European Journal of Endocrinology, 2025, **192**, K44–K49
https://doi.org/10.1093/ejendo/lvaf090
Advance access publication 29 April 2025
Brief Report

Sex differences between mid-life glycaemic traits and brain volume at age 70: a population-based study

Nasri Fatih,[1] Alun Hughes,[1] Carole H. Sudre,[1] Nishi Chaturvedi,[1] Victoria Garfield,[1,2] Richard J. Silverwood,[3] George Ploubidis,[3] Thomas D. Parker,[4] Kirsty Lu,[4] David M. Cash,[4] Ian B. Malone,[4] Andrew Wong,[1] Josephine Barnes,[4] Marcus Richards,[1] Nick C. Fox,[4,5] Jonathan M. Schott,[4,†] and Sarah-Naomi James[1,4,*†]

[1]MRC Unit for Lifelong Health and Ageing at UCL, Institute of Cardiovascular Science, London WC1E 7HB, United Kingdom
[2]Department of Pharmacology & Therapeutics, Institute of Systems, Molecular & Integrative Biology, University of Liverpool, Liverpool L69 7BE, United Kingdom
[3]Centre for Longitudinal Studies, UCL Social Research Institute, University College London, London WC1H 0AL, United Kingdom
[4]Dementia Research Centre, UCL Queen Square Institute of Neurology, University College London, London WC1N 3AR, United Kingdom
[5]UK Dementia Research Institute at UCL, University College London, London NW1 3BT, United Kingdom

*Corresponding author: MRC Unit for Lifelong Health and Ageing at UCL, Institute of Cardiovascular Science, London WC1E 7HB, UK.
Email: sarah.n.james@ucl.ac.uk

Abstract

Higher HbA1c in mid-to-later life has been associated with smaller whole brain volume (WBV) in older women but not men. We explored whether this association was replicated using different markers of (i) glycaemic health [fasting glucose, insulin resistance (HOMA2-IR), and β-cell function (HOMA-%B)] and (ii) brain structure (white or grey matter volume). 453 participants (51% men) from the 1946 British Birth Cohort had glycaemic measures (at age 60–64) and MRI measures (at age ~70). In women, higher fasting glucose and insulin resistance at age ~60 were weakly associated with lower WBV at age ~70 [eg, fasting glucose: β* = −0.07 (95% CI: −0.13, −0.01), $P = .02$]. No associations emerged for men for any glycaemic marker. HOMA-%B was not associated with brain outcomes in either sex. Women's later-life brain health may be more vulnerable to midlife hyperglycaemia.

Keywords: neuroendocrinology, diabetes mellitus, insulin, brain structure

Significance

Using data from the National Health Survey of Health and Development (NSHD) (n~450), we found that different glycaemic markers in mid-life were associated with poorer brain health later in life in women but not in men. For the relationship between fasting glucose and WBV in women, a 1 SD increase of fasting glucose (1.1 mmol/L) in women was equivalent to around 6 months of WBV aging. Although this may be small for a single individual, such effect may be important at a population level. There was no strong evidence of a relationship between glycaemic markers and preferential tissue loss. These findings suggest that management of hyperglycaemia and insulin resistance in mid-life may confer protection of women's brain health.

Introduction

A previous study in a British birth cohort demonstrated that elevated HbA_{1c} throughout mid- and later-life was associated with smaller WBV at age ~70 only in females.[1] However, it remains unknown whether other glycaemia-related pathophysiological markers, such as insulin resistance (HOMA2-IR), beta cell function (HOMA%B), and fasting glucose are (i) also related to smaller later-life whole brain volume, (ii) affect females preferentially; and (iii) predict preferential tissue loss of grey matter (GM) and white matter (WM). We aimed to answer these questions and to provide insights into the mechanism by which dysglycaemia at age 60–64 may be differentially associated with brain health in men and women.

Methods

Information on the sample, exposures, outcomes and analytical approach are found in Supplementary Material 1. Ethical approval for the neuroscience sub-study was granted by the

† J.M.S. and S.-N.J. contributed equally as last authors.

Received: October 17, 2024. **Revised:** March 31, 2025. **Editorial Decision:** April 7, 2025

Table 1. Sample characteristics for the participants considered in these analyses ($n = 453$). .

Participant characteristics	*n*	Males	*n*	Females
Standardised childhood cognition score	231	0.36 (0.73)	222	0.44 (0.74)
Education		231		221
No qualifications		24 (10%)		31 (14%)
Below O-levels (vocational)		17 (7%)		17 (8%)
O-levels and equivalents		38 (17%)		56 (25%)
A-levels and equivalents		83 (36%)		79 (36%)
Degree or higher		69 (30%)		38 (17%)
Adult socioeconomic position		231		222
Non-manual (Class I–IIIN)		193 (84%)		193 (87%)
Manual (Class IIIM-V)		38 (16%)		29 (13%)
Childhood socioeconomic position		231		218
Non-manual (Class I–IIIN)		142 (61%)		120 (55%)
Manual (Class IIIM-V)		89 (39%)		98 (45%)
Characteristics, age 60-64				
HbA_{1c}, %	215	5.71 (0.47)	209	5.8 (0.55)
HbA_{1c}, mmol/mol	215	39.91 (5.15)	215	38.8 (6)
Fasting glucose, mmol/L	227	5.9 (0.9)	212	5.5 (1.1)
Fasting insulin	135	44 (42)	137	35 (24)
HOMA2-IR	135	1.1 (0.8)	137	0.9 (0.5)
HOMA−%B,	135	68.1 (28.9)	137	67.2 (31.4)
Diabetes medication use	231	10 (4%)	222	6 (2.7%)
Waist–hip ratio	231	0.96 (0.06)	222	0.86 (0.06)
Smoking status		231		215
Current smokers		4 (2%)		5 (2%)
Ex-smokers		120 (52%)		86 (40%)
Never smoker		107 (46%)		124 (58%)
Alcohol (units/week)		231		222
≤14		181 (78%)		203 (91%)
>14		50 (22%)		19 (9%)
Exercise levels		229		219
Inactive		125 (55%)		107 (49%)
Moderately active		38 (17%)		47 (21%)
Most active		66 (28%)		65 (30%)
Brain imaging markers measured at age ~70				
Mean age at scanning, years	231	70.7 (0.7)	222	70.7 (0.7)
Whole brain volume (WBV), mL	231	1152.4 (87.0)	222	1047.3 (82.1)
White matter volume (WM), mL	231	439.6 (2.8)	222	394.3 (2.8)
Grey matter volume (GM), mL	231	649.6 (3.4)	222	602.6 (3)
Total intracranial volume (TIV), mL	231	1519.8 (106.8)	222	1343.1 (92.6)

Values presented are pre-imputation data: *n* (%), mean (SD), or median (IQR). % are calculated against the max data available for that specific measure for the pooled sample. As described above, the number of participants considered had to have been part of Insight 46 and have volumetric imaging data available which amounted to 453 participants of which 231 were males and 222 were females. Whole brain volume, white matter volume, and grey matter volume measurements reported are unadjusted for total intercranial volume for these descriptions. Values are *n* (%) or mean (SD).
HOMA2-IR, Homeostatic Model Assessment for Insulin Resistance; HOMA-%B, Homeostatic Model Assessment for β cell function; SD, Standard deviation.

National Research Ethics Service (NRES) Committee London (14/LO/1173). All participants gave written informed consent and this project complies with the Declaration of Helsinki.

Results

Data were available for up to 453 participants (Figure S1), with demographic and clinical characteristics shown in Table 1. The analytical sample was evenly split by sex and on average exhibited normal insulin sensitivity with mildly reduced pancreatic β-cell function.

Inter-correlations of glycaemic traits at age 60-64

There were positive relationships between HbA_{1c}, glucose and HOMA2-IR in both sexes, with a slightly stronger association demonstrated in males (for example, the correlation between glucose and HbA_{1c} was $r = 0.60$ in males vs $r = 0.54$ in females; Figure 1). The positive correlation between HOMA2-IR and HOMA%B was stronger in males ($r = 0.79$) than females ($r = 0.55$), but the negative correlation between glucose and HOMA%B was stronger in females ($r = -0.37$) than males ($r = -0.17$).

Associations between glycaemic traits at age 60-64 and whole brain volume at age 70

Glucose

There was an association between higher glucose and lower WBV in females [$\beta^* = -0.07$ (95% CI: −0.13, −0.01); $P = 0.02$] but not in males [$\beta^* = -0.05$ (−0.14, 0.03); $P = .2$; Figure S2, Table S1).

HbA_{1c}

As previously described,[1] there was a significant association between higher HbA_{1c} at age 60-64 and smaller WBV in females only (Figure S2, Table S1).

No significant associations emerged between HOMA-%B and WBV, in either sex ($P > 0.05$) (Figure S2, Table S1).

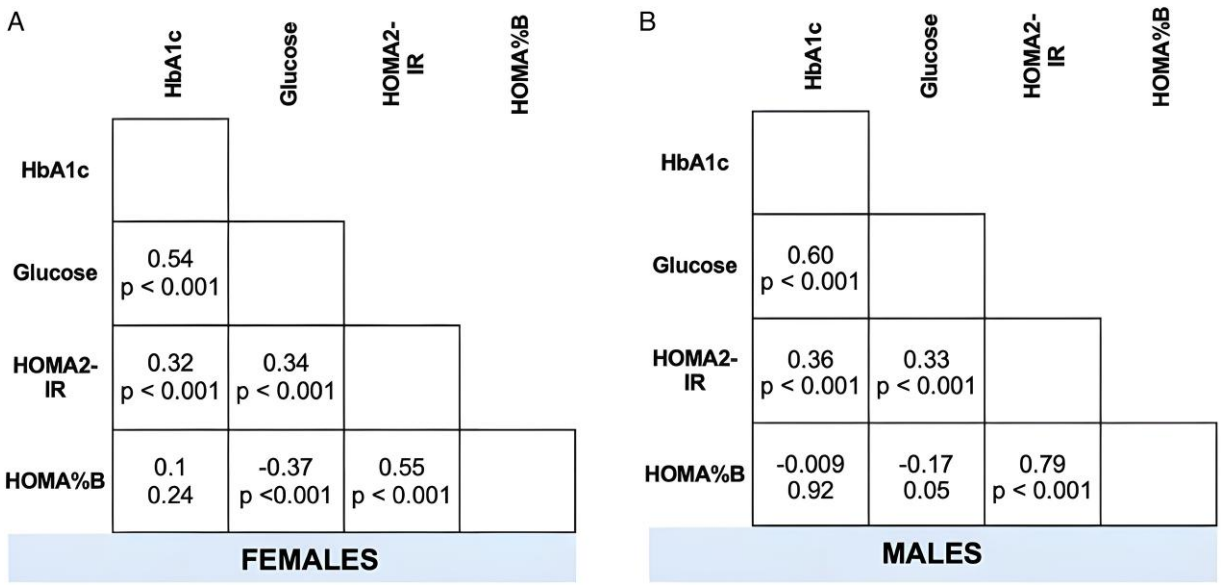

Figure 1. Correlation matrix displaying the correlation between the glycaemic markers HbA1c, glucose, HOMA2-IR, and HOMA%B. On the first row, the *r* value represents the direction of correlation (from a Pearson's correlation). In the second row, the *P* value represents the strength of any association. A) Provides the correlation matrix for the variables in females and B) provides the correlation matrix for the variables in males.

Insulin resistance (HOMA2-IR)

The association between greater HOMA2-IR and smaller WBV was statistically significant in females [β* = −0.12 (−0.2, −0.002); *P* = .04], but not in males [β* = −0.06 (−0.16, 0.05); *P* = 0.31; Figure S2]. Overall, in females, effect sizes of the relationship between significant standardized glycaemic traits at age 60-64 and WBV were ordered as follows: HOMA2-IR (β=−0.12), HbA_{1c} (β=−0.09), and glucose (β= −0.07). None of these relationships were statistically significant in males. Adjustments for confounders did not materially change associations (Table S1).

Associations between glycaemic traits and brain tissue type

Glucose

In females, there was an association between higher glucose with smaller GM [β* = −0.04 (−0.08, −0.002) *P* = 0.04] and WM [β* = −0.06 (−0.1, −0.02) *P* = 0.02] volumes, with a slightly stronger coefficient observed for WM volumes (Figure 2, Table S1). In males, no associations between glucose and GM or WM volume emerged (*P* > .05).

HbA_{1c}

In females, there was an association between higher HbA_{1c} and smaller WM [β* = −0.06 (−0.12, −0.004) *P* = 0.04], but not between HbA_{1c} and GM volume [β* = −0.03 (−0.07, 0.006) *P* = 0.1; Figure 2, Table S1], although the confidence intervals for the GM and WM volume relationships in females overlapped, suggesting that the difference may not be substantial. In males, no associations between glucose and GM or WM volume were identified.

Beta cell function (HOMA-%B)

There were no associations between HOMA-%B and GM or WM volume, in either sex (*P* > 0.05; Figure 2, Table S1).

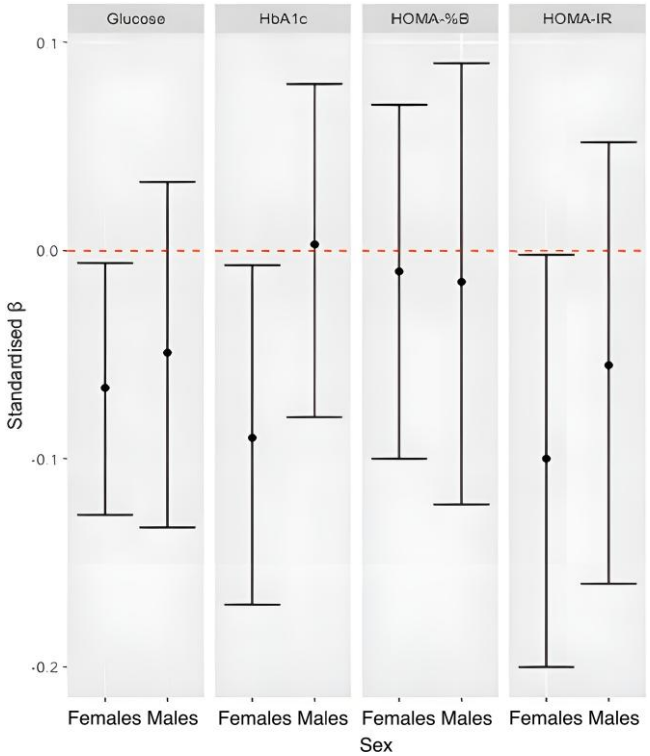

Figure 2. Forest plots displaying the associations between glycaemic traits at age 60-64 (glucose, HbA1c, HOMA-%B, HOMA-IR) with whole brain volumes at age 69-71, stratified by sex. The estimates presented are standardized regression coefficients for the fully confounder-adjusted models (adjusted for total intercranial volume, age at scan, cognitive measures, socio-economic position, waist-to-hip ratio, physical exercise, alcohol status and smoking status). Standardized coefficients are presented here to facilitate comparison.

Insulin resistance (HOMA2-IR)

In females higher HOMA2-IR was associated with smaller GM volumes [β* = −0.05 (−0.1, −0.007); *P* = 0.04], the

association with WM volumes was unconvincing, despite a similar effect size [$\beta^* = -0.05$ (−0.13, 0.04); $P = 0.27$; Figure 2, Table S1]. In males, there were no associations between HOMA2-IR and GM or WM volume.

Overall, adjustments for confounders did not materially change associations (Table S1). Inference was unaffected when analyses were repeated with complete case data (Table S2).

Discussion

In a population-based British birth cohort, biomarkers of hyperglycaemia (glucose, HbA1c) and IR (HOMA2-IR) at 60–64 were linked to smaller brain volumes ∼10 years later in females but not males, with no discernible preference for tissue type. A measure of pancreatic β-cell function (HOMA-%B) was not associated with brain volume in either sex. We previously reported that longitudinal measures of HbA_{1c} across midlife to older age were associated with smaller whole brain volume at age ∼70 in females but not in males. (i) We now show that other related, but mechanistically distinct,[2] glycaemic traits (ie, glucose and IR) also follow this sex-specific trend. The results are consistent with growing evidence that poor glycaemic health, even if only mildly abnormal,[3,4] is associated with poorer subsequent brain health independent of diabetes,[5,6] and that females may be more vulnerable.[1,7,8]

Sex-specific vulnerability to poor glycaemic health may stem from multiple factors. A key mechanism is the rapid decline of oestrogen in postmenopausal females, which normally protects against inflammation, oxidative stress, and vascular dysfunction. Its withdrawal may heighten susceptibility to hyperglycaemia.[9] Other factors include sex differences in adiposity, as higher abdominal fat is linked to poorer brain health[10] and gender-related roles, with diabetic female caregivers less likely to meet glycaemic targets or receive screenings for complications.[11] Other issues may also be important in sex differences: these include variation in glycosylation rates,[12,13] differences in erythrocyte environments,[14] and heterogeneity in erythrocyte lifespan.[15]

There were no associations between HOMA-%B and brain volume metrics in either sex. HOMA-%B is a measure of β cell response or insulin secretion in the pancreas, which may not necessarily reflect glycaemia.[16] Although in some cases, β cell dysfunction is the primary mechanism underlying diabetes, in many others, this feature appears in the latter stages of the condition. The small degree of variance in HOMA-%B in NSHD may have limited the ability to detect a relationship between HOMA-%B and brain outcomes.[17]

Previous studies addressing whether diabetes is associated with preferential tissue loss have yielded inconsistent results.[3,6,18-20] In this study, there was no convincing evidence of an association between glycaemic traits and preferential GM or WM tissue loss.

Strengths and weaknesses

Using data from a national birth cohort with a range of measured confounders, allowed for a clearer characterization of the link between glycaemic traits and smaller brain volume in females. Another strength is the cohort's uniform birth timing, minimizing age-related confounding.

Ascertainment bias is a potential limitation, as neuroimaging participants were generally more educated, from higher SEP, and in better health.[21] Differential survival, particularly among unhealthy males, may have influenced the sex-specific findings.[22] Fewer participants had HOMA measures, reducing statistical power to detect associations. We also did not examine glycaemic markers and white matter lesion (WML) volume since we previously failed to observe an association with HbA1c.[1] Future studies examining the association of glycaemic markers with more subtle measures of WML, such as their shape and distribution may be warranted. The 9- to 13-year gap between glycaemic and brain measures may introduce biases from disease progression and survival effects.

The effect sizes are quite small; taking the relationship between fasting glucose and WBV as an example ($\beta^* = -0.07$), 1 SD increase of fasting glucose (1.1 mmol/L) in females is equivalent to equivalent to a brain that is 6 months older, as measured in UK Biobank. Nevertheless, even small effects may have a significant impact on public health at the population level. Our findings are also consistent with emerging evidence suggestive of a sex-specific effect of diabetes and hyperglycaemia on brain health.[1,7,8] This issue merits further research.

Conclusions

The findings indicate that, similarly to HbA_{1c}, there are differences by sex in adverse associations between glycaemic measures (ie, fasting glucose and Insulin resistance) in late midlife and subsequent brain volume, with females being more susceptible. There was no compelling evidence of preferential tissue loss associated with the glycaemic markers in either sex. Our findings emphasize the importance of maintaining optimal blood glucose levels in the population for brain health in later life.

Acknowledgments

We are very grateful to those study members who helped in the design of the study through focus groups, and to the participants both for their contributions to Insight 46 and for their commitments to research over the last seven decades.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

Funding

This study is principally funded by grants from Alzheimer's Research UK (ARUK-PG2014-1946, ARUK-PG2017-1946), the Medical Research Council (UK) (CSUB19166, MC_UU_12019/1, MC_UU_12019/3), the Wolfson Foundation (PR/ylr/18575). Some researchers are supported by the National Institute for Health and Care Research UCL Queen Square Institute of Neurology, University College London (J.M.S., N.C.F.), University College London Hospitals Biomedical Research Centre (J.M.S.), Wolfson Foundation, and UK Dementia Research Institute (J.M.S., N.C.F.). J.B. is supported by an Alzheimer's Research UK Senior Fellowship. T.D.P. was supported by a Wellcome Trust Clinical Research Fellowship (200109/Z/15/Z). C.H.S. is supported by the Alzheimer's Society (AS-JF-17-011). The funders of the study had no role in study design, data collection, analysis, or interpretation, or report writing. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Authors' contributions

Nasri Fatih (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Project administration [equal], Visualization [equal], Writing—original draft [equal]), Alun Hughes (Formal analysis [equal], Methodology [equal], Resources [equal], Supervision [equal], Writing—review & editing [equal]), Carole Sudre (Conceptualization [equal], Software [equal], Supervision [equal], Writing—review & editing [equal]), Nishi Chaturvedi (Conceptualization [equal], Data curation [equal], Funding acquisition [equal], Resources [equal], Supervision [equal], Writing—review & editing [equal]), Victoria Garfield (Methodology [equal], Supervision [equal], Writing—review & editing [equal]), Richard Silverwood (Formal analysis [equal], Methodology [equal], Supervision [equal], Writing—review & editing [equal]), George Ploudibis (Formal analysis [equal], Methodology [equal], Writing—review & editing [equal]), Thomas Parker (Data curation [equal], Project administration [equal], Resources [equal], Writing—review & editing [equal]), Kirsty Lu (Data curation [equal], Project administration [equal], Supervision [equal], Writing—review & editing [equal]), Dave Cash (Data curation [equal], Methodology [equal], Resources [equal], Supervision [equal], Writing—review & editing [equal]), Ian Malone (Data curation [equal], Methodology [equal], Resources [equal], Software [equal], Writing—review & editing [equal]), Andrew Wong (Data curation [equal], Project administration [equal], Resources [equal], Writing—review & editing [equal]), Josephine Barnes (Methodology [equal], Resources [equal], Writing—review & editing [equal]), Marcus Richards (Conceptualization [equal], Funding acquisition [equal], Investigation [equal], Resources [equal], Writing—review & editing [equal]), Nick Fox (Conceptualization [equal], Funding acquisition [equal], Investigation [equal], Resources [equal], Writing—review & editing [equal]), Jonathan Schott (Conceptualization [equal], Funding acquisition [equal], Methodology [equal], Resources [equal], Writing—review & editing [equal]), and Sarah-Naomi James (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Resources [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal])

All authors made substantial contributions to the conception of the study. N.F. conducted the analysis of the data under the supervision of N.C., A.H., and S.-N.J. and with statistical advice from R.J.S. and G.P. M.R., N.C.F., and J.M.S. provided funding. S.-N.J., T.D.P., K.L., D.M.C., I.B.M., A.W., J.B., C.H.S., M.R., N.C.F., J.M.S. were responsible for acquisition of the data. N.C. and V.G. were crucial for their insight to help interpret the data. N.F., A.H., and S.-N.J. wrote the first draft of the manuscript. All authors reviewed, revised and approved the manuscript.

Conflict of interest: N.C.F. has consulted for Biogen, Ionis, Eli Lilly and Roche and has served on a Data Safety Monitoring Committee for Biogen. J.M.S. has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), has consulted for Roche Pharmaceuticals, Biogen, and Eli Lilly, given educational lectures sponsored by GE, Eli Lilly and Biogen, and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. The remaining authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Data availability

Anonymized data will be shared by request from qualified investigators (skylark.ucl.ac.uk/NSHD/doku.php).

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