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Longitudinal Sleep Trajectories as Predictors of Neurodegeneration Biomarkers and Cognitive Decline

An 8-year serial polysomnography–Simoa biomarker study in the KoGES community cohort

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KEY MESSAGE

Take-home

An 8-year rise in plasma p-tau217 together with high nocturnal hypoxic burden jointly predicts memory decline in community-dwelling older adults — older adults — nominating sleep-related hypoxia as a modifiable target for prodromal-phase dementia prevention.

1 · BACKGROUND

Sleep disturbance — particularly **sleep-disordered breathing (SDB)** and nocturnal nocturnal intermittent hypoxia — is increasingly recognized as a **modifiable modifiable contributor**, not merely a symptom, of neurodegeneration.

Ultrasensitive Simoa now enables scalable, **longitudinal** plasma measurement of **p-tau217, Aβ42/40, GFAP, and NfL**.

Q1. Is it the *level*, or the *trajectory*, of a plasma biomarker that marks incipient cognitive decline?

Q2. Does sleep act as an *effect modifier* of the biomarker–cognition link?

2 · METHODS

Cohort. KoGES Ansan sleep sub-study — community-dwelling older adults with serial in-laboratory PSG and Simoa plasma biomarkers at **baseline (ag1)** and **~8-year follow-up (ag3; mean 8.1 y)**.

Design. Extreme-group phenotype contrast: **Poor memory** (ag3 z < -1.0, n = 173) vs **Good memory** (ag3 z > +1.0, n = 180).

Biomarkers. p-tau217, p-tau217/Aβ42, Aβ40, Aβ42, Aβ42/40, GFAP, NfL — natural-log transformed transformed and standardized.

Sleep domains (7). Respiratory / Architecture / Quantity / Chronotype / Insomnia / Sleepiness / Quality — log1p-transformed.

Statistics. Multivariable logistic & linear regression with **HC3 robust SE**. Moderation via **Firth penalized logistic**. Multiplicity via **BH FDR within domain**; interaction against **Bonferroni α/7 = 0.007**.

Adjustment (Model 2). Age, sex, education, APOE ε4, BMI, diabetes, hypertension, dyslipidemia, smoking, alcohol, physical activity, BDI. Pre-registered in **SAP v1.2** (Python; seed 2026).

3 · COHORT — Table 1

Baseline characteristics and cognitive status by outcome

Characteristicsa	Overall (n=353)	Poor memory (n=173)	Good memory (n=180)	P value
Age at baseline ^b , y	56.26 (4.24)	56.36 (4.15)	56.16 (4.34)	0.662
Age at SNSB-II assessment, y	64.24 (4.40)	64.35 (4.34)	64.13 (4.47)	0.640
Follow-up duration ^c , y	8.09 (0.63)	8.08 (0.66)	8.10 (0.61)	0.778
Sex				0.607
Female	161	76 (43.93%)	85 (47.22%)	
Male	192	97 (56.07%)	95 (52.78%)	
APOE4 allele (n=314) ^d				0.956
non-carrier	253	125 (72.25%)	128 (71.11%)	
carrier	61	31 (17.92%)	30 (16.67%)	
Education, y	11.46 (3.50)	12.03 (3.32)	10.91 (3.58)	0.002
Body mass index, kg/m ²	24.80 (2.98)	24.73 (2.77)	24.88 (3.17)	0.644
Diabetes	60 (17.00%)	30 (17.34%)	30 (16.67%)	0.979
Hypertension	102 (28.90%)	50 (28.90%)	52 (28.89%)	0.909
Hyperlipidemia	106 (30.03%)	50 (28.90%)	56 (31.11%)	0.736
Physical activity ^e	179 (50.71%)	91 (52.60%)	88 (48.89%)	0.555
Smoking status				0.983
Never smoker	214	105 (60.69%)	109 (60.56%)	
Past smoker	91	44 (25.43%)	47 (26.11%)	
Current smoker	48	24 (13.87%)	24 (13.33%)	
Alcohol consumption status				0.425
No drinker	153	79 (45.66%)	74 (41.11%)	
Past drinker	21	12 (6.94%)	9 (5.00%)	
Current drinker	179	82 (47.40%)	97 (53.89%)	
Beck's Depression Inventory	6.83 (6.19)	6.61 (5.90)	7.04 (6.46)	0.518
MMSE at baseline	27.89 (1.62)	27.37 (1.69)	28.39 (1.38)	<0.001
MMSE at 1st follow-up	28.06 (1.58)	27.59 (1.61)	28.47 (1.43)	<0.001
MMSE at SNSB-II assessment	27.58 (1.81)	26.97 (1.88)	28.16 (1.52)	<0.001
SNSB-II domain Z-score, mean (SD)				
Attention	0.03 (1.07)	-0.26 (1.08)	0.32 (0.98)	<0.001
Language	0.33 (1.11)	-0.22 (1.25)	0.87 (0.59)	<0.001
Visuospatial	-0.03 (1.09)	-0.52 (1.32)	0.44 (0.45)	<0.001
Frontal executive	0.59 (1.09)	0.05 (1.11)	1.10 (0.78)	<0.001
Memory (defining outcome)	0.03 (1.58)	-1.52 (0.41)	1.52 (0.43)	<0.001

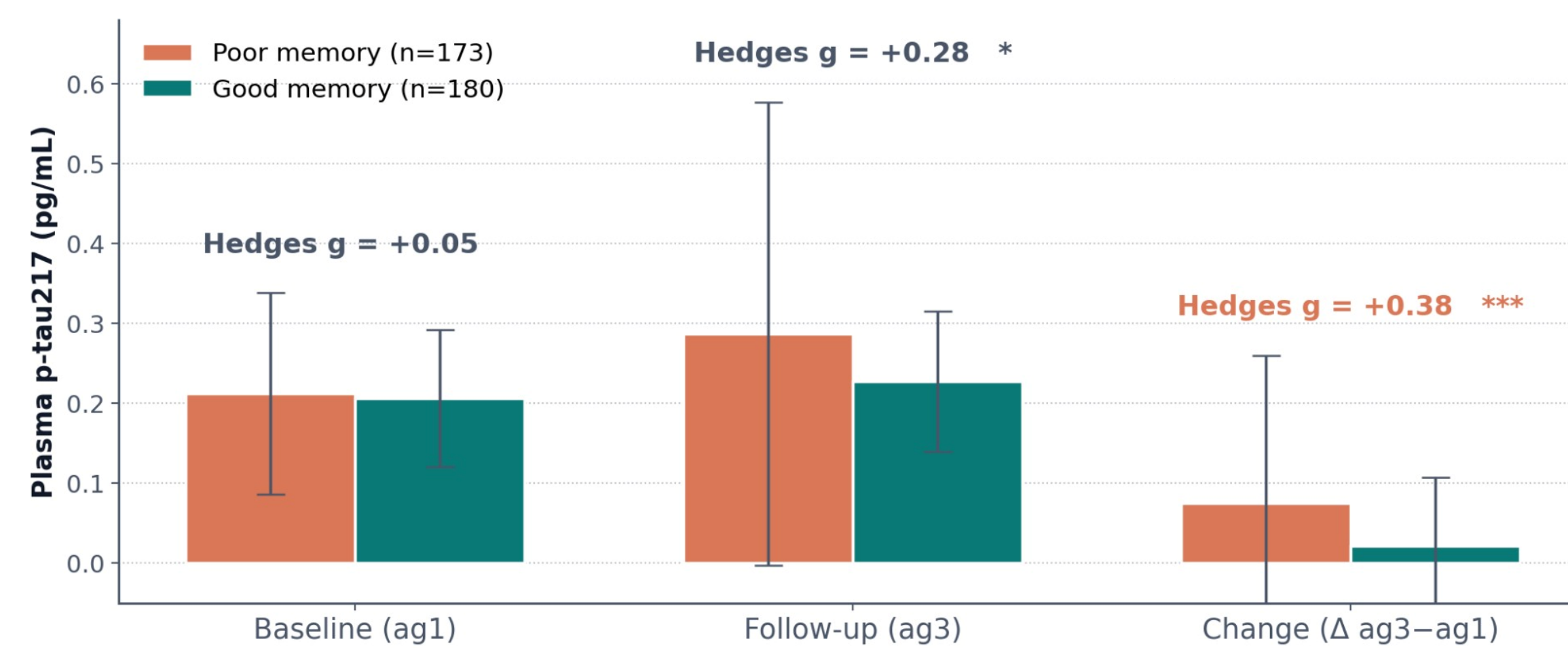
^aMean (SD) or n (%). ^bBaseline 2011–14; 1st FU 2015–18; 2nd FU 2019–22. ^cPSG participation. ^dMissing data may cause discrepancies. ^eRegular exercise engagement.

P-values: *Test / †2 with Yates; bold P<0.05.

SNSB-II = Seoul Neuropsychological Screening Battery 2nd ed.; APOE4 = apolipoprotein ε4; MMSE = Mini-Mental State Examination.

4 · TRAJECTORY BEATS LEVEL

Baseline p-tau217 was **uninformative**; its **8-year rise** was significantly greater in decliners in decliners (Hedges g = **+0.38**, p < 0.001).



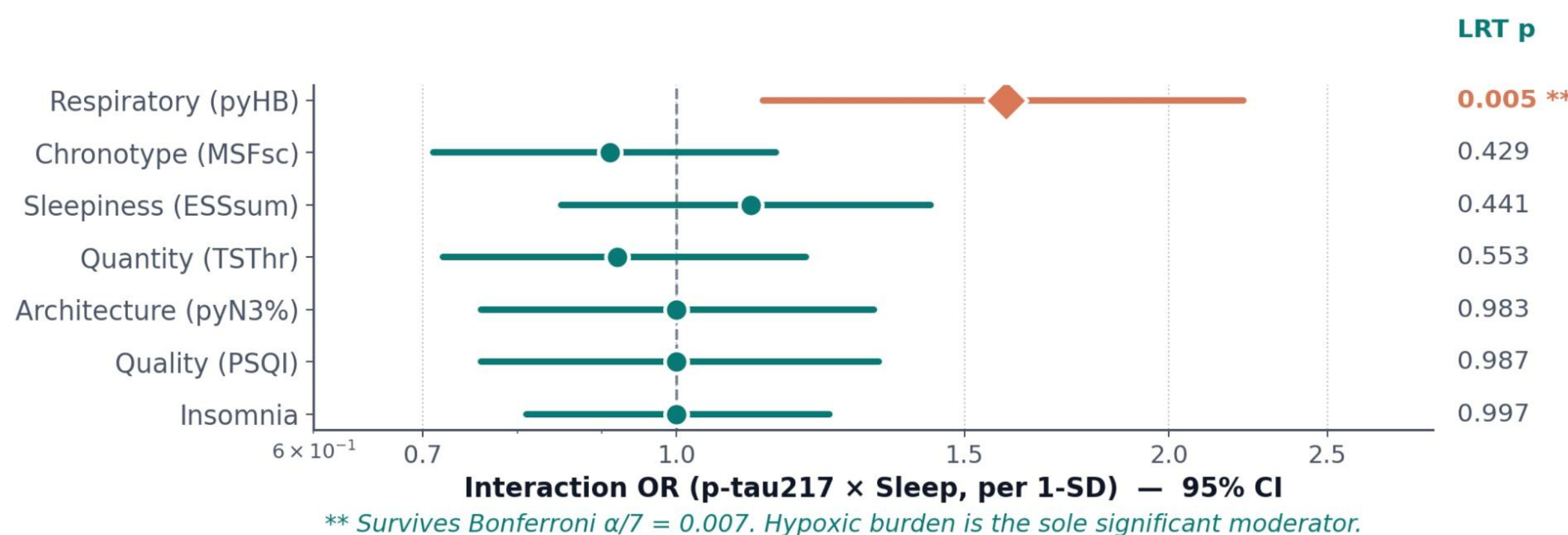
Adjustment-attenuation cascade (Table 4)

p-tau217 exposure	Model	OR (95% CI) / 1-SD	p
Baseline (ag1)	Unadjusted	0.98 (0.79–1.22)	0.881
Baseline (ag1)	Model 2 (full)	0.93 (0.72–1.20)	0.568
Follow-up (ag3)	Unadjusted	1.22 (0.98–1.52)	0.076
Follow-up (ag3)	Model 2 (full)	1.19 (0.92–1.55)	0.193
Change (Δ ag3–ag1)	Unadjusted	1.37 (1.09–1.73)	0.007
Change (Δ ag3–ag1)	Model 2 (full)	1.34 (1.04–1.73)	0.022

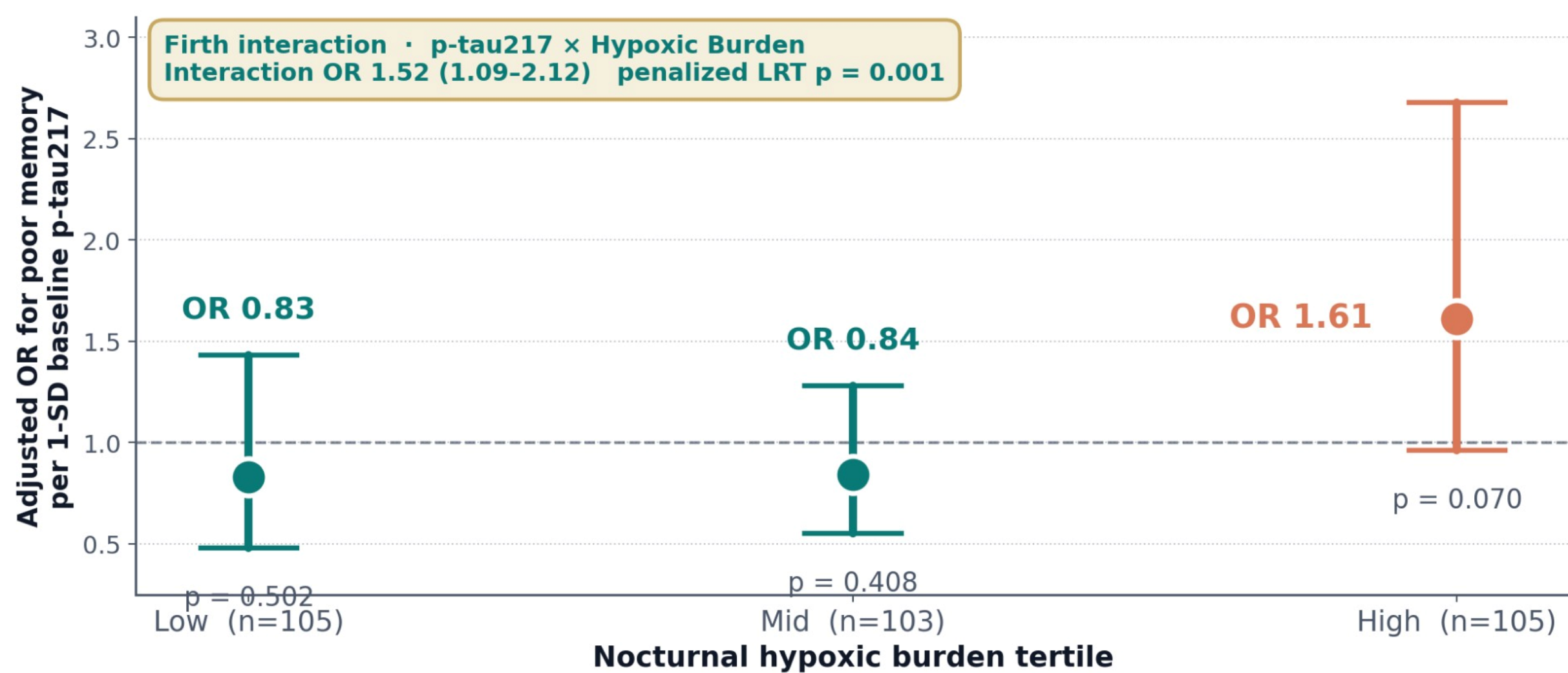
Firth-penalized logistic regression, log-standardized p-tau217. **Δ signal is adjustment-robust**; baseline and concurrent levels are not.

5 · HYPOXIC BURDEN AS A MODIFIER

Among 7 pre-specified domains, **only nocturnal hypoxic burden** significantly modified modified the effect — sole moderator surviving **Bonferroni α/7 = 0.007**.



Tertile-stratified: baseline p-tau217 → poor memory (Table 7)



Baseline p-tau217 predicted decline only in the **high-hypoxic-burden tertile** (adj OR 1.61, (adj OR 1.61, p = 0.070). Interpret alongside Firth penalized LRT p = 0.001.

6 · LONGITUDINAL SLEEP Δ → BIOMARKER Δ

Within-person **ΔSDB/hypoxia** tracked **ΔGFAP** (astrocytic) and **ΔNfL** (axonal), **adjusted for baseline biomarker + Model 2**.

	Δp-tau217	Δp-tau217/Aβ42	ΔAβ42/40	ΔGFAP	ΔNfL
ΔREM-AHI	-0.012	-0.014	+0.005	-0.036 **	-0.050 **
ΔPOD	+0.008	+0.010	+0.002	-0.037 **	-0.020
ΔODI	-0.010	-0.008	-0.004	-0.034 **	-0.018
ΔAHI	-0.005	+0.006	+0.003	-0.036 **	-0.022
ΔAOD100	+0.010	+0.011	-0.001	-0.036 **	-0.015
ΔSupAHI	+0.007	+0.008	+0.002	-0.029 *	-0.012
ΔCT	-0.008	-0.006	+0.004	-0.021 *	-0.010

Figure 4. Standardized β for Δ respiratory metrics (rows) predicting each Δ biomarker (cols). ΔGFAP: all 7 metrics survive within-domain FDR; ΔNfL ← ΔREM-AHI only.

7 · CONCLUSIONS

① TRAJECTORY, NOT LEVEL

The **longitudinal rise in plasma p-tau217** — not its baseline value — distinguished future decliners (adj OR **1.34/1-SD Δ**, p = 0.022). Argues for **serial, not one-off**, plasma sampling.

② HYPOXIC BURDEN AS “SECOND HIT”

Baseline p-tau217 predicted decline **only** under high nocturnal hypoxic burden (Firth OR **1.52**, LRT p = **0.001**). Plausible: hypoxia-driven **BBB dysfunction**, impaired **glymphatic clearance**, direct **tau phosphorylation**.

③ DYNAMIC COUPLING

ΔSDB/hypoxia tracked **ΔGFAP & ΔNfL** (Figure 4). Two independent analyses (moderation & Δ–Δ) converge on the **respiratory/hypoxia domain**.

CLINICAL & PREVENTIVE IMPLICATIONS

A high-risk phenotype — **elevated/rising p-tau217 + high hypoxic burden** — identifies individuals in whom (a) plasma-biomarker prognostic value is greatest, and (b) a **modifiable exposure** (SDB, PAP-treatable) coincides with vulnerability.

If replicated, findings support **pairing serial plasma biomarkers with PSG hypoxic-burden assessment**, targeting SDB in the prodromal phase.

Hypoxic burden — **continuous, physiologically interpretable, treatable** — is **directly actionable** and motivates interventional testing.

8 · STRENGTHS & LIMITATIONS

STRENGTHS

- Serial **in-laboratory PSG** + serial Simoa over ~8 y
- Pre-registered SAP with **domain-structured FDR** + Bonferroni
- HC3 robust SE**, winsorized sensitivity, Firth penalized inference
- Moderation & Δ–Δ converge on **respiratory/hypoxia domain**

LIMITATIONS

- Extreme-group sampling** inflates within-design contrasts
- Observational design — **causal inference limited**
- Δ–Δ are **hypothesis-generating** (regression-to-mean)
- Single-cohort / single-ethnicity — **external validation required**

ACKNOWLEDGEMENTS

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