Brain health across the entire glycaemic spectrum: the UK Biobank

Running title: Glycaemia and brain health: the UK Biobank

Victoria Garfield PhD[1], Aliki-Eleni Farmaki PhD[1], Sophie V. Eastwood MRCGP[1],

Rohini Mathur PhD[2], Christopher T. Rentsch PhD[2], Krishnan Bhaskaran PhD[2], Liam

Smeeth PhD[2], Nish Chaturvedi MD[1]

[1]MRC Unit for Lifelong Health and Ageing at UCL, Institute of Cardiovascular

Science, University College London, 1-19 Torrington Place, London, United

Kingdom, WC1E 7HB

[2]Department of Non-communicable Disease Epidemiology, London School of

Hygiene & Tropical Medicine, Keppel Street, London, United Kingdom, WC1E 7HT

Corresponding author: Dr Victoria Garfield, 1-19 Torrington Place, London, WC1E

7HB, United Kingdom, Tel.: +442035495589, email: v.garfield@ucl.ac.uk

Title characters (with spaces): 128

Running head characters (with spaces): 42

Main text word count: 3357

Number of tables and figures: 5

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ABSTRACT

Objective: To understand the relationship across the glycaemic spectrum, with brain health. We hypothesised that individuals with increasingly higher HbA_{1c} would be more likely to have worse brain health outcomes in comparison to normoglycaemic individuals.

Methods: UK Biobank participants. HbA_{1c} and diabetes diagnosis define baseline glycaemic categories. Outcomes: incident vascular dementia (VD), Alzheimer's dementia (AD), hippocampal volume (HV), white matter hyperintensity (WMH) volume, cognitive function and decline. Reference group: normoglycaemic individuals (HbA_{1c} 35-<42 mmol/mol).

Results: Pre- and known diabetes increased incident VD, (HR 1.54, 95%CI=1.04;2.28 and 2.97, 95%CI=2.26;3.90). Known diabetes increased AD risk (HR 1.84, 95%CI=1.44;2.36). Pre- and known diabetes elevated risks of cognitive decline (OR 1.42, 1.48;2.96 and 1.39, 1.04;1.75). Pre-diabetes, undiagnosed and known diabetes conferred higher WMH volumes (4%, 26%, 5%,) and lower HV (22.4mm^3, 15.2mm^3, 62.2mm^3). Low-normal HbA_{1c} had 2% lower WMH volume and 13.6mm^3 greater HV.

Interpretation: Pre and known diabetes increase VD risks; known diabetes increases AD risk. Low-normal HbA_{1c} associates with more favourable neuroimaging outcomes. Our findings may have implications for cardiovascular medication in hyperglycaemia for brain health.

INTRODUCTION

Type-2 diabetes and, more generally, hyperglycaemic states, have been associated with poorer cognitive function (such as learning and memory)[1,2], increased risk of dementia[2,3] and alterations in key brain structures, particularly the hippocampus[4]. It is also important to explore how low-normal levels (vs. normal glycaemic levels) of glycated haemoglobin (HbA_{1c}) relate to brain health outcomes, which has not been investigated in a population-based study, to date. 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 brain health outcomes or lesser glycaemic states.

Memory loss is the most conclusively reported adverse effect of hyperglycaemia on cognitive function[6], yet hyperglycaemia also associates with worse processing speed, attention, concentration and executive functions [7]. Hippocampal atrophy is a crucial feature of age-related memory loss and the hippocampus is reportedly more vulnerable to the neurotoxic consequences of diabetes[8,9]. Evidence relating diabetes to the presence and progression of white matter hyperintensities is equivocal[10], but some research suggests that those with diabetes have greater volumes of white matter hyperintensities[11,12]. 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, our aim was to investigate, in a single large-scale study, the associations between five glycaemic states across the entire spectrum (low-normal HbA_{1c}, normoglycaemia, pre-diabetes, undiagnosed diabetes and known diabetes) and a breadth of brain health outcomes including: 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 those with increasingly higher HbA_{1c} would have worse outcomes compared to those with normal glycaemic levels.

METHODS

Sample

Full details of the UK Biobank (UKB) cohort have been described elsewhere[13]. 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). Figure 1 depicts our study design.

Informed consent and ethical approval

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (MREC) and informed consent has been obtained from participants.

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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[14] HbA_{1c} assays were performed using five Bio-Rad Variant II Turbo analysers, outlined in detail in the UK Biobank protocol[15]. 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-<48 mmol/mol), normoglycaemic (≥35 & <42 mmol/mol), and low HbA_{1c} (<35 mmol/mol) – based on criteria by Ginde and colleagues [16].

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. [17], which was based on linked UK hospital admission, mortality and primary care data. Here we focus on vascular dementia (n=412) and AD (n=749); frontotemporal dementia cases were excluded (n=95).

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[18]. 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=18,578.

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)[19] 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 449,973.

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[20]. 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=18,809).

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 [21]) 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; medications were captured and classified according to British National Formulary (BNF) chapters.

Exclusion criteria

Those who had AD, vascular or frontotemporal dementia or cognitive impairment prior to their recorded date of baseline assessment (2006-2010), as captured by self-report, nurse interview or HES were excluded.

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

Analyses were performed in RStudio, version 1.1.456 and STATA version 15.

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

449,973 individuals were included in the study, of whom 210,309 had low-normal

HbA$_{1c}$ levels, 198,969 had normoglycaemic levels, 15,229 had pre-diabetes, 3279

had undiagnosed diabetes and 22,187 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 (VD)

We do not present results from the undiagnosed diabetes group, as the number of

cases for both AD and VD was <20. Pre-diabetes and low-normal HbA$_{1c}$ were not

associated with AD in a basic or fully-adjusted model (Fig 2). However, known

diabetes was strongly associated with excess AD risk on minimal adjustment and

this remained robust in a fully-adjusted model (HR 1.84, 95%CI=1.44;2.36). People

with pre-diabetes had elevated risks of VD, as did those with known diabetes (HR

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1.75, 95% CI=1.19;2.59 and HR 3.73, 95% CI=2.90;4.80, respectively) (Fig 2), but low-normal HbA$_{1c}$ was not associated with VD (Fig 2).

Adjustment for health-related measures attenuated associations between glycaemia and VD, but this remained large at 54% increased risk of VD in pre-diabetes and almost 3-fold excess risk 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 1.75 (95% CI=1.19;2.59) and 3.73 (95% CI= 2.90;4.80) for pre-diabetes and known diabetes, respectively. Additional adjustment for antihypertensive therapy only (in addition to Model 1), resulted in HR 1.61 (95% CI= 1.09; 2.39) for pre-diabetes and 3.04 (95% CI= 2.34;3.95) for known diabetes. We also performed sensitivity analyses for both AD and VD in which we included both systolic blood pressure (SBP) alongside antihypertensives in our multiply-adjusted models. However, as the results remained qualitatively the same, albeit with less precision due to a smaller number of cases, we do not present these estimates.

Glycaemia and hippocampal and white matter hyperintensity volumes
Low-normal 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 (Fig 3). Multivariable adjustment, specifically when antihypertensive therapy was added, markedly attenuated associations for pre and known diabetes, but less so for undiagnosed diabetes, for WMH volume only. Thus pre-diabetes, undiagnosed diabetes and known diabetes were associated with greater WMH volumes (4%, 26%

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and 5% respectively), and smaller hippocampal volumes ($22mm^3$, $15mm^3$, $62mm^3$) in

fully-adjusted models. Those with low-normal 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-normal 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, while pre-diabetes was related to 1%

slower reaction times on multivariate adjustment (Table 2). Low-normal HbA_{1c} and

undiagnosed diabetes were not associated with visual memory scores, but those

with known diabetes made 3% 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 (Fig 4), 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 42% and 39% 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 = 0.95; 0.99). This remained

identical upon multivariate adjustment for age, sex, deprivation, smoking, statins,

antihypertensives and CVD.

DISCUSSION

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 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 may be somewhat beneficial in relation to subclinical measures of brain health, such as certain neuroimaging parameters.

It is striking that pre-diabetes and known diabetes both increase the risk of VD, cognitive decline and to a slightly lesser extent AD, in comparison to normoglycaemic individuals. A recent meta-analysis suggests excess dementia risk in pre-diabetes [22] 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 [23,24]. 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 [25,26], prompts consideration of identification and early intervention in such individuals.

Mid-life hypertension increases dementia risk [27,28] and is associated with greater WMH volumes [29]. A recent review of antihypertensive therapy and cerebral small

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vessel disease (SVD) trials showed that antihypertensive therapy protects against progression of white matter hyperintensities [30]. 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 [31]. 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 [32], 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 somewhat 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 [11,12] 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 [33]. However, discrimination between VD and

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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 [34]. Briefly, a combination of genetic, environmental and vascular risk factors results 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 [34]. Just how these pathways act synergistically or independently remains unclear.

Another novel finding is that low-normal HbA$_{1c}$ levels were associated with greater hippocampal volume and lower WMH volume, in comparison with normoglycaemic individuals. Participants with low-normal 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-normal HbA$_{1c}$ and white matter hyperintensity volumes, but this was not the case for 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

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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. Our findings also indicate that pathways to brain health in association with persistently lower 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 associates with 1% slower reaction times, whereas undiagnosed and known diabetes were 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 [35]. We show that there are apparent effects at least cross-sectionally, in pre-diabetes and undiagnosed diabetes, in comparison to normoglycaemia. The association we observed between glycaemia and visual memory was somewhat paradoxical, as known diabetes was associated with 3% 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 18,809 participants who had follow-up visual memory data we found that pre-diabetes and known diabetes conferred a 42% and 39% excess risk of cognitive decline on multivariate adjustment. While only 32 people with pre-diabetes, and 42 people with known diabetes experienced cognitive decline during the study 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

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previous observations [36]. 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 [36].

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, but we acknowledge that completely accurate diagnoses of dementia in particular, remain a challenge. 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. Somewhat weaker associations with AD and hippocampal 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} on white matter and hippocampal volume are intriguing and require further investigation.

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ACKNOWLEGDEMENTS

AUTHOR CONTRIBUTIONS

Literature search: VG; study design: VG, NC; data analysis: VG, SVE, A-EF; data interpretation: VG, NC, LS, KB; Writing: VG, NC; commenting on the draft: VG, A-EF, SVE, RM, CTR, KB, LS, NC. VG guarantees the work carried out, had access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The UK Biobank data are publicly available to all bona fide researchers at https://www.ukbiobank.ac.uk.

DUALITY OF INTEREST

KB reports grants from Diabetes UK, grants from British Heart Foundation, during the conduct of the study; grants from Medical Research Council, outside the submitted work. LS reports grants from BHF and Diabetes UK, during the conduct of the study; grants from Wellcome, grants from MRC, grants from NIHR, grants from GSK, grants from BHF, outside the submitted work; and is a Trustee of the British Heart Foundation. NC reports grants from Diabetes UK, grants from British Heart Foundation, during the conduct of the study; personal fees from AstraZeneca, grants from the Medical Research Council, outside the submitted work. The remaining authors declare that there are no conflicts of interest.

FUNDING

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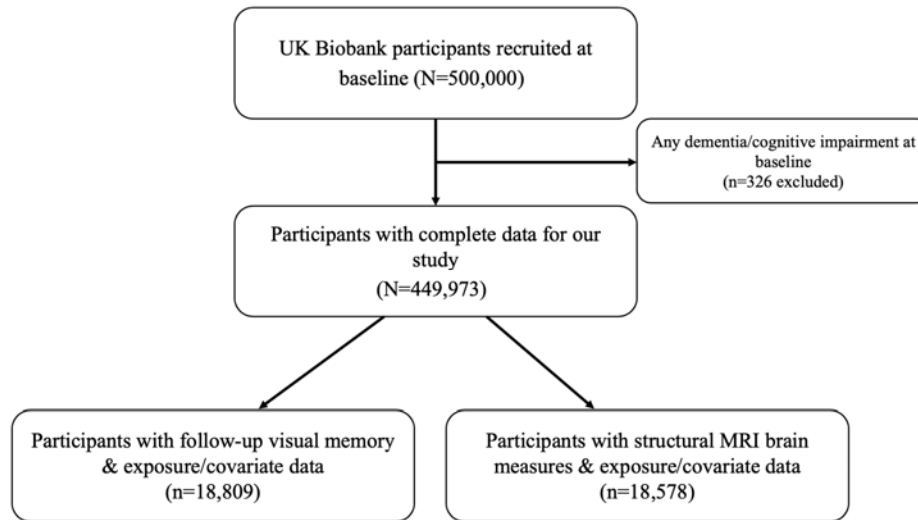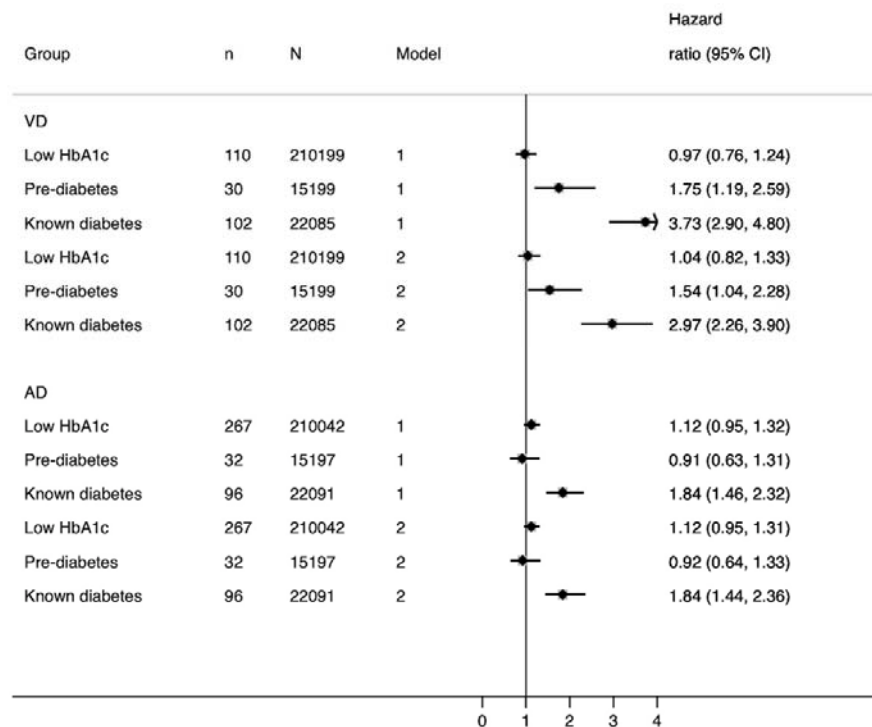
Fig 1. Study design

Fig. 2. Association between glycaemia and incident Alzheimer's and vascular dementia in UK Biobank (N=449,973)

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

Fig. 3. Association between glycaemia and, hippocampal and white matter hyperintensity volumes in a UKB subsample (N=18,578)
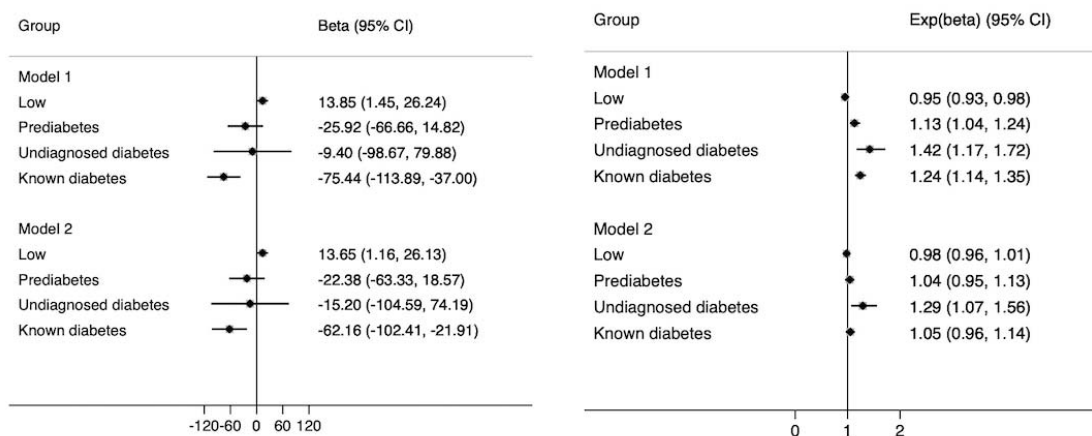
Note. Model 1= adjusted for age + sex + deprivation + ethnicity + educational attainment, Model 2= Model 1 + BMI + CVD + statins + antihypertensives + smoking, 95%CI = 95% confidence interval.

Fig. 4. Association between glycaemia and cognitive decline in a UKB subsample
(N=18,809)

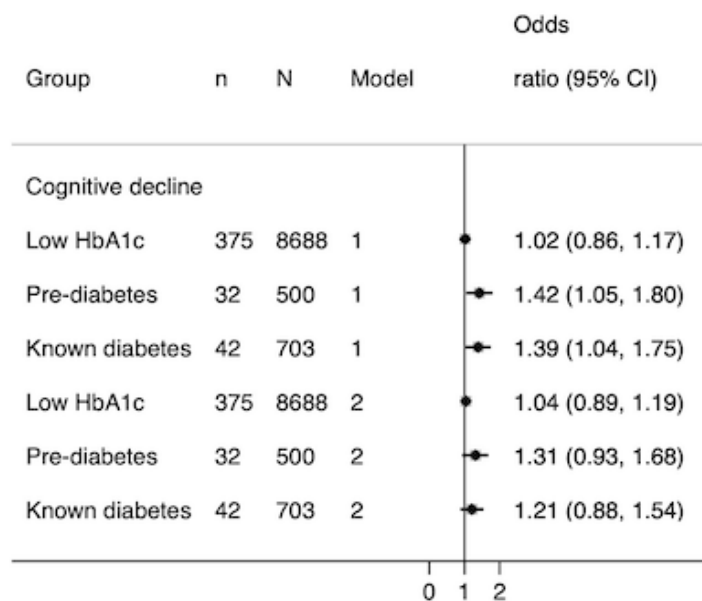| Group	n	N	Model	Odds ratio (95% CI)
Cognitive decline				
Low HbA1c	375	8688	1	1.02 (0.86, 1.17)
Pre-diabetes	32	500	1	1.42 (1.05, 1.80)
Known diabetes	42	703	1	1.39 (1.04, 1.75)
Low HbA1c	375	8688	2	1.04 (0.89, 1.19)
Pre-diabetes	32	500	2	1.31 (0.93, 1.68)
Known diabetes	42	703	2	1.21 (0.88, 1.54)

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

Table 1. Baseline characteristics and outcomes across the glycaemic spectrum, N= 449,973

	Low HbA$_{1c}$ (210309)	Normoglycaemic (198969)	Pre-diabetes (15229)	Undiagnosed (3279)	Known (22187)
Age - Mean(SD)	54.4(8.2)	58.1(7.5)	60.1(6.8)	58.5(7.3)	59.8(7.1)
Men N(%)	94447 (45)	87597 (44)	7205 (47)	1967 (60)	13862 (62)
Education years - Mean(SD)	15.5(4.9)	14.7(5.2)	13.8(5.3)	13.9(5.2)	13.7(5.3)
Ethnicity N(%)					
White European	204186 (97.1)	189305 (95.1)	13435 (88.2)	2837 (86.5)	19880 (89.6)
South Asian	1514 (0.7)	2904 (1.5)	519 (3.4)	165 (5)	1003 (4.5)
African Caribbean	1499 (0.7)	2636 (1.3)	670 (4.4)	148 (4.5)	558 (2.5)
Mixed or other	3110 (1.5)	4124 (2.1)	605 (4)	129 (3.9)	746 (3.4)
Deprivation N(%)					
Least deprived	44865 (21)	40688 (20)	2583 (17)	501 (15)	3354 (15)
2nd least deprived	43902 (21)	40490 (20)	2769 (18)	531 (16)	3728 (17)
Median deprivation level	42853 (20)	40498 (20)	2824 (18)	606 (18)	4105 (18)
2nd most deprived	41925 (20)	39377 (20)	3198 (21)	676 (21)	4672 (21)
Most deprived	36764 (17)	37916 (19)	3855 (25)	965 (29)	6328 (28)
Smoking N(%)					
Never smoker	148515 (71)	127610 (64)	8539 (56)	1824 (56)	12188 (55)
Current smoker	16908 (8)	24476 (12)	2474 (16)	500 (15)	2386 (11)
Ex-smoker	44886 (21)	46883 (24)	4216 (28)	955 (29)	7613 (34)
BMI kg/m^2 - Mean(SD)	26.5(4.2)	27.6(4.7)	30.3(5.5)	32(5.7)	31.4(5.8)
HbA1c mmol/mol - Mean(SD)	32.1(2.3)	37.4(1.8)	43.8(1.5)	58.7(15.1)	53.1(13.9)
HbA1c % - Mean(SD)	5.1(0.2)	5.6(0.2)	6.2(0.1)	7.5(1.4)	7(1.3)
		Cognitive function at baseline			
RT - milliseconds -Mean(SD)	545.7(108.9)	565.4(116)	584.1(129.3)	579.5(127)	587.5(129.6)
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			
AD N(%)	267 (0.1)	349 (0.2)	32 (0.2)	5 (0.2)	96 (0.4)
VD N(%)	110 (0.1)	165 (0.1)	30 (0.2)	5 (0.2)	102 (0.5)
Statins N(%)	18450 (9)	36447 (18)	5195 (34)	983 (30)	17022 (77)
Antihypertensives N(%)	28757 (14)	43287 (22)	5731 (38)	1127 (34)	14435 (65)
Baseline CVD N(%)	7974 (4)	14559 (7)	2364 (15)	450 (14)	4803 (22)
		Follow-up sub-sample of n=18,809			
Cognitive decline N(%)	375 (4)	361 (4)	32 (6)	8 (0.2)	42 (6)
		Imaging sub-sample of n=18,578			
n	9978	7669	400	79	452
WMHV mm^3 -Median(IQR)	2268 (3187)	2965 (4449)	3948 (5216)	4275 (7183)	4089 (6252)
HV mm^3 - Mean(SD)	3884.3 (432.3)	3817.3 (432.1)	3766.3 (453.3)	3864.3 (570.9)	3766.1 (445.9)

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, SD=standard deviation.

Table 2. Association between glycaemia and baseline cognitive function, N=449,973

Group	Reaction time Expß (95% CI)	Visual memory 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 (0.96;1.01)
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 (0.98;1.01)
Undiagnosed T2DM	1.02 (1.01;1.02)	1.00 (0.98;1.03)
Known T2DM	1.02 (1.01;1.02)	0.97 (0.96;0.98)

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.