Received: 26 May 2021 | Accepted: 2 August 2021

DOI: 10.1111/dme.14668

DIABETIC Medicine

RESEARCH ARTICLE

Glycated haemoglobin (HbA_{1c}), diabetes and neuropsychological performance in community-dwelling older adults

Adam H. Dyer[1,2,3] | **Robert Briggs**[1] | **Eamon Laird**[2] | **Leane Hoey**[4] | **Catherine F. Hughes**[4] | **Helene McNulty**[4] | **Mary Ward**[4] | **JJ Strain**[4] | **Anne M Molloy**[5] | **Conal Cunningham**[1,2] | **Kevin McCarroll**[1,2]

[1]Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland

[2]Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Ireland

[3]Wellcome-HRB Clinical Research Facility, St James's Hospital, Dublin, Ireland

[4]The Nutrition Innovation Centre for Food and Health (NICHE), School of Biomedical Sciences, Ulster University, Coleraine, Northern Ireland, UK

[5]School of Medicine, Trinity College Dublin, Dublin, Ireland

Correspondence
Dr Adam H. Dyer MB BCh BAO MSc MRCPI, Mercer's Institute for Successful Ageing (MISA), St James's Hospital, Dublin, Ireland.
Email: dyera@tcd.ie

Funding information
Health Research Board; Irish Department of Agriculture, Food and the Marine; Department for Employment and Learning, Northern Ireland

Abstract

Aims: Given that diabetes is associated with cognitive impairment and dementia in later life, we aimed to investigate the relationship between glycated haemoglobin (HbA_{1c}), diabetes and domain-specific neuropsychological performance in older adults.

Methods: Cross-sectional cohort study using data from the Trinity-Ulster-Department of Agriculture (TUDA) study. Participants underwent detailed cognitive and neuropsychological assessment using the Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB) and Repeatable Assessment for Neuropsychological Status (RBANS). Linear regression was used to assess associations between HbA_{1c}, diabetes status and neuropsychological performance, with adjustment for important clinical covariates.

Results: Of 4938 older adults (74.1 ± 8.3 years; 66.9% female), 16.3% ($n = 803$) had diabetes ($HbA_{1c} \geq 6.5\%$; 48 mmol/mol), with prediabetes ($HbA_{1c} \geq 5.7\%$–6.4%; 39–47 mmol/mol) present in 28.3% ($n = 1395$). Increasing HbA_{1c} concentration was associated with poorer overall performance on the FAB [β: −0.01 (−0.02, −0.00); $p = 0.04$ per % increase] and RBANS [$\beta = -0.66$ (−1.19, −0.13); $p = 0.02$ per % increase]. Increasing HbA_{1c} was also associated with poorer performance on immediate memory, visuo-spatial, language and attention RBANS domains. Diabetes was associated poorer performance on neuropsychological tests of immediate memory, language, visual-spatial and attention.

Conclusions: Both increasing HbA_{1c} and the presence of diabetes were associated with poorer cognitive and domain-specific performance in older adults. HbA_{1c}, and not just diabetes status per se, may represent an important target in the promotion of optimal brain health in older adults.

KEYWORDS

cognition, diabetes, glycated haemoglobin, HbA_{1c}, neuropsychology

1 | INTRODUCTION

Diabetes is one of the most potent risk factors for the development of dementia in later life.[1–4] Recent estimates suggest that diabetes poses nearly as great a risk for developing dementia as APOE4 status, the most prevalent genetic risk factor for sporadic Alzheimer's Disease (AD).[5] While the diabetes-dementia link has been well established, comparatively less research has investigated the relationship between diabetes and specific domains of cognitive function in older people. This may be particularly relevant in identifying individuals at risk who could benefit from early interventions aimed at the prevention of dementia. Such interventions, though successful in high-risk individuals, have not been typically assessed in those with hyperglycaemia and/or diabetes.[6–8]

Glycated haemoglobin (HbA_{1c}) reflects average glucose concentrations over the preceding 3 months and has clinical utility not only in diabetes diagnosis but also in the identification of individuals at risk of diabetes.[9,10] Few studies have specifically explored the relationship between HbA_{1c} and cognitive function, particularly in those without diabetes or in those with prediabetes, conditions which may represent an important target for early intervention. Notably, in the ACCORD-MIND study, a 1% increase in HbA_{1c} was associated with significantly poorer performance in the Digit Symbol Substitution Test (DSST) and the Mini-Mental State Examination (MMSE).[11] Similarly, studies in those with diabetes have identified a significant relationship between hyperglycaemia and poorer performance in tests of perceptual speed and visuo-spatial tasks.[12] Thus, elevated HbA_{1c} may represent an important target for early intervention, rather than focussing on diabetes status alone.

Evidence is beginning to emerge from studies such as in the English Longitudinal Study of Ageing (ELSA) and the Health and Retirement Study (HRS) that HbA_{1c} may be associated with poorer cognitive function in older adults independent of diabetes status.[13,14] Similarly, some studies in patients without diabetes have demonstrated a relationship between greater HbA_{1c} and poorer cognitive function.[15] While such studies have identified significant associations with commonly used global tests of cognition, the relationship of HbA_{1c} with more detailed measures of domain-specific neuropsychological function is less well explored and may be important in identifying older adults at greater risk of future cognitive decline.

The Trinity-Ulster-Department of Agriculture (TUDA) study recruited over 5000 older adults without a diagnosis of dementia to undergo detailed health, metabolic and cognitive assessments. Previous research from this cohort has highlighted the importance of hyperglycaemia (above a certain cut-point) with metformin use as a potential predictor of cognitive dysfunction.[16] However, the relationship between increasing HbA_{1c} and domain-specific cognitive performance in those with normoglycaemia, prediabetes or diabetes has not been assessed. The aim of the current study was to investigate the cross-sectional relationship of HbA_{1c}oncentration with domain-specific cognitive function in TUDA participants.

What's new?

- Diabetes is a risk factor for dementia in later life, but the relationship between HbA_{1c} and domain-specific neuropsychological performance in older adults is less well explored.
- Increasing HbA_{1c} concentration was associated with poorer overall and domain-specific neuropsychological performance in older adults
- Similarly, diabetes was associated with poorer performance on immediate memory, visual-spatial, language and attention domains.

2 | METHODS

2.1 | Study design

The current study consisted of an analysis of data from the TUDA study which was conducted between 2008 and 2012 (ClinicalTrials.gov identifier: NCT02664584) and has been described elsewhere.[17–19] Briefly, participants were recruited from general practise and hospital outpatient clinics in Northern Ireland and the Republic of Ireland. Inclusion criteria included age ≥60 years and not having an existing diagnosis of dementia. Participants were recruited as part of three subcohorts: (i) cognitive subcohort: from geriatric medicine clinics/day hospital at St James's Hospital, Dublin; (ii) bone subcohort: participants with a diagnosis of osteopenia/osteoporosis (as per World Health Organisation criteria) from a specialist bone health service at St James's Hospital, Dublin and (iii) hypertensive subcohort: individuals with a diagnosis of hypertension recruited from general practises in the catchment area of the Western and Northern Health and Social Care trusts in Northern Ireland. Ethical approval was obtained from the Office for Research Ethics Committees Northern Ireland (ref: 08/NIR03/113), and the Research Ethics Committee in St James's Hospital, Dublin, Ireland.

2.2 | Health and lifestyle assessment

Comprehensive assessment of health, lifestyle and medical comorbidity was undertaken via a 90-min interview. Weight (electronic scales from Brosch Direct Ltd.) and height (wall-mounted stadiometer from Seca Ltd.) were recorded in standard fashion. Participants were asked a series of questions on their medical history including diagnosis of diabetes, hypertension, ischaemic heart disease, atrial fibrillation, congestive cardiac failure and cerebrovascular disease (stroke or transient ischaemic attack). Participants were also asked about alcohol and smoking history and to provide a list of the current medications they were taking, coded as per the Anatomical Therapeutic Classification (ATC) System. A history of hypertension was defined as any known history of hypertension or being currently prescribed medication used to treat hypertension (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretrics). Hyperlipidaemia was considered to be a known history of the same or being prescribed lipid-lowering therapy.

2.3 | Blood sampling and analysis

Blood samples were obtained and processed within 4 h of collection. HbA_{1c} was measured in both jurisdictions in participating hospital laboratories using the Bio-Rad Variant II Turbo analyser (Bio-Rad Laboratory Inc.), traceable to the International Federation for Clinical Chemistry (IFCC) reference method. Results are reported as both IFCC units in mmol/L and as Diabetes Control and Complications Trial (DCCT) units in %. Blood samples were additionally analysed for total cholesterol and total triglycerides (in mmol/L) in the hospital laboratories.

2.4 | Diabetes

Diabetes was defined by one or more of the following: (i) self-reported diagnosis of diabetes, (ii) use of diabetes medication (oral hypoglycaemic/insulin) or (iii) $HbA_{1c} \geq 48$ mmol/L (6.5%). Prediabetes was defined as an HbA_{1c} 39.0–47.0 mmol/L (5.7%–6.4%) without meeting the criteria for diabetes (i.e. formal diagnosis or antidiabetic medication as above) according to American Diabetes Association (ADA) Criteria.[20] Diabetes medications were identified via the ATC Codes 'A10A' and 'A10B' and 'A10X' referring to 'insulins and analogues', 'blood glucose-lowering drugs" and 'other drugs used in diabetes', respectively. Those who did not meet the criteria for either prediabetes or diabetes were deemed to be 'normoglycaemic'.

2.5 | Cognitive assessment

Cognitive assessment was undertaken by trained assessors in a standardised fashion at both study sites. The Mini-Mental State Examination (MMSE) was used as an assessment of global cognitive function and is the most widely used cognitive screening tool in health research and clinical practise.[21] The Frontal Assessment Battery (FAB) tool was used to assess frontal lobe executive function and specifically in the areas of conceptualisation (assessing similarities), mental flexibility (verbal fluency), motor programming ('Luria' test), resistance to interference (conflicting instructions), inhibitory control (via a go-no-go paradigm) and environmental autonomy (prehension behaviour). It is scored out of a total of 18.[22] The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) was used as a detailed neuropsychological assessment of five cognitive domains, including immediate memory (Index I), visual-spatial (Index II), language (Index III), attention (Index IV) and delayed memory (Index V), with each domain scored from 100.[23] The RBANS was administered by trained assessors who underwent identical training at each study site. Index scores were calculated in a standardised fashion in addition to a total score reflecting overall performance on the five domains.[23] Participants also underwent assessment for current anxiety and depressive symptoms using the Hospital Anxiety and Depression Scale (HADS) and Centre for Epidemiological Studies Depression scale (CES-D), respectively.[24,25] Standard cut-offs were applied with a score of ≥16 indicating depression (CES-D) and a score of ≥11 indicating anxiety (HADS).[19]

2.6 | Statistical analysis

All statistical analysis was conducted using STATA v. 15.0 (STATACorp) with an alpha level of $p < 0.05$ considered statistically significant. Data were inspected for normality of distribution by examining Q-q plots and histograms. Data which were not normally distributed underwent natural log transformation. Descriptive statistics are reported as means with standard deviations, and medians with interquartile ranges as appropriate, in addition to proportions and percentages. Between-group differences for those with diabetes, prediabetes and without either (i.e. normoglycaemic) were analysed using ANOVA, Kruskal–Wallis test and Chi-square tests as appropriate.

Linear regression was used to assess the relationship between HbA_{1c} (in %) and cognitive function, with HbA_{1c} (%) as the independent variable and cognitive test outcome (total MMSE score, natural log-transformed FAB score, RBANS total and RBANS index scores) as the dependent variable.

TABLE 1 Characteristics of TUDA Participants by diabetes status

Characteristics	Normoglycaemic ($N = 2740$)	Prediabetes ($n = 1395$)	Diabetes ($n = 803$)	p value
Age (years)	73.3 (8.4)	75.7 (8.1)	74.0 (7.8)	<0.001
Sex (female)	1872 (68.3%)	998 (71.5%)	431 (53.7%)	<0.001
Body mass index	26.9 (5.0)	28.5 (5.4)	30.4 (5.6%)	<0.001
Waist–hip ratio	0.90 (0.1)	0.91 (0.1)	0.95 (0.1)	<0.001
Education (years)	16.2 (3.0)	15.8 (2.9)	15.6 (2.7)	<0.001
Smoking (current)	323 (11.8%)	181 (13.0%)	92 (11.5%)	0.12
Alcohol (current)	1681 (61.3%)	742 (53.2%)	387 (48.2%)	<0.001
Systolic blood pressure (mmHg)	144.6 (21.1)	144.7 (21.1)	144.9 (21.4)	0.90
Diastolic blood pressure (mmHg)	79.1 (11.0)	78.0 (11.2)	76.2 (11.7)	<0.001
Hypertension	1885 (68.8%)	1029 (73.8%)	680 (84.68%)	<0.001
Hypercholesterolaemia	1472 (53.7%)	889 (63.7%)	666 (82.9%)	<0.001
Myocardial infarction	220 (8.0%)	148 (10.6%)	129 (16.1%)	<0.001
Atrial fibrillation	319 (11.7%)	218 (15.6%)	117 (14.6%)	<0.001
Ischaemic heart disease	375 (13.7%)	233 (16.7%)	195 (24.3%)	<0.001
Cerebrovascular disease	346 (12.6%)	245 (17.6%)	162 (20.2%)	<0.001
HbA_{1c} (mmol/l)	36.1 (2.3)	41.8 (1.9)	54.7 (13.6)	<0.001
HbA_{1c} (%)	5.5% (0.2%)	6.0% (0.2%)	7.2% (1.3%)	<0.001
MMSE score	27.2 (2.6)	26.9 (2.6)	26.8 (2.7)	<0.001
FAB score	16 (14–17)	16 (14–17)	16 (14–17)	<0.001
RBANS	86.7 (17.2)	83.9 (16.9)	82.7 (15.6)	<0.001
Index I score (immediate memory)	90.5 (17.8)	88.8 (17.7)	86.0 (16.9)	<0.001
Index II score (visual spatial)	89.5 (20.3)	86.0 (19.3)	86.6 (19.4)	<0.001
Index III score (language)	90.8 (13.0)	89.4 (13.8)	88.7 (12.7)	<0.001
Index IV score (Attention)	89.5 (17.5)	86.8 (17.5)	85.2 (17.3)	<0.001
Index V score (delayed memory)	87.03 (18.6)	85.7 (18.7)	85.2 (17.6)	0.01
Known diabetes ($n = 603$)				
Diabetes duration (years)			9.3 (6)	
Diabetes treatment			362 (55.2%)	
Metformin			218 (33.3%)	
Sulfonylurea			30 (4.6%)	
Thiazolodinedione			8 (1.2%)	
GLP−1 Analogue			35 (5.4%)	
DPP−4 inhibitor			117 (17.9%)	

Note: Data presented as means with standard deviations in addition to proportions with percentages. Between-group differences were analysed using ANOVA, Kruskal–Wallis and Chi-square tests as appropriate.

Abbreviations: DPP-4, Dipeptidylpeptidase 4; FAB, Frontal Assessment Battery; GLP-1, Glucagon-Like Peptide 1; HbA_{1c}, glycated haemoglobin; MMSE, Mini-Mental State Examination; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

TABLE 2 Relationship between HbA_{1c} (in %) and Cognitive Function in the TUDA Cohort

	Model 1		Model 2		Model 3		Model 4	
	β (CI)	*p*	β (CI)	*p*	β (CI)	*P*	β (CI)	*p*
MMSE								
HbA_{1c} (%/)	−0.12 (−0.21, −0.03)	0.02	−0.09 (−0.18, 0.01)	0.04	−0.05 (−0.14, 0.04)	0.24	−0.06 (−0.14, 0.04)	0.24
$_{ln}$FAB								
HbA_{1c} (%)	−0.01 (−0.02, −0.01)	0.001	−0.01 (−0.02, −0.00)	0.005	−0.01 (−0.01, −0.00)	0.04	−0.01 (−0.02, −0.00)	0.04
RBANS total								
HbA_{1c} (%)	−1.56 (−2.15, −0.96)	<0.001	−1.14 (−1.68, −0.60)	<0.001	−0.89 (−1.43, −0.34)	0.001	−0.66 (−1.19, −0.13)	0.02
RBANS index I (immediate memory)								
HbA_{1c} (%)	−1.87 (−2.48, −1.26)	<0.001	−1.31 (−1.90, −0.72)	<0.001	−0.88 (−1.47, −0.29)	0.004	−0.88 (−1.48, −0.29)	0.004
RBANS index II (visual-spatial)								
HbA_{1c} (%)	−1.14 (−1.83, −0.43)	0.002	−1.08 (−1.71, −0.43)	0.001	−0.77 (−1.42, −0.13)	0.02	−0.87 (−1.42, −0.13)	0.02
RBANS index III (language)								
HbA_{1c} (%)	−0.72 (−1.17, −0.26)	0.002	−0.70 (−1.13, −0.26)	0.002	−0.48 (−0.93, −0.04)	0.03	−0.48 (−0.93, −0.04)	0.03
RBANS index IV (attention)								
HbA_{1c} (%)	−1.68 (−2.30, −1.06)	<0.001	−1.22 (−1.78, −0.66)	<0.001	−0.89 (−1.49, −0.32)	0.002	−0.89 (−1.45, −0.32)	0.01
RBANS index V (delayed memory)								
HbA_{1c} (%)	−0.71 (−1.36, −0.07)	0.03	−0.35 (−0.97, 0.28)	0.28	0.16 (−0.48, 0.79)	0.63	0.16 (−0.48, 0.79)	0.63

Note: Linear models are presented both unadjusted (Model 1) and with adjustments made for age, sex, body mass index, level of education (years) and a family history of dementia (Model 2). Model 3 further adjusts for hypertension, hyperlipidaemia, cardiovascular and cerebrovascular disease. Model 4 further adjusts for alcohol and smoking status as well as screened anxiety and depression symptoms.

Abbreviations: $_{ln}$FAB, log-transformed Fontal Assessment Battery; MMSE, Mini-Mental State Examination; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

TABLE 3 Relationship between diabetes status and cognitive function in the TUDA cohort

	Model 1		Model 2		Model 3		Model 4	
	β (CI)	*p*	β (CI)	*p*	β (CI)	*p*	β (CI)	*p*
MMSE								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−0.28 (−0.45, −0.11)	0.001	−0.00 (−0.16, 0.16)	0.98	0.02 (−0.14, 0.18)	0.83	0.03 (−0.14, 0.19)	0.68
Diabetes	−0.31 (−0.52, −0.11)	0.003	−0.15 (−0.35, 0.05)	0.14	−0.09 (−0.29, 0.11)	0.39	−0.07 (−0.27, 0.12)	0.53
$_{ln}$FAB								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−0.03 (−0.04, −0.01)	0.001	−0.002 (−0.02, 0.01)	0.73	−0.00 (−0.02, 0.01)	0.82	0.00 (−0.01, 0.02)	0.98
Diabetes	−0.03 (−0.05, −0.01)	<0.001	−0.02 (−0.04, −0.00)	0.03	−0.02 (−0.04, 0.00)	0.06	−0.02 (−0.03, 0.00)	0.11
RBANS total								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−2.78 (−3.88, −1.67)	<0.001	−0.77 (−1.539, 0.587)	0.12	−0.58 (−1.55, 0.41)	0.25	−0.34 (−1.30, 0.63)	0.49
Diabetes	−4.06 (−5.42, −2.70)	<0.001	−2.26 (−3.49, −1.04)	0.001	−1.63 (−2.87, −0.39)	0.01	−1.23 (−2.46, 0.00)	0.05
RBANS index I (immediate memory)								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−1.76 (−2.90, −0.63)	0.002	−0.61 (−1.69, 0.47)	0.27	−0.40 (−1.49, 0.68)	0.47	−0.24 (−1.31, 0.83)	0.66
Diabetes	−4.58 (−5.96, −3.20)	<0.001	−2.57 (−3.90, −1.22)	0.001	−1.91 (−3.28, −0.55)	0.01	−1.65 (−3.01, −0.29)	0.02
RBANS index II (visual spatial)								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−3.51 (−4.80, −2.21)	<0.001	−1.27 (−2.43, −0.11)	0.03	−1.17 (−2.33, −0.01)	0.05	−0.95 (−2.10, 0.20)	0.11
Diabetes	−2.94 (−4.53, −1.04)	<0.001	−2.33 (−3.78, −0.89)	0.002	−2.00 (−3.48, −0.53)	0.01	−1.71 (−3.18, −0.25)	0.02
RBANS index III (language)								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−1.41 (−2.25, −0.56)	0.001	−0.53 (−1.34, 0.27)	0.19	−0.48 (−1.28, 0.32)	0.25	−0.39 (−1.19, 0.41)	0.34
Diabetes	−2.13 (−3.17, −1.10)	<0.001	−1.52 (−2.52, −0.52)	0.003	−1.29 (−2.29, −0.27)	0.01	−1.10 (−2.11, −0.08)	0.03
RBANS index IV (attention)								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−2.66 (−3.80, −1.52)	<0.001	−0.65 (−1.67, 0.37)	0.21	−0.53 (−1.55, 0.49)	0.31	−0.33 (−1.34, 0.68)	0.52

(Continues)

TABLE 3 (Continued)

	Model 1		Model 2		Model 3		Model 4	
	β (CI)	*p*	β (CI)	*p*	β (CI)	*p*	β (CI)	*p*
Diabetes	−4.39 (−5.80, −2.99)	<0.001	−2.56 (−3.84, −1.29)	0.001	−2.17 (−3.46, −0.88)	0.001	−1.84 (−3.13, −0.56)	0.01
RBANS index V (delayed memory)								
Normoglycaemic	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Prediabetes	−1.42 (−2.62, −0.21)	0.02	0.17 (−0.97, 1.31)	0.77	0.43 (−0.71, 1.57)	0.46	0.61 (−0.52, 1.75)	0.29
Diabetes	−1.91 (−3.38, −0.44)	0.01	−0.17 (−1.58, 1.25)	0.82	0.61 (−0.84, 2.05)	0.41	0.93 (−0.51, 2.36)	0.21

Note: Linear models are presented both unadjusted (Model 1) and with adjustments made for age, sex, body mass index, level of education (years) and a family history of dementia (Model 2). Model 3 further adjusts for hypertension, hyperlipidaemia, cardiovascular and cerebrovascular disease. Model 4 further adjusts for alcohol and smoking status as well as screened anxiety and depression symptoms.

Abbreviations: $_{ln}$FAB, log-transformed Fontal Assessment Battery; MMSE, Mini-Mental State Examination; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

In the first instance, the association was tested unadjusted (Model 1) and then followed by adjustment for age, sex, body mass index, an education level (age finished formal education), family history of dementia and study subcohort (Model 2). Further adjustment accounted for cardiovascular risk factors which may impact on the relationship between HbA_{1c} and cognition including hyperlipidaemia, hypertension, a history of cardiovascular (composite of either ischaemic heart disease, previous myocardial infarction, atrial fibrillation or congestive cardiac failure) or cerebrovascular disease (composite of either previous transient ischaemic attack or previous stroke) (Model 3). Models were further adjusted for probable anxiety and depression in addition to alcohol use and smoking status (Model 4).

For all linear analysis, residual vs fit plots were examined to ensure normal distribution of residuals and variance inflation factors computed for linear models to examine for multicollinearity. Results for all models are reported as beta coefficients (β) with the corresponding 95% confidence interval (CI).

3 | RESULTS

3.1 | Participant characteristics and diabetes prevalence

Of 5186 participants, those with missing data for HbA_{1c} ($n = 171$) and cognitive assessment ($n = 77$) were excluded and the remaining 4938 participants included in the current analysis (mean age: 74.1 ± 8.3 years; 66.9% female). Participants with missing data were significantly younger (71.7 ± 7.5 years, $t = -3.71$, $p < 0.001$) with a lower BMI (26.9 ± 5.8 vs. 27.9 ± 5.4, $t = -2.4$, $p = 0.01$) with a greater proportion of females (75% female; $\chi^2 = 7.1$, $p = 0.01$) than included individuals. The prevalence of diabetes was 16.3% ($n = 803$) with prediabetes present in 28.3% ($n = 1395$) as per the above criteria. Of those with diabetes, 81.3% ($n = 653$) had a self-reported diagnosis with 18.7% ($n = 150$) diagnosed based on HbA_{1c}. No participants with a normal HbA_{1c} and without a diagnosis of diabetes were taking glucose lowering medications. Detailed characteristics of participants by diabetes status are presented in Table 1.

Of those with diabetes, 55.2% (362/653) were prescribed metformin, 33.3% (218/653) a sulfonylurea, 4.6% (30/653) a thiazolidinedione, 1.2% (8/653) a glucagon-like peptide 1 analogue, 5.4% (35/653) a dipeptidylpeptidase 4 inhibitor and 17.9% (117/653) insulin. Of those with a known diagnosis of diabetes ($n = 653$), the mean duration of the disease was 9.3 ± 8.6 years. The mean HbA_{1c} of all participants with diabetes was 54.7 mmol/L (±13.5)/7.4% (±1.3) (see Table 1).

3.2 | HbA_{1c}, overall and doman-specific neuropsychological performance

Increasing HbA_{1c} was associated with significantly poorer performance (in unadjusted models) on all three cognitive measures (MMSE, FAB, RBANS) as well as on indices of I–IV on the RBANS (Table 2). While some associations were attenuated after adjustment, increasing HbA_{1c} remained significantly associated with poorer performance on the overall FAB [β: −0.01

(−0.02, −0.00) per %, $p = 0.04$] and the RBANS [β: −0.66 (−1.19, −0.13) per %, $p = 0.03$] scores in fully adjusted models. Additionally, increasing HbA_{1c} was associated with poorer performance on immediate memory [β: −0.88 (−1.48, −0.29) per %, $p = 0.004$], visuo-spatial [β: −0.77 (−1.42, −0.13) per %, $p = 0.02$], language [β: −0.48 (−0.93, −0.04) per %, $p = 0.03$] and attention [β: −0.89 (−1.45, −0.32) per %, $p = 0.01$] RBANS domains. Full results are presented in Table 2.

3.3 | Prediabetes, diabetes and cognitive performance

We further examined whether prediabetes or diabetes was associated with poorer cognitive performance compared to normoglycaemic participants. While prediabetes (vs normoglycaemia) was associated with poorer performance on the all three assessments in addition to indices I–IV of the RBANS, these associations were attenuated following robust covariate adjustment. Unadjusted, diabetes (vs. normoglycaemia) was associated with significantly poorer performance on the overall FAB [β: −0.03 (−0.04, −0.01), $p = 0.001$] and RBANS [β: −4.06 (−5.42, −2.70), $p < 0.001$] scores in addition to indices I–IV of the RBANS. While these associations were attenuated under fully adjusted models, the associations between diabetes and poorer performance on immediate memory [β: −1.65 (−3.01, −0.29), $p = 0.02$], visual-spatial [β: −1.71 (−3.18, −0.25), $p = 0.02$], language [β: −1.10 (−2.11, −0.08), $p = 0.03$] and attention [β: −1.84 (−3.13, −0.56), $p = 0.01$] domains persisted following robust covariate adjustment. Full results are given in Table 3.

4 | DISCUSSION

In the current study of nearly 5000 older adults from the TUDA study, increasing HbA_{1c} was associated with poorer overall cognitive performance on the FAB and RBANS. Additionally, increasing HbA_{1c} was significantly associated with poorer domain-specific cognitive performance on RBANS domains I (immediate memory), II (visual-spatial), III (language) and IV (attention). While diabetes was not associated with overall FAB and RBANS scores following covariate adjustment, diabetes was associated with poorer performance on immediate memory, visual-spatial, language and attention RBANS domains. These findings highlight the potential importance and value of HbA_{1c} and diabetes as a target that could be addressed in promoting optimal brain health in older adults.

To date, previous research has focussed only on the association between diabetes or prediabetes and cognitive function, with few studies specifically exploring the relationship with HbA_{1c}. Furthermore, in studies examining the association between HbA_{1c} and cognition, neuropsychological assessments have typically been fewer and less detailed than in this current study.[13–15] In one of the most detailed studies to date in this area, Zheng et al. demonstrated that HbA_{1c} concentration was inversely associated with global cognition, memory and executive function.[13] The findings of the current study are thus in line with the previous research, adding important new evidence to support the association between HbA_{1c} and cognitive performance. These findings are also in good agreement with the findings from other studies, such as those from the Health and Retirement Study (HRS) which identified a significant impact of HbA_{1c} concentrations on episodic memory, as well as studies examining the impact of HbA_{1c} on cognitive decline in older adults without diabetes.[14,15] While our findings are largely confirmatory of these previous analyses, they add further evidence to support the potential of HbA_{1c} as a modifiable risk factor to promote optimal brain health in older adults.

The current results demonstrating poorer domain-specific neuropsychological performance in those with diabetes are also consistent with previous reports that have shown the impact of diabetes on neuropsychological tests of attention and memory.[26–28] This association may be worthy of further research, particularly in younger adults with midlife diabetes who may be at risk of future cognitive decline. Both the current study and the majority of the previous research linking hyperglycaemia, diabetes and cognitive function have been undertaken in older individuals. Recent studies have demonstrated cross-sectional relationships between diabetes and tests of neuropsychological function in midlife.[29,30] Furthermore, studies should focus on HbA_{1c} in midlife and longitudinal change in specific domains of cognitive function in order to identify individuals who may be most at-risk of later decline. By excluding those with a known diagnosis of dementia, the TUDA study was designed to reflect both the normal range of cognitive function in ageing in addition to mild cognitive impairment. Thus, our sample may be biased to include individuals with better cognitive function than similarly aged individuals in more representative population studies.

One of the strengths of this study is the detailed nature of cognitive tests used. Previous studies examining the impact of HbA_{1c} on cognition have been limited by both fewer and less comprehensive cognitive testing, often relying only on global cognition measures or screening tests such as MMSE. The inclusion of a detailed neuropsychological battery of tests (using the RBANS) in the current study is a particular strength. This battery allowed

us not only to examine the relationship between HbA_{1c} and global cognition but also the association in greater detail by incorporating tests of specific cognitive domains. Furthermore, the current study was able to control for a large number of covariates and potential confounders including assessments of educational attainment, depression, anxiety and mood, and also a history of cardiovascular disease and other risk factors known to be associated with dementia risk.

The biggest limitation of the current study is the cross-sectional design, therefore no causality can be inferred from the results. Thus, the results of the current study cannot confirm whether increased HbA_{1c} results in poorer cognitive performance. Importantly, the association may vary by age and could be time- or exposure-dependent, potentially only acting as a risk factor during a particular window of susceptibility. For instance, diabetes is known to act as a risk factor for dementia in midlife, but not necessarily in later life.[29,30] Future studies are needed to assess individuals using sensitive neuropsychological tests earlier in life who would be followed up longitudinally to gauge the impact of HbA_{1c} on a cognitive decline over time.

A further limitation of the current study again centres around its cross-sectional nature. No inference can be made as to the potential influence of duration of hyperglycaemia as we have no historical data on previous HbA_{1c} or duration of undiagnosed diabetes or prediabetes. Similarly, the current study had no data on other risk factors for poorer cognition in individuals with diabetes such as albuminuria and did not consider lifestyle risk factors such as exercise and diet, which are known to be important in the promotion of optimal brain health in older adults.[6,7] Furthermore, it must be acknowledged that the effect sizes observed in the current study are rather small, particularly for the FAB. However, our findings add further evidence to the potential utility of HbA_{1c} and diabetes as an important factor in the optimal promotion of brain health in older adults, worthy of further study in a longitudinal fashion, particularly in younger and middle-aged individuals with diabetes.

5 | CONCLUSION

This study demonstrated a significant association between increasing HbA_{1c} and poorer cognitive performance in a study of nearly 5000 older adults. The results indicate that regardless of diabetes status, increasing HbA_{1c} is associated with poorer cognitive function. Importantly, these results suggest that HbA_{1c} may be a risk factor for cognitive decline in older adults and might be an appropriate target for strategies used to promote brain health.

ACKNOWLEDGEMENTS

The Trinity-Ulster-Department of Agriculture (TUDA) study was supported by government funding from the Irish Department of Agriculture, Food and the Marine and Health Research Board (under the Food Institutional Research Measure to H.M) and from the Northern Ireland Department for Employment and Learning (under its Strengthening the All-Island Research Base initiative). The authors wish to acknowledge all of the TUDA study participants. Dr Dyer additionally wishes to acknowledge the support of the Wellcome-HRB Clinical Research Facility at St James's Hospital.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ORCID

Adam H. Dyer https://orcid.org/0000-0003-1356-510X
Robert Briggs https://orcid.org/0000-0001-9585-2692

REFERENCES

1. 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.
2. Leibson CL, Rocca WA, Hanson VA, 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.
3. Knopman DS, Gottesman RF, Sharrett AR, 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.
4. 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.
5. Gottesman RF, Albert MS, Alonso A, 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.
6. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and alzheimer disease. *Nat Rev Neurol*. 2018;14:653-666.
7. Ngandu T, Lehtisalo J, Solomon A, 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.
8. 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.
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010;33(Suppl 1):S62-S69.
10. Selvin E, Steffes MW, Zhu H, et al. Glycated haemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010;362:800-811.

11. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycaemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes – memory in diabetes (ACCORD-MIND) trial. *Diabetes Care*. 2009;32(2):221-226.
12. Morris JK, Vidoni AD, Honea RA, et al. Impaired glycaemia increases disease progression in mild cognitive impairment. *Neurobiol Aging*. 2014;35(3):585-589.
13. Zheng F, Yan L, Yang Z, Zhong B, Xie W. HbA_{1c}, diabetes and cognitive decline: the english longitudinal study of ageing. *Diabetologia*. 2018;61(4):839-848.
14. Pappas C, Andel R, Infurna FJ, Seetharaman S. Glycated haemoglobin (HbA_{1c}), diabetes and trajectories of change in episodic memory performance. *J Epidemiol Community Health*. 2017;71(2):115-120.
15. Ravona-Springer R, Moshier E, Schmeidler J, et al. Changes in glycemic control are associated with changes in cognition in non-diabetic elderly. *J Alzheimers Dis*. 2012;30(2):299-309.
16. Porter K, Ward M, Hughes CF, et al. Hyperglycaemia and metformin use are associated with B vitamin deficiency and cognitive dysfunction in older adults. *J Clin Endocrinol Metab*. 2019;104(10):4837.
17. McCann A, McNulty H, Rigby J, et al. Effect of area-level socioeconomic deprivation on risk of cognitive dysfunction in older adults. *J Am Geriatr Soc*. 2018;66(7):1269-1275.
18. Ntlholang O, McCarroll K, Laird E, et al. The relationship between adiposity and cognitive function in a large community-dwelling population: data from the Trinity Ulster Department of Agriculture (TUDA) ageing cohort Study. *Br J Nutr*. 2018;120(5):1-11.
19. Moore K, Hughes CF, Hoey L, et al. B-vitamins in relation to depression in older adults over 60 years of age: the trinity ulster department of agriculture (TUDA) cohort study. *J Am Med Dir Assoc*. 2019;20(5):551-557.
20. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2020. *Diabetes Care*. 2020;43(Supp 1):S14-31.
21. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
22. Dubois B, Slachevsky A, Litvan I, et al. The FAB: a frontal assessment battery at bedside. *Neurology*. 2000;55:161-226.
23. Randolph C, Tierney MC, Mohr E, Chase TN. The repeatable battery for the assessment of neuropsychological status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998;20:310-319.
24. Radloff L, Locke B. The community mental health assessment survey and the CES-D Scale. In: Weissman M, Myers J, Ross C, eds. *Community Surveys of Psychiatric Disorders*. Rutgers University Press; 1986.
25. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361e370.
26. Moheet A, Mangia S, Seaquist ER. Impact of diabetes on cognitive function and brain structure. *Ann N Y Acad Sci*. 2015;1353:60-71.
27. Palta P, Schnieder ALC, Jan Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. *J Int Neuropsychol Soc*. 2014;20(3):28-91.
28. Koekkoek PS, Ruis C, van den Donk M, et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes – the ADDITION-Netherlands study: a cluster randomized trial. *J Neurol Sci*. 2012;214(1–2):71-77.
29. Dyer AH, McKenna L, Gamage G, et al. Cognitive performance in midlife type 2 diabetes: results from the ENBIND study. *Diabet Med*. 2021;38(6):e14412.
30. Dyer AH, McKenna L, Batten I, et al. Peripheral inflammation and cognitive performance in middle-aged adults with and without type 2 diabetes: results from the ENBIND study. *Front Aging Neurosci*. 2020;12: 605878.

How to cite this article: Dyer AH, Briggs R, Laird E, et al. Glycated haemoglobin (HbA_{1c}), diabetes and neuropsychological performance in community-dwelling older adults. *Diabet Med*. 2021;00:e14668. https://doi.org/10.1111/dme.14668