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ORIGINAL ARTICLE

The impact of type 2 diabetes and body mass index on cerebral structure is modulated by brain reserve

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Background and purpose: Body mass index (BMI), hyperglycaemia and type 2 diabetes and their interactive effects are associated with brain volume atrophy in ageing. It remains to be established if these risk factors are particularly concerning in individuals with high or low brain volumes.

Methods: Demographics, venous blood and magnetic resonance imaging data were collected for 494 healthy community-living adults aged 53–78 (mean 65) years, as part of the Personality and Total Health Through Life study. Associations between BMI, blood glucose, diabetes status and brain volume (whole brain, grey matter, white matter and subcortical structures) were investigated using quantile regression.

Results: Quantile regression revealed vulnerability to BMI × glucose interactions particularly in lower volumes and significant main effects for type 2 diabetes particularly in higher volumes. Diabetes was most strongly associated with brain volumes. The association between BMI, blood glucose and diabetes was not consistent across the full range of brain volumes.

Conclusion: Explicit investigation of the upper and lower boundaries of brain volume distributions was valuable. We found evidence of protective reserve from higher brain volumes and that a combination of high BMI and higher blood glucose was particularly concerning for individuals with lower brain volumes.

Introduction

Brain tissue loss occurs throughout the adult lifespan but increases progressively with age. By the age of 80 years, typical shrinkage is estimated to be around 10% of original total brain volume and is an important contributor to loss of cognitive function [1]. Better understanding of how modifiable risk factors contribute to neurodegeneration is critical to the development of strategies aimed at optimizing healthy brain ageing and at decreasing the risk of dementia. There is substantial evidence indicating that type 2 diabetes mellitus (T2D) and overweight/obesity [often measured as body mass index (BMI)] are both associated with accelerated brain atrophy, neurodegeneration and increased risk of cognitive decline [2]. However, although they co-occur and share a number of pathological features, it is not clear whether one or the other contributes more to neurodegeneration. Moreover, it is not well understood whether their effect is uniform across cerebral structures and individuals [3].

Type 2 diabetes is associated with lower total brain volume and accelerated brain atrophy throughout life [2,4]. This amounts to approximately 1.5% lower brain volume in adults with T2D, equivalent to 3 years of age-associated atrophy [5]. There is growing evidence that high blood glucose levels in the non-diabetic range are also implicated in brain tissue loss well before the onset of clinical T2D [6].

High BMI is also associated with lower total brain volume and accelerated brain atrophy over time,

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amounting to approximately 6% lower brain volume in adults with obesity, who experience 20% more atrophy per year than individuals of normal weight [2]. As obesity and T2D are highly comorbid, overlap in their pathophysiology and share several pathways to affect cerebral health, it is unresolved which contributes most to neurodegenerative processes and the extent to which they interact.

A promising new approach is to focus on blood glucose levels, because blood glucose in the normal range can impact cerebral health. To our knowledge, the only study to have examined in detail the overlap in effects between high BMI and T2D, and also consider blood glucose, suggested that T2D effects on white matter may be secondary to comorbid obesity. However, these conclusions are limited by a small sample and a unique focus on white matter [4]. It is unclear whether grey matter might be differentially affected. For example, brain regions with high insulin receptor density, such as the hippocampus [7], may be particularly vulnerable to hyperinsulinaemia from both T2D and obesity. Investigation of structures with low insulin receptor density that are also vulnerable to hyperglycaemia, such as the thalamus [8], may therefore help to distinguish the effects of T2D from those of obesity.

A growing body of evidence suggests that those with smaller intracranial, total brain and subcortical volumes may be at increased risk of subsequent brain atrophy and pathological cognitive decline [2,9]. Lower volumes appear to be associated with increased vulnerability to physical and psychological risk factors and consequent neurodegeneration [10]. This can be framed as a limited reserve for coping with the additional impact of high blood glucose, T2D and high BMI. Conversely, larger brain volumes may constitute protective reserve [11]. The aim of this study was therefore to investigate the association between BMI, blood glucose, T2D and brain volume in a large sample of community-living middle- and older-aged individuals.

Methods

Study population

This cross-sectional study focused on a recent wave (wave 4) of the Personality and Total Health (PATH) Through Life study, which is a large longitudinal study investigating ageing, health, cognition and other individual characteristics across the lifespan, described in detail elsewhere [12]. Briefly, a large cohort of healthy community-living adults provided self-report, blood and magnetic resonance imaging data at 4-year intervals over a 12-year period. The current study focused on follow-up data for cohorts aged 40–45 (n = 2530) and 60–64 (n = 2551) years at baseline. Participants were excluded on the basis of unavailable magnetic resonance imaging data at the wave of interest (wave 4) and history of neurological disorders (epilepsy, Parkinson's disease, stroke or dementia) at any time during the PATH study, resulting in a final sample of 494 (40s, n = 266, 60s, n = 228; Supporting Information). Included/excluded subjects differed only in years of education (included, mean 14.13 years; excluded, mean 14.41 years; $t(617)$ = 2.239, P = <0.02). Participants provided written, informed consent. This study was approved by the human research ethics committees of the Australian National University and the University of New South Wales.

Measurements

Body mass index was computed based on self-reports of weight and height with the formula weight (kg)/height (m^2). Venous blood was collected following an overnight fast and plasma glucose was measured on an LX20 Analyzer (Beckman, Beckman Coulter Life Sciences, Indianapolis, IA, USA) by an oxygen rate method. Diabetic status was defined by non-overlapping categories of T2D (self-reported or two or more fasting blood glucose measurements during the study >7 mmol/L), impaired fasting glucose (IFG) (not T2D and two or more blood glucose measurements during the study ≥5.6 mmol/L) or normal fasting glucose (NFG) (not T2D or IFG, two or more blood glucose measurements during the study <5.6 mmol/L), following American Diabetes Association guidelines. Years of education, smoking (ever versus never smoked) and neurological exclusion criterion (listed previously) were obtained by self-report. Hypertension was assessed by self-reported use of antihypertensive medication or two blood pressure measurements taken 3 min apart while participants were seated (systolic > 140 mmHg, diastolic > 90 mmHg). Physical activity (PA), expressed as metabolic equivalents, was calculated from self-reported hours of PA (mild PA × 3) + (-moderate PA × 6) + (vigorous PA × 9), following the ratio in Ainsworth *et al.* [13]. Acquisition parameters for magnetic resonance imaging scans are described in detail elsewhere [14] and in the Supporting Information. Briefly, scans were three-dimensional structural fast-field echo sequence T1-weighted, analyzed using the longitudinal pipeline of Freesurfer v5.3 on a Linux workstation [15]. This study focused on wave 4 total brain, grey matter, thalamus (left + right), white matter and corpus callosum volume.

Statistical analyses

Analyses were carried out in R version 3.2.0 (Vienna, Austria). Main effects models for each brain volume (total, grey matter, thalamus, white matter and corpus callosum) were fit with BMI, glucose and diabetes status (NFG/IFG/T2D) as predictors. Separate models were fit for the BMI × glucose and BMI × diabetes status interactions, to allow separate interpretation of main effects and interactions. All models controlled for intracranial volume, sex, age, cohort (40s/60s), years of education, hypertension (yes/no), smoking status (ever/never) and PA (metabolic equivalents). Linear regression and corresponding quantile models were fit with quantreg v5.21 [16].

Comparison of quantile submodels against the linear results provided insight into whether predictors had a constant association across the whole range of brain volumes, taking into account heterogeneity of variance in ways that alternative approaches, which may deal with such non-linearity, such as spline models, could not. Wald tests of equality of slopes indicated whether models (joint test) and/or slopes (non-joint test) for each submodel within the quantile regression differed from one another. Linear and quantile models explained variance in distinct ways, thus we used the Akaike information criterion and −2 log likelihood via the chi-square ratio test.

Four groups were specified with cut-off points of tau 0.25, 0.5 and 0.75 to allow comparison of the centre, upper 25th percentile and lower 25th percentile of the distribution. Three cut-off points were chosen to maintain sufficient power at each tau. Alpha was adjusted for multiple comparisons at <0.05 or <0.01 (conservatively, linear model and four quantile slopes = 0.05/4 = 0.01).

Results

Just over half (n = 251, 50.81%) of participants were male. Around 20% (n = 95) had IFG and 10% (n = 46) had T2D. Further participant characteristics can be seen in Table 1 and quartile cut-off points can be seen in Table 2. Wald tests indicated that quantile submodel fit differed significantly for main effects and interactions in grey matter [quantile regression analysis of deviance (24,1224) = 1.70, P = 0.02 and quantile regression analysis of deviance (26,1222) = 1.76, P = 0.01, respectively] (Table S1). The −2 log likelihood and Akaike information criterion fit indices similarly indicated a trend for superior fit in quartile models regarding grey matter volume (Table S2). Accordingly, main effects from linear model coefficients will be reported to provide context for whole-sample trends (for comparison with other literature that takes a linear approach), but the better-fitting quartile models will form the basis of interpretation and conclusions.

Table 1 Participant characteristics

	All	NFG	IFG	T2D
Age (years)	64.66 (9.79)	63.66 (9.63)	65.79 (9.98)	69.99 (8.74)
BMI	27.22 (4.83)	26.48 (4.55)	28.44 (4.81)	30.34 (5.2)
Glucose (mmol/L)	5.45 (1.21)	5.05 (0.45)	5.92 (0.68)	7.53 (2.68)
Total brain volume (mm^3)	1119.57 (112.36)	1124.94 (112.72)	1123.92 (105.95)	1069.36 (112.48)
Grey matter volume (mm^3)	587.9 (55.14)	590.22 (55.2)	589.96 (52.06)	565.88 (57.16)
Thalamus volume (mm^3)	15.54 (1.61)	15.62 (1.62)	15.61 (1.58)	14.85 (1.46)
White matter volume (mm^3)	502.42 (60.85)	505.14 (61.37)	504.35 (57.26)	477.64 (59.74)
Corpus callosum volume (mm^3)	2.86 (0.54)	2.91 (0.55)	2.81 (0.44)	2.55 (0.49)
METs	48.88 (46.67)	47.68 (46.55)	57.23 (50.72)	40.91 (36.33)
Gender: male	251 (50.81%)	159 (45.04%)	64 (67.37%)	28 (60.87%)
Gender: female	243 (49.19%)	194 (54.96%)	31 (32.63%)	18 (39.13%)
Smoking: no	273 (56.76%)	195 (56.69%)	51 (55.43%)	27 (60%)
Smoking: yes	208 (43.24%)	149 (43.31%)	41 (44.57%)	18 (40%)

Due to missing data, some counts may not sum to the total sample size. BMI, body mass index; IFG, impaired fasting glucose; MET, metabolic equivalent; NFG, normal fasting glucose; T2D, type 2 diabetes. Data are given as mean (SD) and n (%).

Table 2 Brain volume quartiles

	τ 0.25	τ 0.5	τ 0.75	
Total brain volume (mL)	[773, 1040]	[1040, 1120]	[1120, 1190]	[1190, 1500]
Grey matter volume (mL)	[423, 547]	[547, 586]	[586, 625]	[625, 754]
Thalamus volume (mL)	[12, 15.1]	[15.1, 16.3]	[16.3, 17.4]	[17.4, 21.7]
White matter volume (mL)	[330, 461]	[461, 500]	[500, 539]	[539, 744]
Corpus callosum volume (mL)	[0.98, 2.49]	[2.49, 2.83]	[2.83, 3.23]	[3.23, 4.8]

Main effect associations with blood glucose and diabetes

Blood glucose was significantly associated with grey matter [$\tau = 0.50$, $b = 3.98$, 95% confidence interval (CI), −6.23, −1.74] and thalamus (significance at $\tau = 0.25$, $b = -0.09$, 95% CI, −0.18, −0.01) volume (Fig. 1). In fully adjusted models, participants with T2D had 28.28 mL (95% CI,−47.21, −9.36) lower total brain volume, 9.45 mL (95% CI, −21.69, 2.77)

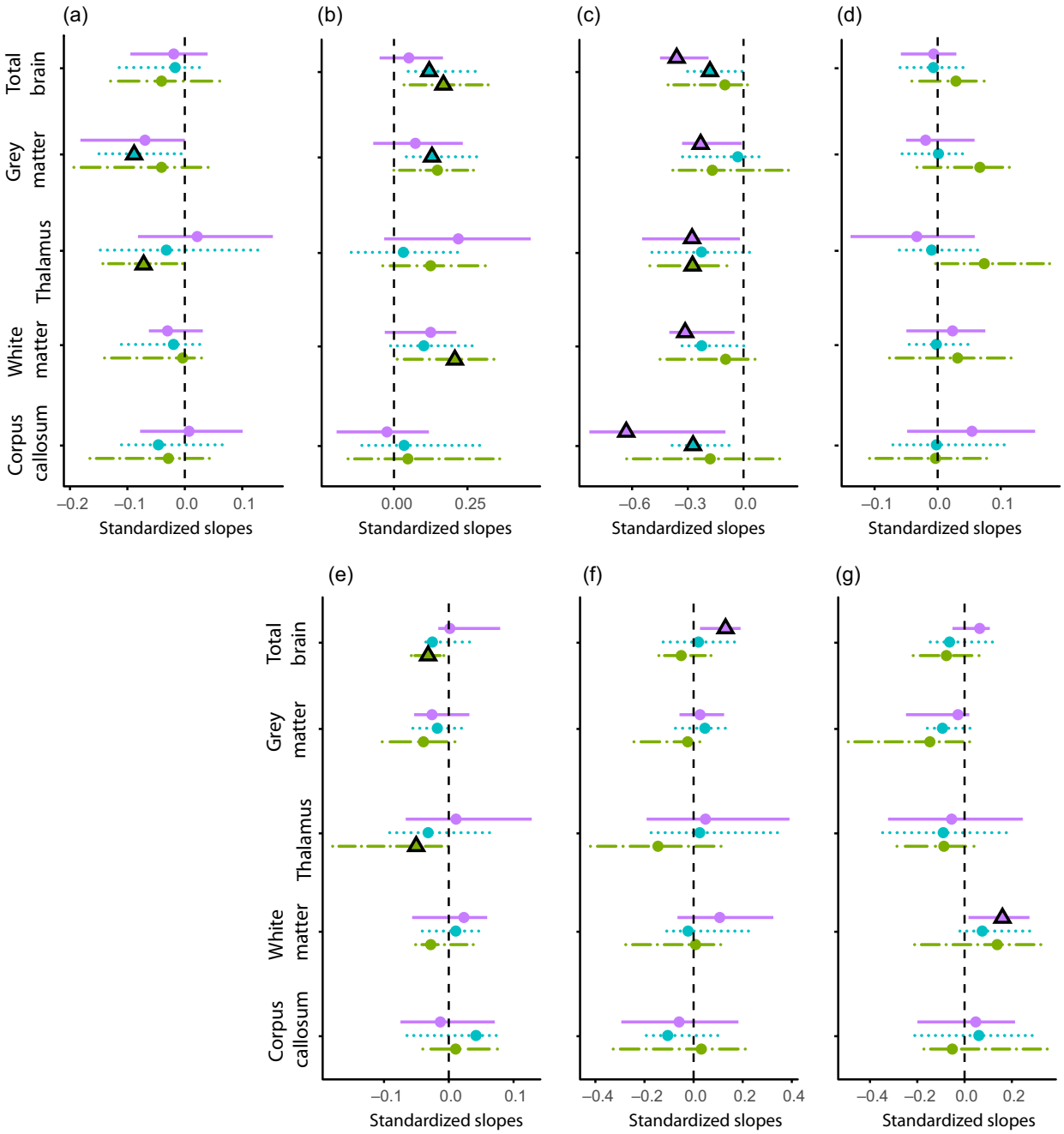

Figure 1 Model slopes and significance. Points are regression slopes with 95% bootstrap confidence intervals (2500 replicates). ▲, significant ($\alpha < 0.05$); ●, non-significant; solid lines, highest (tau 0.75); dotted lines, middle (tau 0.50); dotted and dashed lines, lowest (tau 0.25). Tau is the boundary between quartiles ([0–25%], (25–50%], (50–75%] and (75–100%]), corresponding to the slope at the 25th, 50th and 75th of each percentile. All models control for intracranial volume, sex, age, cohort, years of education, hypertension and diabetes status. (a) Glucose; (b) impaired fasting glucose (IFG) [vs. normal fasting glucose (NFG)]; (c) type 2 diabetes (T2D) (vs. NFG); (d) body mass index (BMI); (e) glucose × BMI; (f) IFG × BMI; (g) T2D × BMI. [Color figure can be viewed at wileyonlinelibrary.com]

lower grey matter volume, 0.44 mL (95% CI, −0.91, 0.04) lower thalamus volume, 16.23 mL (95% CI, −29.23, −3.23) lower white matter volume and 0.17 mL (95% CI, −0.36, 0.01) lower corpus callosum volume. The association between T2D and smaller brain volumes was most pronounced in the 75th percentile (Fig. 1), indicating that the significant impact of T2D on brain volume was driven by the upper end of the distribution.

Main effect associations with body mass index

The main effect for BMI was not significantly associated with any brain volume, although there was a trend for individuals in the 25th percentile to have a positive association with brain volumes, whereas those in the 50th and 75th percentiles were closer to neutral or negative associations (Fig. 1).

Interactions between body mass index, blood glucose levels and type 2 diabetes

Body mass index and blood glucose interacted to predict volumes. Significance was not uniform across quartiles. In the 25th percentile, the BMI × glucose interaction was associated with lower volume, specifically 0.61 mL (95% CI, −1.22, −0.01) lower total brain and 0.01 mL (95% CI, −0.02, −0.01) lower thalamus matter volume and borderline significance for grey matter volume. This indicated that the combination of high BMI and high blood glucose was a risk factor particular to individuals with low brain volumes at baseline. BMI and diabetes status significantly interacted in the 75th percentile. Each additional unit of BMI was associated with 3 mL (95% CI, 1.04, 5.02) greater total brain volume in individuals with IFG, adding to the main effect trend for higher total brain volume associated with IFG. In white matter, having T2D (rather than NFG) mitigated the main effect negative association between BMI and brain volume by 2 mL (95% CI, 0.06, 4.04) per unit BMI (Fig. 1).

Sensitivity analyses

Additional models (Supporting Information) were run with outliers removed, without covariates, without or with adjustment for diabetes, with additional adjustment for PA and with an additional adjustment for cholesterol. The pattern of associations was broadly consistent. Analyses were repeated with quantile splits based on intracranial volume rather than individual brain regions to partially address whether these effects were more likely to be due to smaller pre-morbid head size or neurodegeneration. Although broadly similar, some divergence indicated that the current results were probably explained by a mix of initial brain volume and prior pathological shrinkage.

Discussion

This study's main findings were that BMI and glucose interact in their associations with brain volumes and that these associations depend on the brain volumes (large or small) of those investigated. A quantile approach, which allows investigation of the lower and upper distribution of brain volumes, provided better model fit and more nuanced information than a linear model. This approach indicated a more complex pattern of associations that differed depending on whether participants had a particularly high or low (intracranial volume adjusted) total brain, grey matter, thalamus, white matter or corpus callosum volume.

Type 2 diabetes was associated with lower brain volumes [2,4] and contributed more to neurodegeneration than BMI in both white and grey matter. BMI was not directly associated with neurodegeneration, even in the corpus callosum, contrary to previous studies [17].

However, significant interactions with glucose and T2D status indicate that a combination of high BMI and higher blood glucose was particularly concerning for individuals with lower brain volumes, seen in total brain volumes and specifically in the thalamus. This may be indicative of an ongoing atrophy process putatively linked to high glucose and BMI within these individuals or, alternatively, diminished reserve in lower volumes leading to increased vulnerability. Lack of significance in sensitivity analyses using intracranial volume as a proxy for pre-morbid brain size suggests that these effects are more likely to be due to neurodegenerative processes than initially smaller brain size. This possibility would be most convincingly clarified via comparison of monozygotic twins with differential glycaemic histories.

Results supported the presence of protective reserve associated with larger brain volumes [11]. In individuals with larger brain volumes only, a combination of IFG and high BMI was positively associated with total brain volume in individuals with IFG, although the magnitude of the effect was small (<1% total brain volume per unit BMI). This may be indicative of protective compensatory pre-diabetic metabolic changes to blood glucose metabolism in higher body weights or, conversely, pathological volume increase associated with inflammation from chronically high blood glucose levels. If the latter is the case, there was

little indication that this persists in T2D. Although T2D was universally significantly associated with lower volumes in the largest volumes, the association was (barring the thalamus) consistently lower in magnitude and non-significant in those with the lowest volumes. This may indicate that previous atrophy processes leave limited room for additional neurodegenerative effects. Together, this suggests simultaneous protective or compensatory processes preserving brain volume in some individuals and exhaustion of degenerative processes, but the nature of these processes remains unclear.

The thalamus has a comparatively lower insulin receptor density than other well-studied grey matter structures such as the hippocampus [7,8] and so may be more clearly associated with hyperglycaemia (rather than hyperinsulinaemia). The relationship between thalamus volume and T2D was of similar magnitude as in other insulin-receptor-rich structures reported elsewhere (here, thalamus volume was 5% lower in T2D; elsewhere, hippocampus volume was ~4.4% lower in T2D [18]), demonstrating that the thalamus is vulnerable to type 2 as well as type 1 diabetes [8]. Interestingly, the association between glucose and thalamus volume was significant only in the lowest percentile, whereas it was associated with both the lowest and highest percentile in T2D. Together with significant interactions between BMI and glucose in this percentile, this suggests that the thalamus may be a useful structure for isolating the potential impact of hyperglycaemia (absent hyperinsulinaemia) on grey matter, but only in individuals with low reserve. Similarly, this indicates some differentiation in the association between the thalamus and high blood glucose *per se* versus T2D. This supports our previous findings that T2D and high glucose levels are not necessarily synonymous due to glycaemic management and so can have differing impacts on the brain [19].

This study has a number of strengths and limitations. Although cross-sectional, cohort effects in the current study were limited by the use of two narrow age bands and controlling for both cohort and time in all models. Further, although the sample was combined in the interests of statistical power and analytical clarity, it is possible that different mechanisms underlie BMI in different cohorts (e.g. skeletal muscle loss in the 60s). Although brain volumes and rates of overweight and T2D were on a par with global estimates [20], this limited variability at the lower ranges of BMI possibly obscured the influence of low BMI and was reflected in a small proportion of the youngest cohort having T2D, although the number of individuals with IFG or T2D was sufficient for analysis when the cohorts were combined. The impact of this on model precision and significance could be investigated by quota sampling across the range of BMI and NFG/IFG/T2D, at the cost of generalizability. High levels of education limit generalizability, but the presence of significant associations in this healthy, highly educated community-living sample indicates the importance of the association between blood glucose and BMI on brain volumes in ageing.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Figure S4. Quantile model stability across sensitivity analyses: interactions.

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