

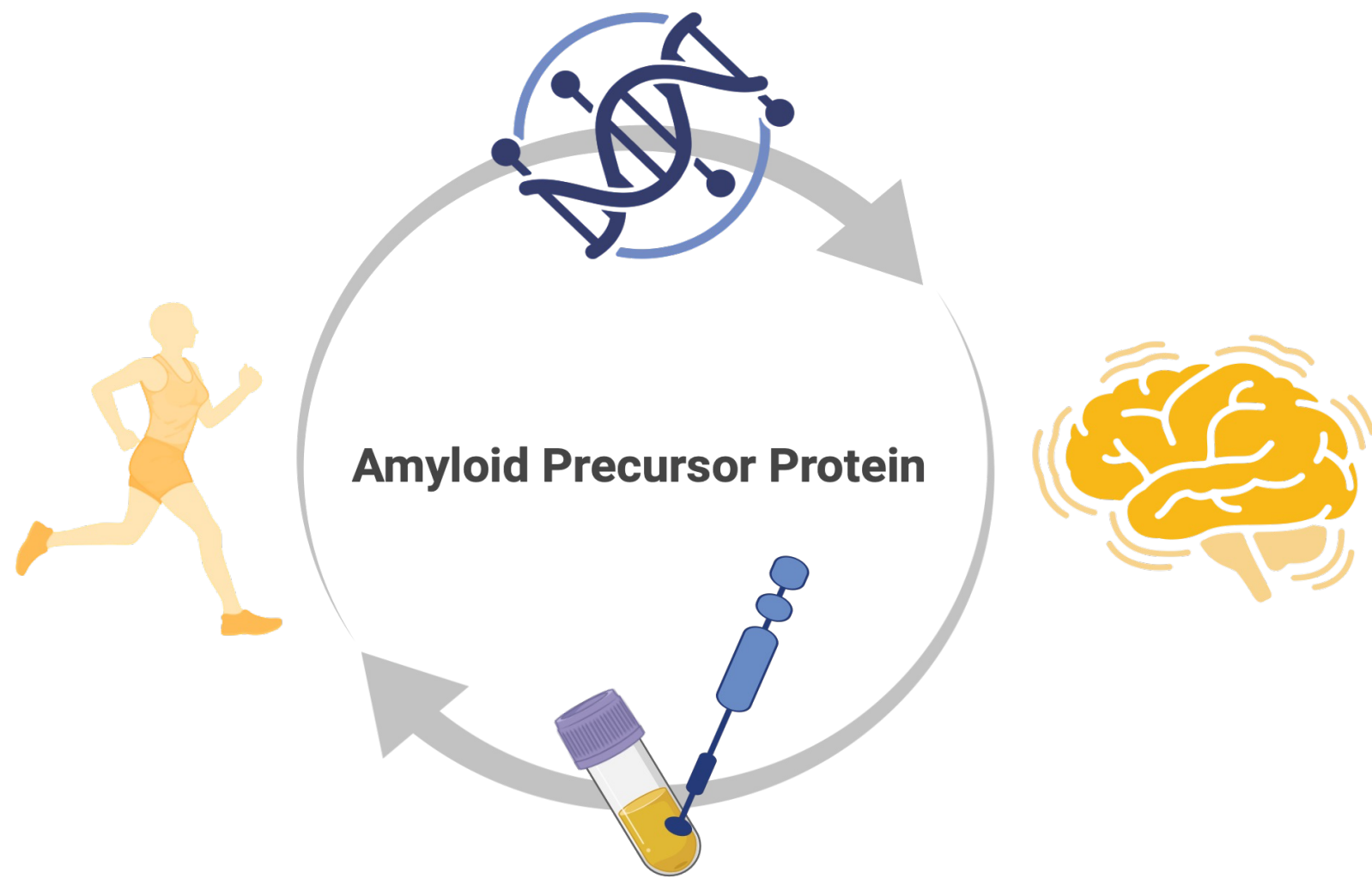
# Methylation and Protein Levels of the *APP* Gene in relation to Cognitive Function After A Six-month Aerobic Exercise Trial in Women with Breast Cancer

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## Background & Purpose

- Amyloid Precursor Protein (*APP*) gene dysregulation and Amyloid  $\beta$  ( $A\beta$ ) accumulation are associated with increased cognitive impairment but have been understudied in cancer-related cognitive decline.
- This study investigated how *APP* gene methylation and  $A\beta$  protein levels change with aerobic exercise and their potential mediating or moderating effects on the relationship between aerobic exercise and cognitive changes.



## Method

- This longitudinal analysis focused on a subsample with pre- and post-intervention methylation data from the Exercise Program in Cancer and Cognition (EPICC) trial.
- Variables of Interest
  - DNA methylation (from peripheral blood)
    - M-values from 81 CpG sites within or near the *APP* gene (Positive / Negative = higher methylated/unmethylated signals)
  - Plasma Protein
    - $A\beta$ 1-40 /  $A\beta$ 1-42 / APP669-711 / APP669-711: $A\beta$ 1-42 /  $A\beta$ 1-40: $A\beta$ 1-42 / Composite Biomarker (sum of  $A\beta$ 1-40: $A\beta$ 1-42 and APP669-711: $A\beta$ 1-42 with 1:1 weight)
  - Objectively measured Cognitive Composite Scores (Higher = Better)
- Statistical Analysis using R (version 4.4)
  - Linear regression with linear mixed-effects modeling
  - Moderation and Serial mediation (with 5,000 bootstrapped samples)



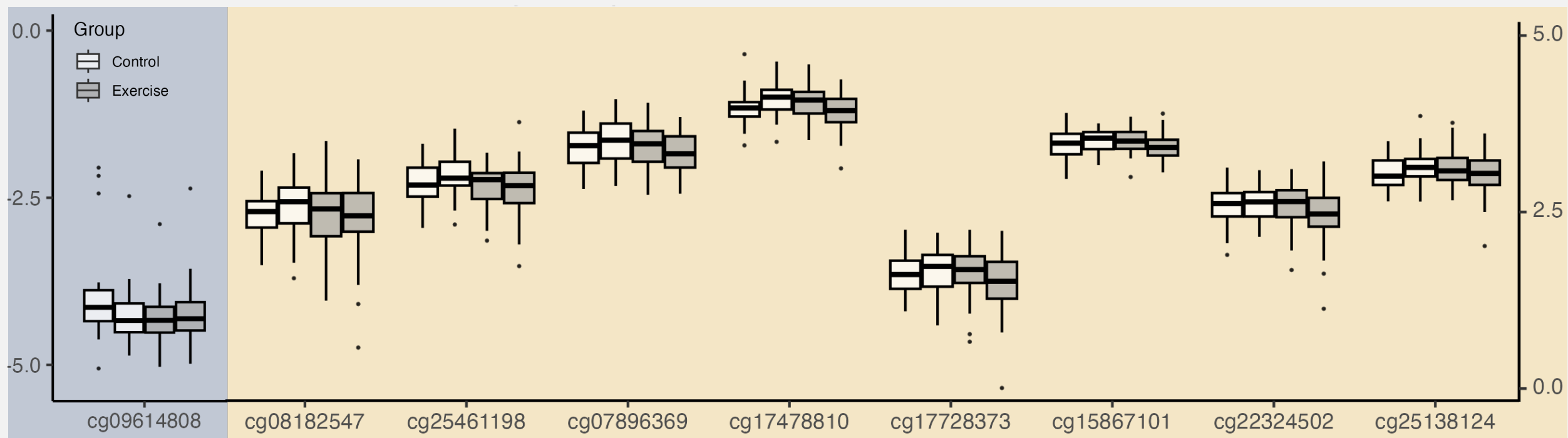
Publications from EPICC trial main finding (left) and protocol (right)

**Table 1. Sample Characteristics (N=64)**

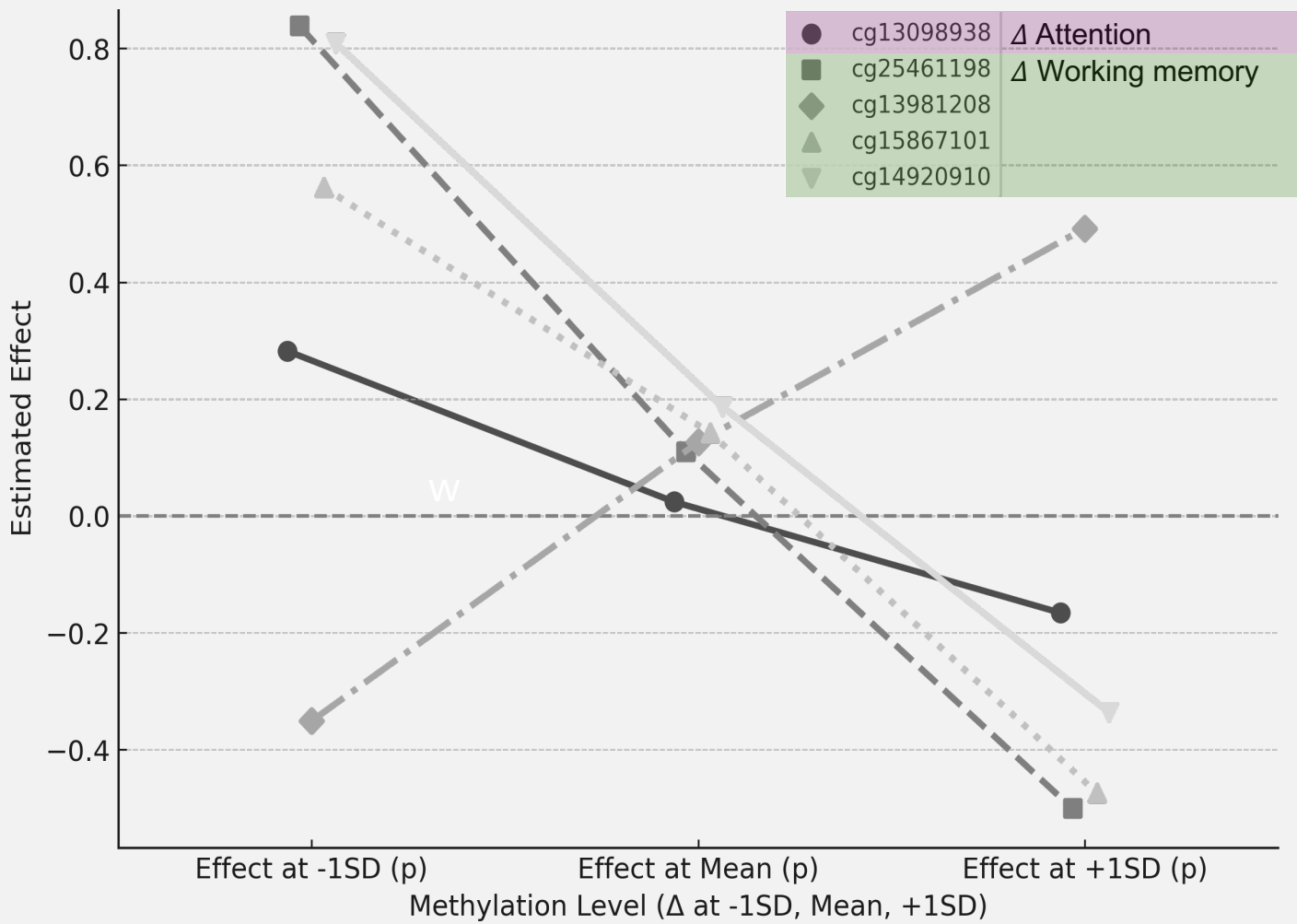
	Mean (SD)/n (%)
Age [years]	62.2 (8.03)
Education [years]	16.2 (2.60)
Body mass index [kg/m <sup>2</sup> ]	31.3 (6.84)
Endocrine therapy [days]	54.0 (127.81)
Disease stage	
Ductal carcinoma in situ	11 (17.2)
I	40 (62.5)
IIa	9 (14.1)
IIb	2 (3.1)
IIIa	2 (3.1)
Chemotherapy [Yes]	7 (10.9)

## Findings

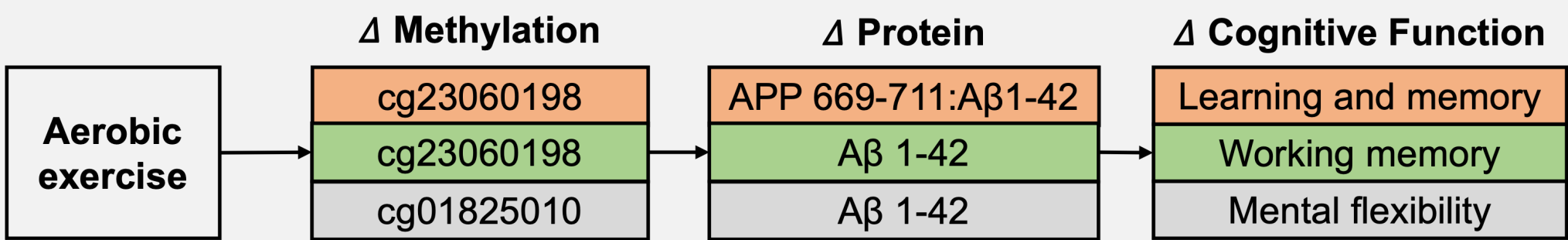
- Aerobic exercise affected methylation at nine CpG sites depending on the CpG-site methylation status at pre-intervention, but not protein.
- Time effects were observed for APP 669-711, the APP 669-711: $A\beta$  1-42 ratio, and the Composite Biomarker, all showing increases over six months across both groups.



**Figure 1.** Boxplots showing CpG site-specific methylation M-values by group, with pre- and post-intervention values side by side.



**Figure 2.** Simple slopes for moderation effects of changes in ( $\Delta$ ) methylation.



**Figure 3.** Serial mediation of aerobic exercise -  $\Delta$  methylation -  $\Delta$  protein -  $\Delta$  cognitive function

## Conclusion

- Aerobic exercise altered DNA methylation at multiple CpG sites across the *APP* gene and Site-specific methylation changes may moderate cognitive benefits of aerobic exercise.
- DNA methylation profiles and  $A\beta$  ratio may help predict and explain individual variability in the cognitive response to aerobic exercise among postmenopausal women with breast cancer.