Menopause Timing, Epigenetic Age Acceleration, & Late-Life Cognition:

A Mediation Analysis in the Health and Retirement Study

Brittany T. Morin & Jacqueline M. Torres

University of California, San Francisco

SCAN ME

BACKGROUND

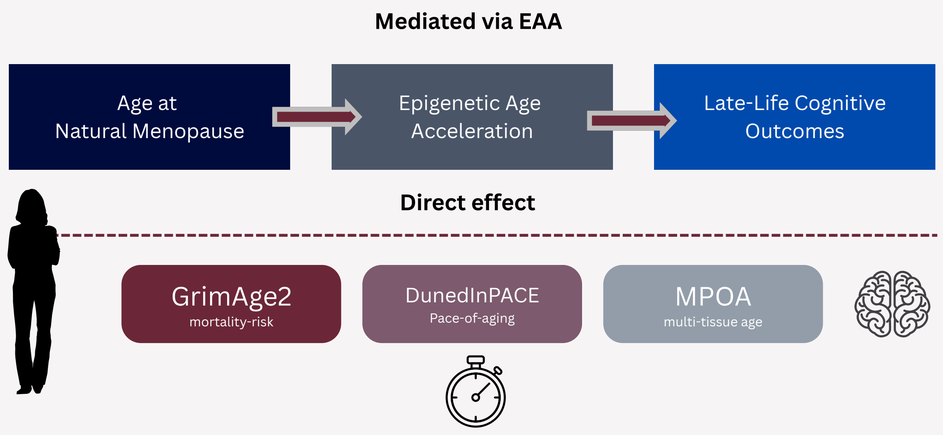
Reproductive aging is a key component of the female exposome, the cumulative biological and environmental exposures shaping women's health across the life course.

Earlier menopause has been associated with accelerated cognitive decline, yet the biological mechanisms linking reproductive aging to late-life cognition remain poorly characterized.

Epigenetic age acceleration (EAA), defined as the discrepancy between biological and chronological age measured by DNA methylation-based clocks, represents a plausible mechanistic pathway, given that both menopause timing and cognitive aging are shaped by cumulative hormonal exposures.

The Critical Window Hypothesis posits that the timing of hormonal changes during the menopausal transition may have lasting neurological consequences.

CONCEPTUAL FRAMEWORK



STUDY SAMPLE

Characteristic	N = 1,286 (models: N = 1,135)
Data Source	HRS 2016 VBS
HRS waves harmonized	2008-2022 (8 waves)
Epigenetic clocks	Grimage2, MPOA, DunedInPACE
Cognitive outcomes	Word recall, TICS
Mediation method	Parametric g-formula
Bootstrap replicates	1,000 (BC 95% CI)

OBJECTIVES

Examine whether EAA mediates the relationship between age at natural menopause and late-life cognitive outcomes

Test three epigenetic clocks as candidate mediators: GrimAge2, MPOA, and DunedinPACE

Assess two cognitive outcomes: delayed word recall (memory) and TICS (general cognition)

EXPOSURE → MEDIATOR ASSOCIATION

Each additional year of later menopause was significantly associated with:

- Lower **GrimAge2** acceleration (β = −0.075, p = 0.022), lower mortality risk
- Lower **DunedinPACE** (β = −0.003, p = 0.001), slower biological aging pace
- Lower **MPOA** (β = −0.001, p = 0.037), slower multi-tissue epigenetic age

METHODS

Study Sample

Health and Retirement Study (HRS) 2016 Innovation Subsample;

- N = 1,286 postmenopausal women with venous blood epigenetic data.
- N = 1,135 with complete covariate data contributing to models.
- Menopause history harmonized across 8 HRS waves (2008–2022).

Exposure

Age at natural menopause (continuous). Natural menopause defined as 12+ months of amenorrhea not due to surgery, chemotherapy, or radiation.

Cognitive Outcomes

- Delayed word recall — memory domain
- Telephone Interview for Cognitive Status (TICS) — general cognition

Epigenetic Mediators

- GrimAge2 — mortality-risk clock
- DunedinPACE — pace-of-aging clock
- MPOA — multi-tissue epigenetic age

Statistical Analysis

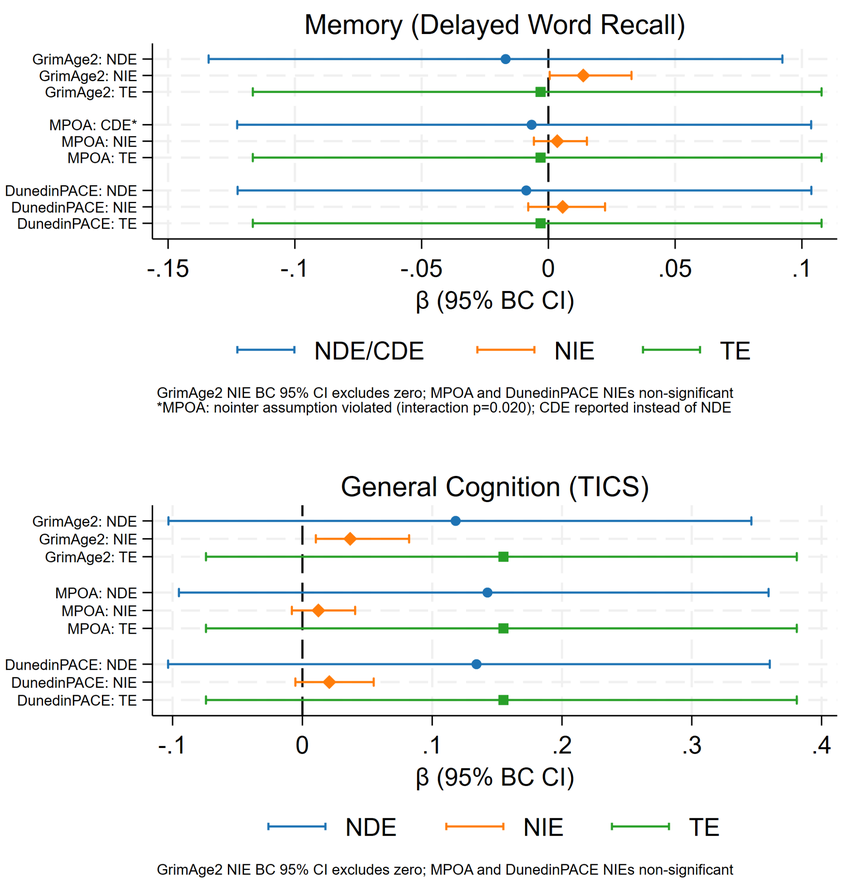
Causal mediation estimated using the parametric g-formula with bias-corrected (BC) bootstrap 95% confidence intervals (1,000 replications). Total effect decomposed into natural direct effect (NDE) and natural indirect effect (NIE).

Covariates

Age, race/ethnicity, education, BMI, APOE status, childhood SES

RESULTS

Menopause Timing and Late-Life Cognition:
Epigenetic Age Acceleration as an Indirect Pathway



GrimAge2 NIE BC 95% CI excludes zero; MPOA and DunedinPACE NIEs non-significant
*MPOA: nointer assumption violated (interaction p=0.020); CDE reported instead of NDE

GrimAge2 NIE BC 95% CI excludes zero; MPOA and DunedinPACE NIEs non-significant

NDE=Natural Direct Effect; CDE=Controlled Direct Effect;
NIE=Natural Indirect Effect via EAA; TE=Total Effect
BC bootstrap 95% CIs, 1000 replications. N=1,135 (HRS 2016 VBS subsample).
Continuous exposure: age at menopause centered at 45 years.
*MPOA/dwrecall: exposure-mediator interaction present (p=0.020); CDE reported.

KEY FINDINGS

- **Earlier menopause predicts faster biological aging:** significant a-paths for all three clocks (GrimAge2, DunedinPACE, and MPOA)
- **Total effects of menopause age on cognition were small and non-significant:**
  - Word recall: β = −0.023, 95% CI (−0.050, 0.003), p = 0.084
  - TICS: β = −0.006, 95% CI (−0.058, 0.046), p = 0.817
- **GrimAge2 emerged as the primary mediating clock:** NIEs were statistically significant for both outcomes.
  - Word recall: NIE = 0.014, BC 95% CI (0.001, 0.033)
  - TICS: NIE = 0.037, BC 95% CI (0.010, 0.082)
- **MPOA and DunedinPACE NIEs directionally consistent but non-significant (all BC 95% CIs included zero).**
- **Power analyses:** ~2,100–3,100 observations needed for 80% power to detect GrimAge2-mediated effects at observed magnitude.

CONCLUSIONS

GrimAge2-indexed biological aging is a candidate mechanistic pathway linking reproductive aging to late-life cognition, with significant NIEs for both outcomes — though total effect estimates were small and imprecise in this subsample, suggesting competing pathways warrant investigation.

Powered detection of mediated effects requires substantially larger samples (~2,100–3,100 for GrimAge2 pathways; larger for MPOA and DunedinPACE).

These findings motivate larger epigenetic cohort studies to disentangle competing pathways and clarify the role of menopause timing in dementia risk.

DISCUSSION

These findings position GrimAge2-indexed biological aging as a biologically plausible candidate pathway linking reproductive aging to late-life cognition, with significant NIEs for both outcomes. The presence of significant NIEs alongside null total effects suggests competing or offsetting pathways attenuating the net association. Situating menopause timing within the female exposome framework underscores the broader relevance of cumulative reproductive exposures for brain health and dementia risk.

Limitations

- Cross-sectional epigenetic data; direction of temporality assumed
- Self-reported age at menopause; N = 1,135 limits power for mediation
- Smoking history and cardiovascular comorbidities not yet incorporated

Future Directions

- Longitudinal epigenetic data to establish temporal ordering
- Leverage larger epigenetic cohorts for powered mediation inference
- Incorporation of smoking history and cardiovascular comorbidities planned for subsequent analyses
- Incorporate cumulative hormonal exposure measures (reproductive lifespan, HRT timing)
- Explore heterogeneity by APOE-ε4 status, race/ethnicity, and HRT use

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