

Structural and Functional Hypothalamic Changes as Early Features of Neurodegeneration

BACKGROUND

- Although hypothalamic volume is reduced at the time of dementia diagnosis, it is unknown whether this is an early feature, and how this relates to prodromal symptoms of dementia.
- We hypothesise that the hypothalamus is affected early by neurodegeneration and that this is associated with changes to endocrine function, adiposity and sleep.

METHODS

- We used data from 452,808 dementia-free, midlife participants in the UK Biobank, of which 59,039 attended 3T magnetic resonance neuroimaging 10.8 (3.8-17.5) years after baseline.
- We identified four markers of early neurodegeneration:
 - Apolipoprotein E4 (APOE4) homozygotes
 - Participants with a dementia diagnosis during follow-up
 - Raised plasma neurofilament light (NFL, available for a subgroup)
 - Raised glial fibrillary acidic protein (GFAP, available for a subgroup)
- FreeSurfer (v7.4.1 and v6.0.1) was used to segment hypothalamic volume (total and subunits) and hippocampal volume, which were normalised to total intracranial volume.
- Plasma levels of several hypothalamic, pituitary, and peripheral hormones were available at baseline while adiposity (weight circumference) and self-reported sleep were available at baseline and the imaging visit.
- Multivariate regression models were used to explore whether the markers of early neurodegeneration were associated with differences in hypothalamic volume, hormone levels and symptoms. Cox proportional hazards models were used to determine whether hypothalamic volume could predict dementia during follow-up.

Dementia Diagnosis During Follow-up				
	No	Yes	p	
n	445050	7758	-	
Proportion (%)	98.3	1.7	-	
Age	56.3 (8.07)	64.4 (4.46)	<0.001	
Women (%)	53.9	46.4	<0.001	
Body mass index	27.3 (4.7)	27.7 (4.8)	<0.001	
APOE Genotype				
	-/-	4/-	4/4	p
n	315084	103683	10426	-
Proportion (%)	73.4	24.2	2.4	-
Age	56.5 (8.08)	56.4 (8.08)	56.3 (8.11)	<0.001 ^{a,b}
Women (%)	53.5	53.6	52.9	0.43
Body mass index	27.4 (4.72)	27.3 (4.73)	27.1 (4.66)	<0.001 ^{a,b,c}

Table 1. Baseline group differences in age, sex and body mass index among participants with a dementia diagnosis during follow-up and among APOE genotypes.

RESULTS

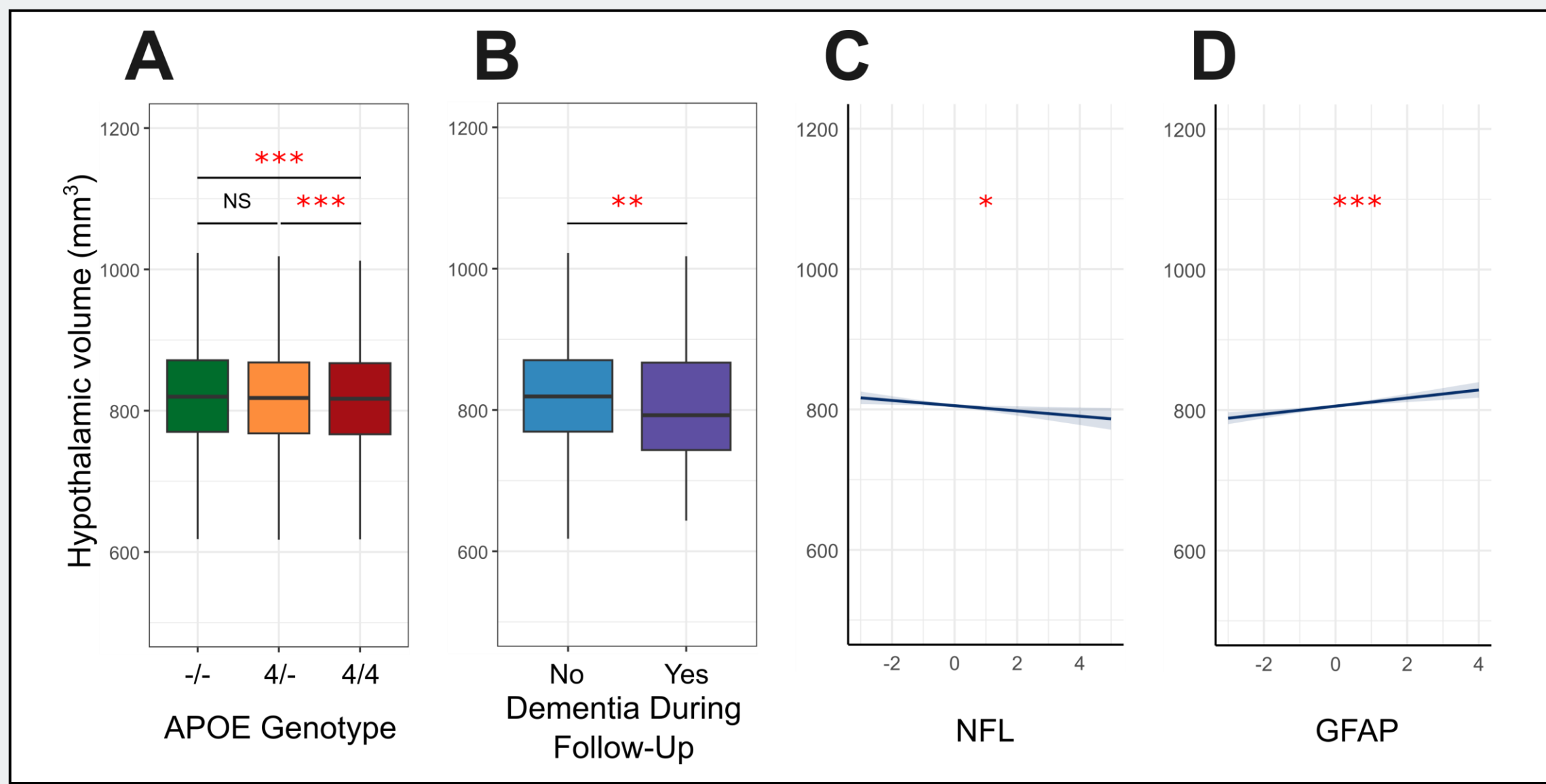


Figure 1: APOE4 (A), Dementia during follow-up (B) and NFL (C) were associated with lower hypothalamic volume, while GFAP (D) was associated with higher volume.

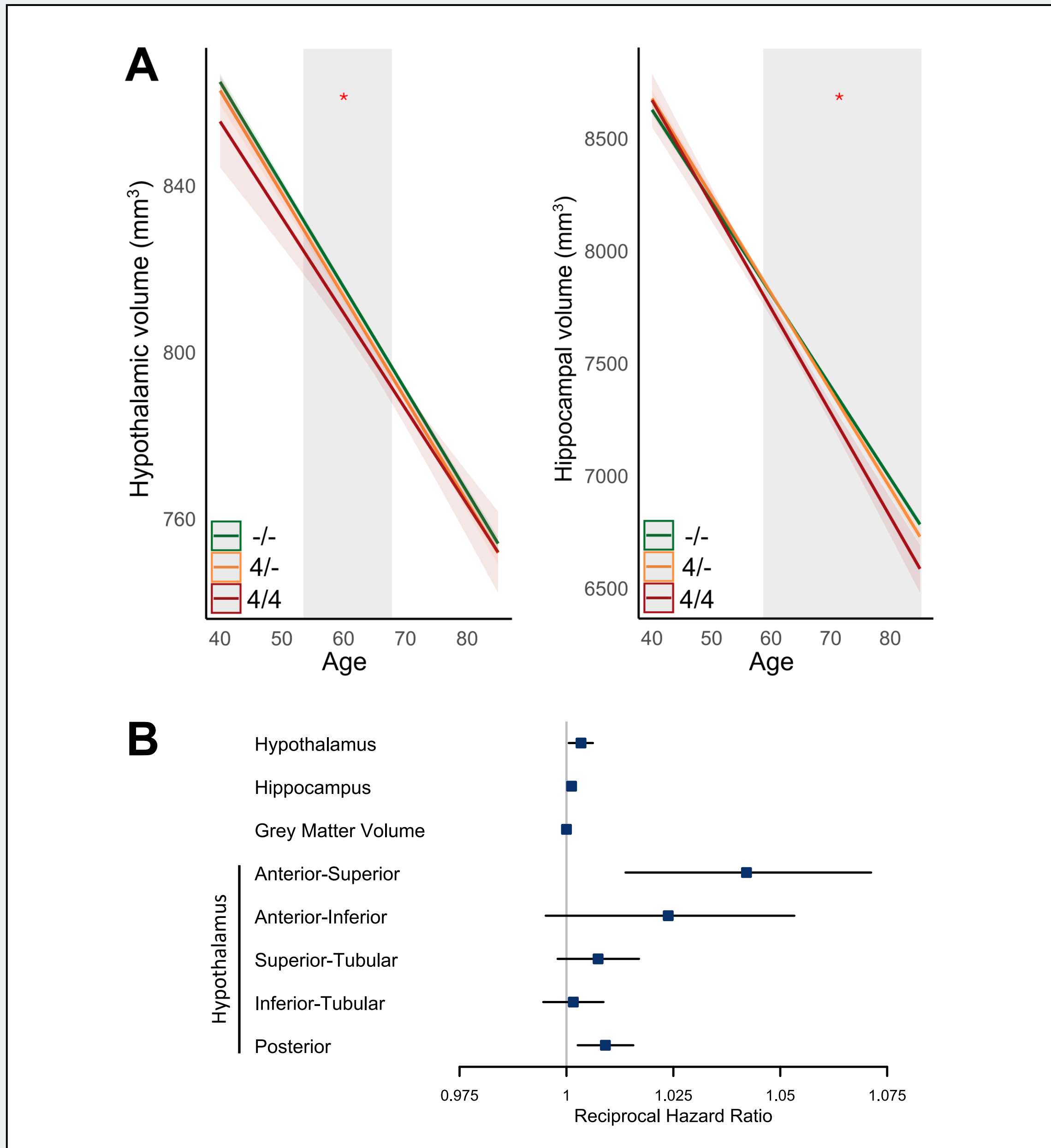


Figure 2A: The differences between APOE4 homozygotes and non-carriers emerged earlier for the hypothalamus than the hippocampus (age 53 vs. 59). **2B:** Hazard ratios for dementia during follow-up were higher for reduced anterior-superior, posterior and total hypothalamic volume, compared with reduced hippocampal volume.

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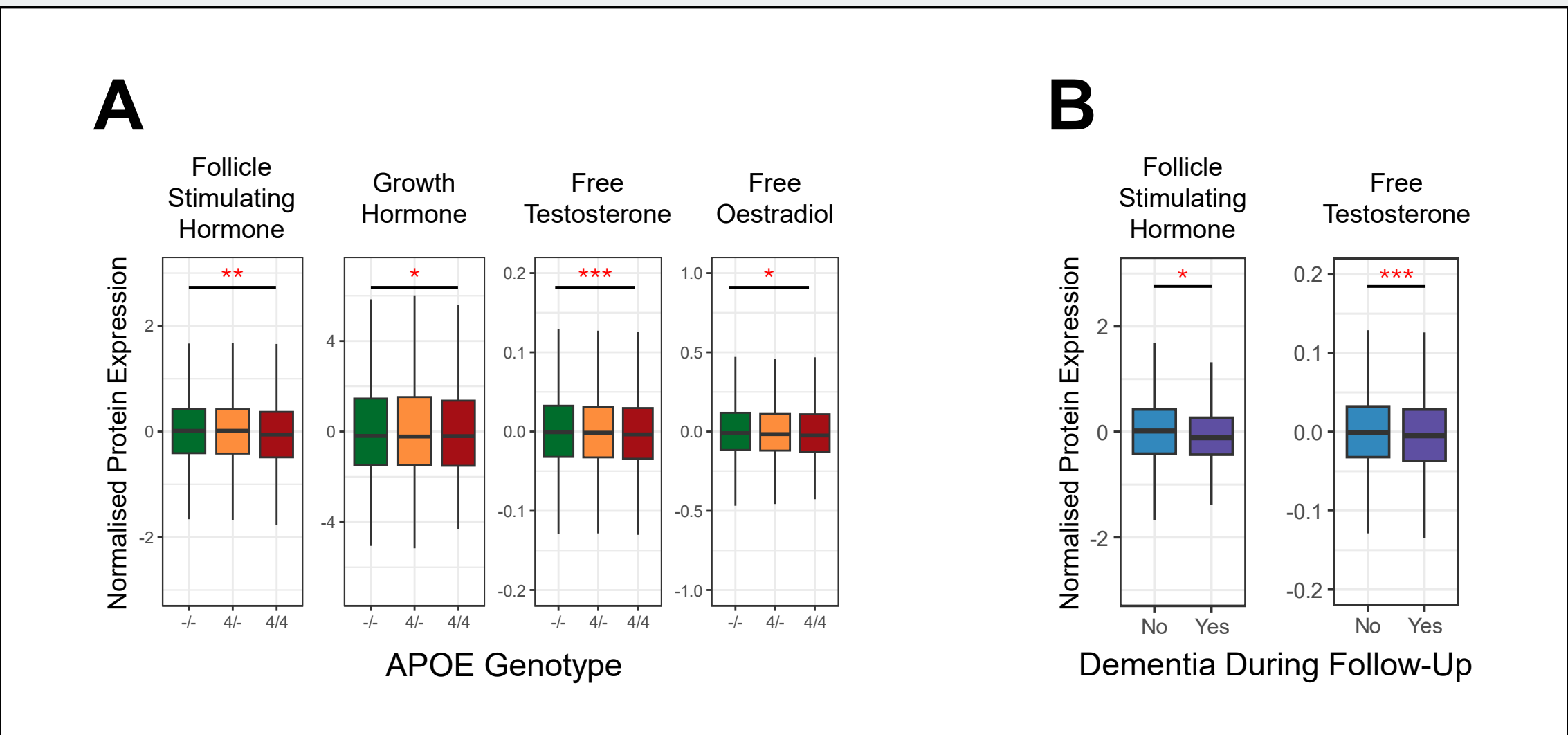


Figure 3A: APOE4 homozygotes had lower follicle-stimulating hormone, growth hormone, free testosterone and free oestradiol. **3B:** Participants who developed dementia during follow-up had lower follicle-stimulating hormone and free testosterone. In contrast, NFL and GFAP were associated with higher levels of all available pituitary proteins.

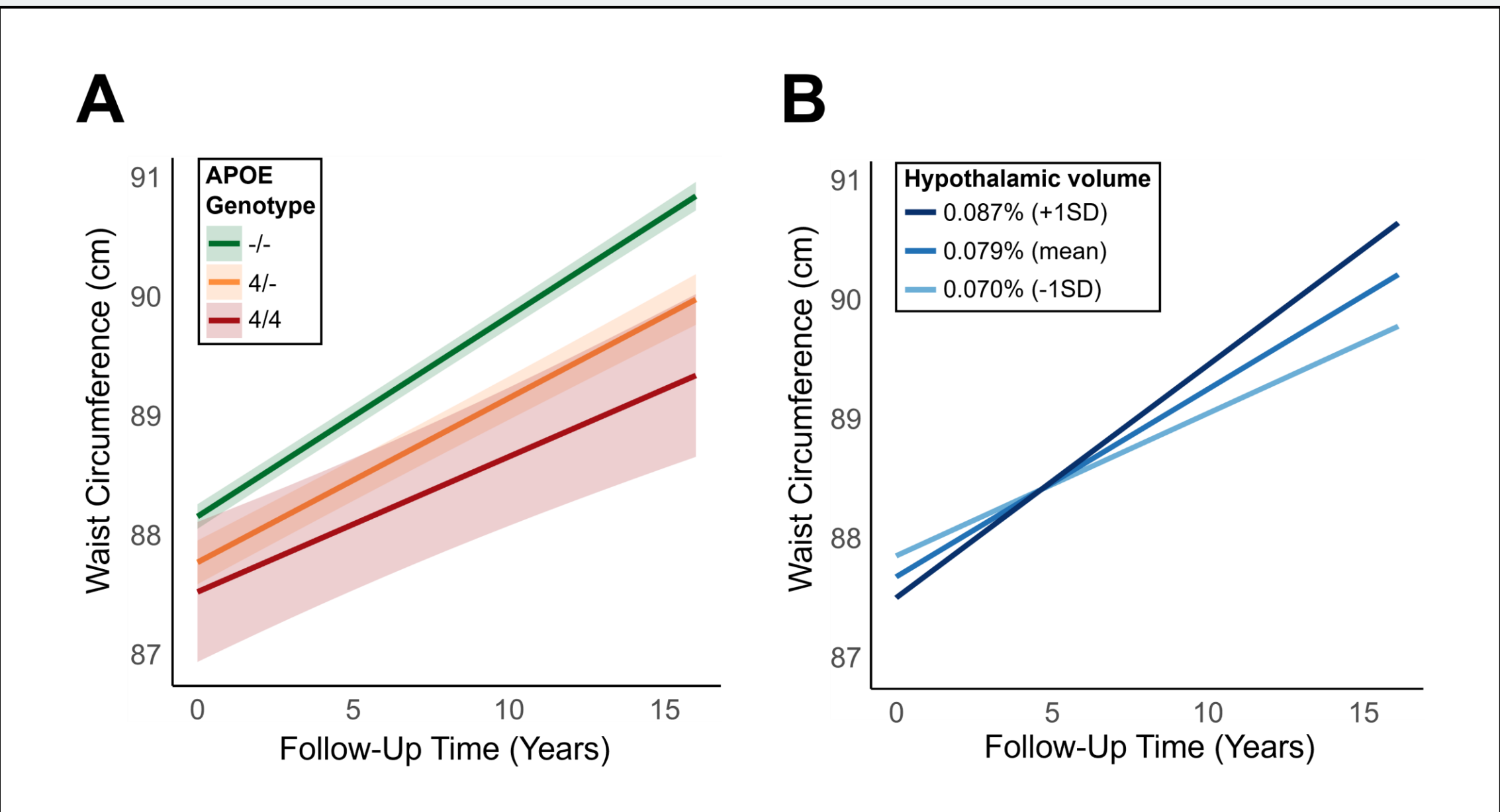


Figure 4: APOE4 (A) and lower hypothalamic volume (B) were associated with reduced gain in adiposity. A similar effect was seen for dementia during follow-up, higher NFL and higher GFAP.

- Dementia during follow-up, NFL, and GFAP were associated with increased sleep duration and daytime somnolence while APOE4 homozygotes experienced less daytime somnolence than non-carriers.

CONCLUSION

- Hypothalamic involvement is an early feature of neurodegeneration and may contribute to prodromal changes to endocrine function, adiposity and sleep.
- Hypothalamic dysfunction may therefore be a previously overlooked driver of pathology and a useful biomarker in people with dementia.

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