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## Research letter

### Brain atrophy in ageing: Estimating effects of blood glucose levels vs. other type 2 diabetes effects

#### Introduction

It is now well documented that ageing is associated with brain shrinkage, particularly in late adulthood [1,2]. From age 60 onwards, the average adult brain atrophies  $\approx 0.5\%/yr$  for the whole brain,  $\approx 0.33\%/yr$  for grey matter and  $\approx 0.62\text{--}0.68\%/yr$  for white matter [3–5]. This may seem small, but cumulatively adds up to substantial volume losses over decades: between the ages of 60 and 70, approximately 54 mL (5%) of total brain volume is lost, a substantial amount when coupled with cumulative atrophy across the lifespan. Type two diabetes mellitus (T2D) is associated with the development of structural brain abnormalities, including increased cerebral atrophy over time [2]. Individuals with T2D have a significantly lower total brain volume (0.1–1.5%), grey matter volume ( $\sim 1\%$ ), and WMV ( $< 1\%$ ) than those with normal fasting glucose (NFG), corresponding to between one and three years of age-associated atrophy [1]. There is mounting evidence that variation of blood glucose in the normal fasting glucose (NFG) range may also impact on brain structure and be associated with cognitive impairment [1,2,6].

Blood glucose levels and T2D are typically related, but it does not follow that an individual with T2D necessarily has high blood glucose levels. Successful glycaemic control following diagnosis can return blood glucose levels to normal. However, glycaemic control is not synonymous with addressing T2D comorbidities, such as obesity or pre-existing vascular damage, which mechanistically link T2D to cerebral atrophy. For example, while blood glucose is associated with both grey and white matter atrophy, obesity has differential effects on grey and white matter in otherwise healthy overweight and obese individuals [7,8]. The current study examined the overlap in the association between blood glucose levels (across the whole range, and in NFG only), T2D and longitudinal brain volumes (total, white matter, and grey matter) in a healthy, community-living ageing population (see Fig. S1, Supplementary material).

#### Materials and methods

##### Study population

Participants were sampled from the Personality and Total Health (PATH) Through Life study, a large longitudinal study investigating ageing, health, cognition and other individual characteristics across the lifespan [9]. This study focuses on a randomly selected sub-sample of the oldest of the PATH cohorts

(aged 60–64 years at baseline) with MRI scans taken on four occasions four years apart ( $M = 4.36$ ,  $SD = 1.58$ ), and fasting blood glucose measurements on three occasions. After exclusions, due to missing data and history of neurological disorders, there were  $n = 279$  participants. They did not differ from the wider PATH sample except for a slightly higher education level ( $M = 14.46$  vs.  $M = 13.71$ ;  $t(294) = 4.284$ ,  $P < 0.01$ ). See supplementary material for additional information on sample selection and inclusion criterion. This study was approved by the Australian National University Ethics Committee. All participants provided written, informed consent.

##### Plasma glucose and brain measures

Venous blood was collected following an overnight fast of at least 10 hours. Plasma glucose was measured on a Beckman LX20 Analyser by an oxygen rate method (Fullerton, California). Diabetic grouping was defined by non-overlapping categories of T2D (self-reported, or two or more fasting blood glucose measures  $> 7$  mmol/L), IFG (not T2D and two or more blood glucose measures  $> 5.6$  mmol/L), or NFG (not T2D or IFG, two or more blood glucose measures  $< 5.6$ ), following American Diabetes Association guidelines [10]. T1-weighted brain scans processed with Freesurfer 5.3 to extract total brain volume (TBV), grey matter (GMV) and white matter (WMV) volume.

##### Statistical analyses

To contrast the effects of blood glucose and diabetes diagnosis, a multilevel model was fitted with diabetic group (NFG, IFG, or T2D) as a predictor of repeated blood glucose measures, which were nested by individual (random intercept model). Overlap was explored via coefficient direction, significance, and a multilevel extension of the Variance Inflation Factor (VIF) from the RMS package (v 4.5).

Exploration of the association between blood glucose and brain volumes proceeded in three modelling steps: (1) blood glucose as key predictor; (2) blood glucose and diabetes diagnosis as key predictors (3) blood glucose as key predictor in individuals with NFG only.

To investigate the association between blood glucose and brain volumes, models (1), (2) and (3) were fit for each of TBV, GMV and WMV, with blood glucose (mmol/L) as a fixed-effect predictor of volume (mL). To investigate the longitudinal between-subject association between blood glucose and change in brain volumes over time, models (1), (2) and (3) were fit for each brain volume, with the interaction between blood glucose (mmol/L) and time (age, centred on 60) as a fixed-effect predictor of volume (mL). All models controlled for time (age centred on 60), gender, years of education, and intracranial volume, hypertension, BMI, smoking

status, and Goldberg depression score (see [Supplementary material \[6,7,9\]](#)).

Alpha was set at 0.05.

## Results

### *Overlap between blood glucose and diabetes diagnosis*

Multilevel modelling of diabetic status throughout the study as a predictor of repeated blood glucose measures showed individuals in the NFG group had an average blood glucose level of 5.11 mmol/L (95% CI [5.022,5.192]). Individuals in IFG and T2D groups had significantly higher blood glucose levels ( $b = 0.76$  mmol/L, 95% CI [0.58,0.94] and  $b = 1.74$  mmol/L, 95% CI [1.55,1.94]). There was moderate but not strong correlation between blood glucose and diabetes group (VIF for glucose = 1.04, IFG = 1.05, T2D = 1.08). Further multilevel models indicated that blood glucose and diabetes group did not significantly interact to predict TBV ( $b = -3.08$  mL, 95% CI [-10.15,3.98]), GMV ( $b = -4.08$  mL, 95% CI [-8.52, 0.35]) or WMV ( $b = 0.94$  mL, 95% CI [-4.38,6.25]).

### *Blood glucose, diabetes group and baseline brain volumes*

Blood glucose was not significantly associated with TBV or WMV ([Table 1](#)). Diabetes group (NFG, IFG, and T2D) was significantly associated with brain volumes; compared to those in the NFG group, participants with T2D had significantly lower TBV ( $b = -30.64$  mL, 95% CI [-44.62, -16.67],  $P < 0.001$ ); lower GMV ( $b = -9.62$  mL, 95% CI [-18.01, -1.24],  $P < 0.05$ ); and lower WMV ( $b = -19.59$  mL, 95% CI [-29.63, -9.54]).

### *Blood glucose, T2D and longitudinal change in brain volumes*

Interactions between blood glucose and time ([Table 1](#)) indicated blood glucose was associated with a significant decrease in TBV each year beyond age 60 ( $\approx 0.43$  mL per 1 mmol/L per year) and GMV ( $\approx 1.45$  mL per 1 mmol/L per year). Interactions between time and diabetic group indicated T2D was significantly associated with GM atrophy only ( $\approx 0.75$  mL per 1 mmol/L per year see [Supplementary material](#)).

## Discussion

This study clarifies the synergetic but not completely overlapping contribution of higher blood glucose levels and T2D on the ageing brain. The main findings were that while a T2D diagnosis was more strongly associated with brain structure than variability in plasma glucose levels, the latter also played a significant role beyond T2D. Indeed, while T2D was associated with total brain, grey matter and white matter volume, when the sample was limited to individuals without diabetes or impaired fasting glucose, an individual with a subtly higher blood glucose in the normal range (e.g. 5.5 mmol/L versus 5 mmol/L) were predicted to have an  $\approx 0.06\%$  comparatively greater decrease in total brain volume each year. In combination with typical age-associated changes in brain volume, additional atrophy of this magnitude may be associated with an increased risk of mild cognitive impairment and Alzheimer's disease.

The current study reaffirmed an association between T2D and blood glucose and brain volumes, and extended previous findings indicating an association between high blood glucose in the normal range and change in brain volume over time [1,2]. Our results emphasize that the association between blood glucose and brain atrophy is important even in healthy individuals. Although

baseline brain volumes and atrophy rates were broadly commensurate with the broader literature, total brain and white matter atrophy in the current sample was markedly (approximately 1–2 mL per year), less than has been previously suggested [3]. Further, average blood glucose levels within individuals with T2D were lower than the diagnostic cut-off for T2D (6.85 mmol/L is less than 7 mmol/L), indicating some degree of post-diagnosis glycaemic control was taking place. Significant findings within this neurologically healthy (due to stringent exclusion criterion) and highly educated [9] sample further highlight the importance of blood glucose as a factor in healthy brain ageing.

We also demonstrated that blood glucose levels and T2D are neither synonymous with one another nor their associations with brain volumes and atrophy. Although high blood glucose is a prerequisite for diagnosis, successful glycaemic control can return blood glucose levels to NFG levels without necessarily altering T2D comorbidities, such as obesity or inflammation [8]. While separating individuals with NFG and T2D into distinct groups for study is a valid approach, the current study highlights the need to carefully consider the relationship between covariates and T2D, and urges caution in synthesising conclusions relating to blood glucose across studies conducted in only NFG or only T2D.

The key strength of the current study was the combination of tight age range and longitudinal follow up from age 60, which would be expected to minimise cohort effects and might provide some support for possible causative links. Although, as in all correlational studies, causation cannot be demonstrated. Moreover, reverse causality cannot be excluded (e.g. poorer cognitive functioning due to decreased brain volumes leading to lifestyle and dietary changes that increase blood glucose, or other risk factors such as obesity). The nature of the relationship between T2D, blood glucose and brain atrophy should therefore be clarified by future experimental work.

## Conclusions

In conclusion, this study showed that the impact of blood glucose on the brain is not exclusive to T2D, and that blood glucose levels even in the normal range can have a significant impact on total brain and grey matter atrophy. These results emphasize the need to consider the role of higher normal blood glucose as a risk factor for brain health.

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## Contributors

Statistical analysis: conducted by Dr. Erin I. Walsh, Australian National University.

Dr. Walsh contributed to the design of the study, conducted all statistical analyses, and managed all aspects of manuscript preparation and submission.

Prof. Sachdev contributed to the design of the study, and provided methodological input and theoretical expertise.

**Table 1**  
Multilevel model coefficients for the association between blood glucose, diabetes group and brain volumes.

	Total brain volume			Grey matter volume			White matter volume		
	[1]	[2]	[3]	[1]	[2]	[3]	[1]	[2]	[3]
<i>Fixed</i>									
Glucose	-0.81[-3.09, 1.47]	0.16[-2.18, 2.50]	2.58[-4.02, 9.17]	-1.56[-2.99, -0.14]*	-1.23[-2.70, 0.25]	1.85[-2.25, 5.95]	0.55[-1.15, 2.25]	1.26[-0.50, 3.02]	0.73[-4.36, 5.81]
Time	-4.26[-4.65, -3.87]***	-4.29[-4.68, -3.90]***	-4.12[-4.61, -3.63]***	-2.87[-3.12, -2.63]***	-2.88[-3.13, -2.64]***	-2.74[-3.04, -2.43]***	-1.15[-1.44, -0.85]***	-1.17[-1.46, -0.88]***	-1.15[-1.53, -0.77]***
IFG		7.25[-5.35, 19.86]			4.28[-3.26, 11.81]			2.97[-6.06, 12.00]	
T2D		-30.64[-44.62, -16.67]***			-9.62[-18.01, -1.24]*			-19.59[-29.63, -9.54]***	
Intercept	370.38[300.68, 440.08]***	352.84[284.73, 420.95]***	357.46[264.50, 450.42]***	248.01[207.09, 288.94]***	240.76[199.78, 281.73]***	229.84[173.71, 285.96]***	112.16[62.30, 162.02]***	101.39[52.30, 150.49]***	114.65[45.85, 183.44]**
<i>Random effects (variance)</i>									
Intercept			1504.85[1227.91, 1777.83]	1384.84[1119.17, 1625.05]					
			1383.79[1069.14, 1692.91]	495.22[400.92, 587.54]	485.13[389.57, 571.12]	489.31[376.58, 599.51]	745.92[605.38, 883.82]	698.23[560.78, 822]	726.9[555.74, 894.38]
Residual	302.55[253.92, 353.03]	302.1[253.59, 352.32]	296.65[238.6, 357.24]	122.18[102.53, 142.81]					
			121.74[102.17, 142.21]						
			116.02[93.38, 139.77]						
			172.74[144.96, 201.83]						
			173.36[145.46, 202.53]						
			178.91[143.68, 216.3]						
<i>Model fit</i>									
AIC	5509.68	5479.36	3617.63	4954.22	4940.9	3258.86	5162.59	5139.64	3411.04
<i>Fixed effects</i>									
Glucose	3.82[-0.36, 8.00]	5.16[0.93, 9.38]*	14.02[2.14, 25.90]*	0.90[-1.75, 3.54]	1.39[-1.29, 4.08]	6.49[-0.96, 13.93]	2.53[-0.63, 5.69]	3.50*[0.29, 6.71]	6.78[-2.44, 16.01]
Time	-1.61[-3.68, 0.46]	-1.43[-3.49, 0.64]	2.87[-3.21, 8.96]	-1.45[-2.77, -0.14]*	-1.38[-2.69, -0.07]*	0.10[-3.72, 3.92]	-0.01[-1.58, 1.56]	0.11[-1.46, 1.68]	2.56[-2.18, 7.29]
Glucose × time	-0.48[-0.85, -0.11]*	-0.52[-0.88, -0.15]**	-1.37[-2.55, -0.18]*	-0.26[-0.49, -0.02]*	-0.27[-0.50, -0.04]*	-0.55[-1.30, 0.19]	-0.21[-0.48, 0.07]	-0.23[-0.51, 0.05]	-0.72[-1.65, 0.20]
IFG			7.09[-5.53, 19.71]		4.19[-3.35, 11.72]			2.90[-6.15, 11.94]	
T2D			-31.61[-45.60, -17.62]***		-10.14[-18.53, -1.75]*			-20.00[-30.07, -9.93]***	
Intercept	343.87[271.24, 416.51]***	324.27[253.20, 395.34]***	300.97[196.06, 405.89]***	233.85[190.97, 276.74]***	225.65[182.71, 268.59]***	206.87[142.87, 270.87]***	100.81[48.58, 153.04]***	88.56[37.04, 140.08]***	84.65[6.0, 163.30]*
<i>Random effects (variance)</i>									
Intercept	1504.85[1227.91, 1777.83]	1384.84[1119.17, 1625.05]	1383.79[1069.14, 1692.91]						
			495.22[400.92, 587.54]						
			485.13[389.57, 571.12]						
			489.31[376.58, 599.51]						
			745.92[605.38, 883.82]	698.23[560.78, 822]					
			726.9[555.74, 894.38]						
Residual	302.55[253.92, 353.03]	302.1[253.59, 352.32]	296.65[238.6, 357.24]	122.18[102.53, 142.81]	121.74[102.17, 142.21]	116.02[93.38, 139.77]	172.74[144.96, 201.83]	173.36[145.46, 202.53]	178.91[143.68, 216.3]
<i>Model fit</i>									
AIC	5,506.74	5,475.33	3,613.74	4,954.03	4,940.14	3,258.84	5,164.58	5,141.06	3,410.34

IFG: Impaired Fasting Glucose; T2D: Type 2 Diabetes. All models control for age, gender, years of education, ICV, hypertension, BMI, smoking status, and Goldberg depression score (coefficients not shown). Values in square brackets are 95% confidence intervals. "Time" is the age variable centred on age at baseline (60); Significance levels are as follows: \*P.

Assoc. Prof Cherbuin, Dr. Shaw and Prof. Anstey contributed to the design of the study, provided methodological input and theoretical expertise, advised on statistical analyses, and contributed to writing and editing of the manuscript.

#### Disclosure of interest

The authors declare that they have no competing interest.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabet.2017.06.004>.

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