Is glycaemia associated with poorer brain health and risk of dementia? Cross sectional and follow-up analysis of the UK Biobank

Running title: Glycaemia and brain health in the UK Biobank

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ABSTRACT

Objective: To understand the relationship across the glycaemic spectrum with incident dementia, brain structure, and cognitive decline.

Research Design and Methods: UK Biobank participants, aged 40-69 at recruitment. HbA_{1c} and diabetes diagnosis define baseline glycaemic categories. Outcomes included incident vascular dementia (VD), Alzheimer's dementia (AD), hippocampal volume (HV), white matter hyperintensity (WMH) volume, cognitive function and decline. All results are in reference to normoglycaemic individuals (HbA_{1c} 35-<42 mmol/mol).

Results: 210433 (47%), 15246 (3%), 3280 (0.7%), 20793 (5%) individuals had low HbA_{1c}, pre-diabetes, undiagnosed diabetes, and known diabetes, respectively. Pre- and known diabetes markedly increased incident VD, (hazard ratios (HR) 1.51, 95%CI=1.01;2.25 and 1.96, 95%CI=1.49;2.58, respectively), less so AD (1.18, 0.92;1.52 and 1.13 0.95,1.33), adjusting for demographic and socioeconomic variables. For VD, multivariate adjustment, driven by antihypertensives, attenuated associations, HR 1.27, 0.84;1.91 and 1.45,1.07;1.97. Pre- and known diabetes conferred elevated risks of cognitive decline (odds ratio OR 1.53, 1.02;2.29 and 1.49, 1.02;2.18, respectively). People with pre-diabetes, undiagnosed and known diabetes had higher WMH volumes (4%, 30%, 3%, respectively), and lower HV (34.51 mm^3, 11.73 mm^3 and 61.13 mm^3 respectively). People with low-normal HbA_{1c} (<35 mmol/mol) had 5% lower WMH volume and 13.6 mm^3 greater HV than normoglycaemic individuals.

Conclusions: Pre and known diabetes increase VD risks, less so AD. Excess VD risks were largely accounted for by treated hypertension. Hyperglycaemic states were associated with adverse, whereas low normal HbA_{1c} was associated with favourable brain structure compared to normoglycaemic individuals. Our findings have implications for cardiovascular medication in hyperglycaemia for brain health.

Type-2 diabetes and, more generally, hyperglycaemic states, have been associated with poorer cognitive function (such as learning and memory)(1), increased risk of dementia(2) and alterations in key brain structures, particularly the hippocampus(3). In contrast, recent evidence from a randomised crossover trial also suggests that, in people with diabetes, even modest hypoglycaemia has a detrimental effect on cognitive function(4). Thus, it is also important to explore how low levels of glycated haemoglobin (HbA_{1c}) relate to these outcomes. A previous paper explored the cross sectional association between baseline diabetes and two cognition measures in the UK Biobank (reaction time and visual memory)(5). The authors found that diabetes was associated with poorer scores on the reaction time test, but paradoxically, better scores on the visual memory test. They did not explore other outcomes or lesser glycaemic states.

Memory loss is the most conclusively reported adverse effect of hyperglycaemia on cognitive function(6). Hippocampal atrophy is a crucial feature of age-related memory loss and the hippocampus is particularly vulnerable to the neurotoxic consequences of diabetes(7). Evidence relating diabetes to the presence and progression of white matter hyperintensities is equivocal(8), but some research suggests that those with diabetes have greater volumes of white matter hyperintensities(9,10). Although there have been numerous studies in this area, the role of glycaemia in brain health across the entire glycaemic spectrum remains unclear, in particular no studies have investigated how lesser hyperglycaemic states relate to these outcomes, as most studies have focused on diagnosed diabetes only.

Thus, the aim of this study was to investigate the associations between five glycaemic states across the entire spectrum (low HbA_{1c}, normoglycaemia, pre-diabetes, undiagnosed diabetes and known diabetes) and Alzheimer's dementia (AD) risk, vascular dementia (VD) risk, baseline cognitive function and cognitive decline, hippocampal volume, and white matter hyperintensities volume in the UK Biobank. We hypothesised that there would be a U-shaped association between glycaemia and our outcomes of interest, such that those with lower and higher HbA_{1c} would have worse outcomes than those with normal glycaemic levels.

RESEARCH DESIGN AND METHODS

Sample

Full details of the UK Biobank (UKB) cohort have been described elsewhere(11). Briefly, UKB consists of ~500,000 men and women from the general UK population between 2006-

2010, aged between 40 and 69 years of age at baseline. Participants have detailed phenotype data on physical (subjective and objective), mental and lifestyle measures, as well as linkages to routinely collected data (e.g. deaths, hospital admissions and cancer registers). Supplemental Figure S1 depicts our study design.

Type-2 diabetes mellitus (diabetes)

Exposure status was defined using baseline data on diabetes and HbA_{1c}. Diabetes was defined using an algorithm of self-report doctor diagnosis and/or medication; this algorithm has been validated against primary care data(12) HbA_{1c} assays were performed using five Bio-Rad Variant II Turbo analysers, outlined in detail in the UK Biobank protocol(13). In this study, values greater than 200 mmol/mol were excluded (n=5), as they were considered to be outliers and clinically implausible. For our analyses we divided participants into the following categories: known diabetes, undiagnosed diabetes (≥48 mmol/mol), pre-diabetes (42-<47 mmol/mol), normoglycaemic (≥35 & <42 mmol/mol), and low HbA_{1c} (<35 mmol/mol – based on criteria by Ginde and colleagues (14).

Dementia

Dementia at baseline was captured using ICD-10 codes in linked hospital episode statistics (HES) data. Incident dementia was algorithmically defined with the method described in Wilkinson et al.(15), which was based on linked UK hospital admission, mortality and primary care data. Here we focus on vascular dementia (n=397) and AD (n=1605); frontotemporal dementia cases were excluded (n=84).

Structural brain MRI outcomes

Structural brain MRI scans have been performed in a subsample of UKB participants using standard protocols, details of which are published(16). Post-processed measures (provided by UKB) used in this study included: hippocampal volume (mm^3), normalised for head size and total volume (mm^3) of white matter hyperintensities (WMH, mm^3). WMH volume was log-transformed as it was positively skewed; thus, we report exponentiated betas for this outcome to ease interpretation. The total maximum sample size for participants with these outcomes in our study was n=18,570.

Cognitive function

For cognitive function we pragmatically selected two measures with adequate sample sizes to represent distinct cognitive domains, namely reaction time (RT) and visual memory. In the visual memory test, respondents had to identify matches from six pairs of cards after memorising their positions on the screen. The number of incorrect matches (errors made) was then recorded, whereby a higher number indicates poorer visual memory. RT was measured as the mean time (in milliseconds) taken to correctly identify matches from 12 rounds of the card game 'Snap', where a longer time indicates slower RTs. As per Lyall et al., (2016)(17) reaction time (RT) was transformed using a log transformation (ln) and visual memory was transformed using an ln+1 equation (due to zero-value inflation). The total sample size for the reaction time and visual memory baseline analyses was 448,791.

Cognitive decline

Using data from a subset of participants with both baseline and follow-up measures of cognitive function, cognitive decline was determined using the Standardised Regression Based method(18). This included regressing follow-up visual memory on baseline visual memory, age, sex, years of education, and time between the two assessments. Subsequently, those whose standardised residual was greater than (absolute value) 1.96 (0.05 type-1 error rate) were assigned as having cognitive decline. Only a proportion of the UKB participants had follow-up visual memory data and complete covariate data (n=17,505).

Covariates

Demographics such as age (years), sex, ethnicity (White European, Asian/Asian British, Black/Black British, Other), deprivation (quintiles of Townsend deprivation index, from 'least deprived' to 'most deprived'), and educational attainment (derived as years of full-time education completed, as per qualifications based on coding from the International Standard Classification of Education (19)) were included. Health behaviours included smoking status (never, current smoker and ex-smoker). Health measures included body mass index (BMI) in kg/m^2, baseline cardiovascular disease (CVD – assigned using baseline self-report, nurse interview and linked hospital inpatient data between 2006 and 2010), anti-hypertensive medication and statin use.

Exclusion criteria

Those who had AD, vascular or frontotemporal dementia or cognitive impairment at baseline (2006-2010), as captured by self-report, nurse interview or HES were excluded (n=493).

Missing data

There were missing data across several variables, all of which had <10% missingness and for this reason we used complete case analysis for this study. The missing data were as follows: ethnicity n=2275, BMI n=3260, reaction time n=5776, visual memory n=4627, deprivation n=623, smoking n=1918, HbA_{1c} n=34,594, antihypertensives and statins n=8589, educational attainment n=9133.

Statistical analyses

All analyses were performed in RStudio, version 1.1.456.

Modelling approach

Cross-sectional cognitive function and structural brain analyses

In the cross-sectional analyses, glycaemia was entered as an exposure and four linear regressions were fitted to explore the relationship with baseline cognition outcomes (reaction time and visual memory). Model 1 consisted of adjustment for demographic measures (age + sex + deprivation + educational attainment + ethnicity), Model 2 was additionally adjusted for standard cardiovascular risk factors (smoking + BMI + CVD + anti-hypertensives + statins). Our modelling approach was identical for structural brain outcomes (hippocampal volume and volume of WMH).

Cognitive decline analyses

Only 4% of UKB participants underwent follow-up cognition testing, so our analyses of cognitive decline were restricted to this sub-population. The same models were fitted as in the analyses of baseline data. Logistic regression was used to investigate the association between glycaemia and binary cognitive decline, with the same modelling strategy as above.

Dementia analyses

Cox proportional hazards models were used to examine the relationships between glycaemia and a) AD and b) vascular dementia. The time scale was time since study entry and participants were followed up until 31 March 2017. The same modelling strategy was used,

as described above. The proportional hazards assumption was assessed using the global test to evaluate the interaction of each covariate with time, alongside Schoenfeld residuals.

RESULTS

Sample characteristics

448,791 individuals were included in the study, of whom 210,433 had low HbA_{1c} levels, 199,078 had normoglycaemic levels, 15,239 had pre-diabetes, 3279 had undiagnosed diabetes and 20,762 had known diabetes. Those with prediabetes and known diabetes were older than the other groups. Those with diabetes (undiagnosed and known) were more likely to be ex-smokers, reside in the most deprived quintile and have higher BMIs (Table 1). Those with known diabetes were most likely to be taking antihypertensives and statins at baseline and had the highest prevalence of CVD.

Glycaemia and AD, and vascular dementia

For these outcomes, we only present results from individuals who were ≥60 years, as there were very few AD and VD cases in the younger group. People with pre-diabetes had elevated risks of both AD and VD as did those with known diabetes (HR 1.20, 95% CI=0.93; 1.55 and HR 1.27, 95% CI=0.84; 1.91, respectively for pre-diabetes and HR 1.10, 95% CI=0.91; 1.33 and HR 1.45, 95% CI=1.07; 1.97, respectively for known diabetes) (Figure 1A and 1B). In contrast, compared to normoglycaemic individuals, fully-adjusted models showed that those with low HbA_{1c} had lower risks of both AD (HR 0.96, 95% CI=0.85; 1.08) and VD (HR 0.89, 95% CI=0.68; 1.15). Associations with AD were weaker than those for VD and did not reach conventional levels of statistical significance. Adjustment for health-related measures attenuated associations between glycaemia and VD, but the magnitude of this effect remained large at 27% increased risk of VD in pre-diabetes and 45% in known diabetes. The key factor responsible for accounting for excess risk for both pre-diabetes and known diabetes in multi-variate models was antihypertensive therapy. Model 1 HRs were 1.51 (95% CI= 1.01; 2.25) and 1.96 (95% CI= 1.49; 2.58) for pre-diabetes and known diabetes, respectively. Additional adjustment for antihypertensive therapy only, resulted in HR 1.41 (95% CI= 0.94; 2.11) for pre-diabetes and 1.70 (95% CI= 1.28; 2.26) for known diabetes.

Glycaemia and hippocampal and white matter hyperintensity volumes

Low HbA_{1c} was associated with lower WMH volume, and greater hippocampal volume than normoglycaemic individuals, while pre, undiagnosed and known diabetes were associated with higher WMH volume and lower hippocampal volume (Figure 2). Multivariable adjustment, specifically when antihypertensive therapy was added, markedly attenuated associations for pre and known diabetes, but less so for undiagnosed diabetes, for WMH only. Thus pre-diabetes, undiagnosed diabetes and known diabetes were associated with greater WMH volumes (4%, 30% and 3% respectively), and smaller hippocampal volumes ($23mm^3$, $13mm^3$, $60mm^3$) in the fully-adjusted models. Those with low HbA_{1c} had 2% lower WMH volume, and $14mm^3$ larger hippocampal volumes than normoglycaemic individuals.

Glycaemia, baseline reaction time and visual memory, and cognitive decline

Those with low HbA_{1c} had reaction times that were no different to the normoglycaemic group; however, both undiagnosed and known diabetes were associated with a 2% slower reaction time (Table 2). Low HbA_{1c} was not associated with visual memory scores, but undiagnosed diabetes related to 1% more errors in the visual memory task, whilst those with known diabetes made 2% fewer errors, compared to the normoglycaemic group (Table 2). In Model 1 (demographics) pre-diabetes and known diabetes were associated with somewhat greater risk of cognitive decline (Figure 1C), but the 95% confidence intervals around the odds ratios were wide. However, in the fully-adjusted model these associations became more pronounced and pre-diabetes and known diabetes related to a 53% and 49% increased risk of cognitive decline, respectively. Upon close inspection of the model, we observed a strong relationship between BMI and cognitive decline, which suggested that those with a higher BMI were less likely to suffer from cognitive decline, OR 0.97 (95%CI = 0.96; 0.99). This remained identical upon multivariate adjustment for age, sex, deprivation, smoking, statins, antihypertensives and CVD.

CONCLUSIONS

In this large sample of middle aged adults we report four key findings; first, people with pre-diabetes and known diabetes have excess risks of clinically important outcomes (cognitive decline and dementia), second, that a key determinant of the excess risk of vascular dementia and cognitive decline in association with hyperglycaemia is antihypertensive medication, third, associations between hyperglycaemia and dementia are stronger for vascular than Alzheimer's dementia and finally, that low normal levels of glycaemia are, if anything, beneficial for brain health.

It is striking that pre-diabetes and known diabetes both increase the risk of VD, cognitive decline and to a lesser extent AD, in comparison to normoglycaemic individuals. A recent meta-analysis suggests excess dementia risk in pre-diabetes (20) but most studies do not make a direct comparison to people with established diabetes, and have been restricted by small numbers of events. Risks of cognitive decline have been more extensively studied, with the majority identifying pre-diabetes as a high-risk state, though few suggest that risks are close to established diabetes (21,22). This has important implications for intervention. With greater numbers of individuals surviving to older age, avoidance or at least postponement of dementia is an increasing therapeutic concern, and, much like the finding of excess CVD risks in people with pre-diabetes (23,24), prompts consideration of identification and early intervention in such individuals.

Mid-life hypertension increases dementia risk (25,26) and is associated with greater WMH volumes (27). A recent review of antihypertensive therapy and cerebral small vessel disease (SVD) trials showed that antihypertensive therapy protects against progression of white matter hyperintensities (28). That we show attenuation of risk of both VD and WMH volume on adjustment for the greater use of antihypertensive medication in hyperglycaemic states can superficially be interpreted as treatment having adverse, not beneficial, effects. However, we suggest that, in this context, receipt of antihypertensive medication is acting as an indicator of longstanding untreated elevated blood pressure and that therefore, treatment is being instituted too late. This is supported by a recent study which suggests that treatment for hypertension should begin as early as the third decade to potentially reduce risk of disease and early mortality (29). Early adulthood blood pressure, measured at around age 43 years, is also more strongly related to WMH volumes at age 70 than blood pressure measured throughout middle age, or indeed contemporaneous with WMH volume assessment (30), highlighting the importance of elevated blood pressure even before middle age. The role of even modest elevations in blood pressure, blood pressure trajectories from young adulthood, and early blood pressure lowering intervention, requires exploration in the context of reducing risks of brain pathology.

We show associations between hyperglycaemic states, from pre-diabetes to established diabetes and all of our outcomes, but these appear stronger with VD and WMH volume than

AD and hippocampal volume, as the latter were resistant to adjustment for CVD risk factors. This is in line with evidence that diabetes is associated with greater WMH volume (9,10) and a study in the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) case-control sample, which revealed that those with diabetes had more than a two-fold excess risk of VD, but there was no association with AD (31). However, discrimination between VD and AD remains challenging and there have been no studies to date, that have investigated the associations lesser hyperglycaemic states and VD/AD in a single study. That we observed a stronger association between glycaemia and VD and WMH, as opposed to hippocampal volume and AD is perhaps suggestive of two distinct, yet related neurological and vascular pathways. This is in turn is supportive of a 'two-hit hypothesis', which has gained popularity more recently (32). Briefly, a combination of genetic, environmental and vascular risk factors result in neurovascular dysfunction, alongside damage to arterioles, small arteries and brain capillaries, either through pathways independent of amyloid-ß (hit one) and/or pathways dependent on amyloid-ß (hit two). These pathways converge on blood vessels and can synchronously or independently cause the neuronal dysfunction associated with dementia (32). Just how these pathways act synergistically or independently remains unclear.

One particular novel finding is that low-normal HbA_{1c} levels were associated with healthier brain structure, i.e. greater hippocampal volume and lower WMH volume, in comparison with normoglycaemic individuals. This group also had 4% and 11% lower risks of AD and VD, respectively. Participants with low HbA_{1c} tended to be younger and healthier than the other groups, were less likely to be smokers, less likely to reside in higher quintiles of deprivation, had lower prevalence of baseline CVD and fewer of them were on statins or antihypertensives. Adjustment for these factors somewhat attenuated the relationship between low HbA_{1c} and VD, and white matter hyperintensity volumes, but this was not the case for AD or hippocampal volume. This may, once again, suggest that distinct mediators operate in the association between glycaemia and AD and atrophy of the brain, compared to factors that mediate the relationship between glycaemia and vascular brain damage. Although our findings preclude us from any temporal or causal claims about this association, it is possible that in middle-aged adults without diabetes (~54 years) HbA_{1c} levels below 35 mmol/mol could confer some protection against hippocampal atrophy, as well as the presence of white matter hyperintensities. Currently, we cannot yet determine whether such protection translates to lower risks of incident dementia in this subgroup. Our findings also indicate that

pathways to brain health in association with persistently low HbA_{1c} in people without diabetes are likely different to those with bouts of hypoglycaemia in people with diabetes.

We also observed that pre-diabetes and undiagnosed diabetes were associated with 1% slower reaction times, whereas known diabetes was associated with 2% slower reaction times. Our finding is supported by an early study of diabetes patients who performed slower on a reaction time task, in comparison to age-matched controls (33). We showed that there are apparent effects at least cross-sectionally, in pre-diabetes and undiagnosed diabetes, even if the association with reaction time is somewhat larger in those with known diabetes, in comparison to normoglycaemia. The association we observed between glycaemia and visual memory was somewhat paradoxical, as known diabetes was associated with 2% fewer incorrect matches on this task. It is possible, however, that other factors common to individuals with diabetes (e.g. effects of medication to control glycaemia) could confer some protection against poorer visual memory.

In the 17,505 participants who had follow-up visual memory data we found that pre-diabetes and known diabetes conferred a 53% and 49% excess risk of cognitive decline on multivariate adjustment. While only 28 people with pre-diabetes, and 37 people with known diabetes experienced cognitive decline in the short span of follow up, the fact that both hyperglycaemic states were associated with adverse effects on brain health compared to normoglycaemic individuals adds confidence to our conclusion that hyperglycaemia adversely effects cognitive function, in line with previous observations (34). We observed that adjustment for BMI substantially increased the odds ratios from our demographics-only model, such that individuals with a higher BMI were less likely to suffer from cognitive decline. This may relate to the 'obesity paradox', whereby those with higher BMIs have lower mortality rates than normal weight individuals, for which several explanations have been proposed (34).

Our study possesses some important strengths. UK Biobank is one of the largest studies to have data on HbA_{1c} across the entire glycaemic spectrum, cognitive function, dementia sub-types and structural brain MRI measures. We used validated algorithms to define diabetes and dementia. However, the visual memory test used for follow-up (and thus to define cognitive decline) did not show good reliability (r=0.16) in UKB. UKB had a low response rate and as a result, may suffer from selection bias, which could mean participants were less

likely to have cognitive problems at study inception. Thus, it is possible that the association between glycaemia and our outcomes may have been underestimated.

In conclusion, we show that both pre-diabetes and known diabetes are detrimental in terms of vascular dementia risk and cognitive decline and these excess risks appear to be driven by treated hypertension. Early identification of hyperglycaemic states before frank diabetes, and intervention is once again highlighted here – but now for brain health. Weaker, but nevertheless not negligible associations with AD and with hippocampal volumes (as distinct from VD and WMH volumes), indicate pathological mechanisms beyond standard CVD risk factors, in association with hyperglycaemia, that affect brain health. Our findings of potential beneficial effects of low normal HbA_{1c} are intriguing and require further investigation.

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Table 1. Baseline characteristics and outcome measures across the glycaemic spectrum in UKB, N= 448,791

	Low HbA_{1c} (210433)	Normoglycaemic (199078)	Pre-diabetes (15239)	Undiagnosed (3279)	Known (20762)
			Exposures and covariates		
Age (Mean/SD)	54.4 (8.2)	58.1 (7.5)	60.1 (6.8)	58.5 (7.3)	60.2 (6.8)
Men N (%)	115955 (55)	111440 (56)	8029 (53)	1312 (40)	7664 (37)
Ethnicity					
White European	204303 (97)	189407 (95)	13444 (88)	2837 (86)	18533 (89)
Asian/Asian British	1517 (0.7)	2907 (1)	519 (3)	165 (5)	980 (5)
Black/Black British	1501 (0.7)	2636 (1)	671 (4)	148 (4)	546 (3)
Other	3112 (1)	4128 (2)	605 (4)	129 (4)	703 (3)
BMI kg/m^2					
(Mean/SD)	26.5 (4.2)	27.6 (4.7)	30.3 (5.5)	32.0 (5.7)	31.6 (5.8)
Smoking N (%)					
Never Smoker	148605 (71)	127690 (64)	8547 (56)	1824 (56)	11264 (54)
Current smoker	16915 (8)	24489 (12)	2474 (16)	500 (15)	2212 (11)
Ex-smoker	44913 (21)	46899 (24)	4218 (28)	955 (29)	7286 (35)
Deprivation					
Least Deprived	44895 (21)	40703 (20)	2584 (17)	501 (15)	3137 (15)
2^{nd} least deprived	43924 (21)	40519 (20)	2769 (18)	531 (16)	3483 (17)
Median	42883 (20)	40530 (20)	2826 (18)	606 (18)	3835 (18)
2^{nd} most deprived	41945 (20)	39396 (20)	3203 (21)	676 (21)	4358 (21)
Most Deprived	36786 (17)	37930 (19)	3857 (25)	965 (29)	5949 (29)
HbA_{1c} (mmol/mol)	32.0 (2.3)	37.4 (1.8)	43.8 (1.5)	58.7 (15.1)	52.2 (13.6)
(%)	5.1 (0.2)	5.6 (0.2)	6.1 (0.1)	7.5 (1.4)	6.9 (1.2)
Antihypertensives					
N (%)	28769 (14)	43312 (22)	5736 (38)	1127 (34)	13637 (66)
Statins N (%)	18452 (9)	36466 (18)	5201 (34)	983 (30)	15991 (77)
Baseline CVD N					
(%)	7963 (4)	14553 (7)	2363 (16)	450 (14)	4546 (22)
Education years					
(Mean/SD)	15.5 (4.9)	14.7 (5.2)	13.8 (5.3)	13.9 (5.2)	13.7 (5.3)
			Cognitive function at baseline		
RT - milliseconds					
(Mean/SD)	545.6 (108.9)	565.3 (115.9)	584.1 (129.3)	579.5 (127.0)	587.6 (129.2)
VM – incorrect					
matches (Mean/SD)	4.0 (3.2)	4.3 (3.4)	4.4 (3.6)	4.4 (3.5)	4.3 (3.6)
			Incident dementia		
VD (N/%)	105 (0.1)	166 (0.1)	30 (0.2)	5 (0.2)	91 (0.4)
AD (N/%)	567 (0.3)	756 (0.4)	75 (0.5)	14 (0.3)	193 (0.9)
			Follow up sub-sample of n=17,505		
Cognitive decline					
(N/%)	358 (4)	334 (4)	28 (6)	–	37 (6)
			Imaging sub-sample of n=18,570		
n	9994	7678	400	79	419
WMHV – mm^3					
(Median/IQR)	2266 (3185)	2966 (4442.5)	3948 (5159.2)	4275 (7052)	4208 (6531)
HV – mm^3	3884.4 (432.2)	3817.1 (432.1)	3766.3 (453.3)	3864.3 (570.9)	3764.6 (432.3)
(Mean/SD)					

Note. BMI=body mass index (kg/m^2), HbA_{1c}= glycated haemoglobin, CVD=cardiovascular disease, RT= reaction time, VM= visual memory, VD= vascular dementia, AD= Alzheimer's disease, WMHV= white matter hyperintensity volume, HV= hippocampal volume, AD= Alzheimer's disease, IQR= interquartile range, low HbA1c <35 mmol/mol, normoglycaemic 35-<42 mmol/mol, pre-diabetes 42-<48 mmol/mol, undiagnosed diabetes ≥48 mmol/mol.

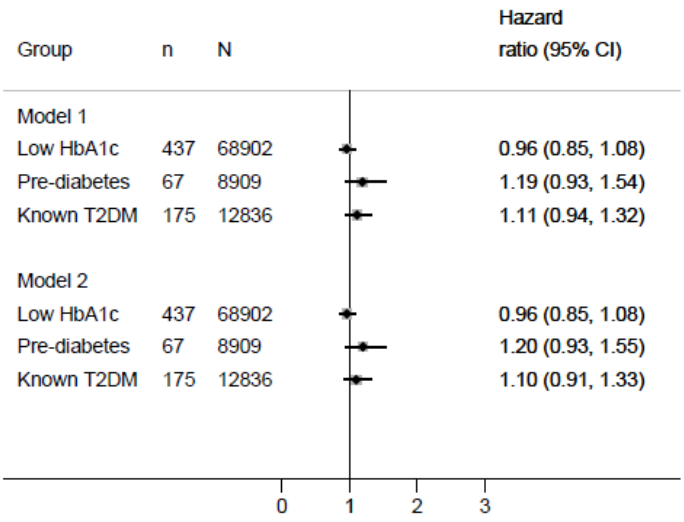
Table 2. Association between glycaemia and baseline cognitive function, N=448,791

	Reaction time	Visual memory
Group	Expß (95% CI)	Expß (95% CI)
	Model 1	
Low HbA_{1c}	1.00 (0.99;1.00)	1.00 (1.00;1.00)
Prediabetes	1.01 (1.01;1.01)	0.99 (0.98;1.00)
Undiagnosed T2DM	1.01 (1.01;1.02)	0.99 (0.97;1.02)
Known T2DM	1.02 (1.01;1.02)	0.97 (0.96;0.98)
	Model 2	
Low HbA_{1c}	1.00 (0.99;1.00)	1.00 (0.99;1.00)
Prediabetes	1.01 (1.01;1.01)	1.00 (0.99;1.01)
Undiagnosed T2DM	1.02 (1.01;1.02)	1.01 (0.99;1.03)
Known T2DM	1.02 (1.01;1.02)	0.98 (0.97;0.99)

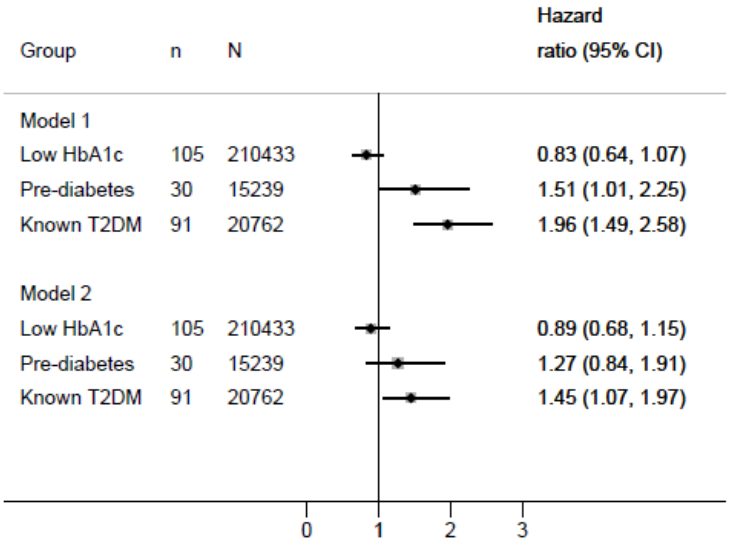
Note. Model 1= adjusted for age + sex + deprivation + ethnicity + educational attainment, Model 2= Model 1 + BMI + CVD + statins + antihypertensives + smoking. Exp(ß) =exponentiated beta, 95% CI = 95% confidence interval.

Figure 1. Association between glycaemia and incident AD, vascular dementia and cognitive decline in UK Biobank

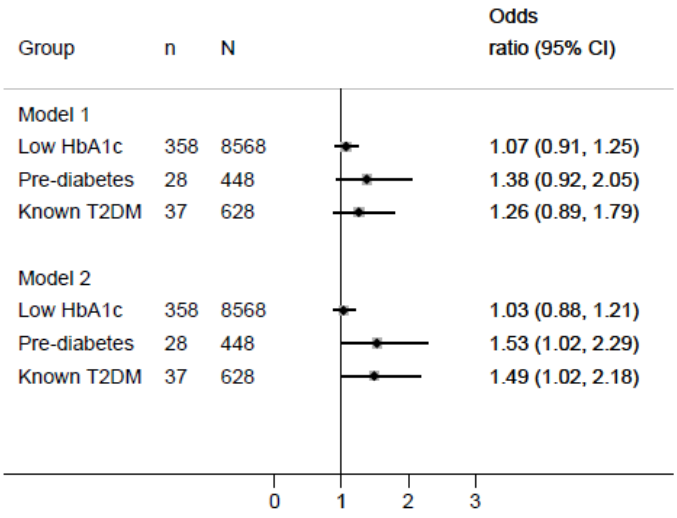
A) Association between glycaemia and incident AD in those ≥60 years (n=193790)



B) Association between glycaemia and incident VD in those ≥60 years (n=194094)

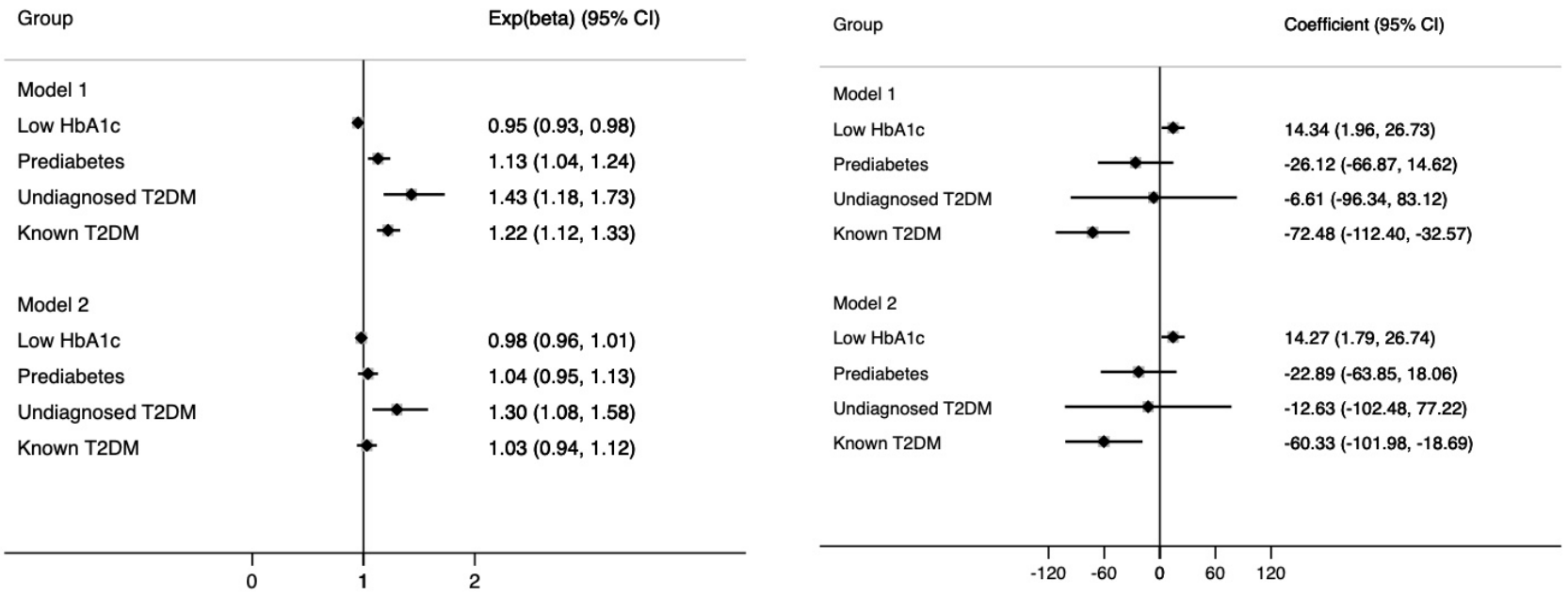


C) Association between glycaemia and cognitive decline in a UKB subsample (N=17,505)



Note. People with normoglycaemia are the comparator group (hazard ratio or odds ratio of 1.00). Model 1= adjusted for age + sex + deprivation + ethnicity + educational attainment, Model 2= Model 1 + BMI + CVD + statins + antihypertensives + smoking. HR= hazard ratio, 95% CI = 95% confidence interval. Reference category= normoglycaemic group (35-42 mmol/mol). Hazard ratios for the undiagnosed T2DM group are not presented (<20 cases for AD, VD and cognitive decline).

Figure 2. Association between glycaemia and white matter hyperintensity volume (left panel), and hippocampal volume (right panel), n=18,570



Note. Individuals with normoglycaemia are the comparator group. Model 1= adjusted for age + sex + deprivation + ethnicity + educational attainment, Model 2= Model 1 + BMI + CVD + statins + antihypertensives + smoking. Coefficient = unstandardized coefficient (mm^3), exp(beta)= exponentiated beta, 95% CI = 95% confidence interval. Low HbA1c <35 mmol/mol.