

# Epigenetic age acceleration from peripheral blood as a novel biomarker of psychosis in female APOE4 carriers with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)

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## Background

- Psychosis occurs in nearly 40-60% of AD cases and has a 10% annual incidence in AD/MCI<sup>1,2</sup>
- More severe disease & stressor to caregivers
- Female APOE4 carriers** are at highest risk
  - Unclear mechanisms → Limited biomarkers and treatments
- Research has begun looking at epigenetics

**Figure 1. DNA methylation's influence on gene transcription<sup>3</sup>**

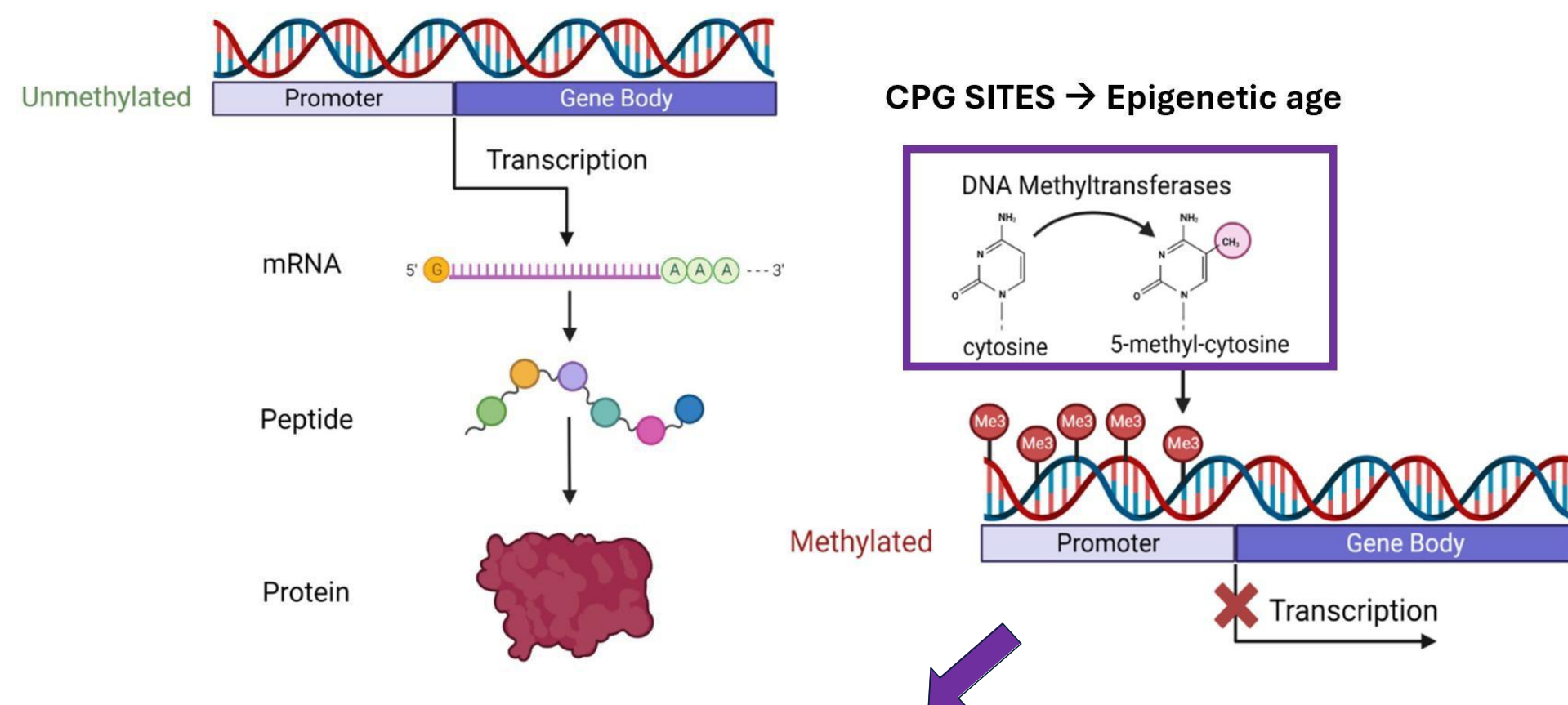


**Table 1. Summary of common epigenetic clocks<sup>4-6</sup>**

| Clock             | Tissue           | # CpGs | Model Trained On            |
|-------------------|------------------|--------|-----------------------------|
| Horvath           | Pan-tissue       | 353    | Chronological Age           |
| Hannum            | Whole blood      | 71     | Chronological Age           |
| Levine (PhenoAge) | Peripheral blood | 513    | Phenotypic Age (healthspan) |

- Epigenetic age acceleration is linked to:
  - Psychosis in schizophrenia<sup>7</sup>
  - Amyloid burden & memory loss in AD<sup>6</sup>
  - Progression from normal cognition to MCI/AD<sup>8</sup>
- Gap:** EAA has not been studied in relation to psychosis in AD/MCI

## Objectives and Hypothesis

- Objective 1:** Explore whether EAA is associated with psychosis in individuals with AD/MCI, and whether this association varies by sex and APOE4 status.
- Objective 2:** Explore whether associations with psychosis differ across epigenetic clock used

**Hypothesis:** EAA is associated with higher odds of psychosis, particularly among female APOE4 carriers

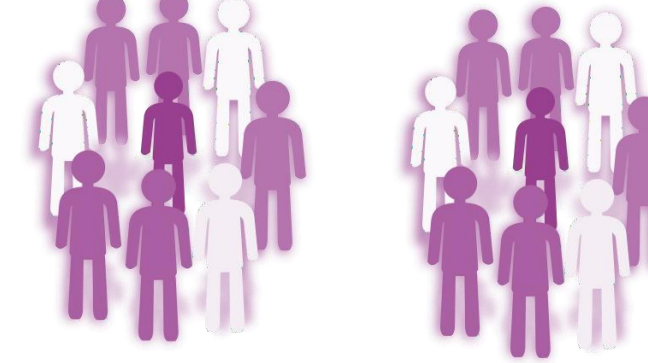
## Methods

### 1: Determine Study Population



- DNA methylation data
- Clinical MCI or AD
- NPIQ/MMSE scores
- Sex
- Date of birth
- APOE genotype

### 2: Create Psychosis Groups using NPIQ Scores



### 3: Calculate EAA for each participant



### 4: Statistical Analysis

#### Model 1: Main Effect Model – Logistic Regression

- Is EAA independently associated with psychosis status?
- #### Model 2: Sex \* APOE4 \* EAA Interaction Model
- Does the association differ based on sex and APOE4 carrier status

Covariates: Chronological age, sex, APOE4, MMSE, smoking status

## Results

### Participant Demographics by Psychosis Status



#### No Psychosis

**N = 364 (87.1%)**  
**Mean age:** 73.74  
**Female:** 41.5%  
**MCI:** 92.6%  
**PhenoAge EAA:** -0.18±0.35

**MMSE: 27.54\***  
**NPIQ: 2.24\***

**\*Significant difference (P < .05)**

#### Psychosis

**N = 54 (12.9%)**  
**Mean Age:** 75.46  
**Female:** 40.7%  
**MCI:** 85.2%  
**PhenoAge EAA:** +1.20±1.20

**MMSE: 26.69\***  
**NPIQ: 5.09\***



**Table 2. Associations Between EAA and Psychosis Across Three Epigenetic Clocks**

| Clock    | Model        | Predictor                                       | Odds Ratio (95% CI)      | P-value       |
|----------|--------------|-------------------------------------------------|--------------------------|---------------|
| Horvath  | Main Effects | EAA                                             | 1.13 (0.90, 1.43)        | 0.294         |
|          | Interaction  | EAA * Female * APOE4 Carrier Interaction        | 1.14 (0.44, 2.93)        | 0.787         |
| PhenoAge | Main Effects | EAA                                             | 1.11 (0.90, 1.37)        | 0.316         |
|          | Interaction  | <b>EAA * Female * APOE4 Carrier Interaction</b> | <b>3.04 (1.26, 7.34)</b> | <b>0.013*</b> |
| Hannum   | Main Effects | EAA                                             | 0.98 (0.80, 1.21)        | 0.865         |
|          | Interaction  | EAA * Female * APOE4 Carrier Interaction        | 1.64 (0.65, 4.11)        | 0.292         |

Abbreviations: EAA = Epigenetic Age Acceleration, MMSE = Mini-Mental State Examination. The main effect of DNAm age acceleration is derived from a main effects-only model. The 3-way interaction term is derived from the full interaction model, with all main effects and lower order interactions included. The reference group are male APOE4 non-carriers. Odds ratios reported per 5 year increases in EAA.

**Table 3. Subgroup Analysis of Psychosis Odds per 5-Year Increase in PhenoAge EAA**

| Group                       | Group Total N | No Psychosis N (MCI/AD) | Psychosis N (MCI/AD) | Odds Ratio (95% CI)      | P-value       |
|-----------------------------|---------------|-------------------------|----------------------|--------------------------|---------------|
| Male Non-carrier            | 119           | 108 (105/3)             | 11 (9/2)             | 1.36 (0.87, 2.11)        | 0.180         |
| Male APOE4-carrier          | 126           | 105 (91/14)             | 21 (18/3)            | 0.88 (0.63, 1.24)        | 0.459         |
| Female Non-carrier          | 89            | 78 (77/1)               | 11 (9/2)             | 0.89 (0.56, 1.42)        | 0.630         |
| <b>Female APOE4-carrier</b> | <b>84</b>     | <b>73 (64/9)</b>        | <b>11 (10/1)</b>     | <b>1.76 (1.07, 2.89)</b> | <b>0.025*</b> |

Odds ratios are calculated per 5 year increase in DNAm PhenoAge EAA and adjusted for chronological age and MMSE scores. Values in parentheses represent the number of participants with MCI and AD, respectively.

## Discussion

Our findings suggest that accelerated biological aging may contribute to psychosis risk in Alzheimer's disease, but only within specific patient subgroups. The association between EAA and psychosis was restricted to **female APOE4 carriers** and was observed only with the **PhenoAge clock**, highlighting potential differences in the biological pathways captured by epigenetic aging measures. Higher MMSE scores were protective against psychosis.

These results identify PhenoAge as a promising biomarker candidate and support future studies investigating the molecular mechanisms linking epigenetic aging, APOE4, and psychosis in AD. Future research should also examine whether interventions that slow or reverse epigenetic aging can reduce psychosis risk or improve clinical outcomes. These findings should be interpreted cautiously given limitations related to cohort heterogeneity, symptom ascertainment, methylation variability, and small subgroup sample sizes.

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