

The effect of hormone replacement therapy on brain structure, neurovascular function and cognition

BACKGROUND

- Studies examining the cognitive effects of hormone replacement therapy (HRT) for menopausal symptoms have been mixed, with some suggesting that HRT increases dementia risk.
- We assessed the effect of HRT on brain structure, neurovascular function and cognition using data from the PREVENT-Dementia study.

METHODS

- Cognitively healthy women (n=388, 40-60 years) were classified using the STRAW+10 criteria as: HRT-users (HRT-U), peri- or post-menopausal non-hormone users (HRT-NU), and pre-menopausal non-hormone users (PRE).
- Episodic memory, was derived using a principal component analysis of the COGNITO neuropsychological battery.
- Self-reported vascular risk factors, depression and sleep, were collected using questionnaires.
- Follicle stimulating hormone (FSH), a proxy of circulating sex-hormones, was analysed using fasting blood samples.
- Total grey matter (GMV), white matter (WMV), white matter hyperintensity (WMHV) volumes, and grey matter cerebral blood flow (GMCBF) were extracted from 3T magnetic resonance imaging (T1-weighted, FLAIR, and ASL) using FreeSurfer (v7.1.0), SPM12 and FSL.
- R Studio was used for imputation of missing data, and robust linear regression models.

	Pre-menopausal	HRT non-users	HRT users	p
N	127	201	60	-
Age	46 (4)	54 (4)	53 (3)	<0.001 *#
Years of Education	17.4 (3.9)	16.1 (3.5)	17.3 (2.9)	0.002 *‡
Body Mass Index	28 (7)	28 (6)	26 (5)	0.18
Current or Past Smoker (%)	39	38	48	0.37
Alcohol (units/week)	10 (10)	11 (14)	12 (12)	0.37
Follicle Stimulating Hormone (IU/L)	8 (5)	73 (30)	44 (31)	<0.001 *#‡
Hypertension (%)	8	9	12	0.70
Diabetes (%)	3	4	2	0.78
Hyperlipidaemia (%)	9	14	8	0.20
Depression (%)	33	29	35	0.63
Anxiety (%)	17	18	22	0.77
Sleep Disorder (%)	8	21	20	0.006 *#
Depressive Symptoms (CESD Total)	9 (8)	10 (9)	8 (7)	0.25
Sleep Dysfunction (PSQI Total)	5.9 (3.2)	6.8 (3.4)	6.5 (3.9)	0.04 *
APOE4 Carriers (%)	43	34	42	0.23

Table 1. HRT-U and HRT-NU were older, had higher FSH and more sleep problems than PRE, while HRT-NU had lower education than HRT-U and PRE. *PRE vs. HRT-NU, #PRE vs. HRT-U, ‡HRT-NU vs. HRT-U.

AUTHORS

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RESULTS

- HRT-NU had worse episodic memory than HRT-U (p=0.01) and PRE (p<0.001), adjusting for age, education, depression and sleep.
- HRT-U had lower WMV than HRT-NU (p(FDR)=0.01) with a similar trend compared to PRE (p=0.03, p(FDR)=0.10), even adjusting for age, education, intracranial volume and vascular risk.
- In HRT-U, lower FSH level (suggesting a higher HRT dose) was associated with lower GMV (p(FDR)=0.001).
- There were no significant group differences in GMV, WMHV or GMCBF.

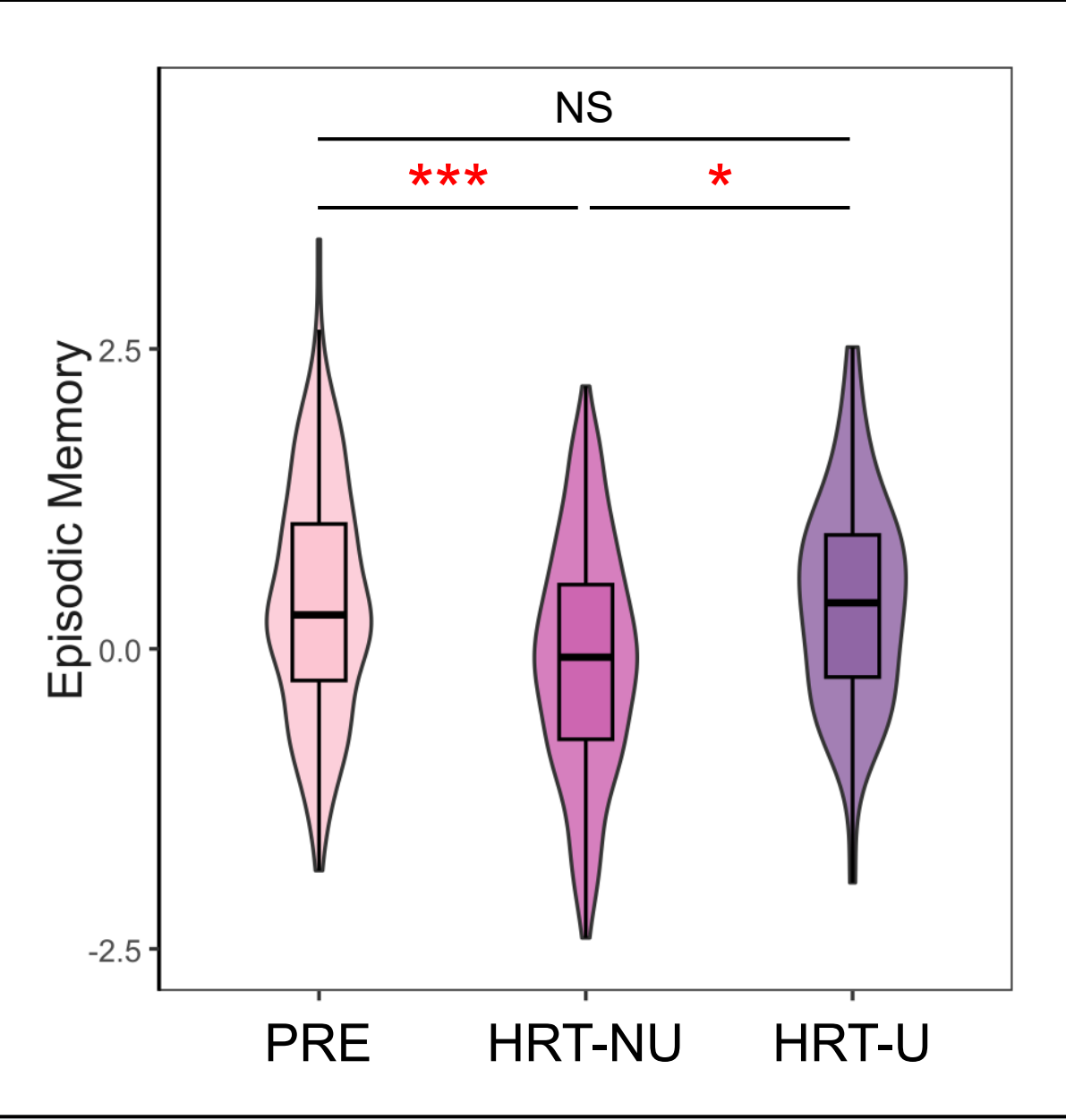


Figure 1: HRT-NU had worse episodic memory than HRT-U and PRE.

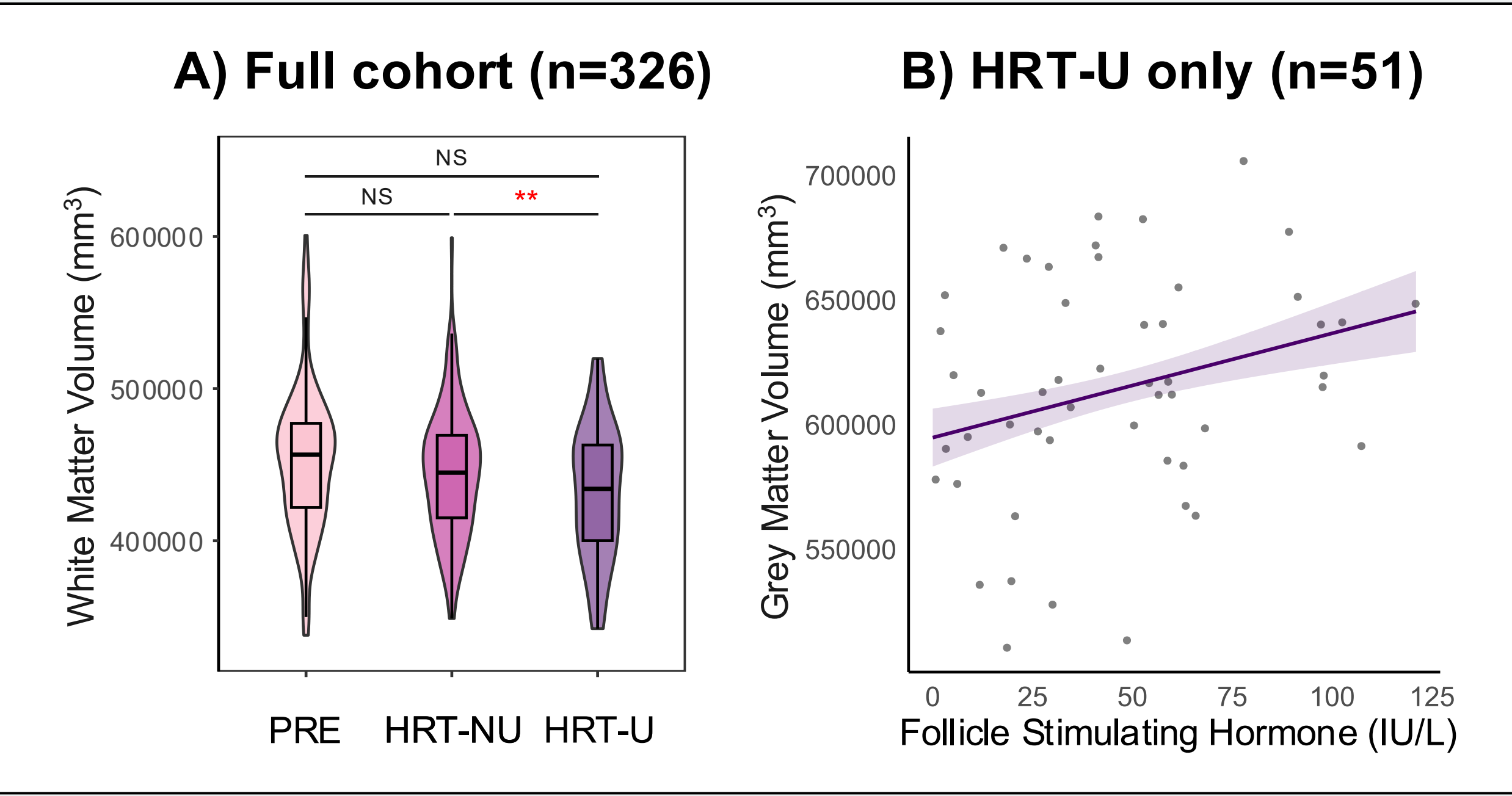


Figure 2A: HRT was associated with lower WMV. **2B:** Lower FSH, indicating a higher HRT dose, was associated with lower GMV volume.

CONCLUSION

- Although HRT-U had better episodic memory than HRT-NU, they also had lower WMV and a hormone dose-dependent reduction in GMV.
- Ongoing follow-up of these women will reveal whether this effect translates to a higher dementia risk.

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