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: 3551

Number of tables and figures: 5

Number of references: 40

ABSTRACT

Aims: To understand the relationship between glycated haemoglobin (HbA_{1c}) and brain health, across the entire glycaemic spectrum. We hypothesised that individuals with increasingly higher HbA_{1c} would be more likely to have worse brain health outcomes in comparison to normoglycaemic individuals.

Materials and methods: We used data from the UK Biobank cohort, which recruited 500,000 individuals aged 40-69 years. HbA_{1c} and diabetes diagnosis were used to define baseline glycaemic categories. Our outcomes included: incident all-cause dementia, vascular dementia (VD), Alzheimer's dementia (AD), hippocampal volume (HV), white matter hyperintensity (WMH) volume, cognitive function and decline. The reference group was normoglycaemic individuals (HbA_{1c} 35-<42 mmol/mol). Our maximum analytical sample had 449,973 individuals with complete data.

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 all-cause and AD risk (HR 1.91, 95%CI=1.66;2.21 and HR 1.84, 95%CI=1.44;2.36, respectively). 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 (3%, 22%, 7%,) and lower HV (36mm^3, 80mm^3, 82mm^3), whereas low-normal HbA_{1c} had 1% lower WMH volume and 12mm^3 greater HV.

Conclusion: Both pre-diabetes and known diabetes are harmful in terms of vascular dementia, cognitive decline and AD risks, as well as lower hippocampal volume. Associations appeared to be somewhat driven by antihypertensive medication, which implies that certain cardiovascular drugs may ameliorate some of the excess risk. Low-normal HbA_{1c} levels, however, associate with more favourable brain health outcomes and warrant more in-depth investigation.

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]. However, 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.

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 (see Supplementary Material). 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.

Type-2 diabetes mellitus (diabetes)

Exposure status was defined using baseline data on diabetes and HbA_{1c} (see Supplementary material). Diabetes was defined using an algorithm of self-report doctor diagnosis and/or medication; this algorithm has been validated against primary care data[16] . 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[18].

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 indicated poorer visual memory. Participants also completed a timed assessment of symbol matching which was similar to the card game 'Snap'. RT was measured as the mean time (in milliseconds) taken to correctly identify matches from trials that had matching symbol pairs. A higher score (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.

Neuroimaging outcomes

Structural brain MRI scans have been performed in a subsample of UKB participants using standard protocols (see Supplementary Material)[20]. Post-processed measures (provided by UKB) used in this study included: hippocampal volume (mm^3 - normalised for head size) and total volume 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 maximum sample size for these outcomes in our study was n=35,418.

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.[21], which was based on linked UK hospital admission, mortality and primary care data. Coded diagnoses were compared against clinical expert adjudication of full-text medical records. Here we focus on all-cause dementia (n=2,023) (see Supplementary Material), vascular dementia (n=412) and AD (n=749). Frontotemporal dementia cases were only included in all-cause dementia analyses (n=95).

Cognitive decline

Using data from a subset of participants who had both baseline and follow-up measures of cognitive function, cognitive decline was determined using the Standardised Regression Based method[22]. This included regressing follow-up visual memory on baseline visual memory, as well as age, sex, years of education, and time between the two assessments. 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). This was because a sub-sample underwent repeat cognitive assessment between the summers of 2012 and 2013, who all lived within 35 kilometres of the Stockport (England) UKB centre. The response rate was 21% to the email or letter invitation.

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 [23]) 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

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

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 analyses

Cognitive function and neuroimaging outcomes

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), whilst Model 2 was additionally adjusted for standard cardiovascular risk factors (smoking + BMI + CVD + anti-hypertensives + statins). Our modelling approach was identical for neuroimaging outcomes (hippocampal volume and volume of WMH).

Longitudinal analyses

Dementia

Cox proportional hazards models were used to examine the relationships between glycaemia and a) all-cause dementia, b) AD and c) 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.

Cognitive decline

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

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.

Cross-sectional results

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, on multivariate adjustment pre-diabetes was related to 1% slower reaction times (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 were associated with 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.

Longitudinal results

Glycaemia and all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VD)

We do not present results from the undiagnosed diabetes group, as the number of cases for all-cause dementia, AD and VD was <20. Pre-diabetes and low-normal HbA_{1c} were not associated with all-cause dementia or AD in basic or fully-adjusted models (Fig 2). However, known diabetes was strongly associated with excess all-cause dementia and AD risk on minimal adjustment and this remained robust in fully-adjusted models (HR 1.91, 95%CI = 1.66;2.21 and HR 1.84, 95%CI=1.44;2.36, respectively). People with pre-diabetes had elevated risks of VD, as did those with known diabetes (HR 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 the associations between glycaemia and VD. However, this remained large at 54% increased risk of VD for pre-diabetes and almost 3-fold excess risk for known diabetes. In multivariate models the key factor responsible for accounting for excess risk for both pre-diabetes and known diabetes was antihypertensive therapy. Model 1 HRs were 1.75 (95% CI=1.19;2.59) for pre-diabetes and 3.73 (95% CI= 2.90;4.80) for known diabetes. 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 all-

cause dementia, AD and VD in which we included both systolic blood pressure (SBP) alongside antihypertensives in multiply-adjusted models. As the results remained qualitatively identical, albeit with less precision due to a smaller number of cases, we do not present these estimates. Additional analyses of confounding by age are in Supplementary Table S1.

Glycaemia and hippocampal and white matter hyperintensity volumes

Low-normal HbA_{1c} was associated with lower WMH volume and greater hippocampal volume compared with normoglycaemic individuals. Pre-, undiagnosed and known diabetes were associated with higher WMH volume and lower hippocampal volume (Fig 3). Multivariable adjustment, specifically the addition of antihypertensive therapy, markedly attenuated associations with WMH volume for pre and known diabetes, but less so for undiagnosed diabetes. Thus pre-diabetes, undiagnosed diabetes and known diabetes were associated with greater WMH volumes (3%, 22% and 7% respectively), and smaller hippocampal volumes (36mm^3, 80mm^3, 82mm^3) in fully-adjusted models. Those with low-normal HbA_{1c} had 1% lower WMH volume (which did not reach conventional levels of statistical significance on multiple adjustment), and 12mm^3 larger hippocampal volumes than normoglycaemic individuals.

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, 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 all-cause and Alzheimer's dementia. Fourth, we observed that low-normal levels of glycaemia may be somewhat beneficial in relation to subclinical measures of brain health, such as certain neuroimaging parameters.

We observed that pre-diabetes associates with 1% slower reaction times, whereas undiagnosed and known diabetes associate with 2% slower reaction times. This finding is supported by an early study of diabetes patients who performed slower on a reaction time task, in comparison to age-matched controls[24]. We show that there are apparent associations at least cross-sectionally, with 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 perhaps confer some protection against poorer visual memory.

Another novel finding is that in minimally-adjusted models 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 (from 4% to 1% and did not reach conventional levels of statistical significance), 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 preclude us from drawing 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. However, these findings warrant replication to determine whether this is true and if so, what the underlying mechanisms may be. Our results 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.

It is striking that in comparison to normoglycaemic individuals, pre-diabetes and known diabetes both increase the risk of VD, cognitive decline and to a slightly lesser extent all-cause dementia and AD. A recent meta-analysis suggests excess dementia risk in pre-diabetes[25] 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[26,27]. 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. Therefore, much like the finding of excess CVD risks in people with pre-diabetes[28,29], this result prompts consideration of identification and early intervention in such individuals.

Mid-life hypertension increases dementia risk[30,31] and is associated with greater WMH volumes[32]. A recent review of antihypertensive therapy and cerebral small vessel disease (SVD) trials showed that antihypertensive therapy protects against progression of white matter hyperintensities[33]. That we show attenuation of the risk of both VD and WMH volume on adjustment for 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 acts 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[34]. 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 [35]. This

serves to highlight 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, with the exception of all-cause dementia, for which excess risks only emerged in relation with known diabetes. Individuals with diagnosed and thus, treated diabetes had lower HbA_{1c} levels than the undiagnosed group, which is expected. Those with established diabetes have elevated HbA_{1c} for around 10 years before diagnosis. Long-term elevation of HbA_{1c} is likely associated with worse brain health. Hyperglycaemic states appeared to associate somewhat more strongly 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, showing that those with diabetes had more than a two-fold excess risk of VD, but no association with AD[36]. Discrimination between VD and AD remains challenging and to date, no studies have investigated the associations between 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[37]. 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[37]. Just how these pathways act synergistically or independently remains unclear.

In the 18,809 participants who had follow-up visual memory data we found that pre-diabetes and known diabetes conferred 42% and 39% excess risks 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 negatively affects cognitive function, in line with previous observations[38]. 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[38]. Importantly, once diagnosed, diabetes remains a lifelong condition and these individuals are at increased risk of complications. However, while higher BMI in midlife is associated with greater risk of cognitive decline, the reverse occurs in older age, supported by evidence of an inverse relationship between BMI and dementia mortality[40]. The explanation is that weight loss occurs as a result of chronically ill health[39].

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 neuroimaging measures. We used validated algorithms to define diabetes and dementia, but we acknowledge that completely accurate diagnoses of dementia in particular, remain a challenge. The algorithm used to define dementia in UKB was most accurate for all-cause dementia, followed by AD and then VD[21]. 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 and cognitive decline risk, which appear to be driven by treated hypertension. Somewhat weaker associations with all-cause dementia and AD indicate that pathological mechanisms beyond standard CVD risk factors may affect brain health, in association with hyperglycaemia. Our findings of low-normal HbA_{1c} associated with favourable white matter hyperintensity and hippocampal volumes are intriguing and require further investigation.

ACKNOWLEGDEMENTS

This work was conducted under the approved UK Biobank project number 7661. We thank the volunteer participants of the UK Biobank, and the UK Biobank researchers.

AUTHOR CONTRIBUTIONS

Literature search: VG; study design: VG, NC; data analysis: VG, SVE; 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

This work was jointly funded by Diabetes UK and British Heart Foundation grant 15/0005250. KB holds a Sir Henry Dale Fellowship funded by Wellcome and the Royal Society (grant number 107731/Z/15/Z).

REFERENCES

1. Rory J McCrimmon, Christopher M Ryan BMF. Diabetes and Cognitive Dysfunction. Lancet 2012;379:2291–99.

2. Xue M, Xu W, Ou YN, et al. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. Ageing Res. Rev. 2019;55:100944.

3. Ravona-Springer R, Luo X, Schmeidler J, et al. Diabetes is associated with increased rate of cognitive decline in questionably demented elderly. Dement. Geriatr. Cogn. Disord. 2010;29(1):68–74.

4. Rosenberg J, Lechea N, Pentang GN, Shah NJ. What magnetic resonance imaging reveals – A systematic review of the relationship between type II diabetes and associated brain distortions of structure and cognitive functioning. Front. Neuroendocrinol. 2018;52:79-112.

5. Lyall DM, Celis-morales CA, Anderson J, et al. Associations between single and multiple cardiometabolic diseases and cognitive abilities in 474 129 UK Biobank participants. 2017;38:577–583.

6. Ryan CM, Geckle M. Why is learning and memory dysfunction in Type 2 diabetes limited to older adults? Diabetes. Metab. Res. Rev. 2000;16(5):308–315.

7. Biessels GJ, Nobili F, Teunissen CE, et al. Understanding multifactorial brain changes in type 2 diabetes: a biomarker perspective. Lancet Neurol. 2020;19(8):699–710.

8. Gold SM, Dziobek I, Sweat V, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. Diabetologia 2007;50(4):711–719.

9. Fotuhi M, Do D, Jack C. Modifiable factors that alter the size of the hippocampus with ageing. Nat. Rev. Neurol. 2012;8(4):189–202.

10. Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: A systematic review. Lancet Diabetes Endocrinol. 2015;3(1):75–89.

11. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J. Am. Heart Assoc. 2015;4(6):001140.

12. Mankovsky B, Zherdova N, van den Berg E, et al. Cognitive functioning and structural brain abnormalities in people with Type 2 diabetes mellitus. Diabet. Med. 2018;35(12):1663–1670.

13. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med. 2015;12(3):1–10.

14. Swanson JM. The UK Biobank and selection bias. Lancet 2012;380(9837):110.

15. UK Biobank. UK Biobank: Protocol for a large-scale prospective epidemiological resource. UKBB-PROT-09-06 (Main Phase) 2007;06(March):1–112.Available from: https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf

16. Eastwood S V., Mathur R, Atkinson M, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK Biobank. PLoS One 2016;11(9): e0162388.

17. Tierney A, Fry D, Almond R, et al. UK Biobank Biomarker Enhancement Project Companion Document to Accompany HbA1c Biomarker Data . 2018;1–8. Available from: https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_hb1ac.pdf

18. Ginde AA, Cagliero E, Nathan DM, Camargo CA. Value of Risk Stratification to Increase the Predictive Validity of HbA1c in Screening for Undiagnosed Diabetes in the US Population. 2008;1346–1353.

19. Lyall DM, Cullen B, Allerhand M, et al. Cognitive test scores in UK biobank: Data reduction in 480,416 participants and longitudinal stability in 20,346 participants. PLoS One 2016;11(4):1–10.

20. Littlejohns TJ, Holliday J, Gibson LM, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. Nat. Commun. 2020;11(1):1–12.

21. Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank : a validation study of primary care, hospital admissions and mortality data. Eur. J. Epidemiol. 2019;34:557–565.

22. Frerichs RJ, Tuokko HA. A comparison of methods for measuring cognitive change in older adults. Arch. Clin. Neuropsychol. 2005;20(3):321–333.

23. International Standard Classification of EducationI S C E D 1997 . 1997.Available from: http://www.unesco.org/education/information/nfsunesco/doc/isced_1997.htm

24. Subramanian N, Chandrasekar S. REACTION TIME IN CLINICAL DIABETES MELLITUS. 1984;2–5.

25. Xue M, Xu W, Ou YN, et al. Diabetes mellitus and risks of cognitive impairment and

dementia: A systematic review and meta-analysis of 144 prospective studies. Ageing Res. Rev. 2019;55:100944.

26. Euser SM, Sattar N, Witteman JCM, et al. A prospective analysis of elevated fasting glucose levels and cognitive function in older people: Results from PROSPER and the Rotterdam Study. Diabetes 2010;59(7):1601–1607.

27. Marseglia A, Fratiglioni L, Kalpouzos G, et al. Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: A population-based cohort study. Alzheimer's Dement. 2019;15(1):25–33.

28. Glumer C, Jorgensen T, Borch-Johnsen K. Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. Diabetes Care 2003;26(8):2335–2340.

29. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N. Engl. J. Med. 2008;359(15):1577–1589.

30. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4(8):487–499.

31. Whitmer RA, Sidney S, Selby J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64(2):277 LP – 281.

32. Lane CA, Barnes J, Nicholas JM, et al. Associations between Vascular Risk across Adulthood and Brain Pathology in Late Life: Evidence from a British Birth Cohort. JAMA Neurol. 2019;1–9.

33. Van Middelaar T, Argillander TE, Schreuder FHBM, et al. Effect of antihypertensive medication on cerebral small vessel disease: A systematic review and meta-analysis. Stroke 2018;49(6):1531–1533.

34. Yano Y, Reis JP, Lewis CE, et al. Association of Blood Pressure Patterns in Young Adulthood With Cardiovascular Disease and Mortality in Middle Age. JAMA Cardiol.

2020;5(4):382–389.A

35. Lane CA, Barnes J, Nicholas JM, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. Lancet Neurol. 2019;18(10):942–952.

36. Doney ASF, Bonney W, Jefferson E, et al. Investigating the relationship between type 2 diabetes and dementia using electronic medical records in the GoDARTS bioresource. Diabetes Care 2019;42(10):1973–1980.

37. Kisler K, Nelson AR, Montagne A, Zlokovic B V. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat. Rev. Neurosci. 2017;18(7):419–434.A

38. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. Diabetes Care 2013;36(SUPPL.2)

39. Singh-Manoux A, Dugravot A, Shipley M, et al. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. Alzheimer's Dement. 2018;14(2):178–186.

40. Bhaskaran K, dos-Santos-Silva I, Leon DA, et al. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. Lancet Diabetes Endocrinol. 2018;6(12):944–953.

Fig 1. Study design

Fig. 2. Association between glycaemia and incident all-cause, 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=35,418)

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)

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)	*P-value*
Age - Mean(SD)	54.4(8.2)	58.1(7.5)	60.1(6.8)	58.5(7.3)	59.8(7.1)	<0.001
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)	<0.001
Ethnicity N(%)						<0.001
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(%)						<0.001
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(%)						<0.001
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)	<0.001
BMI kg/m² - Mean(SD)	26.5(4.2)	27.6(4.7)	30.3(5.5)	32(5.7)	31.4(5.8)	<0.001
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)	<0.001
HbA1c % - Mean(SD)	5.1(0.2)	5.6(0.2)	6.2(0.1)	7.5(1.4)	7(1.3)	<0.001
Statins N(%)	18450 (9)	36447 (18)	5195 (34)	983 (30)	17022 (77)	<0.001
Antihypertensives N(%)	28757 (14)	43287 (22)	5731 (38)	1127 (34)	14435 (65)	<0.001
Baseline CVD N(%)	7974 (4)	14559 (7)	2364 (15)	450 (14)	4803 (22)	<0.001
			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)	<0.001
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)	<0.001
			Incident dementia			
All-cause dementia N(%)	678 (0.3)	920 (0.5)	110 (0.7)	16 (0.5)	299 (1.3)	<0.001
AD N(%)	267 (0.1)	349 (0.2)	32 (0.2)	5 (0.2)	96 (0.4)	<0.001
VD N(%)	110 (0.1)	165 (0.1)	30 (0.2)	5 (0.2)	102 (0.5)	<0.001
			Follow-up sub-sample of n=18,809			
Cognitive decline N(%)	375 (4)	361 (4)	32 (6)	8 (0.2)	42 (6)	<0.001
			Imaging sub-sample of n=35,418			
n	9978	7669	400	79	452	
WMHV mm³ - Median(IQR)	2268 (3187)	2965 (4449)	3948 (5216)	4275 (7183)	4089 (6252)	<0.001

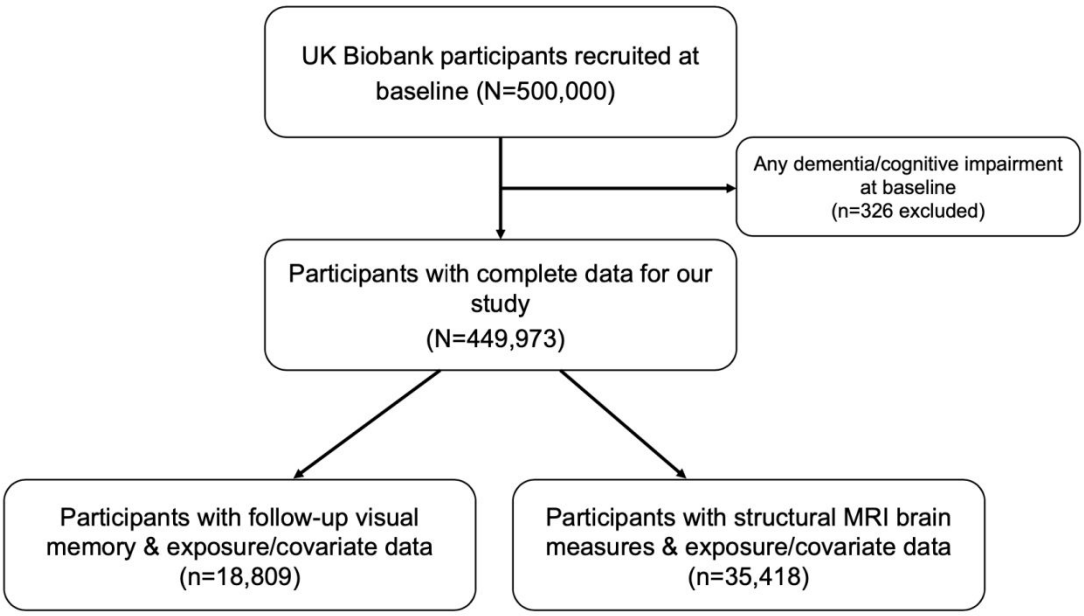
HV mm³ - Mean(SD)	3884.3 (432.3)	3817.3 (432.1)	3766.3 (453.3)	3864.3 (570.9)	3766.1 (445.9)	<0.001

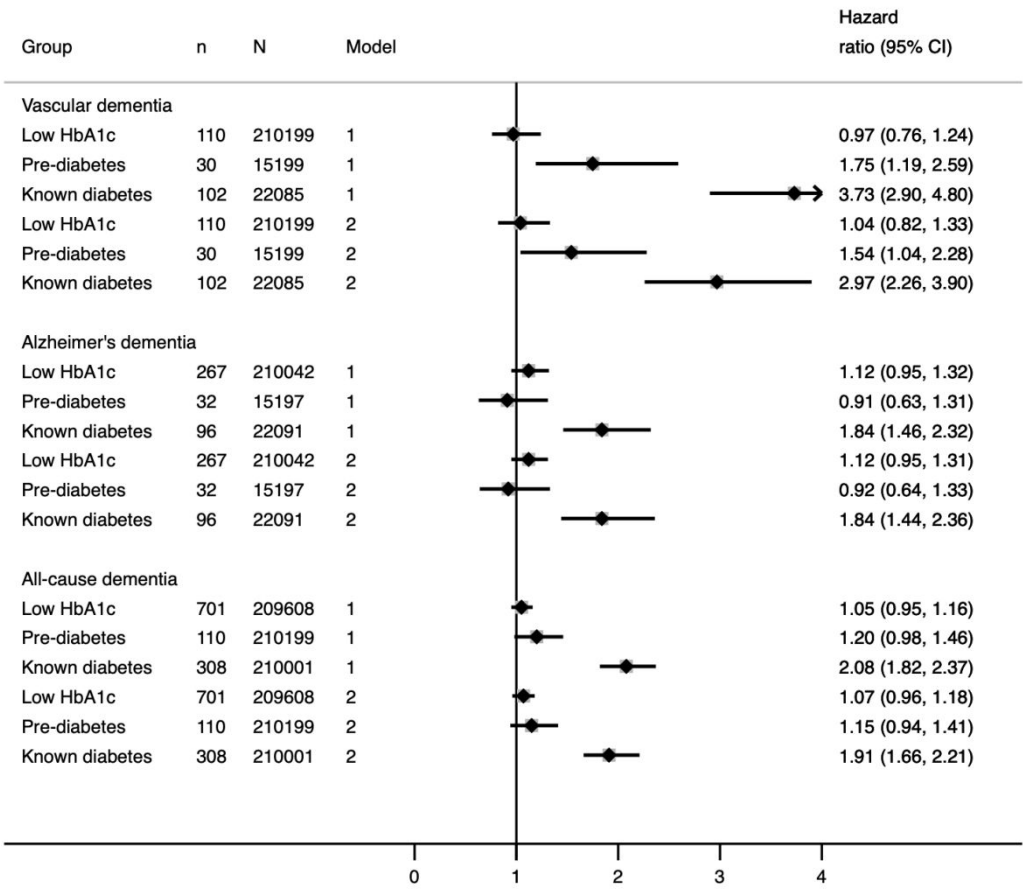
Note. BMI=body mass index (kg/m^2), HbA_{1c}= glycated haemoglobin, CVD=cardiovascular disease, RT= reaction time, VM= visual memory, VD= vascular dementia, AD= Alzheimer's disease, WMHV= white matter hyperintensity volume, HV= hippocampal volume, AD= Alzheimer's disease, IQR= interquartile range, low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

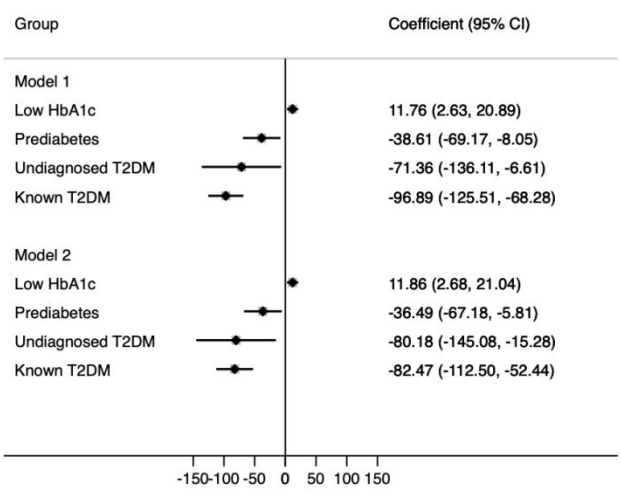
Table 2. Association between glycaemia and baseline cognitive function, N=449,973

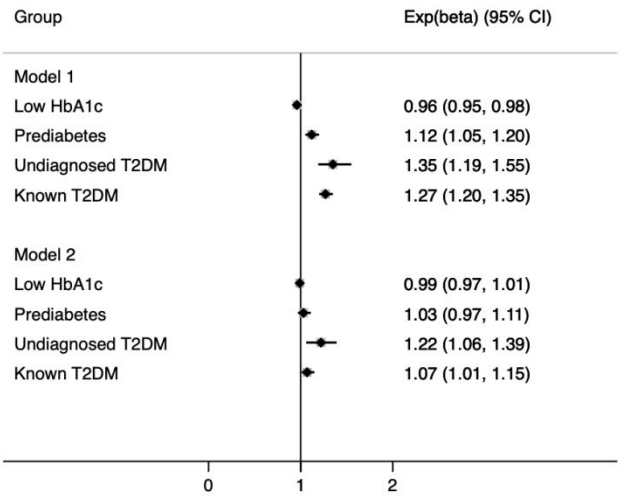
	Reaction time	Visual memory
Group	Expß (95% CI)	Expß (95% CI)
	Model 1	
Low HbA_{1c}	1.00 (0.99;1.00)	1.00 (1.00;1.00)
Prediabetes	1.01 (1.01;1.01)	0.99 (0.98;1.00)
Undiagnosed T2DM	1.01 (1.01;1.02)	0.99 (0.96;1.01)
Known T2DM	1.02 (1.01;1.02)	0.97 (0.96;0.98)
	Model 2	
Low HbA_{1c}	1.00 (0.99;1.00)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

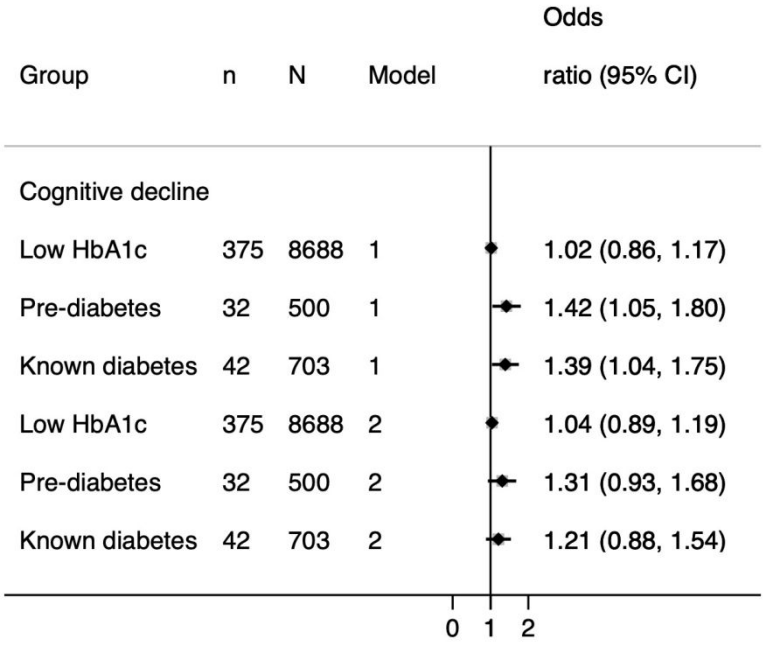
Note. Model 1= adjusted for age + sex + deprivation + ethnicity + educational attainment, Model 2= Model 1 + BMI + CVD + statins + antihypertensives + smoking. Exp(ß) =exponentiated beta, 95% CI = 95% confidence interval.


UK Biobank participants recruited at baseline (N=500,000)
Any dementia/cognitive impairment at baseline (n=326 excluded)
Participants with complete data for our study (N=449,973)
Participants with follow-up visual memory & exposure/covariate data (n=18,809)
Participants with structural MRI brain measures & exposure/covariate data (n=35,418)


Group n N Model Hazard ratio (95% CI)
Vascular dementia
Low HbA1c 110 210199 1 0.97 (0.76, 1.24)
Pre-diabetes 30 15199 1 1.75 (1.19, 2.59)
Known diabetes 102 22085 1 3.73 (2.90, 4.80)
Low HbA1c 110 210199 2 1.04 (0.82, 1.33)
Pre-diabetes 30 15199 2 1.54 (1.04, 2.28)
Known diabetes 102 22085 2 2.97 (2.26, 3.90)
Alzheimer's dementia
Low HbA1c 267 210042 1 1.12 (0.95, 1.32)
Pre-diabetes 32 15197 1 0.91 (0.63, 1.31)
Known diabetes 96 22091 1 1.84 (1.46, 2.32)
Low HbA1c 267 210042 2 1.12 (0.95, 1.31)
Pre-diabetes 32 15197 2 0.92 (0.64, 1.33)
Known diabetes 96 22091 2 1.84 (1.44, 2.36)
All-cause dementia
Low HbA1c 701 209608 1 1.05 (0.95, 1.16)
Pre-diabetes 110 210199 1 1.20 (0.98, 1.46)
Known diabetes 308 210001 1 2.08 (1.82, 2.37)
Low HbA1c 701 209608 2 1.07 (0.96, 1.18)
Pre-diabetes 110 210199 2 1.15 (0.94, 1.41)
Known diabetes 308 210001 2 1.91 (1.66, 2.21)
0
1
2
3
4


Group
Coefficient (95% CI)
Model 1
Low HbA1c
11.76 (2.63, 20.89)
Prediabetes
-38.61 (-69.17, -8.05)
Undiagnosed T2DM
-71.36 (-136.11, -6.61)
Known T2DM
-96.89 (-125.51, -68.28)
Model 2
Low HbA1c
11.86 (2.68, 21.04)
Prediabetes
-36.49 (-67.18, -5.81)
Undiagnosed T2DM
-80.18 (-145.08, -15.28)
Known T2DM
-82.47 (-112.50, -52.44)
-150 -100 -50 0 50 100 150


Group
Exp(beta) (95% CI)
Model 1
Low HbA1c
0.96 (0.95, 0.98)
Prediabetes
1.12 (1.05, 1.20)
Undiagnosed T2DM
1.35 (1.19, 1.55)
Known T2DM
1.27 (1.20, 1.35)
Model 2
Low HbA1c
0.99 (0.97, 1.01)
Prediabetes
1.03 (0.97, 1.11)
Undiagnosed T2DM
1.22 (1.06, 1.39)
Known T2DM
1.07 (1.01, 1.15)
0 1 2


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)
0 1 2