

APOE-ε4, exercise, and subjective sleep quality in middle-aged adults at elevated risk for Alzheimer's disease: Findings from PAAD-2

Chadsley M. Wessinger¹, Kyoung Shin Park^{2,1}, Alexis B. Slutsky-Ganesh^{3,1}, William B. Karper¹, Jeffrey D. Labban^{4,1}, Samantha L. DuBois^{5,1}, Samuel W. Kibildis^{6,1}, Jarod C. Vance^{7,1}, Hadassah Som-Pimpong^{8,1}, Bryan Montero-Herrera¹, Brittany D. Armstrong¹, Marcus Roman^{5,1}, Laurie Wideman¹, & Jennifer L. Etnier¹

¹University of North Carolina at Greensboro, NC, USA; ²Emory University School of Medicine, GA, USA; ³North Carolina Agricultural and Technical State University, NC, USA; ⁴University of Tennessee, TN, USA; ⁵Appalachian State University, NC, USA; ⁶Athens-Clarke County Unified Government, GA, USA; ⁷Longwood University, VA, USA; ⁸Meharry Medical College, TN, USA

Background

- Sleep disturbance and the apolipoprotein E (APOE) ε4 allele are established risk factors for Alzheimer's disease (AD).^{1,2}
- Regular physical activity (PA) may mitigate sleep disturbance, particularly during midlife (40-65 years),³ an important life stage for lifestyle changes to lower AD risk.
- However, it remains unclear whether the relationship between PA and sleep differs by genetic risk in this age group or across sleep quality domains.
- We investigated the effects of a 12-month PA intervention on subjective sleep quality as a function of APOE-ε4 carriage in cognitively unimpaired (MoCA ≥26) middle-aged adults with a family history of AD (FH+).

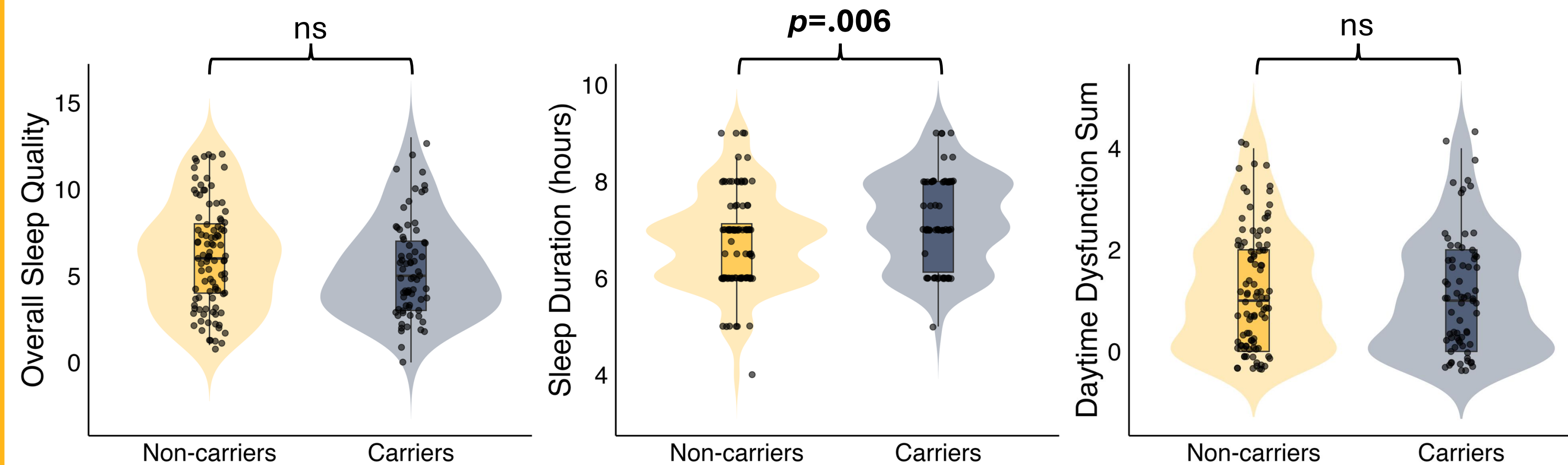
Methods

- Middle-aged adults (N=171, 56.3±6.3 yrs, 86% female) were randomized to an exercise or usual-care control group for 12 months (NCT03876314; NIH01AG058919).⁴
- Exercise consisted of virtual aerobic and resistance training 3 days/week; control participants received monthly educational materials.
- APOE-ε4 carriage was determined from saliva (70 carriers, 96 non-carriers).
- Sleep quality, duration, and daytime dysfunction were assessed via the Pittsburgh Sleep Quality Index (PSQI) at pre- and post-test.
 - Higher PSQI scores reflect worse sleep quality and greater daytime dysfunction.
- Longitudinal mixed-effects models with random intercepts estimated Time*Group*APOE-ε4 interactions under maximum likelihood estimation.

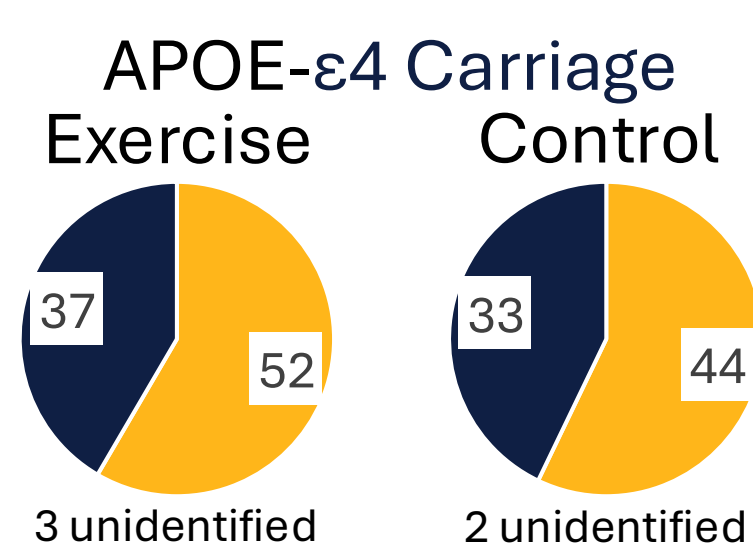
Results

Baseline

● Non-carriers ● Carriers



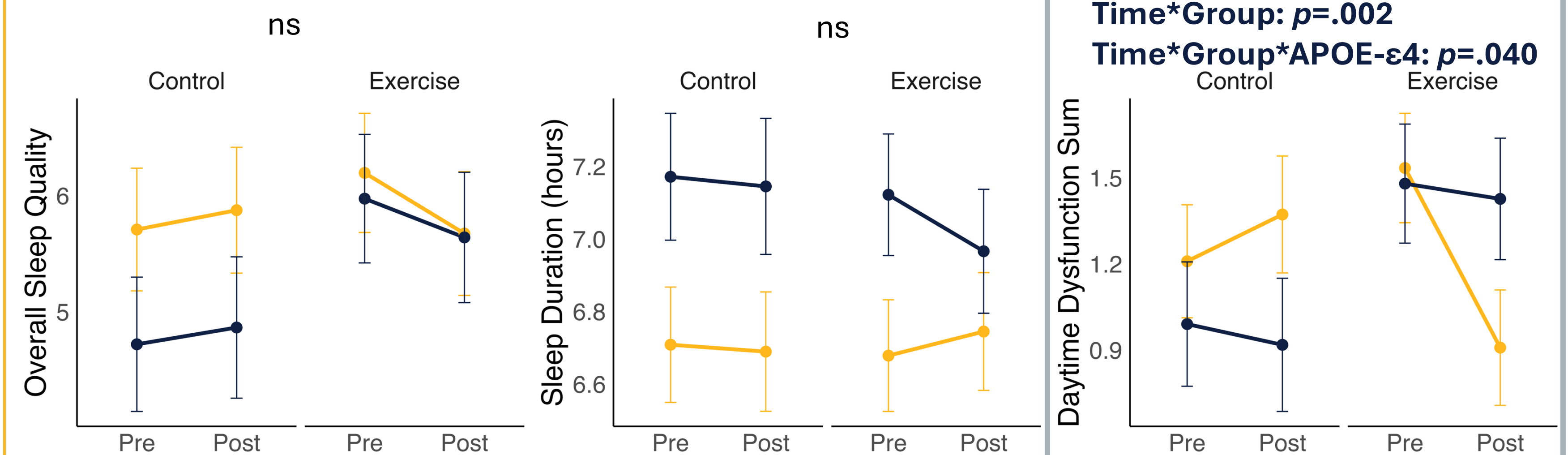
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	Exercise (n=92)	Control (n=79)
Age, yrs	56.2±6.5	56.5±6.1
BMI, kg/m ²	29.4±6.4	27.8±5.2
Sex, % female	86%	86%

- APOE-ε4 carriers reported 26 more minutes of sleep than non-carriers (p=.006).
- No exercise vs control between group differences in covariates (age, BMI, sex, APOE-ε4 carriage) or sleep-related outcome variables (all p>.05).

Changes



- Intervention adherence varied by cohort (cohort 1: 61%; cohort 2: 58%; cohorts 3-11: 74%).
 - Variation may be explained by impacts of COVID-19 (see Etnier, Armstrong, et al.'s poster)
- Significant Time*Group (p=.002) and Time*Group*APOE-ε4 (p=.040) interactions were observed for subjective daytime dysfunction.
 - From pre- to post-test, APOE-ε4 non-carriers in the exercise group reported improvements in subjective daytime dysfunction (Δ=0.626, d=0.77, p=.0007).
- No significant Time*Group or Time*Group*APOE-ε4 interactions were observed for other outcome variables (all p>.05).

Discussion

- In this predominately female sample of middle-aged adults with a FH+, 12-months of exercise improved subjective daytime dysfunction in APOE-ε4 non-carriers, but not in controls or carriers.
- Only daytime dysfunction improved, albeit in APOE-ε4 non-carriers only, suggesting exercise may enhance daytime functioning even in the absence of changes to overall sleep quality or duration.
- APOE-ε4 carriage may moderate sleep-related benefits of PA, likely through APOE-ε4-related neuroinflammation,⁵ potentially reflecting a higher threshold for exercise-induced improvements among APOE-ε4 carriers.
- Given the subjective nature of the PSQI, replication leveraging objective sleep quality measures (e.g., polysomnography) are necessary and the predominantly female sample prohibits generalization to broader samples.
- More targeted lifestyle interventions (e.g., greater exercise dose) may be needed to improve sleep-related daytime functioning in those at elevated genetic risk for AD.

References

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GREENSBORO
Department of Kinesiology

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