

Sleep Quality and Cardiovascular Burden Moderates the Association Between Neuroinflammation and Cognitive-Functional Decline

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BACKGROUND

- Poor sleep is a modifiable risk factor for cognitive and functional decline.
- Sleep disruption is associated with vascular dysregulation, cardiovascular disease (CVD) risk, and inflammation, each of which independently contribute to cognitive decline and dementia.
- However, the combined influence of poor sleep, vascular burden, and neuroinflammatory processes on cognitive trajectories in AD remains unclear.
- Plasma glial fibrillary acidic protein (GFAP), a peripheral marker of astrocytic reactivity, may provide insight into the neuroinflammatory pathways linking sleep, cardiovascular health, and cognitive decline.
- This study investigated whether sleep characteristics and CVD burden modify longitudinal associations between GFAP and cognitive-functional decline in older adults.

METHODS

Participants

- N = 129 participants from the 1Florida Alzheimer's Disease Research Center

Table 1. Sample Demographics

	Mean	SD
Age (years)	64.9	7.73
Education (years)	13.83	3.06
CVD Burden	2.35	1.44
Geriatric Depression Scale (GDS)	2.62	2.58
GFAP	152.24	106.23
Global Sleep Quality (0-21)	6.81	4.07
Subjective Sleep Quality-C1 (0-4)	0.99	0.87
Sleep Duration-C3 (0-4)	1.08	0.89
Habitual Sleep Efficiency-C4 (0-4)	0.95	1.14
CDR Sum of Boxes (CDR-SB)	1.11	1.18
	N	%
Male	70	54.30%
APOE Status		
No ε4 Alleles	86	67.70%

Methods

- Linear mixed effects models with:
 - Predictor:** GFAP
 - Moderators:**
 - Subjective Sleep Quality, Sleep Duration, Habitual Sleep Efficiency, Global Sleep Quality measured by the Pittsburgh Sleep Quality Index (PSQI).
 - CVD burden (count of cardiometabolic and vascular risk indicators, including self-reported diagnoses, recent smoking and obesity [BMI ≥ 30]).
 - Outcome:** Cognitive-functional decline measured by the Clinical Dementia Rating Scale, Sum of Boxes (CDR-SB), reflecting combined cognitive and functional severity across three visits.
 - Covariates:** age, sex, education, depression, APOE ε4 status
- Post-hoc simple slope analyses clarified interactions.
- Benjamini-Hochberg false discovery rate (FDR) correction was applied to adjust for multiple comparisons.

RESULTS

Figure 1. Interaction of GFAP and Global Sleep Quality by CVD Burden

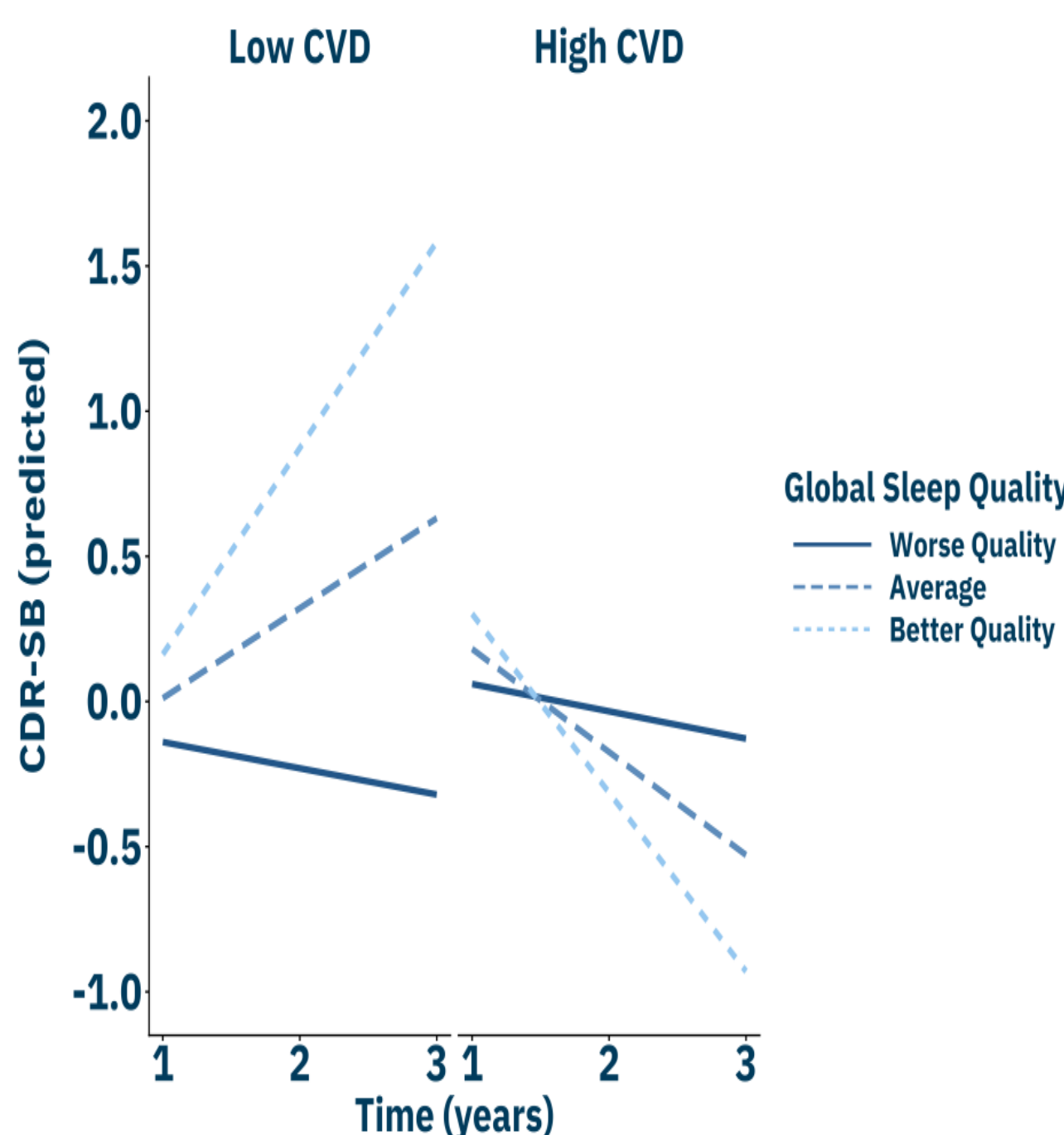


Figure 2. Interaction of GFAP and Subjective Sleep Quality by CVD Burden

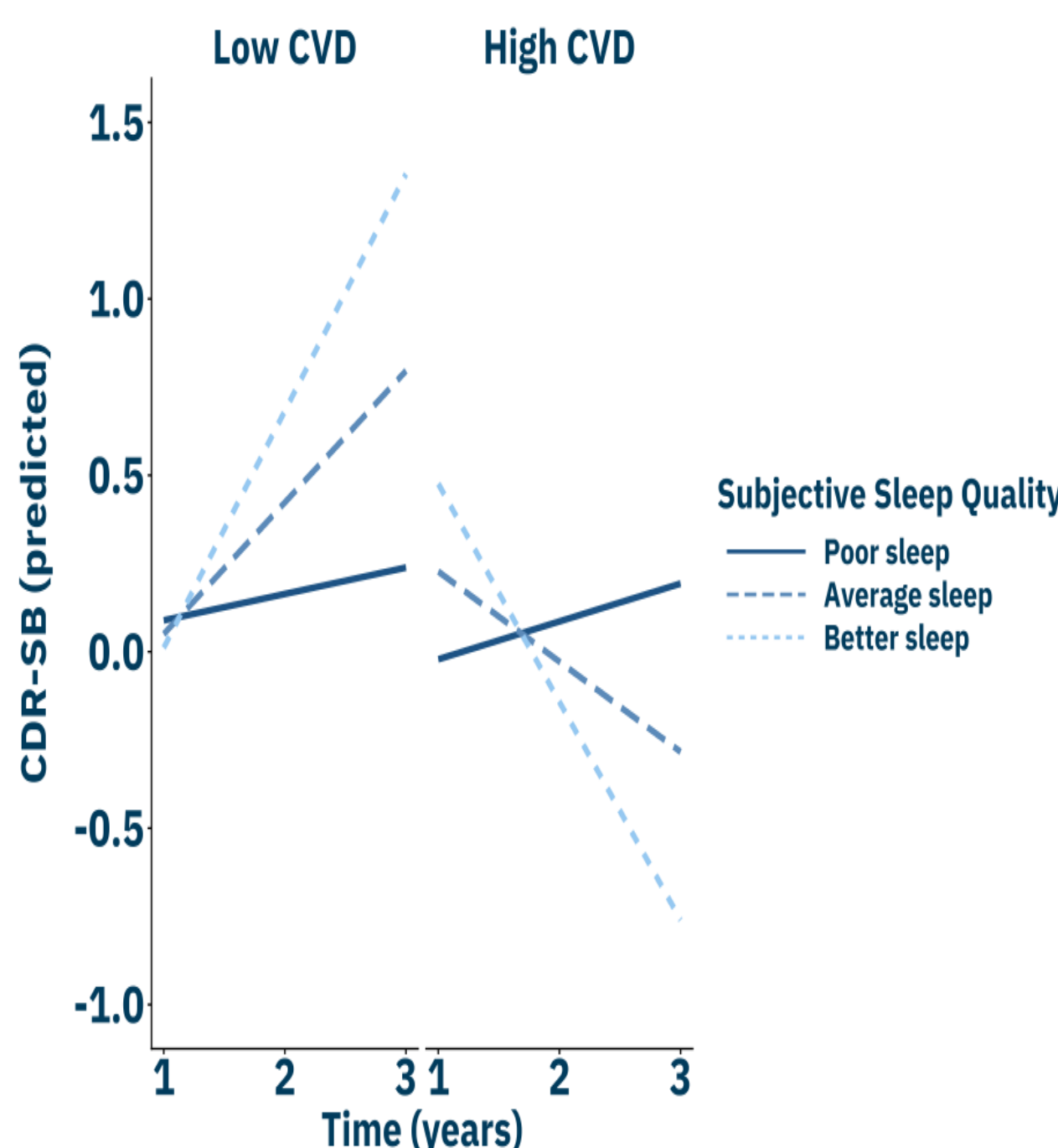


Figure 3. Interaction of GFAP and Sleep Duration by CVD Burden

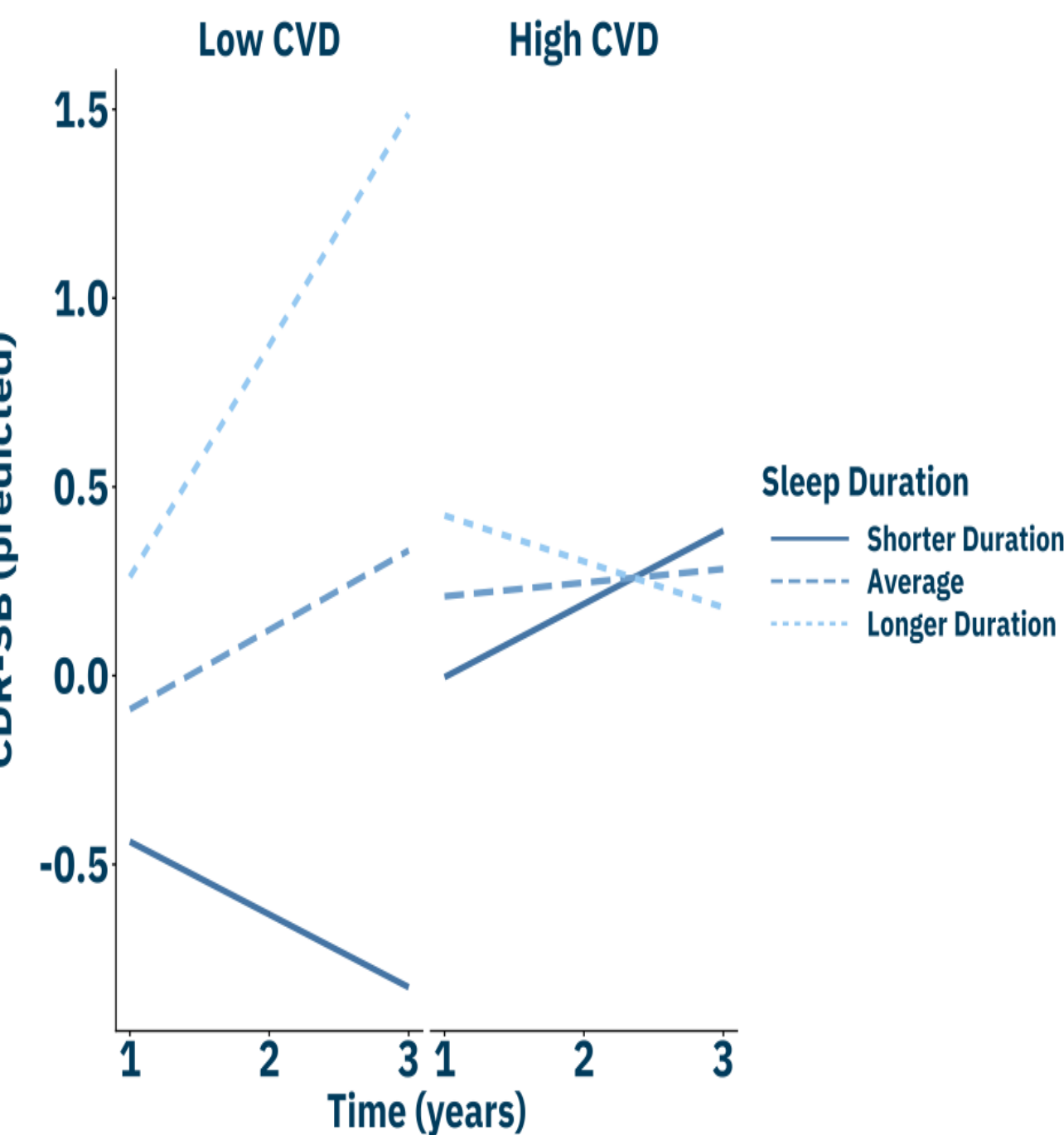
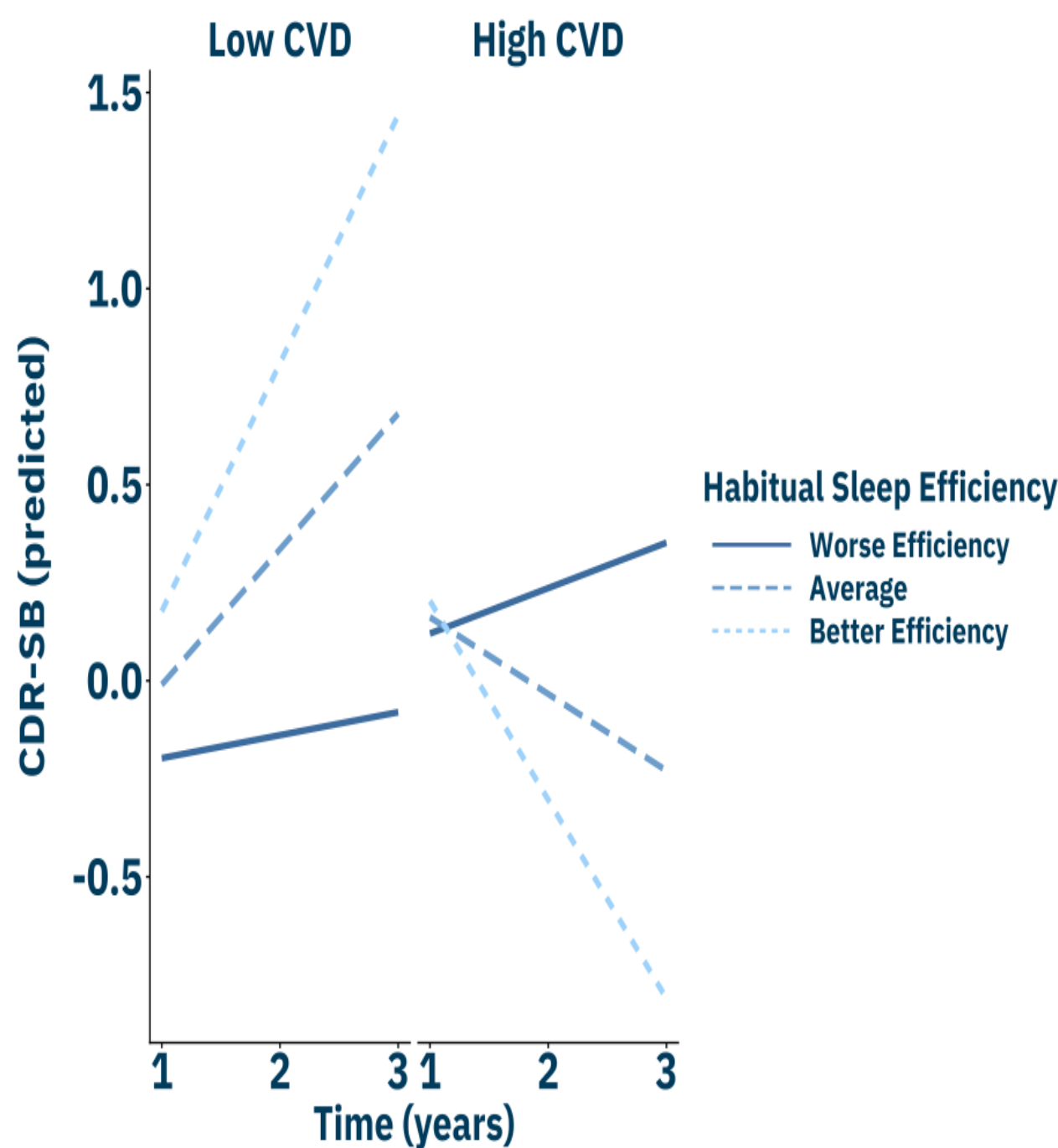


Figure 4. Interaction of GFAP and Habitual Sleep Efficiency by CVD Burden



***Note.** CDR-SB values are displayed in standardized (z-scored) units. Figures depict predicted CDR-SB trajectories over time at high GFAP (+1SD), stratified by sleep characteristics and CVD burden.

RESULTS (cont.)

Higher plasma GFAP levels was associated with greater cognitive-functional decline over time ($\beta = 0.18$, $pFDR = .02$).

Global Sleep Quality x CVD Burden ($\beta = 0.29$, $pFDR < .01$)

- At lower CVD burden, higher plasma GFAP levels were associated with greater decline at better ($\beta = 0.71$, $p < .001$) and average ($\beta = 0.31$, $p = .01$) global sleep quality, whereas these associations were attenuated and reversed at higher CVD burden (*better*: $\beta = -0.62$, $p = .01$; *average*: $\beta = -0.36$, $p = .01$; *poor*: $\beta = -0.10$, $p = .61$).

Subjective Sleep Quality x CVD Burden ($\beta = 0.31$, $pFDR < .01$)

- At lower CVD burden, higher plasma GFAP levels were associated with greater decline at better ($\beta = 0.67$, $p < .01$) and average sleep quality ($\beta = 0.37$, $p < .01$), whereas these associations attenuated and reversed at higher CVD burden (*better*: $\beta = -0.62$, $p = .01$; *average*: $\beta = -0.27$, $p = .05$; *poor*: $\beta = 0.11$, $p = .52$).

Sleep Duration x CVD Burden ($\beta = 0.22$, $pFDR = .02$)

- At lower CVD burden, higher plasma GFAP levels were associated with greater decline at longer duration ($\beta = 0.61$, $p < .01$), whereas this association was no longer significant at higher CVD burden (*longer duration*: $\beta = -0.12$, $p = .45$; *average*: $\beta = 0.04$, $p = .80$; *shorter duration*: $\beta = 0.19$, $p = .33$).

Habitual Sleep Efficiency x CVD Burden ($\beta = 0.62$, $pFDR = .02$)

- At lower CVD burden, higher plasma GFAP levels was associated with greater decline at better ($\beta = 0.63$, $p < .01$) and average ($\beta = 0.35$, $p = .01$) habitual sleep efficiency, whereas these associations attenuated and reversed at higher CVD burden (*better*: $\beta = -0.51$, $p = .01$; *average*: $\beta = -0.20$, $p = .14$; *poor*: $\beta = 0.12$, $p = .53$).

CONCLUSIONS

- Higher neuroinflammatory burden was associated with greater cognitive and functional decline over time.
- CVD burden shaped whether sleep characteristics strengthened the association between GFAP and cognitive-functional decline, suggesting that the predictive value of sleep quality for cognitive decline depends on cardiometabolic context.
- Patterns observed at lower CVD burden may reflect processes less tightly linked to GFAP-related neuropathology (e.g., irregular sleep schedules, poor sleep hygiene), reducing the extent to which poorer sleep reflects underlying biological processes.
- At higher CVD burden, poor sleep appears more closely tied to underlying vascular and inflammatory processes.
- These findings suggest that sleep is not a uniform risk factor, but a context-dependent modifier which should not be examined in isolation.**

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