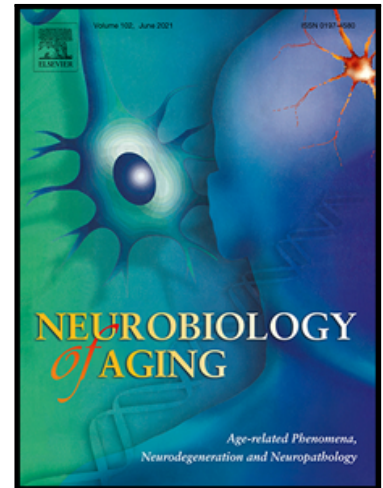


Sex-related differences in whole brain volumes at age 70 in association with hyperglycemia during adult life



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Highlights

- It is unclear whether hyperglycemia in adulthood impacts brain outcomes.
- HbA1c was associated with lower global brain volumes in females but not in males
- No evidence linking hyperglycemia with amyloidosis or cognitive impairments.
- Our findings show target organ damage in female brains with hyperglycemia

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Abstract

Longitudinal studies of the relationship between hyperglycemia and brain health are rare and there is limited information on sex differences in associations. We investigated whether

glycosylated haemoglobin (HbA1c) measured at ages of 53, 60-64 and 69 years, and cumulative glycemic index (CGI), a measure of cumulative glycemic burden, were associated with metrics of brain health in later life.

Participants were from Insight 46, a sub-study of the Medical Research Council National Survey of Health and Development (NSHD) who undertook volumetric MRI, florbetapir amyloid-PET imaging and cognitive assessments at ages of 69-71. Analyses were performed using linear and logistic regression as appropriate, with adjustment for potential confounders. We observed a sex interaction between HbA1c and whole brain volume (WBV) at all three time points. Following stratification of our sample, we observed that HbA1c at all ages, and CGI were positively associated with lower WBV exclusively in females. HbA1c (or CGI) was not associated with amyloid status, white matter hyperintensities (WMHs), hippocampal volumes (HV) or cognitive outcomes in either sex.

Higher HbA1c in adulthood is associated with smaller WBV at 69–71 years in females but not in males. This suggests that there may be preferential target organ damage in the brain for females with hyperglycemia.

Keywords: hyperglycemia, diabetes, cognition, amyloidosis, brain, hyperintensities

1. Introduction

Dementia describes a syndrome of debilitating symptoms that impair behaviour and cognition (Duong et al, 2017). Recent reports have estimated that up to 50 million people are living

with dementia globally, with its incidence rising markedly as populations age (Prince et al, 2014). In the absence of effective treatment, research has focused on identifying modifiable risk factors that may contribute to the pathogenesis of the disease prior to its overt presentation. There are numerous studies linking type 2 diabetes (T2D) to various markers of brain pathology, and most robustly to small/large vessel disease (Liu et al, 2018; Umemura et al, 2017). Other studies have linked T2D with neurodegeneration (both global and regional) and cognitive decline (Moran et al, 2015; Last et al, 2007; Schneider et al, 2017 van den Berg et al, 2009).

Some evidence has suggested that mid-life diabetes poses the greatest risk for the development of brain pathology and dementia. Mid-life diabetes is associated with lower whole brain volume (WBV) and hippocampal volume (HV) (Roberts et al, 2014). Other studies suggest that cognitive impairment is more severe in those with diabetes in later life (Arnold et al., 2018). Previous studies have also shown that there are sex differences in cardiovascular mortality and degree of target organ damage with diabetes (Ezekowitz et al., 2020); Gómez-Marcos et al, 2015). Females with diabetes are at a higher risk of coronary heart disease and stroke than males (Huxley et al, 2006; Peters et al, 2014; de Simone et al, 2017). Females with diabetes have a higher risk of developing vascular dementia (Chatterjee et al, 2016) and have been found to have smaller brains than females without diabetes (Espeland et al, 2015). One study reported that diabetes is associated with lower hippocampal volumes in females but not in males (Hempel et al, 2012).

Hyperglycemia is a mechanistic marker of diabetes associated with cognitive deficits, small vessel disease and neurodegeneration (Cox et al, 2005, Liu et al, 2018, Schneider et al, 2017). There are various hypothesised pathways through which hyperglycemia can damage the brain (Stehouwer et al, 2018). In line with findings of sex differences in target organ damage in diabetes, hyperglycemia in females has been associated with higher risk of cardiovascular

disease when compared to males (Du et al, 2016), but few studies have explored sex differences in associations between hyperglycemia (especially across different time points) and markers of brain pathology.

The MRC National Survey of Health and Development (NSHD) is a national birth cohort of people born in the UK during the same week in 1946 (Kuh et al, 2016). The longitudinal span of the study, now running over 7 decades, is unique, and participants have been repeatedly phenotyped for social and clinical characteristics throughout their lifetime. Using Insight 46, a neuroscience sub-study of NSHD, we investigated whether higher levels of glycated haemoglobin (HbA1c), even within the normal range, and cumulative glycemic burden over mid-life to late life, were associated with adverse cognitive and brain imaging outcomes at age 69-71.

We hypothesised that higher HbA1c across the different time-points (and greater GCI) would be associated with higher WMHVs, smaller global and hippocampal brain volumes, amyloid positivity, and worse cognitive outcomes at age 69-71 and that the strength of any associations would differ by sex.

2.Methods

2.1 Standard protocol approvals, registrations, and patient consents

The study was approved by the National Research Ethics Service Committee London (REC reference 14/LO/1173) and all participants provided written informed consent.

2.2 Sample

The NSHD is a British birth cohort originally consisting of 5,362 males and females born across mainland Britain during the same week in 1946 (Kuh et al, 2016). There have been 24 waves of data collections across childhood and adulthood with participants most recently assessed at age 68–69. Insight 46 is a neuroscience sub-study of this cohort consisting of 502 participants who underwent further assessments between May 2015 and January 2018. Inclusion into the sub-study was based solely on maximising the life course data available within NSHD. Participants were selected at random from those who attended a clinic-based assessment at age 60–64, had childhood and adulthood data available and were willing to attend a clinic visit in London. A more detailed description of the Insight 46 inclusion criteria have previously been described (Lane et al, 2017).

2.3 Investigations

2.3.1 Neuroimaging protocol

Neuroimaging was performed using a single Biograph mMR 3T PET-MRI scanner (Siemens Healthcare, Erlangen), with simultaneous acquisition of dynamic PET-MRI data, including volumetric (1.1 mm isotropic) T1-weighted and T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) sequences. The full imaging protocol has been described previously (Lane et al, 2017). PET data were acquired continuously in list mode, during and following injection of 370 MBq ^{18}F florbetapir (Avid Radiopharmaceuticals, Philadelphia, PA).

Amyloid burden was assessed over a 10-min period, around 50 min after injection. Positive or negative A β was determined using a Gaussian mixture model applied to SUVR values, taking the 99th percentile of the Ab-negative Gaussian as the cut-off point (0.6104).

Volumetric T1-weighted and FLAIR images underwent visual quality control before processing using automated pipelines whole-brain volume (WBV) segmentation using Multi-Atlas Propagation and Segmentation (Leung et al, 2011), hippocampal volume (HV) using Similarity and Truth Estimation for Propagated Segmentations (Cardoso et al, 2013) with appropriate manual editing, and total intracranial volume (TIV) using Statistical Parametric Mapping 12 (Malone et al, 2015). A validated, unsupervised, automated algorithm, Bayesian Model Selection (BaMoS), (Sudre et al, 2015) was used to segment white matter hyperintensities jointly from 3D T1 and FLAIR images, followed by visual quality control, generating a global white matter hyperintensity volume (WMHV) including subcortical grey matter but excluding infratentorial regions.

For imaging analyses, participants also needed acceptable quality amyloid PET and MRI of acceptable quality as determined by visual assessment. For WMHV and brain volume analyses, individuals with white matter pathologies not considered to be of vascular origin (e.g., demyelination) or cortical infarcts inappropriately segmented were excluded.

2.3.2 Cognitive outcome measures

Cognitive function at age 69-71 was assessed using the Preclinical Alzheimer Cognitive Composite (PACC). The PACC is a composite measure derived from four cognitive assessments: Mini Mental Status Examination total score, Logical Memory delayed recall score, Digit Symbol Substitution Test score, and the Face-Name Associative Memory Exam total score. This is described in details by Lu et al, 2019.

2.3.3 Life course and clinical variables

HbA1c was measured in non-fasting blood samples at age 53, overnight fasting blood samples at age 60–64 years, and non-fasting blood samples at age 69–71. Cumulative glycemic index (CGI) was calculated by multiplying the number of HbA1c units above normal at each cycle by the number of months between the midpoints of the preceding and succeeding cycle intervals (Orchard, 1997). T2D status and prescription medication for diabetes (including insulin) were based on questionnaire self-reported diagnosis at ages 36, 53, 60–64 and 69–71.

Childhood socioeconomic position (cSEP) was measured as father's occupational social class recorded at age 4–5 (or if missing at age 11). Adult socioeconomic position (aSEP) was measured by the occupation of head of household at 53 years. These were coded according to the UK Registrar General's Standard Occupational Classification, then classified into 6 categories: unskilled, partly skilled, skilled manual, skilled nonmanual, intermediate, professional. Childhood cognitive function was derived from four tests of verbal and non-verbal ability administered to the participants at ages 8, 11 and 15 (Pigeon, 1964).

Educational attainment was represented as the highest educational or training qualification achieved by age 43, grouped into 5 categories: no qualification, below O-levels (vocational), O-levels and equivalents, A-levels and equivalents, higher education (degree and equivalents). Smoking status was assessed through questionnaire-based self-report (available at ages 53, 60–64 and 69) and was classified into three groups: smokers, ex-smokers and non-smokers at each age. Physical activity level (available at ages 53, 60–64 and 69) was ascertained by self-report and classified into any physical activity (participants exercised at least once a week) or no physical activity (no physical activity in a week). Body mass index (BMI) was defined as $\text{weight(kg)}/\text{height(m}^2\text{)}$ using height and weight measurements collected by trained nurses during each time point assessment to a standard protocol. *APOE* genotyping

was performed based on the two single nucleotide polymorphisms, rs439358 and rs7412, and individuals were subsequently categorised as *APOE*- ϵ 4 carriers or non-carriers.

2.4 Statistical analysis

Statistical analyses were conducted in Stata version 15.1. For continuous variables that were normally distributed, means and standard deviations were reported. For skewed data, the median and the range were reported. For categorical variables, frequency and percentages were reported.

The associations between each HbA1c and cumulative glycemic index (CGI) measures with brain imaging and cognitive outcomes were tested through a series of linear regression models. Confounders were identified through a directed cyclic graph (supplementary figure 1) on the basis of a literature review exploring the association between hyperglycemia and brain outcomes. Potential confounders were considered to be sex, age at neuroimaging scanning, cSEP, adulthood socioeconomic position (aSEP), childhood cognition, education, BMI, physical activity level and smoking status. For each association a minimally adjusted model (Model 1) was first constructed. Model 1 was adjusted for sex and age at scan. For WBV, total HV and WMHV, this model additionally adjusted for TIV. Model 2 further adjusted for social factors related to cognition (cSEP, aSEP, childhood cognition and education). Model 3 was the fully confounder-adjusted model and further included lifestyle factors (BMI, physical exercise, smoking status at measured at each time point respectively). Prior to running model 1, interaction terms between each HbA1c indicator and sex were examined. Models were subsequently sex-stratified if this term was statistically significant (likelihood ratio test, $p < 0.05$). When amyloid status was used as an outcome, interaction terms between HbA1c and *APOE* ϵ 4 were also explored. If any of the interaction terms were significant, the sample was stratified accordingly.

Owing to its skewed distribution, WMHV was log transformed prior to analysis and associations are reported as % change in WMHV. To control for the effect of diabetic medication (including insulin) on blood sugar levels, a value 11 mmol/mol (1%) was added to the HbA1c value of any participants receiving hypoglycemic medication at a given time point. The 1% addition is consistent with a previous clinical review that reported the effectiveness of antidiabetic drugs to range from 0.9-1% (Chaudhury et al, 2017). Moreover, the addition of 11mmol/mol, approximately 1SD reflects the approach used for blood pressure (BP), where again a rough 1SD is added to the measured HbA1c, reflecting longstanding exposure to elevated HbA1c.

One participant was excluded from the analysis for having an HbA1c value of more than 3SD from the mean suggesting a potential error in measurement. Multiple imputation for missing data was performed using the Multivariate Imputation by Chained Equations (MICE) method by fully conditional specification (50 imputed datasets) under the assumption of missing at random. MICE results are presented below but previously checked for concordance with the complete case data and the pattern of effects were similar. In addition, a sensitivity analysis was performed using measured HbA1c whereby the effects of diabetes medication were omitted. This had no significant effect on the findings.

For all analyses, the conventional level of 5% was used to represent statistical significance.

3. Results

Following multiple imputation, the final analysis consisted of data for 454 participants. All 454 participants had available data for WBV, HV and WMHV and 446 (91%) had usable data for amyloid analysis (see figure 1). For complete case analysis, see supplementary table 3 and table 4 in the appendix.

Demographic and clinical characteristics are shown in table 1. Participants were aged 70 years (SD = 0.7), 52% were male and 82 participants (18.3%) met the threshold to be considered amyloid positive. HbA1c levels were similar across each sweep (see table 1). There was no significant difference in mean HbA1c values between males and females at any age: age 53 (M=36.7 mmol/mol (SD = 4.7), F=37.4 mmol/mol (SD = 4.9)), age 60-64 (M=37.1 mmol/mol (SD = 5.4), F=37.6 mmol/mol (SD = 5.6)) and age 69 (M=37.7 mmol/mol (SD = 5.8), F = 38 mmol/mol (SD = 6.2)). See supplementary table 1 for additional comparisons between males and females.

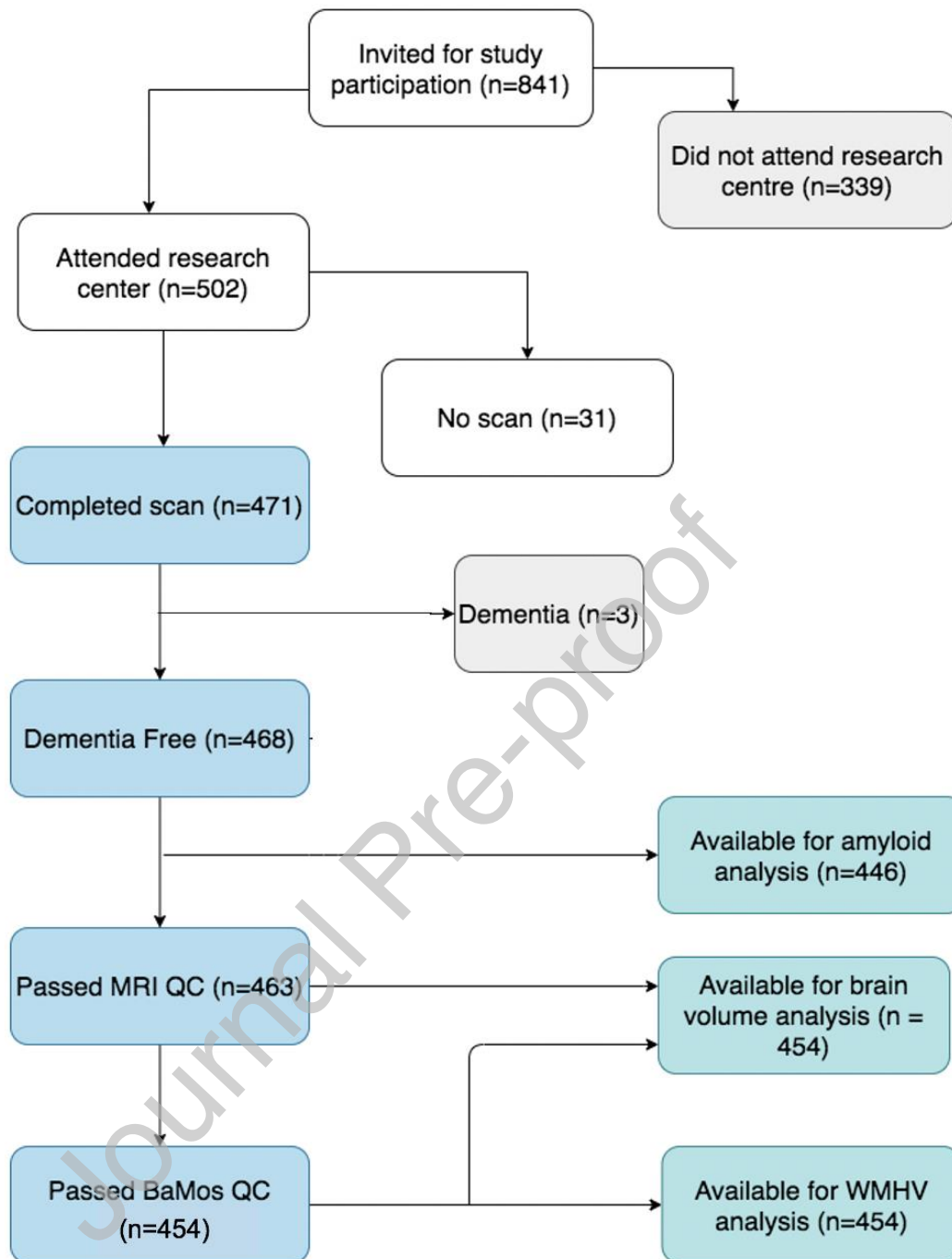


Figure 1. Flowchart providing an overview of Insight 46 recruitment from the NSHD cohort and summary of imaging data available. BaMoS, Bayesian Model Selection; MRI, magnetic resonance imaging; MCI, mild cognitive impairment; NSHD, National Survey of Health and Development; PET, positron emission tomography; QC, quality control; WMHV, white matter hyperintensity volume.

Characteristics		Males	Females
Age at scanning, years (SD)		70.7 (0.7)	70.7 (0.7)
Amyloid positive n (%)		45 (54%)	37 (46%)
Amyloid SUVR (SD)		0.60 (0.07)	0.58 (0.07)
Whole brain volume, mL (SD) – unadjusted for Total Intracranial volume (TIV)		1152.4 (87.0)	1047.3 (82.1)
Hippocampal volume, mL (SD)		6.5 (0.6)	6.0 (0.7)
White matter hyperintensity volume, mL (SD)		1.10 (1)	1.22 (1.01)
Total intracranial volume, mL (SD)		1519.8 (106.8)	1343.1 (92.6)
Preclinical Alzheimer Cognitive Composite z score (SD)		-0.16 (0.7)	0.16 (0.7)
Standardised childhood cognition score (SD)		0.36 (0.75)	0.45 (0.74)
Systolic blood pressure at 69, mm Hg		134.9 (15.9)	130.9 (16.4)
APOE ε4 carrier (1 or 2 alleles) n (%)		74 (54%)	62 (46%)
HbA1c levels % (SD)	<i>At 53 years of age</i>	5.5 (0.4)	5.6 (0.5)
		36.7 (4.7)	37.4 (4.9)
HbA1c mmol/mol (SD)	<i>At 60–64 years of age</i>	5.5 (0.5)	5.6 (0.5)
		37.1 (5.4)	37.6 (5.6)
	<i>At 69 years of age</i>	5.5 (0.5)	5.6 (0.5)
		37.3 (5.8)	37.9 (6.2)
Self-reported diagnosis of diabetes (n (%))	<i>At 53 years of age</i>	14 (52%)	13 (48%)
	<i>At 60–64 years of age</i>	16 (60%)	11 (40%)
	<i>At 69 years of age</i>	17 (63%)	10 (37%)
Diabetes medication use (n (%))	<i>At 53 years of age</i>	1 (50%)	1 (50%)
	<i>At 60–64 years of age</i>	10 (63%)	6 (37%)
	<i>At 69 years of age</i>	15 (6%)	14 (6%)
Smoking status at 69	<i>Current Smokers</i>	4 (44 %)	5 (56 %)
	<i>Ex-smokers</i>	120 (58%)	86 (42%)
	<i>No smoking history</i>	107 (46%)	124 (54%)
Body-mass index, kg/m ²	<i>At 53 years of age</i>	27.1 (3.4)	26.7 (4.7)
	<i>At 60–64 years of age</i>	26.6 (3.5)	27.3 (4.7)
	<i>At 69 years of age</i>	27.8 (3.6)	27.2 (5.1)

Adult socioeconomic position	<i>Non-manual (Class I–III)</i>	29 (6%)	92 (20%)
	<i>Manual (Class IV–VI)</i>	206 (46%)	129 (28%)
Childhood socioeconomic position	<i>Non-manual (Class I–III)</i>	87 (19%)	88 (19%)
	<i>Manual (Class IV–VI)</i>	147 (33%)	129 (29%)

Table 1. Demographic and clinical characteristics of females and males. These are pre-imputation, so the statistics were generated. The number of females is 221 and the number of males is 233. Values are n, mean (SD), n (%), or median (IQR).

3.1 Associations between HbA1c and PET amyloid status:

There were no significant associations between HbA1c at any time-point investigated, or CGI, on amyloid status at age 69-71 with or without adjustment for potential confounders (Table 2). There was also no evidence of an interaction with either sex (p interaction for all >0.7) or APOE status (p interaction for all > 0.5).

3.2 Associations between HbA1c and WMHV:

There were no significant associations between HbA1c at any time-point, or CGI, and WMHV at age 69-71 with or without adjustment for potential confounders (see table 2). There was also no evidence of an interaction with sex (p interaction for all >0.7).

3.3 Associations between HbA1c and WBV:

Interaction analysis revealed a difference between males and females in the association between HbA1c and WBV at age 53 ($\beta = 118.1$, CI (50.9, 120.2), $p = 0.001$), age 60-64 ($\beta = 94.6$, CI (34.9, 154.3), $p = 0.002$), and age 69 ($\beta = 102.1$, CI (47.2, 156.9), $p < 0.001$), so a stratified analysis was performed. Higher HbA1c at each time point was associated with lower mean WBV at age 69-71 in females, but not in males (Figure 2). These associations were negligibly affected by adjustment for potential confounders. Analysis of association between CGI and WBV showed essentially similar findings with a negative association between cumulative HbA1c in females and no evidence of an association in males (figure 3). As a sensitivity analysis, we replicated this analysis after excluding the participants with

diabetes. The associations between HbA1c and WBV in females remained similar (supplementary table 2).

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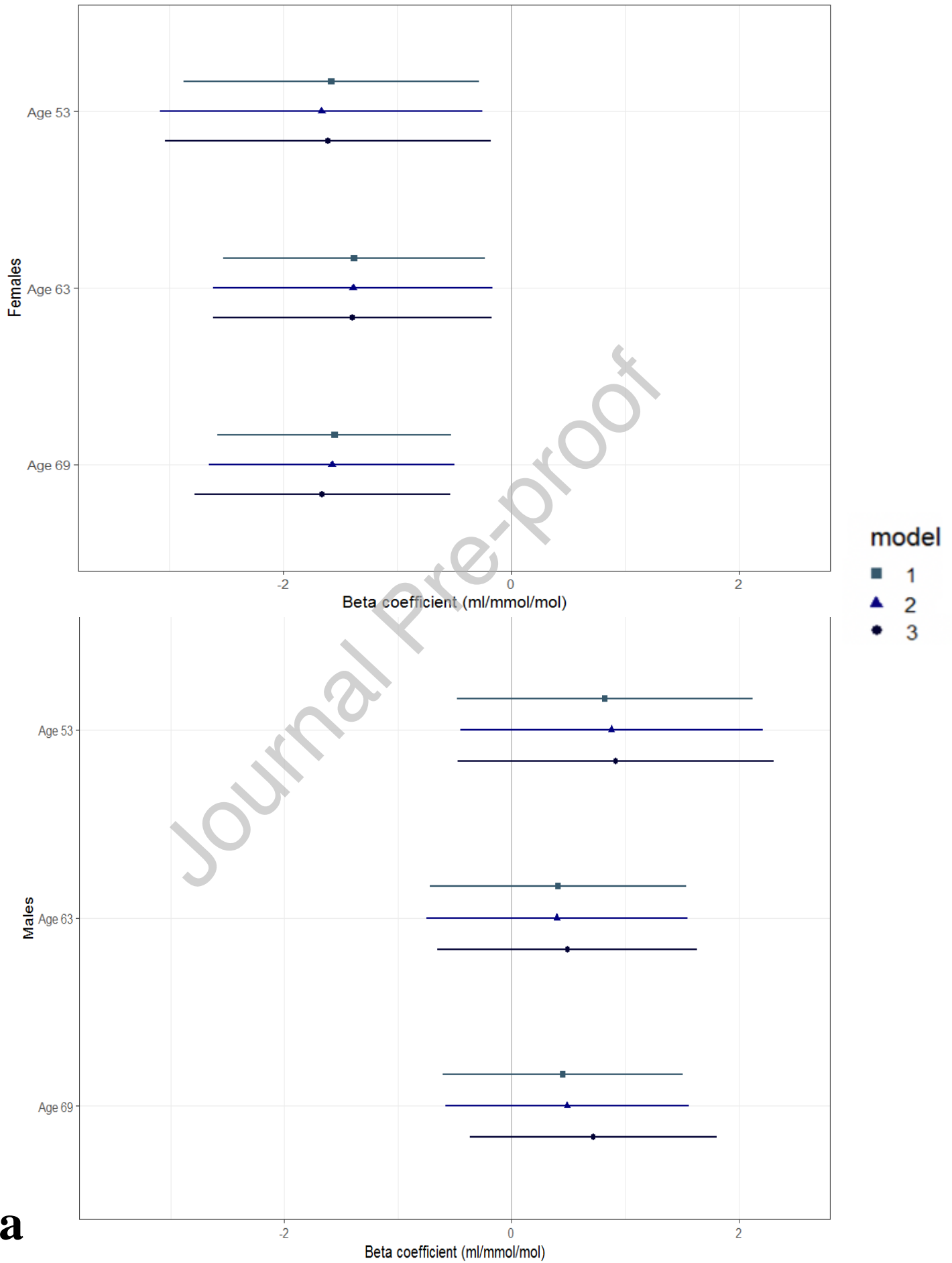
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Figure 2. Forest plots showing the associations between HbA1c levels across all ages and WBV stratified by sex. Graph a represents these associations in females and graph b represents these associations in males. Model 1: minimally adjusted model for TIV and age at scanning. Model 2: Model 1 + adjustments for cSEP, aSEP, education and childhood cognition. Model 3: Model 2 + adjustments for BMI, physical activity and smoking status.

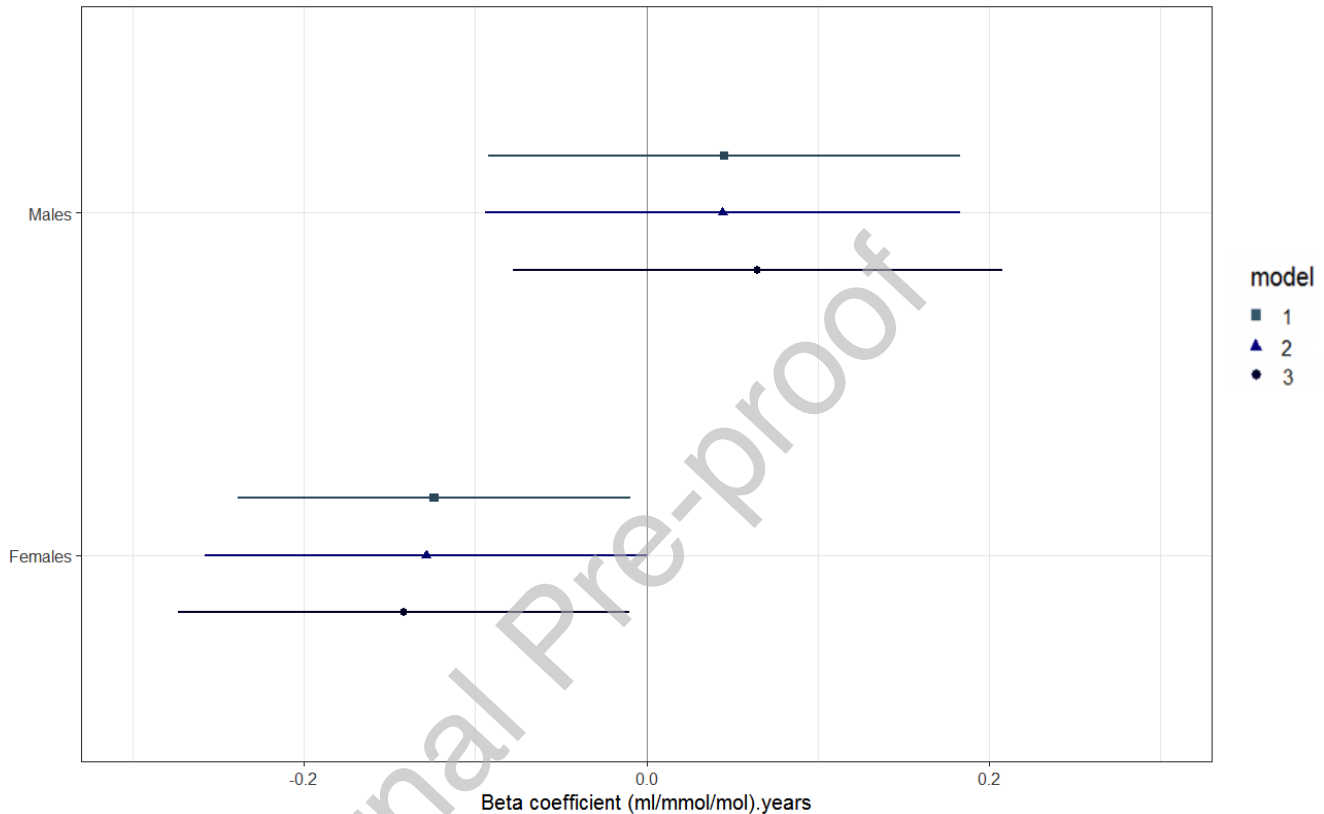


Figure 3. Forest plots showing the associations between CGI and WBV volume at 69–71 years of age. Model 1: minimally adjusted model for TIV and age at scanning. Model 2: Model 1 + adjustments for cSEP, aSEP, education and childhood cognition. Model 3: Model 2 + adjustments for BMI, physical activity and smoking statuses.

3.4 Associations between HbA1c and hippocampal volume:

There were no significant associations between HbA1c at any time-point and HV at age 69–71 with or without adjustment for potential confounders (Table 2). Findings for CGI were similar and there was no evidence of a sex interaction for either HbA1c or CGI (all interaction P values > 0.1).

3.5 Associations between HbA1c and cognitive outcomes:

There were no associations between HbA1c at any time-pointed and the PACC cognitive scores at age 69-71 with or without adjustment for potential confounders (Table 2). Findings for CGI were similar and there was no evidence of a sex interaction for either HbA1c or CGI (all interaction P values>0.7).

		WMHV ($\mu\text{L}/(\text{mol}/\text{mol})$)				HV ($\mu\text{L}/(\text{mol}/\text{mol})$)				Amyloid status				PACC			
		β	95% CI		p	β	95% CI		p	OR	95% CI		p	β	95% CI		p
Age 53	M1	-2.780	-23.208	17.649	0.79	-1.454	-13.070	10.163	0.81	1.23	0.71	2.15	0.5	-0.001	-0.014	0.013	0.94
	M2	-1.813	-22.947	19.322	0.87	-1.987	-13.899	9.925	0.74	1.24	0.70	2.20	0.5	0.0001	-0.012	0.013	0.97
	M3	-2.814	-24.554	18.927	0.80	-2.051	-14.211	10.110	0.74	1.24	0.69	2.22	0.5	0.000	-0.013	0.013	0.97
Age 60-64	M1	1.240	-16.637	19.116	0.89	0.411	-8.627	9.909	0.94	1.15	0.71	1.87	0.6	-0.002	-0.014	0.011	0.80
	M2	1.782	-16.528	20.093	0.85	-0.357	-9.399	9.448	0.95	1.15	0.72	1.87	0.6	0.0001	-0.011	0.011	0.98
	M3	0.076	-18.541	18.693	0.99	-0.703	-11.377	8.027	0.89	1.18	0.71	1.93	0.5	0.000	-0.011	0.012	0.94
Age 69	M1	4.072	-12.401	20.544	0.63	0.641	-12.093	2.836	0.22	1.00	0.72	1.40	>0.9	-0.001	-0.012	0.010	0.82
	M2	4.766	-12.083	21.615	0.58	0.025	-12.012	3.328	0.27	0.98	0.70	1.40	>0.9	-0.001	-0.011	0.010	0.92
	M3	2.662	-14.665	19.989	0.76	-1.675	-11.532	4.147	0.36	1.06	0.75	1.49	>0.8	0.001	-0.010	0.011	0.91
CGI	M1	0.101	-0.092	0.294	0.30	-5.554	-14.512	3.403	0.22	1.04	0.86	1.27	0.7	-0.016	-0.150	0.119	0.82
	M2	0.294	-0.091	0.308	0.29	-5.210	-14.414	3.993	0.27	1.04	0.85	1.27	0.7	-0.006	-0.127	0.115	0.92
	M3	0.098	-0.107	0.303	0.35	-4.431	-13.838	4.976	0.36	1.04	0.85	1.28	0.7	0.007	-0.116	0.131	0.91

Table 2. Regression analyses between HbA1c and cumulative glycemic index (CGI) with cognitive and brain imaging outcomes. The outcomes presented are white matter hyperintensities volume (WMHV), hippocampal volume (HV), Amyloid status and Preclinical Alzheimer Cognitive Composite (PACC). For WMHV and HV, the models were as follow = Model 1: minimally adjusted model for TIV, sex and age at scanning. Model 2: Model 1 + adjustments for cSEP, aSEP, education and childhood cognition. Model 3: Model 2 + adjustments for BMI, physical activity and smoking statuses. For Amyloid status and PACC - Model 1: minimally adjusted model for sex and age at scanning. Model 2: Model 1 + adjustments for cSEP, aSEP, education and childhood cognition. Model 3: Model 2 + adjustments for BMI, physical activity and smoking status. OR - Odds ratio

4. Discussion

In this longitudinal study, we observed a sex difference in the association between HbA1c measured in adulthood and WBV during late life. Elevated HbA1c at 53, 60-64 and 69 years, even within the normal range, was associated with lower WBV at age 70-72 in females, but not in males. A similar interaction was observed between higher cumulative glycemic exposure and WBV. We found no evidence of an association between HbA1c levels, or CGI and β -amyloid status, WMHV, HV and cognitive outcomes in either sex separately or combined.

Previous cross-sectional studies have reported that diabetes and pre-diabetes are associated with impaired brain structure (Furlano, Horst, & Nagamatsu, 2021) and elevated HbA1c has been reported to be associated with reduced WBV (Schneider et al, 2017). We demonstrate that elevated glycemic levels measured at successive time points throughout midlife and early late-life predict lower WBV in females at age 69-71. There was no evidence that the strength of association differed over the period of mid-life to early late-life. This contrasts with some previous work showing that mid-life diabetes was associated with worse brain and cognitive outcomes later in life (Roberts et al, 2014). Our finding of a sex difference in associations between HbA1c and WBV is in keeping with previous studies that have found sex differences in susceptibility to target organ damage in T2D. One previous study reported that T2D was associated with a greater reduction in hippocampal volumes in females than in males (Hempel et al. 2012). Females with diabetes also have a higher risk of vascular disease as well as renal and cardiac target organ damage (Gómez-Marcos et al, 2015; de Simone et al, 2017). A greater burden of vascular disease, particularly SVD, could contribute to brain atrophy (Wardlaw et al, 2013), although the lack of an increase in WMH in association with elevated HbA1c in our study seems inconsistent with this being a major mechanism. Schneider et al. (Schneider et al, 2017) also found no evidence that increased WMH mediated the association between HbA1c and lower brain volume in the Atherosclerosis Risk in Communities Neurocognitive Study.

There are multiple possible explanations for these differences by sex: one is that poorer brain outcomes are related to the natural decline of oestrogen experienced by females after the menopause. Oestrogen is a sex hormone thought to have an important neuroprotective effect supporting important neuronal functions (Cutter et al, 2003). A sex-related differences in inflammatory responses linked to T2D is another possible explanation.

Hyperglycemia results in the formation of advanced glycosylation end products which in turn can result in the chronic stimulation of cytokines and inflammation. Increased inflammation and advanced glycosylated end products are known to promote neurodegeneration (Roriz-Filho et al., 2009, Sims-Robinson et al., 2010) and there is evidence of sex differences in inflammation in T2D, with females showing higher levels of C-reactive protein compared to males (de Rekeneire et al, 2006).

We originally hypothesised that elevated HbA1c and glycemic burden would be associated with WMHV, a cardinal measure of cerebral SVD. This was based on known mechanistic pathways linking hyperglycemia to cerebral microvascular remodelling and damage to the blood-brain barrier. Our findings did not show a convincing association between HbA1c at any time point and WMHV, and there was also no evidence of an association between CGI and WMHV. This is consistent with some studies (Reitz et al, 2017; Schneider et al, 2017), although others have failed to observe an association between elevated HbA1c and WMHV (de Havenon et al, 2019). This inconsistency in the literature may be explained by variability in the methods with not all studies adjusting for all potentially important confounders such as demographic (i.e, age, sex and education) and clinical factors (i.e depression and vascular risk).

Alternatively, it is possible that the volumetric parameter for WMHs we used was insufficiently sensitive to detect an association between hyperglycemia and WMHs, or that it fails to discriminate between different etiologies (Last et al, 2007). One study found that although people with T2D did not differ from controls on traditional WMH measures (i.e., total WMH volume), they displayed more non-punctuate WMH and there was a difference in shape (eccentricity) of punctuate deep WMH (de Bresser et al, 2018). A future analysis of the location and shape of the WMH lesions in this cohort may therefore be warranted.

We did not find any convincing associations between elevated HbA1c and cognition as assessed by the PACC. Previous evidence on this relationship is mixed: some studies report that poorer glycemic control, as measured by higher HbA1c levels, is associated with worse cognitive function (van Harten et al., 2007), while others report no convincing associations (Cosway et al, 2001, Christman et al, 2011). These inconsistencies may be attributable to the heterogeneity in the cognitive measures used by different studies. We also failed to observe an association between raised HbA1c and amyloidosis. This finding is consistent with previous studies that failed to observe an association between HbA1c levels and A β positivity

rates despite observing an association between hyperglycemia and neurodegeneration (Byun et al, 2017). This finding suggests that hyperglycemia may affect brain outcomes through non-amylogenic pathways

A major strength of this study is the uniqueness of our cohort and the rich longitudinal data acquired over decades of adult life; however, it also has several limitations. Insight 46 participants were selected based on previous clinic attendance, among other criteria. We have previously reported that this selection results in a bias towards those with higher SEP, more education, better cognitive function, and better health (James et al, 2018). This may explain some of the negative findings observed as the cohort is cognitively normal, limiting the extent of pathology. In addition, 957 NSHD participants had died before the 2015 sweep, so differential survival may have also biased our results toward the null (Kuh et al, 2016). An inherent weakness of a birth cohort design is that it is subject to secular influences, and this post-war cohort is likely to have characteristics and exposures that differ from modern day cohorts, especially in terms of lifestyle and diet. This could make it difficult to generalise our findings to other younger cohorts. Another important limitation is that our sample is exclusively white British, and thus may not be representative of other populations. This is particularly important since both rates of T2D, and AD have been shown to vary based on ethnicity (Mehta et al, 2008, Tillin et al, 2012).

In conclusion, this longitudinal study found that elevated HbA1c from mid-life onwards was associated with lower WBV in females but not in males. This suggests that raised HbA1c in the normal range is preferentially linked to target organ damage in the female brain. Future work should explore potential mediators in these associations and focus on the development of sex-specific prevention strategies against brain volume loss.

5. Competing interests:

JS has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), has consulted for Roche Pharmaceuticals, Biogen and Eli Lilly, and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) provide the PET β -amyloid

tracer for Insight 46 (Florbetapir) but had no part in the design of the study. All other authors have no competing interests to declare.

6. Acknowledgement

All authors contributed to this study. NF, SJ and AH were involved in the conceptualisation of the study. TP, CL, and KL performed the data collection, NF was involved in the formal analysis of the data, SJ, AH, NC and NF were involved in the interpretation of the data. NF drafted the manuscript and AH, SJ, NC, CL, TP, KL, DC, IM, RS, AW, JB, CS, MR, NF, and JS critically reviewed and amended the manuscript.

7. Additional Contributions, availability of data and materials.

We thank National Survey of Health and Development study members for their lifelong participation and past and present members of the National Survey of Health and Development study team who helped to collect the data. Data used in this publication are available to bona fide researchers on request to the National Survey of Health and Development Data Sharing Committee via a standard application procedure. Further details can be found at <http://www.nshd.mrc.ac.uk/data>. <https://doi.org/10.5522/nshd/q102>; <https://doi.org/10.5522/nshd/q103>.

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9. Disclosures

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