

Hormone Replacement Therapy is Associated with Lower Odds of Limbic-predominant Age-related TDP-43 Encephalopathy Neuropathological Change (LATE-NC)

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INTRODUCTION

- LATE neuropathological change (LATE-NC) is a dementia subtype that clinically resembles Alzheimer’s disease (AD) and becomes more prevalent with age.^{1,2}
- Because women generally live longer than men, they face a higher lifetime risk for LATE.³
- Recent findings from The 90+ Study suggest that long-term use (15+ years) of hormone replacement therapy (HRT) is associated with reduced odds of LATE-NC.⁴
- **Objective:** To replicate the findings from The 90+ Study on the potential protective effect of HRT against neurodegenerative dementia using ROS-MAP data.

METHODS

- Women participants (N=1416)
 - From the Religious Orders Study (ROS) or the Rush Memory and Aging Project (MAP) longitudinal cohort
 - Age ≥65 yrs at death & neuropathological evaluation
- HRT (exposure) - defined as "yes" if answered “yes” or “suspect” to:
 - Did you ever take any type of estrogen hormonal medication?
 - Are you currently taking HRT?
 - Taking an estrogen medication at visit.
- HRT related variables factors:
 - HRT duration
 - Last use of HRT to death
 - Start of HRT to menopause
 - Mode of HRT
- Neuropathology:
 - LATE-NC (outcome): TDP-43 pathology in amygdala, limbic or neocortical regions
 - AD neuropathological changes (ADNC): high likelihood based on NIA-AA criteria⁵
- Analysis:
 - Logistic regression analyses used to estimate ORs and 95% CIs for the association between HRT and LATE-NC
 - Model 1: Unadjusted
 - Model 2: Adjusted for age at baseline, age at death, and education
 - Model 3: Model 2 + ADNC

Hormone replacement therapy use is associated with lower odds of LATE neuropathology, a common cause of dementia in older adults

Table 1. Characteristics of The Study Population.

	Women		
	no HRT (N = 782)	HRT (N = 634)	Total (N= 1416)
Mean (SD)			
Age baseline (y)	81.8 (7.0)	79.2 (6.9)	80.6 (7.0)
Age at death (y)	90.9 (6.5)	90.1 (6.4)	90.6 (6.5)
Baseline to death (y)	9.2 (5.8)	10.9 (6.0)	10.0 (6.0)
MMSE to death	1.2 (1.6)	1.2 (1.6)	1.2 (1.6)
Education (y)	15.9 (3.4)	16.1 (3.3)	16.0 (3.4)
Last MMSE score	20.1 (9.5)	20.3 (9.6)	20.2 (9.6)
Number (%)			
LATE-NC			
No TDP pathology	316 (42)	291 (48)	607 (45)
Any TDP pathology	430 (58)	321 (52)	751 (55)
ADNC			
No, low, intermediate	576 (74)	489 (77)	1065 (75)
High likelihood	203 (26)	145 (23)	348 (25)

Figure 1. Odds of LATE-NC in relation to HRT.

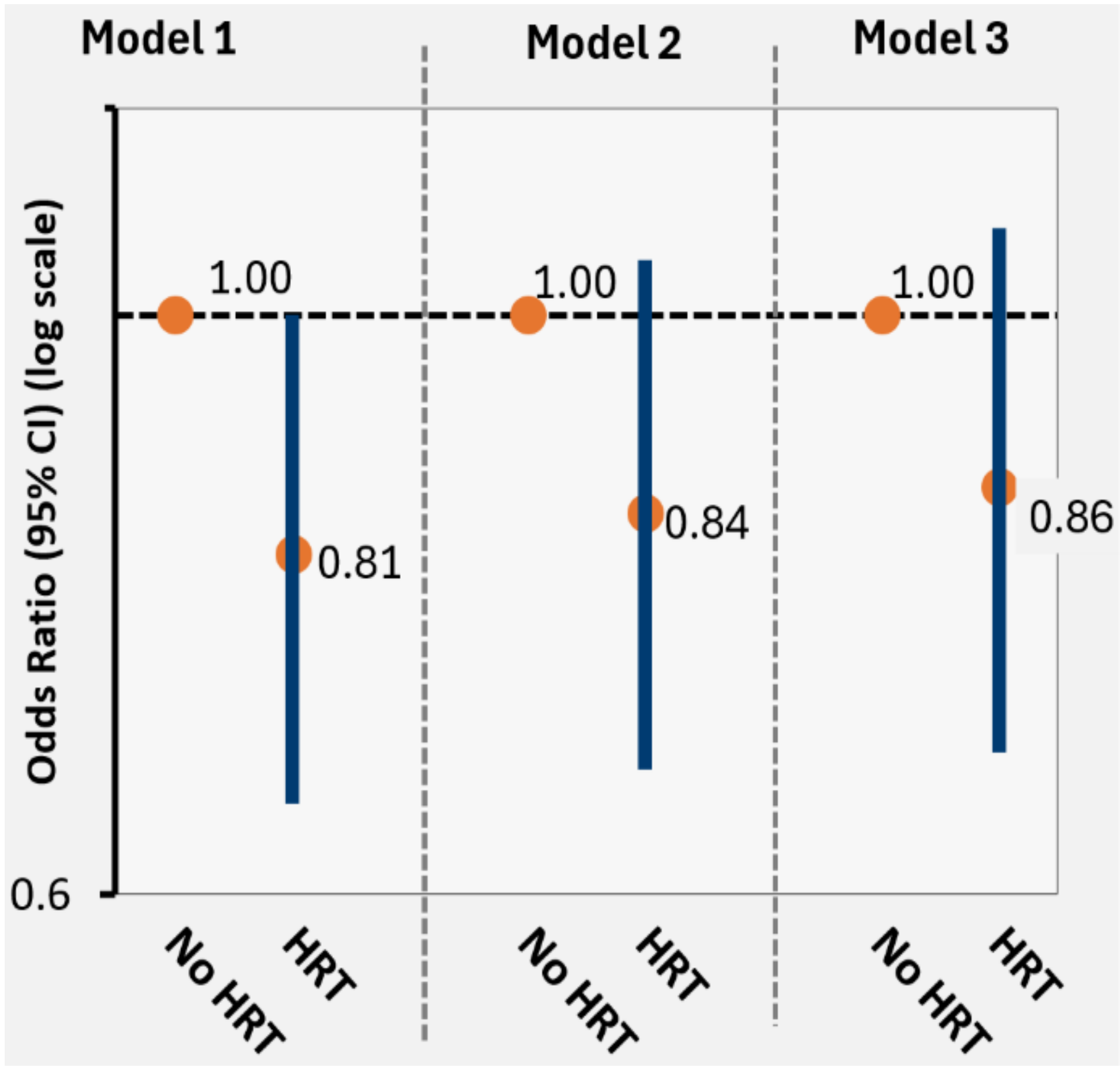
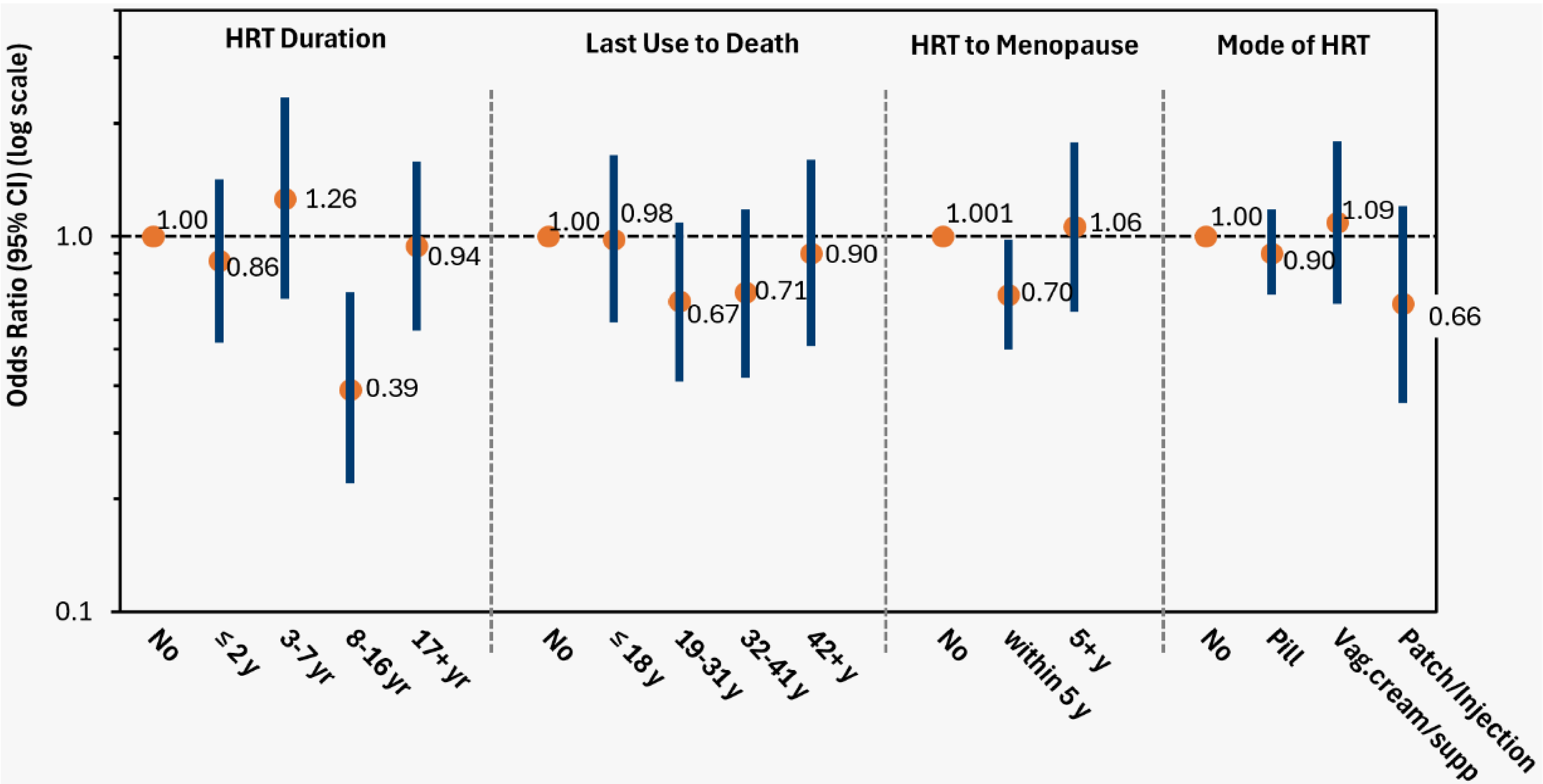


Figure 2. Odds of LATE-NC in relation to duration, recency, timing, and mode of HRT use (Model 3).



RESULTS

- The prevalence of LATE-NC was 52% in women who used HRT, 58% in women who did not use HRT (*Table 1*)
- HRT use was associated with lower odds of LATE-NC in the unadjusted model. This trend persisted after adjusting for covariates in Model 2 and Model 3, although attenuated and no longer significant. (*Figure 1*)
- HRT duration of 8-16 years was significantly associated with reduced odds of LATE-NC, even after full adjustment. (*Figure 2*)
- HRT use 19-31 and 32-41 years before death showed lower odds of LATE-NC. However, this association was not significant. (*Figure 2*)
- HRT use within 5 years before or after menopause was significantly associated with lower odds of LATE-NC, even after full adjustment. (*Figure 2*)
- HRT mode (patches/injections) showed lower odds of LATE-NC. However, this association was not significant. (*Figure 2*)

DISCUSSION

- Findings are consistent with prior research from The 90+ Study.
- **Long-term HRT use:** Both studies show lower LATE-NC risk with extended use (90+ Study: ≥15 years; ROS-MAP: 8–16 years).
- **Timing of HRT:** Both are consistent: 90+ Study shows benefit with use ~29 years before death; ROS-MAP shows 19–31 years before death plus a critical window around menopause (±5 years).
- **Reproductive factors:** No association with LATE-NC in 90+ Study or ROS-MAP.
- **Strengths:** Large sample size with comprehensive HRT & neuropathology data.
- **Limitations:** Unable to assess the separate effects of estrogen, progesterone, or their combination. Autopsy study participants may not be representative of the general population.

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