a detailed neuropsychological assessment battery. Our findings are particularly

striking given the fact that the study is one of the first to include such a young cohort of participants free from any diabetes-related complications.

Whilst the greater likelihood of MoCA error seen in the present study was striking and survived robust adjustment for covariates, it is notable that we assessed a population free from any objective cognitive impairment. Similarly, we demonstrated small but significant differences in specific memory performance in type 2 diabetes. Such differences, whilst statistically significant, are slightly smaller than those observed in other studies, nearly all of which focused on older individuals (in addition to including those with diabetes-related complications) than the present study [22].

The statistically significant differences observed, whilst not clinically significant in terms of objective cognitive impairment, may be part of the cognitive decrements noted in individuals with type 2 diabetes across the lifespan [23]. Understanding the longitudinal trajectories of these cognitive decrements may be crucial in selecting out those with type 2 diabetes most at risk of later cognitive decline. Such early decrements, which may not be clinically significant, may in fact act as a marker of those individuals at risk of later cognitive decline.

The lack of clinically significant impairment in the present study may be reflective of the high-performing nature of the cohort under study in our analysis. Notably, our participants were young, had a high level of education, a short duration of diabetes and were free from diabetes-related complications.

We demonstrated a significant effect of type 2 diabetes on performance on the paired associates learning task, a task with significant working memory demands. This task is arguably the most demanding and performance has been linked to a variety of brain regions

including the prefrontal cortex, medial temporal cortex, hippocampus, parietal cortex, posterior cortical visual areas and the basal ganglia [24,25]. Performance on this task has previously been associated with metabolic control in older adults with type 2 diabetes [25]. In addition to later risk of cognitive impairment and accumulation of cerebrospinal fluid biomarkers of Alzheimer's disease [21].

Notably, structural neuroimaging studies in type 2 diabetes have demonstrated a reduced volume in the hippocampus, basal ganglia, and the cortex, including the medial temporal lobe [26,27], the same areas targeted by the paired associates learning task. The relationship between regional brain volumes in structural neuroimaging studies conducted in those with midlife type 2 diabetes is an important consideration for future research. However, at present, our findings echo previous structural neuroimaging research implicating brain regions such as the medial temporal lobe, basal ganglia and hippocampus in type 2 diabetes. The longitudinal consequences of these associations are worthy of further study.

The cognitive complications of type 2 diabetes are typically underappreciated in comparison to other diabetes-related complications [28]. Increasing awareness may be particularly important in diabetes self-management, where future approaches may involve the use of self-administered computerized assessment batteries. However, such assessment must also take into account that most individuals with midlife type 2 diabetes will not develop cognitive impairment and care must be taken to avoid additional psychological burden. Even in the present study, the size of cognitive decrements are small, and little is known about the longitudinal consequences of such decrements. Further studies are required to track the exact trajectories of these decrements in order to identify an optimal frequency (e.g. annual or bi-annual), the specific composition and the setting of cognitive screening in type 2 diabetes.

Whilst current guidelines [29] propose annual screening in older adults, the optimal screening approach for midlife type 2 diabetes is yet to be clarified.

We observed no association between type 2 diabetes and neuropsychological measures of executive function. Such findings may be surprising given previous studies demonstrating an effect of type 2 diabetes in midlife on executive function [22,23]. Whilst our findings may be explained by the nature of our cohort, it may also be that the tests of executive function were not sufficiently extensive to demonstrate such a deficit. Whilst our battery was custom-designed to balance tolerability/test duration and specific domains implicated in type 2 diabetes, a more extensive neuropsychological battery may have yielded differing results.

An important limitation of the present study is its cross-sectional nature. Future follow-up waves of ENBIND will clarify the impact of midlife type 2 diabetes on later cognitive decline. Finally, we must also acknowledge that whilst the study was conducted in samples matched for educational attainment, premorbid IQ may have influenced cognitive performance. By examining this cohort longitudinally, we aim to provide long-term assessment of people with type 2 diabetes in midlife to examine the impact of these cognitive decrements on later cognitive decline.

In conclusion, we report that type 2 diabetes in midlife, even in those with uncomplicated type 2 diabetes, is associated with subtle cognitive decrements in overall/domain-specific cognitive function. Our findings add novel insight into the relationship between type 2 diabetes and cognitive function in midlife, during the exact window when type 2 diabetes is acting as a risk factor for later cognitive decline and dementia. Further understanding of such



decrements may be important in selecting out those most at risk of later cognitive decline for potential preventative interventions.

### **Funding sources**

This work was funded by a grant from the Meath Foundation.

### **Competing interests**

None declared.

### **Acknowledgements**

The authors would like to acknowledge the study participants and staff at Tallaght University Hospital (in particular Ms Marian Hughes and Ms Mary Kelly for administrative support).

### **References**

1. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. *J Diabetes Investig* 2013; **4**: 640–650.
2. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999; **53**:1937–1942.
3. Liebson CL, Rocca WA, Hanson VA, Cha R, Kokmen E, O'Brien PC *et al*. The risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Ann N Y Acad Sci* 1997; **826**:422–427.
4. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM *et al*. Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia

in the Atherosclerosis Risk in Communities (AIRC) Cohort. *JAMA Neurol* 2017; **74**: 1246–1254

5. Knopman DS, Gottesman RF, Sharrett AR, Tapia AL, DavisThomas S, Windham BG *et al.* Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: The Atherosclerosis Risk in Communities Study. *Alzheimers Dement* 2018; **14**: 1406–1415.
6. Van den Berg E, de Craen AJ, Biessels GJ, Gussekloo J, Wstendorp RGJ. The impact of diabetes mellitus on cognitive decline in the oldest old: a prospective population based study. *Diabetologia* 2006; **49**: 2015–2023
7. Pelimanni E, Jehkonen M. Type 2 diabetes and Cognitive Functions in Middle Age: A Meta-Analysis. *J Int Neuropsychol Soc* 2018; **21**: 1–16.
8. Aberle I, Kliegel M, Zimprich D. Cognitive development in young-old type-2 diabetes patients: A longitudinal analysis from the “Interdisciplinary Longitudinal Study of Aging”. *Curr Psychol* 2008; **27**: 6–15.
9. Garcia-Casares N, Jorge RE, Garcia-Arnes, Acion L, Berthier ML, Gonzalez-Alegre P *et al.* Cognitive dysfunctions in middle-aged type 2 diabetic patients and neuroimaging correlations: A cross-sectional study. *J Alzheimers Dis* 2014; **42**: 1337–1346.
10. Ryan CM, Geckle MO. Circumscribed cognitive dysfunction in middle-aged adults with type 2 diabetes. *Diabetes Care* 2000; **23**: 1486–1493.
11. Solanki RK, Dubey V, Munshi D. Neurocognitive impairment and comorbid depression in patients of diabetes mellitus. *Int J Diabetes Dev Ctries* 2009; **29**: 133–138.

12. Mehrabian S, Raycheva M, Gateva A, Todorova G, Angelova P, Traykova M *et al.* Cognitive Dysfunction profile and Arterial Stiffness in Type 2 diabetes. *J Neurol Sci.* 2012; **322**: 152–156.
13. Biessels JG, ter Braak EWM, Erkelens DW, Hijman R. Cognitive Function in Patients with Type 2 diabetes Mellitus. *Neurosci Res Comm* 2001; **28**: 11–22.
14. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle Interventions to Prevent Cognitive Impairment, Dementia and Alzheimer Disease. *Nat Rev Neurol* 2018; **14**: 653–666.
15. Ngandu T, Lehtisalo J, Solomon A, Levalahti, Ahtiluoto S, Antikainen R *et al.* A 2 year multi-domain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A Randomised Controlled Trial. *Lancet* 2015; **385**: 2255–2263.
16. Dyer AH, Briggs R, Mockler D, Gibney J, Kennelly SP. Non-pharmacological interventions for cognition in patients with Type 2 diabetes Mellitus: A Systematic Review. *QJM* 2020; **113**: 155–161.
17. Kenny RA, Coen RF, Frewen J, Donoghue O, Cronin H, Savva GM. Normative Values of Cognitive and Physical Function in Older Adults: Findings from The Irish Longitudinal Study of Ageing. *J Am Geriatr Soc* 2013; **61**: S279–S290.
18. Briggs R, Carey D, O'Halloran, Kenny RA, Kennelly SP. Validation of the 8-item Centre for Epidemiological Studies Depression Scale in a Cohort of Community-Dwelling Older People: Data from The Irish Longitudinal Study on Ageing (TILDA). *Eur Geriatr Med* 2018; **9**: 121–126.
19. Meijer JW, Smith AJ, Sonderen EV, Groothoff JW, Eisma WH, Links TP. Symptom Scoring Systems to Diagnose Distal Polyneuropathy in Diabetes: The Diabetic Neuropathy Symptom Score. *Diabet Med* 2002; **19**: 962–965.

20. Lowe C, Rabbit P. Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. Cambridge Neuropsychological Test Automated Battery. International Study of Post-Operative Cognitive Dysfunction. *Neuropsychologia* 1998; **36**: 915–932.
21. Soldan A, Pettigrew C, Moghekar A, Albert M, BIOCARD Research Team. Computerized cognitive tests are associated with biomarkers of Alzheimer’s disease in cognitively normal individuals 10 years prior. *J Int Neuropsychol Soc* 2016; **22**: 968–977.
22. Palta P, Schneider ALC, Jan Biessels, Touradji P, Hill-Briggs, F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six domains and the most frequently reported neuropsychological tests within domains. *J Int Neuropsychol Soc* 2014; **20**: 278–291.
23. Jan Biessels G, Despa F. Cognitive Decline and Dementia in Diabetes Mellitus: Mechanisms and Clinical Implications. *Nat Rev Endocrinol* 2018; **14**: 591–604.
24. Owen AM, Sahakian BJ, Semple J, Polkey CE, Robbins TW. Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* 1995; **33**: 1–24.
25. Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MWJ. Improving metabolic control leads to better working memory in adults with type 2 diabetes. *Diabetes Care* 2006; **29**: 345–351.
26. Bernardes G, Ijzerman RG, ten Kulve JS, Barkhof F, Diamant M, Veltman DJ *et al*. Cortical and subcortical gray matter structural alterations in normoglycemic obese and type 2 diabetes patients: relationship with adiposity, glucose and insulin. *Metab Brain Dis* 2018; **33**: 1211–1222.

27. Moran C, Phan TG, Chen J, Blizzard L, Beare R, Venn A *et al.* Brain Atrophy in Type 2 diabetes: regional distribution and influence on cognition. *Diabetes Care* 2013; **36**: 4036–4042.
28. Dolan C, Glynn R, Griffin S, Conroy C, Loftus C, Wiehe PC *et al.* Brain Complications of Diabetes Mellitus: A Cross-Sectional Study of Awareness Among Individuals with Diabetes and the General Population in Ireland. *Diabet Med* 2018; **35**: 871–879.
29. American Diabetes Association. Older Adults: Standards of Medical Care in diabetes-2019. *Diabetes Care* 2019; **42**: S139–S147.

**Table 1** Baseline characteristics of ENBIND participants, presented by study group with appropriate univariate analysis

| Characteristic                              | Midlife type 2 diabetes<br>( <i>n</i> = 102) | Healthy controls<br>( <i>n</i> = 50) | <i>P</i> |
|---|--|--------------------------------------|----------|
| Age, years                                  | 53 ± 8                                       | 52 ± 8                               | 0.59     |
| Women, <i>n</i> (%)                         | 47 (47)                                      | 29 (59)                              | 0.15     |
| Educational attainment, <i>n</i><br>(%)     |  |                                      | 0.40     |
| Primary                                     | 13 (13)                                      | 3 (6.0)                              |          |
| Secondary                                   | 71 (70)                                      | 36 (72)                              |          |
| Tertiary                                    | 18 (18)                                      | 11 (22)                              |          |
| BMI, kg/m <sup>2</sup>                      | 32.3 ± 7.7                                   | 26.6 ± 3.3                           | <0.001   |
| Family history of<br>dementia, <i>n</i> (%) | 23 (23)                                      | 13 (26)                              | 0.52     |
| Hypertension, <i>n</i> (%)                  | 55 (54)                                      | 6 (12)                               | <0.001   |
| Hyperlipidaemia, <i>n</i> (%)               | 62 (61)                                      | 4 (8.0)                              | <0.001   |
| HbA <sub>1c</sub> , mmol/mol                | 61 ± 19                                      | 37 ± 3                               | <0.001   |
| HbA <sub>1c</sub> , %                       | 7.7 ± 1.8                                    | 5.5 ± 0.3                            | <0.001   |
| No. of daily medications                    | 4 (2–5)                                      | 0 (0–1)                              | <0.001   |
| Diagnosis duration, years                   | 6 (2–11)                                     | -                                    | -        |
| Diabetes treatment, <i>n</i> (%)            |  |                                      |          |
| Metformin                                   |  |                                      |          |
| Alone                                       | 27 (27)                                      |                                      |          |
| Combination                                 | 41 (40)                                      |                                      |          |
| Glicazide                                   |  |                                      |          |
| Alone                                       | 2 (2.0)                                      |                                      |          |
| Combination                                 | 15 (15)                                      |                                      |          |
| DPP-4 inhibitors                            |  |                                      |          |

|                               |         |
|-------------------------------|---------|
| <b>Alone</b>                  | 0 (0)   |
| <b>Combination</b>            | 17 (17) |
| <b>SGLT2 inhibitors</b>       |         |
| <b>Alone</b>                  | 0       |
| <b>Combination</b>            | 10 (10) |
| <b>GLP-1 analogues</b>        |         |
| <b>Alone</b>                  | 3 (2.9) |
| <b>Combination</b>            | 21 (24) |
| <b>Insulin</b>                |         |
| <b>Alone</b>                  | 2 (2.0) |
| <b>Combination</b>            | 6 (6.0) |
| <b>No diabetes medication</b> | 2 (2.0) |

---

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2.

Data are presented as means  $\pm$  SD or medians (interquartile ranges), unless otherwise indicated.

Table 2 Greater likelihood of error on the Montreal Cognitive Assessment in those with type 2 diabetes

| Independent variable     | IRR (95% CI)      | <i>P</i> | IRR (95% CI)      | <i>P</i> | IRR (95% CI)      | <i>P</i> |
|--------------------------|-------------------|----------|-------------------|----------|-------------------|----------|
|                          | Model 1           |          | Model 2           |          | Model 3           |          |
|                          | (unadjusted)      |          | (adjusted)        |          | (adjusted)        |          |
| Type 2 diabetes          | 2.37 (1.53, 3.64) | <0.001   | 2.44 (1.54, 3.87) | <0.001   | 2.09 (1.49, 2.93) | <0.001   |
| Age (years)              |                   |          | 1.21 (1.07, 1.37) | 0.002    | 1.13 (1.03, 1.23) | 0.008    |
| Sex                      |                   |          | 0.83 (0.60, 1.13) | 0.233    | 0.89 (0.70, 1.14) | 0.369    |
| Education                |                   |          |                   |          |                   |          |
| Primary                  |                   |          | 1.00              |          | 1 (Reference)     |          |
| Secondary                |                   |          | (Reference)       | 0.013    | 0.67 (0.46, 0.99) | 0.046    |
| Tertiary                 |                   |          | 0.66 (0.48, 0.92) | 0.002    | 0.50 (0.30, 0.86) | 0.012    |
| BMI (kg/m <sup>2</sup> ) |                   |          | 0.98 (0.95, 1.00) | 0.076    | 0.97 (0.88, 1.07) | 0.595    |
| Hypertension             |                   |          |                   |          | 0.85 (0.60, 1.20) | 0.355    |
| Hyperlipidaemia          |                   |          |                   |          | 1.16 (0.83, 1.65) | 0.383    |

IRR, incidence rate ratio.

Poisson regression was used to assess associations with likelihood of error on the Montreal Cognitive Assessment (MoCA) test. Under both unadjusted and adjusted models type 2 diabetes mellitus was associated with greater likelihood of error on the MoCA test. Associations were tested unadjusted (Model 1), followed by adjustment for age, sex, education, BMI (Model 2) and further adjustment for hypertension and hyperlipidaemia (Model 3).



Table 3 Performance on the Cambridge Neuropsychological Assessment Battery

| Domain/test  | Type 2<br>diabetes<br>(n = 100) | Controls<br>(n = 49) | $\beta$ (95% CI)<br>for type 2<br>diabetes | Standardized $\beta$<br>for type 2<br>diabetes | <i>P</i>    | $\beta$ (95% CI)<br>for type 2<br>diabetes<br>Mellitus | Standardized $\beta$<br>for type 2<br>diabetes | <i>P</i>    | $\beta$ (95% CI)<br>for type 2<br>diabetes | Standardized $\beta$<br>for type 2<br>diabetes | <i>P</i>                            |
|--|---------------------------------|----------------------|--|--|-------------|--|--|-------------|--|--|-------------------------------------|
|  |                                 |                      | <b>Model 1</b><br><b>(unadjusted)</b>      |  |             |  | <b>Model 2</b><br><b>(adjusted)</b>            |             |  |  | <b>Model 3</b><br><b>(adjusted)</b> |
| Memory (z-score)   | -0.05 ±<br>1.51                 | 0.14 ± 0.54          | -0.19<br>(-0.37, -<br>0.01)                | -0.17  | <b>0.04</b> | -0.20<br>(-0.39,<br>0.01)                              | -0.18  | <b>0.04</b> | -0.21<br>(-0.42, -<br>0.01)                | -0.19  | <b>0.04</b>                         |
| <b>Paired associates<br/>learning<br/>(1st attempt memory<br/>score)</b> | 10.29 ±<br>4.52                 | 11.63 ±<br>4.32      | -1.34<br>(-2.88, 0.19)                     | -0.15  | 0.08        | -1.97<br>(-3.51,<br>0.43)                              | -0.21  | <b>0.01</b> | -2.21<br>(-3.86, -<br>0.55)                | -0.24  | <b>0.01</b>                         |
| <b>Spatial working memory<br/>(strategy score)</b>                       | 8.53 ±<br>2.50                  | 8.55 ± 2.93          | -0.02<br>(-0.93, 0.89)                     | -0.00  | 0.97        | 0.36<br>(-0.59,<br>1.26)                               | 0.06   | 0.48        | 0.16<br>(-0.21, 0.54)                      | 0.08   | 0.39                                |
| <b>Delayed pattern</b>   | 77.95 ±                         | 81.44 ±              | -3.48                                      | -0.11  | 0.18        | -4.08  | -0.13  | 0.14        | -0.34                                      | -0.16  | 0.11                                |

|   |                 |                 |                        |       |      |                        |       |      |                        |       |       |
|---|-----------------|-----------------|------------------------|-------|------|------------------------|-------|------|------------------------|-------|-------|
| <b>recognition</b><br><b>(percentage correct)</b>                                 | 14.33           | 14.89           | (-8.62, 1.66)          |       |      | (-9.57, 1.41)          |       |      | (-0.75, 0.07)          |       |       |
| Executive<br>function/attention<br>(z-score)                                      | -0.04 ±<br>0.08 | 0.08 ± 0.86     | -0.12<br>(-0.41, 0.17) | -0.07 | 0.43 | -0.16<br>(-0.47, 0.15) | -0.09 | 0.31 | -0.22<br>(-0.55, 0.11) | -0.13 | -0.19 |
| <b>Stockings of Cambridge</b><br><b>(problems solved on 1st</b><br><b>choice)</b> | 8.62 ±<br>3.38  | 9.27 ± 3.18     | -0.64<br>(-1.79, 0.50) | -0.09 | 0.27 | -0.74<br>(-1.93, 0.45) | -0.10 | 0.22 | -0.37<br>(-0.66, 0.12) | -0.13 | 0.17  |
| <b>Rapid visual processing</b><br><b>(signal detection)</b>                       | 0.89 ±<br>0.52  | 0.89 ± 0.60     | -0.00<br>(-0.02, 0.02) | -0.02 | 0.85 | -0.00<br>(-0.02, 0.02) | -0.03 | 0.78 | -0.15<br>(-0.56, 0.27) | -0.07 | 0.49  |
| <b>Reaction time task, ms</b>   | 422.3 ±<br>53.9 | 409.5 ±<br>45.2 | 13.42<br>(-4.3, 31.1)  | 0.12  | 0.14 | 14.45<br>(-4.8, 33.7)  | 0.13  | 0.14 | 16.39<br>(-4.3, 37.1)  | 0.15  | 0.12  |

Table summarizes performance of those with type 2 diabetes vs healthy controls. Linear regression model results are presented as  $\beta$  coefficients and corresponding 95% CI as well as standardized  $\beta$  values for effect of study group on test score. Associations were tested unadjusted (Model 1), then adjusted for age, sex, education, BMI (Model 2) with further adjustment for hypertension and hyperlipidaemia (Model 3).