



Sleep Disturbance Linked to Subjective Cognitive Complaints and Slower Processing Speed in APOE ϵ 4 Carriers In Midlife: PAAD2 Baseline Data

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BACKGROUND

- Sleep disturbance and the apolipoprotein E (APOE) ϵ 4 allele are both established risk factors for Alzheimer's disease (AD).¹
- Evidence suggests sleep pathology may exacerbate AD pathophysiology particularly during **midlife (40–65 years)** — a critical window to detect preclinical cognitive changes.²
- APOE ϵ 4 carriers exhibit accelerated slow-wave sleep decline,³ and sleep disturbance is bidirectionally linked to amyloid accumulation in preclinical AD,⁴ providing biological context for genotype-dependent moderation of the sleep–cognition relationship.
- It remains unclear whether the sleep–cognition relationship differs by APOE ϵ 4 genotype in midlife, or whether this manifests in subjective or objective measures of cognition.
- In this cross-sectional study, we tested whether **sleep quality interacts with APOE ϵ 4 carriage** to predict subjective and cognitive measures of cognition in cognitively unimpaired middle-aged adults with a family history of AD.

METHODS

- We analyzed baseline data of cognitively unimpaired, middle-aged adults with a family history of AD, enrolled in a clinical trial (NCT03876314).⁵
 - N = 174 (88.5% Female, 88.5% White/Caucasian, Education = 16.8 ± 2.39 years)
 - Age $M \pm SD = 56.1 \pm 6.28$ [Range: 40 – 66 years]
 - Montreal Cognitive Assessment (MoCA) Score = 27.9 ± 1.7
- Participants completed the **Pittsburg Sleep Quality Index (PSQI)** via REDCap survey with higher scores indicating greater sleep disturbance.⁶
- APOE ϵ 4 genotype** was determined from saliva samples (70 carriers vs. 104 non-carriers) excluding 3 heterozygous carriers with ϵ 2.
- Subjective cognitive complaints (SCC)** were measured via **Everyday Cognition Scale (ECog-12)** with higher score indicating greater complaints.⁷
- Processing speed** was measured by **Symbol Digit Modalities Test (SDMT)**, while **Episodic memory composite** (Delayed Recall of Auditory Verbal Learning, Logical Memory, Complex Figure, Paired Associates Tests) and **executive function composite** (Trail Making B, Digits Span Backward, Flanker, Dimensional Change Cart Sort) were each computed as z-score averages.

- Linear regression models** tested the PSQI $\times$ APOE ϵ 4 interaction on each cognitive outcome with potential covariates (age, sex, education, pulse pressure). Significant interactions decomposed via simple slope analyses.

Table 1. Sample Characteristics

Variable	Total (N = 174)	ϵ 4 Carriers (n = 70)	Non-carriers (n = 104)
Age (years)	56.2 ± 6.46	55.6 ± 6.36	56.6 ± 6.53
Female (%)	88.5%	85.7%	90.4%
White/Caucasian (%)	88.5%	88.6%	88.5%
Education (years)	16.8 ± 2.39	16.8 ± 2.46	16.8 ± 2.36
PSQI Score	5.7 ± 2.95	5.3 ± 2.72	6.0 ± 3.06
ECog-12 score	1.44 ± 0.48	1.43 ± 0.49	1.44 ± 0.47
SDMT score	59.7 ± 11.5	59.1 ± 10.9	60.2 ± 11.9
Pulse Pressure (mmHg)	40.6 ± 13.5	42.3 ± 10.1	39.5 ± 15.4

RESULTS

- Significant PSQI $\times$ APOE ϵ 4 interactions on ECog-12 and SDMT but not on episodic memory composite ($b = 0.01$, $p = .800$) or executive function composite ($b = 0.00$, $p = .995$). See Table 2 and Figures 1–2.
- Simple slope analyses for ECog-12 and SDMT:
 - In APOE ϵ 4 carriers only, higher PSQI (greater sleep disturbance) $\rightarrow$ higher ECog-12 (more SCC [$b = 0.06$, $p = .01$]) $\rightarrow$ lower SDMT (slower processing speed [$b = -1.13$, $p = .03$])
 - In APOE ϵ 4 non-carriers, all $p > .60$

Table 2. Linear Regression Results

Outcome	ECog-12 b (SE)	p	SDMT b (SE)	p
Predictor				
PSQI Score	-0.00 (0.02)	.864	0.15 (0.37)	.683
APOE ϵ 4 (Carrier)	-0.29 (0.16)	.072	5.33 (3.87)	.171
PSQI $\times$ APOE ϵ4 †	0.06 (0.03)	.033	-1.31 (0.63)	.039
Age	-0.00 (0.01)	.519	-0.60 (0.15)	<.001
Sex (Female)	0.03 (0.12)	.811	6.36 (2.76)	.023
Race (White)	-0.25 (0.12)	.038	2.83 (2.88)	.328
Education	-0.01 (0.02)	.618	-0.27 (0.38)	.473
Pulse Pressure	-0.00 (0.00)	.343	0.05 (0.09)	.578
R²	0.073		0.125	

† Key interaction term. Bold red = $p < .05$.

Figure 1. PSQI $\times$ APOE ϵ 4 interaction on SCC (ECog-12; $b = 0.06$, $p = .033$). In APOE ϵ 4 carriers, higher PSQI was associated with greater ECog-12 ($b = 0.05$, $p = .012$). Not significant for non-carriers ($p > .60$). Points = partial residuals; shading = 95% CI.

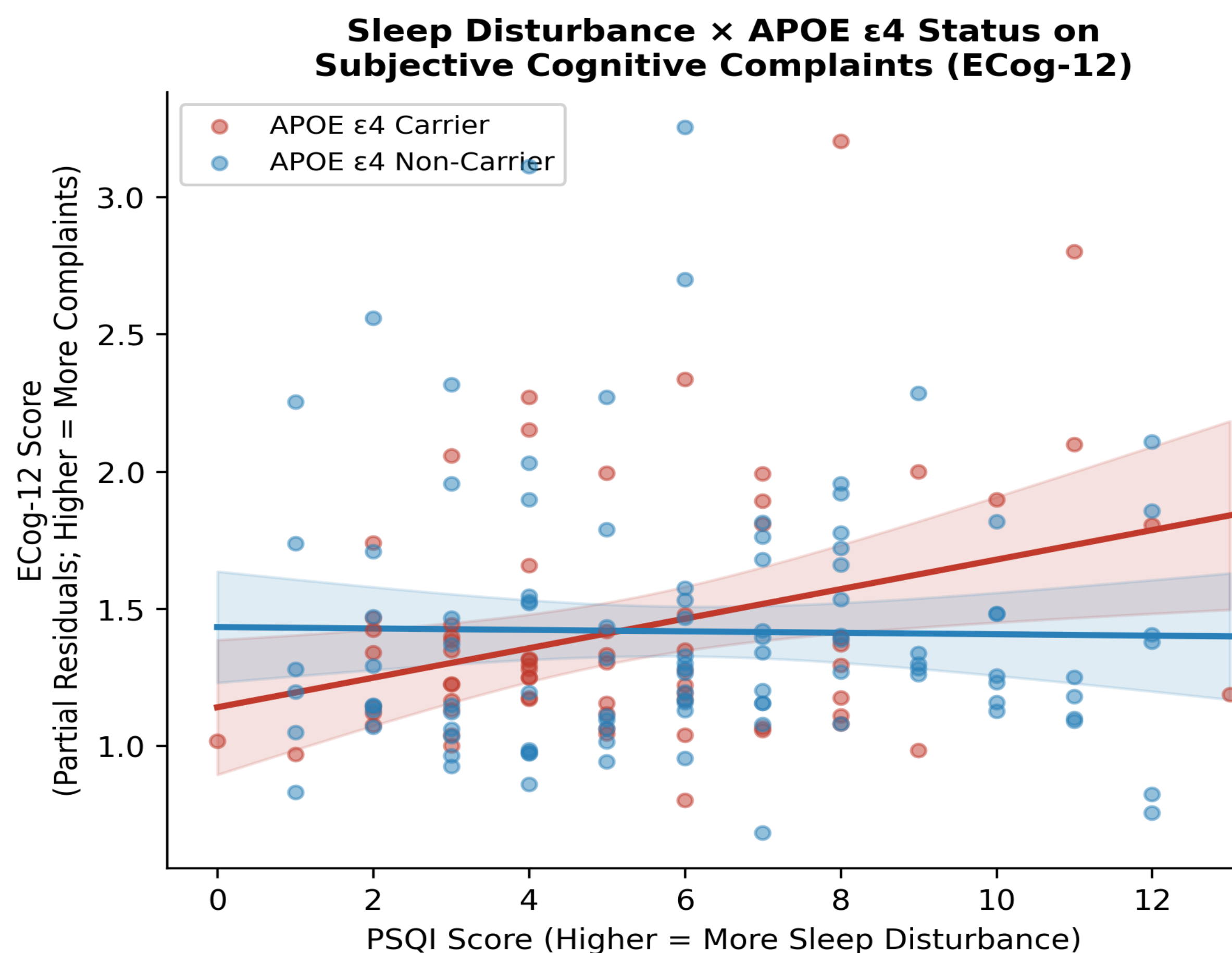
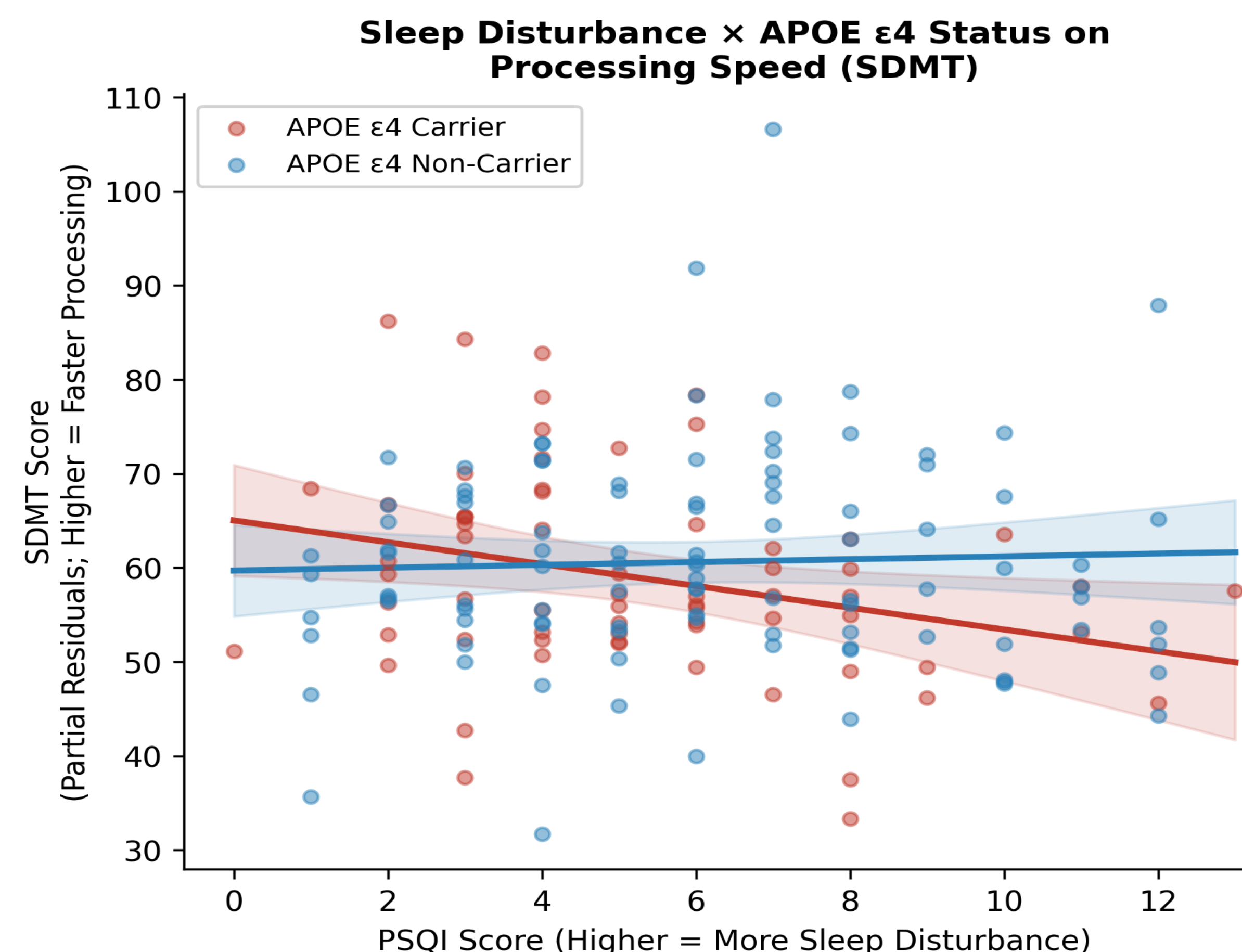


Figure 2. PSQI $\times$ APOE ϵ 4 interaction on processing speed (SDMT; $b = -1.31$, $p = .039$). In APOE ϵ 4 carriers, higher PSQI was associated with lower SDMT score ($b = -1.16$, $p = .024$). Not significant for non-carriers ($p > .60$). Points = partial residuals; shading = 95% CI.



DISCUSSION

- APOE ϵ 4 carriers in midlife appear **uniquely vulnerable** to the cognitive consequences of sleep disturbance, manifesting as greater subjective cognitive complaints and slower processing speed — effects absent in non-carriers.
- These effects appeared in **subjective cognitive complaints (ECog-12)** and **processing speed (SDMT)**, but not in memory or executive function — suggesting these domains may be earlier, more sensitive markers of sleep-related cognitive vulnerability in genetically at-risk individuals.
- Heightened ϵ 4 vulnerability may reflect APOE ϵ 4-associated acceleration of slow-wave sleep decline; each 1% annual slow-wave sleep decrease confers a **27% increased dementia risk**, with ϵ 4 carriers showing the greatest slow-wave sleep loss over time.⁷ A plausible mechanism involves glymphatic clearance: slow-wave activity disruption acutely elevates CSF amyloid- β , and worse subjective sleep quality over multiple nights associates with elevated CSF tau.¹
- Persistent short sleep (≤ 6 h) in midlife independently predicts **30% higher dementia risk**,² reinforcing the clinical importance of targeting sleep health in middle-aged adults at genetic risk.
- Interventions targeting **sleep quality** may be particularly beneficial for APOE ϵ 4 carriers in midlife to mitigate early trajectories of cognitive decline during this critical preclinical window.
- Limitations are the cross-sectional design and the sample predominantly including white females. Thus, generalizability may be limited.

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