Received: 22 March 2023 | Revised: 9 June 2023 | Accepted: 18 June 2023

DOI: 10.1111/dom.15207

ORIGINAL ARTICLE

WILEY

Testing for associations between HbA1c levels, polygenic risk and brain health in UK Biobank ($N = 39\,283$)

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Funding information
UKRI Innovation-HDR-UK Fellowship, Grant/Award Number: MR/S003061/1

Abstract

Aim: To investigate whether continuous HbA1c levels and HbA1c-polygenic risk scores (HbA1c-PRS) are significantly associated with worse brain health independent of type 2 diabetes (T2D) diagnosis (vs. not), by examining brain structure and cognitive test score phenotypes.

Methods: Using UK Biobank data ($n = 39\,283$), we tested whether HbA1c levels and/or HbA1c-PRS were associated with cognitive test scores and brain imaging phenotypes. We adjusted for confounders of age, sex, Townsend deprivation score, level of education, genotyping chip, eight genetic principal components, smoking, alcohol intake frequency, cholesterol medication, body mass index, T2D and apolipoprotein (*APOE*) e4 dosage.

Results: We found an association between higher HbA1c levels and poorer performance on symbol digit substitution scores (standardized beta [β] $= -0.022$, $P = .001$) in the fully adjusted model. We also found an association between higher HbA1c levels and worse brain MRI phenotypes of grey matter (GM; fully-adjusted $\beta = -0.026$, $P < .001$), whole brain volume ($\beta = -0.072$, $P = .0113$) and a general factor of frontal lobe GM ($\beta = -0.022$, $P < .001$) in partially and fully adjusted models. HbA1c-PRS were significantly associated with GM volume in the fully adjusted model ($\beta = -0.010$, $P = .0113$); however, when adjusted for HbA1c levels, the association was not significant.

Conclusions: Our findings suggest that measured HbA1c is associated with poorer cognitive health, and that HbA1c-PRS do not add significant information to this.

KEYWORDS
cohort study, population study, type 2 diabetes

1 | INTRODUCTION

Dementia is a major public health concern of the 21st century, with up to 50 million people living with dementia worldwide, and that number is projected to increase to 150 million by 2050.[1] The prediction of dementia remains elusive, and there is a significant medical demand to identify risk factors and diagnostic methods that can improve the understanding of the disease. There is a growing body of literature that recognizes the association between hyperglycaemia, type 2 diabetes (T2D) and poorer performance on tests of cognitive abilities, as well as poorer

brain health, as measured by MRI scans. For example, a meta-analysis of 122 studies reported that individuals with T2D had a 1.25-1.91 times higher risk of cognitive disorders like dementia.[2] However, there have been instances where no association was reported between diabetes and accelerated cognitive decline in individuals ($n = 596$).[3]

Generally, vascular pathologies are proposed as a potential pathway to dementia, this may pertain to any/all of promotion/inhibited clearance of amyloid, atherosclerosis-related hypoxia or general dysregulation of heart–brain linkage.[4] In people with diabetes, insulin resistance may lead to dysregulation of cerebral glucose metabolism, and MRI has revealed deficits in hippocampal functions mediated by hyperglycaemia.[5] Additionally, inflammation and deficits in the hypothalamic–pituitary–adrenal axis may accelerate cognitive decline.[5] It is unclear if HbA1c is a proxy for poorer cardiometabolic health generally in this context, or if it may be a direct and isolated causal variable toward poorer brain health.

HbA1c provides information regarding the average blood glucose of an individual over the last 2-3 months and is a useful screening tool for diabetes; an HbA1c level of more than 6.5% is a diagnostic for diabetes, and it is a more meaningful measurement of an individual's health, because it remains consistent over a few months compared with blood glucose levels, which fluctuate on a daily basis.[6] HbA1c was found to have a vascular pathway-independent relationship with dementia in individuals with undiagnosed diabetes.[7] There are prior studies showing association between HbA1c and poorer cognitive/brain health; however, these tend to be in comparatively small sample sizes, in people with diabetes only, using cognitive screening tools (rather than sensitive, normative-range tests) and/or not including concurrent measures of structural brain health.[8–10]

Polygenic risk score (PRS) is a method of tallying 'risk' variants for various traits. Previous research has shown, for example, that an Alzheimer's disease PRS associated with non-demented brain health (cognitive scores; structure),[11] that is, in the absence of clinical onset. A heightened genetic risk estimate for HbA1c may be a useful proxy for average lifetime exposure. Genetic influences on HbA1c levels are more stable over the lifetime than absolute measurements of HbA1c. Earlier identification of individuals at risk could be implemented based on common genetic variation before the changes in absolute HbA1c levels or loss of glucose control influence brain health.

The UK Biobank is a large population cohort consisting of more than 500 000 participants; it contains baseline medical, cognitive, socioeconomic and genetic data for the majority of participants, as well as brain imaging data for more than 30 000 participants.[12] The aim of the current study was to investigate whether HbA1c levels and HbA1c-PRS add any meaningful information to the association reported between T2D diagnosis and worse brain health in the UK Biobank cohort.

2 | METHODS

2.1 | Study design and participants

The UK Biobank is a large prospective cohort study consisting of more than 500 000 participants who attended assessment centres to undergo several physical, sociodemographic and medical assessments.[12] In 2014, a subgroup of 100 000 participants were invited for MRI assessments, which are currently ongoing. As of June 2022, MRI data were available for 39 283 participants who attended the MRI assessment centres in Newcastle, Cheadle and Reading with identical protocols. The given project was conducted under UK Biobank application ID 17689 (PI: Lyall).

2.2 | Ethics statement

This study was a secondary data analysis. It was conducted under generic approval from the NHS National Research Ethics Service (approval letter dated 29 June 2021, Ref 21/NW/0157). The UK Biobank is an open access resource that is available to all researchers upon verification from the UK Biobank (http://www.ukbiobank.ac.uk/). All participants in the study provided written informed consent before data collection.[12]

2.3 | HbA1c measurements

HbA1c was measured by the UK Biobank using high-performance liquid chromatography analysis on a Bio-Rad VARIANT II Turbo (measured in mmol/mol).[13] These measurements occurred twice for the purposes of this study - at baseline (2006-2010) and then repeat assessment (on average 4 years later), and when imaging began separately in 2014 (where HbA1c data is not yet available).

2.4 | Imaging data

The study identified brain imaging phenotypes of interest *a priori*, which have previously been linked with cognitive decline related to age or have been reported to be affected in dementia. These outcome measures included white matter (WM), grey matter (GM), white matter hyperintensity (WMH), whole brain volume and overall hippocampal volume.[11] The study also considered general fractional anisotropy (gFA),[14] general factor for mean diffusivity (gMD)[15] and general factor for frontal lobe GM (gFrontal),[16] and these were constructed using principal components analysis by a method described previously.[15] GM and WM volumes were adjusted for skull size and converted to z- scores for interpretation and analysis (i.e. on a per standard deviation [SD] scale). Higher values on WMH and gMD reflect worse health, whereas all other values are such that higher values are healthier.

A 3-T Siemens scanner was used to collect the MRI data; the tissue volumes were derived by the UK Biobank and are used here as image-derived phenotypes. All brain imaging data underwent quality checks by UK Biobank.[17] Further details about MRI data collection and protocols can be found at https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf and https://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf.

2.5 | Cognitive data

The cognitive measures used in the analysis included fluid intelligence ($n = 36\,232$), matrix completion ($n = 26\,450$), symbol digit substitution ($n = 26\,459$), total trail making (TMT) (A + B) ($n = 25\,782$) and the reaction time (RT) ($n = 36\,301$). Most of the cognitive phenotypes were measured as tasks using the computerized version of previously validated cognitive tests.[18] These tasks are MRI specific and have mostly exhibited a good level of reliability and validity.[19] Cognitive test Ns vary slightly because some tests were introduced after the scanning assessment had begun.

2.6 | Covariates

Townsend deprivation indices were derived using the residential postcodes of the participants.[20] The Townsend deprivation index provides information regarding the socioeconomic deprivation of an individual and is based on data collected from car ownership, household overcrowding, owner occupation status and employment status. A higher score on the Townsend deprivation index means a higher level of socioeconomic deprivation. The education level of the participants was divided into whether they had completed a degree or not. We used eight UK Biobank genetic principal components (GPCs).[21] Smoking was coded as ever (vs. never). Alcohol intake frequency was coded on a scale of 0-6, with 1 being never, 6 being almost daily and 0 for unanswered (which was rare; < 5%). Body mass index (BMI) was calculated by the UK Biobank using the equation: weight (measured in kg)/(height [measured in metres])^2. The participants self-reported yes or no in response to the question 'Has a doctor ever told you that you have diabetes?', and where previous research has shown that the vast majority of participants are probable to have T2D rather than type 1 diabetes, with diagnosis after the age of 10 years.[22] In terms of medication, participants self-reported 'Do you regularly take any of the following medications?' (for cholesterol; for blood pressure; insulin; hormone replacement; oral contraceptive), and we coded this into cholesterol versus not, and insulin versus not.

2.7 | Genotyping and quality control

For approximately 50 000 participants in the UK Biobank, genotyping was performed by Affymetrix through a bespoke BiLEVE Axion array, and for the other 450 000 participants in the UK Biobank, genotyping was conducted using the Affymetrix UK Biobank Axiom array. The UK Biobank used 1000 genomes phase 3 and UK10K reference panels to conduct imputation: https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/impute_ukb_v1.pdf. Participants were excluded if they were missing more than 10% of the single nucleotide polymorphisms (SNPs) used to create the score, missing more than 10% of the whole genetic data, their self-reported sex did not match their genetically determined sex, they had purported sex chromosome aneuploidy, were heterozygosity outliers or were not in the European ancestry subset of the UK Biobank. *APOE* e4 genotype dosage was measured using two SNPs: rs7412 and rs429358. *APOE* e4 genotype presence was included because of its previously reported relationship with structural phenotypes of the brain.[23]

2.8 | Polygenic risk score calculation

SNPs were identified from an independent (i.e. the UK Biobank was not included in the analysis) trans-ancestry meta-analysis of genome-wide association studies (GWAS) using a total of 131 datasets, where the summary statistics from only the European ancestry were used.[24] This means that HbA1c-PRS were constructed from non-UK Biobank participants. To select SNPs for the score, the most significant SNP (i.e. with the lowest *P* value) from each genome-wide significant region ($P < 5 \times 10^{-8}$) from the meta-analysis was selected. Only non-ambiguous SNPs were selected for the score. SNPs were checked for strand alignment and had to have an imputation score of less than 0.8. SNP effects were weighted by their reported coefficient.[24] This left 43 SNPs to make the score. The PRS were calculated using plink –score with no-mean-imputation.[25]

2.9 | Statistical analysis

All the assumptions were checked for by visualizing the normality and homoscedasticity of data, and the variables exhibiting non-normal distributions were log-transformed. RT, WMH and TMT were log-transformed because they did not exhibit normal distributions. The scores on the cognitive tests and the brain MRI phenotype volumes were converted to z-scores for analysis (i.e. beta = 1 means a 1 SD difference per change in outcome unit).

First, we used HbA1c (converted to z-scores, i.e. where associations reflect an ~35 mmol/mol difference) measurement levels as the predictor variable and tested the association between HbA1c levels and the outcome measures described above using multiple linear regression models. This was followed by using HbA1c-PRS as the predictor variable in place of baseline HbA1c measurements, and we tested for the association between HbA1c-PRS and the outcome measures described above using multiple linear regression models. Finally, we included both HbA1c and HbA1c-PRS in a multivariate model estimate to test their independent effects. R studio and JASP were used to carry out the data analysis.

2.9.1 | Models

The minority of variables with missing values with missing data (namely, selected 'did not know' or 'choose not to answer') (< 5%) were removed. We used two models: partially adjusted and fully adjusted. In the partially adjusted model, we controlled for age (at MRI) of the participants, sex, eight UK Biobank GPCs and

TABLE 1 Descriptive statistics

Characteristic	Total	Female	Male
n	39 283	20 150	19 133
Mean (SD) age at MRI (y)	64.34 (7.68)	63.61 (7.54)	65.12 (7.76)
Mean (SD) Townsend score	−2.009 (2.64)	−1.96 (2.64)	−2.05 (2.65)
Mean (SD) BMI (kg/m^2)	26.57 (4.44)	26.12 (4.81)	27.04 (3.97)
Mean (SD) HbA1c measurement (mmol/mol)	35.044 (5.14)	34.81 (4.62)	35.28 (5.62)
Participants who reported a T2D diagnosis	2093 (5.3%)	731 (3.6%)	1362 (7.1%)
APOE e4 genotype dosage (expressed as percentage 0%/1%/2%)	73.7%/23.9%/2.3%	(71%/23%/2%)	(72%/22%/2%)
Percentage of participants with a degree	44.8%	42.7%	46.9%
Cholesterol medication (yes/no)	3182 (8.1%)	3182 (15.9%)	0 (0%)
Smoking history (ever vs. never)	14554 (37.4%)	6703 (33.6%)	7.851 (41.4%)
College/university degree vs. not	17599 (44.9%)	8609 (42.8%)	8990 (47.1%)
Alcohol intake			
Daily or almost daily	6795 (17.4%)	2745 (13.7%)	4050 (21.31%)
Three or four times per week	11300 (29%)	5123 (25.6%)	6177 (32.5%)
Once or twice per week	10322 (26.5%)	5433 (27.2%)	4889 (25.7%)
One to three times per month	4458 (11.4%)	2683 (13.4%)	1775 (9.3%)
Special occasions only	3818 (9.8%)	2616 (13.1%)	1202 (6.3%)
Never	2313 (5.9%)	1399 (7%)	914 (4.8%)

Abbreviations: BMI, body mass index; T2D, type 2 diabetes.

genotyping chip. In the fully adjusted model, we additionally controlled for Townsend deprivation score, level of education, smoking, alcohol intake frequency, cholesterol medication, BMI, diabetes and *APOE* e4 dosage. In a supplementary analysis, we also adjusted for HbA1c values in the fully adjusted model (Tables S1 and S2).

3 | RESULTS

3.1 | Descriptive statistics

In $N = 39\,283$, the mean age was 64.34 (SD 7.68) years. The descriptive statistics are provided in Table 1. In $N = 10\,984$ participants with HbA1c measured twice at baseline as well as at repeat assessment (on average, 4 years later at a distinct, non-imaging visit), the Pearson r correlation was $r = 0.77$ ($P < .001$), indicating good stability. All participants who self-reported insulin medication also reported a doctor's diagnosis of diabetes.

3.2 | Cognitive function

There were statistically significant associations between observational HbA1c measurements (converted to z-scores) and fluid intelligence, matrix completion, poorer log RT, log of TMT and symbol digit substitution scores for the partially adjusted model, although the effect sizes were small, ranging from 0.018 to 0.051 SDs (Table 2; per one-SD difference in HbA1c). For the fully adjusted model, only symbol digit substitution had a significant association with HbA1c measurements, although the effect size was small ($\beta = -0.02$; Table 2). Expressed as unstandardized betas this was also −0.02 (i.e. per one-unit increase in HbA1c was associated with a −0.02 lower average raw score). By contrast, there were no significant associations between any HbA1c-PRS and cognitive functions (Table 2).

3.3 | Brain imaging

As shown in Table 3, there were significant associations between HbA1c measurements and GM volume, whole brain volume, log WMH volume, overall hippocampal volume, gFA, gMD and gFrontal in the partially adjusted model; however, the effect sizes were small (ranging from 0.020 to 0.074 SDs). In the fully adjusted model, HbA1c was associated with GM volume, whole brain volume and gFrontal (ranging from 0.022 to 0.072 SDs per SD of HbA1c; Table 3). As can be seen from Table 3, for the partially adjusted model, HbA1c-PRS exhibited a significant association with total GM volume with a small effect size ($\beta = 0.0099$); and similarly for the fully adjusted model, HbA1c-PRS exhibited a significant association with total GM volume with a small effect size ($\beta = 0.01$).

Expressed as unstandardized betas per unit of HbA1c, the above significant fully adjusted effect sizes were, for HbA1c: Symbol digit

TABLE 2 Cognitive functions as outcomes of HbA1c measurements and HbA1c-PRS (converted to z-scores)

	HbA1c model				HbA1c-PRS model			
	Partially adjusted model		Fully adjusted model		Partially adjusted model		Fully adjusted model	
Variable	Standardized beta	*P* value	Standardized beta	*P* value	Standardized beta	*P* value	Standardized beta	*P* value
Fluid intelligence/reasoning score	**−0.018**	**<.001***	0.0099	.121	−0.00697	.18032	−0.0079	.121
Matrix completion score	**−0.024**	**<.001***	−0.005	.497	−0.0073	.2153	−0.0046	.4344
Log reaction time (ms)	**0.024**	**<.001***	0.0071	.258	−0.0034	.4865	−0.006	.206
Log of total trail making score	**0.018**	**.003***	0.004	.57	0.004	.494	0.0069	.253
Symbol digit substitution score	**−0.051**	**<.001***	**−0.022**	**.00129***	−0.0017	.748	0.0014	.793

Note: Models are partially adjusted for age (at MRI), sex, eight UK Biobank GPCs and genotyping chip; and are fully adjusted for sex, age, Townsend deprivation score, level of education, genotyping chip, eight UK Biobank GPCs, smoking, alcohol intake frequency, cholesterol medication, BMI, whether the participant had diabetes at the time of assessment and *APOE* e4 dosage. Bold/* = significant at nominal $P < 0.05$.
Abbreviations: BMI, body mass index; GPCs, genetic principal components; PRS, polygenic risk scores.

TABLE 3 MRI volumetric measures as outcomes of HbA1c measurements and HbA1c-PRS (converted to z-scores)

	HbA1c model				HbA1c-PRS model			
	Partially adjusted model		Fully adjusted model		Partially adjusted model		Fully adjusted model	
Variable	Standardized beta	*P* value	Standardized beta	*P* value	Standardized beta	*P* value	Standardized beta	*P* value
Total grey matter volume adjusted for skull size	**−0.059**	**<.001***	**−0.026**	**7.27 x10^{-07}***	**−0.0099**	**.0158***	**−0.01**	**.0113***
Total white matter volume adjusted for skull size	−0.004	.497	−0.0089	.185	−0.0063	.2299	−0.0055	.309
Whole brain volume adjusted for skull size	**−0.074**	**.002***	**−0.072**	**.0113***	−0.027	.2233	−0.028	.2153
Log WMH volume	**0.049**	**<.001***	0.0099	.1083	−0.002	.6699	0.003	.535
Overall hippocampal volume	**−0.036**	**<.001***	−0.0109	.099	−0.0037	.4693	−0.0017	.744
General fractional anisotropy	**−0.033**	**<.001***	−0.0099	.1583	0.0025	.6444	0.0033	.56
General factor of mean diffusivity	**0.02**	**<.001***	0.0077	.256	−0.0022	.6735	−0.0026	.6355
General factor of frontal lobe grey matter	**−0.043**	**<.001***	**−0.022**	**.000267***	−0.0087	.063	−0.0086	.076

Note: Models are partially adjusted for age (at MRI), sex, eight UK Biobank GPCs and genotyping chip; and are fully adjusted for sex, age, Townsend deprivation score, level of education, genotyping chip, eight UK Biobank GPCs, smoking, alcohol intake frequency, cholesterol medication, BMI, whether the participant had diabetes at the time of assessment and *APOE* e4 dosage. HbA1c-PRS model: * = significant $P < .05$. Bold/* signifies $P < 0.05$.
Abbreviations: BMI, body mass index; GPCs, genetic principal components; PRS, polygenic risk scores; WMH, white matter hyperintensity.

substitution (−0.023 lower score), GM volume (−250.46 mm^3), whole brain volume (−1081.54 mm^3) and gFrontal (−0.004 SDs); and for HbA1c-PRS, GM (−515.71 mm^3 per SD of polygenic risk).

3.4 | Multivariate estimates

When we included observational HbA1c and HbA1c-PRS in the same model, there were no independent significant associations reported between HbA1c-PRS and any variables (i.e. there was no evidence of a significant effect beyond that of measured HbA1c).

3.5 | Interactions

We tested for significant interactions between HbA1c (observational and PRS) and T2D. There were significant interactions for GM ($P = .006$), WM ($P = .009$), gMD ($P = .001$) and gFrontal ($P = .001$).

Analyses were therefore stratified by T2D no/yes status. There were broadly similar effects of HbA1c for GM (non-T2D group HbA1c $\beta = -0.01$, $P = .022$ vs. T2D group $\beta = -0.09$, $P < .001$), whereas for WM the HbA1c association was in the T2D group only ($\beta = -0.07$, $P = .012$) and was null in the non-T2D group ($P = .448$). For gMD, the magnitude was larger in the T2D group, but was ultimately non-significant in each group (non-T2D $\beta = -0.01$, $P = .216$ vs. T2D $\beta = 0.05$, $P = .066$). Finally, for gFrontal, HbA1c had a deleterious association in the non-T2D group only ($\beta = -0.03$, $P < .001$ vs. T2D $P = .427$). There were no interactions between HbA1c-PRS and T2D status (all $P > .05$).

3.6 | Sensitivity analysis

When we excluded all T2D cases outright, the results were very similar to controlling for it. We further corrected significant findings for additional potential brain health risk factors: history of stroke, high blood pressure and depression. The findings were unchanged and differences in effect size were to the third decimal point only.

4 | DISCUSSION

4.1 | Overview

The aim of the current study was to investigate whether HbA1c, and separately, HbA1c-PRS, are associated with worse brain health independent of the well-established links between clinical diabetes and worse brain health (including cognitive and brain structural phenotypes). There is limited research with a large sample that follows a single standard protocol for brain imaging. To this end, the UK Biobank dataset with imaging data for more than 30 000 participants is a significant advancement. This study found that baseline HbA1c was associated with subsequent MRI volumes of GM, whole brain, total hippocampal volume and WMH volumes, as well as gFA, gMD and gFrontal in the partially adjusted model; however, in the fully adjusted model, only GM volume, whole brain volume and gFrontal exhibited a significant averse association with Hba1c. Additionally, HbA1c-PRS were significantly associated with GM volume specifically (in all models).

This study also found that HbA1c measurements from baseline are significantly associated with scores on cognitive test scores (completed at imaging), including fluid intelligence, matrix completion, RT, trail making and symbol digit substitution tests in the partially adjusted model; however, only symbol digit substitution was significant in the fully adjusted model. HbA1c-PRS did not show any such significant relationships. Taken together, these results suggest that HbA1c measurements may be able to indicate early signs of worse brain health before major cognitive impairment; however the use of HbA1c-PRS does not significantly contribute to this. In general, effect sizes and magnitudes were comparatively small, approximately 0.1 SDs difference per SD of HbA1c (itself approximately 35 units mmol/mol).

4.2 | Interpretation

The significant associations reported between HbA1c baseline measurements and poorer performance on tests of cognitive abilities and different brain MRI phenotypes corroborates the association reported between diabetes and poorer brain health. Further, as suggested by previous research, HbA1c levels can be used a biomarker to potentially contribute to the prevention cognitive decline.[26] However, HbA1c-PRS do not add much meaningful information to the relationship reported between T2D and poorer brain health, suggesting that standard clinical measurement for this approach would be sufficient. While we do not suggest changing clinical guidelines explicitly on the basis of this report, management of HbA1c levels (in people with diabetes or not) should be a priority for the maintenance of better cognitive health.

In a similar study by Garfield et al.,[27] using bidirectional Mendelian randomization (MR) analysis, no association was reported between HbA1c SNPs and hippocampal volume, nor WMH, which is consistent with our study. However, their study did not consider any other brain MRI phenotypes, which may be why Garfield et al. reported null results compared with significant results for GM in the current study. In the same study, Garfield et al. also reported no association between RT and HbA1c MR analysis, which is consistent with results in the current study. The current study found that HbA1c-PRS were significantly associated with total GM volume, which is consistent with previous findings showing smaller GM volumes for higher HbA1c values.[28] However, it should be noted that lower volumes in this study may not be indicative of atrophy or neurodegeneration, because the only measurement was cross-sectional measures of brain phenotypes. HbA1c-PRS did not exhibit a significant association with other brain MRI phenotypes, which may be attributed to the fact that genetic associations are generally small in effect. The UK Biobank imaging data may not be statistically powered enough to detect meaningful effect sizes. This warrants the need for further research with larger datasets. It is possible that the HbA1c/brain health association is significantly more complex than the linear findings reported here: it may differ non-linearly by age, sex, HbA1c levels and/or the presence of conditions like T2D.

4.3 | Limitations

The current study may be limited by several factors. The genetic association found in the study may be limited by the fact that there is no standard methodology for calculating genetic risk scores efficiently, with several different approaches having different accountings for linkage disequilibrium, beta shrinkage and GWAS P value thresholding.[11] While this study uses genetic risk scores as a proxy for lifetime exposure to higher HbA1c, it is fundamentally cross-sectional, with associated limitations regarding causality. The HbA1c-PRS is liable to include some degree of pleiotropy (i.e. they are not isolated to HbA1c levels alone).

Participants in the UK Biobank have a lower-than-average frequency of physical health conditions, are more highly educated and live in less socioeconomically deprived areas.[29] Psychotropic medication, or the use of benzodiazepines, was not controlled for in the current study; however, this may influence cognitive test scores.[30] It is possible we have underestimated T2D in the sample based on self-report, where additional NHS records may be informative.

MRI is a labour-intensive process and may lead to a sample bias, because stents and pacemakers are a contraindication to MRI, which may have led to a generally healthy population being scanned.[31] We used a comparatively small number of highly significant SNPs in our genetic risk score, where a more liberal inclusion threshold may yield different results. Another caveat in the UK Biobank cohort is the lack of diversity, thus the findings of this study cannot be extrapolated to all populations.[32] Given that non-white groups are at a higher risk of diabetes in contrast to people with white ancestry,[33] cohort studies of more diverse ancestries are necessary to assess the prevalence and biological pathways related to diabetes and dementia.

5 | CONCLUSIONS

In conclusion, higher HbA1c measurements are associated with differences in brain structure and cognitive abilities in UK Biobank participants, but HbA1c-PRS did not add significant information to this. This suggests that HbA1c measurements could be used in the future along with other assessments to identify individuals with risk of cognitive impairment and decline. It also suggests that keeping glucose levels lower in diabetes could help to mitigate against cognitive decline.

AUTHOR CONTRIBUTIONS

Concept: SR, DML, RJS and NS. Analysis: SR, DML and JW. Write-up: SR and DML. Supervision: DML.

ACKNOWLEDGEMENTS

This research was conducted using the data provided by the UK Biobank resource; we are grateful to the participants of the UK Biobank cohort.

FUNDING INFORMATION

Sanskar Ranglani was funded by University of Glasgow, School of Life Sciences Undergraduate Vacation Scholarship to undertake this research project. Rona J. Strawbridge was funded by a University of Glasgow LKAS Fellowship and a UKRI Innovation-HDR-UK Fellowship (MR/S003061/1).

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15207.

DATA AVAILABILITY STATEMENT

Data are available from the UK Biobank website for a fee via their data access procedure: https://www.ukbiobank.ac.uk/enable-your-research/register.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ranglani S, Ward J, Sattar N, Strawbridge RJ, Lyall DM. Testing for associations between HbA1c levels, polygenic risk and brain health in UK Biobank ($N = 39\,283$). *Diabetes Obes Metab*. 2023;25(11):3136-3143. doi:10.1111/dom.15207