

Better Slow-Wave Sleep Quality Associates With Better Glymphatic Function And Slows Down Cognitive Decline In Preclinical AD

Núria Tort-Colet^{1,2}, Ana Fernández-Arcos^{1,2}, Mariateresa Buongiorno³, Natalia Soldevila-Domenech^{1,2}, Sebastian C. Holst⁴, Michalis Kassinosopoulos¹, Gonzalo Sanchez-Benavides^{1,2}, Oriol Grau-Rivera^{1,2}.

1. Clinical and Risk Factors for Neurodegenerative Diseases Research Group, BarcelonaBeta Brain ResearchCenter, Barcelona, Spain, 2. Hospital del Mar Research Institute, Barcelona, Spain, Barcelona, Spain, 3. Vall d'Hebron Research Institute, Barcelona, Spain, 4. Roche Pharma Research and Early Development, Neuroscience and Rare Diseases, Roche Innovation Center Basel, F. Hoffmann - La Roche Ltd, Basel, Switzerland.

Background

Alzheimer's disease (AD) is characterized by the pathological accumulation of Aβ and tau proteins, detectable decades before cognitive symptoms emerge¹, granting a critical window for prevention strategies.

The glymphatic system plays a key role in clearing these proteins, a process that occurs primarily during slow-wave sleep (SWS)², which is also the sleep stage during which memory consolidation takes place³. Therefore, SWS emerges as a potential modifiable risk factor in AD pathophysiology.

However, whether objective SWS quality associates with glymphatic and cognitive function *over time* in cognitively healthy adults at elevated AD risk remains poorly understood.

Given that AD disproportionately affects women, it is also unknown whether these associations differ by sex, a gap that could help explain women's unequal vulnerability to the disease.

Aim

To test wheter SWS parameters are related to glymphatic function and cognitive trajectories in a cohort of healthy older adults at increased risk of AD.

Methods

Cohort

The study comprised 76 cognitively unimpaired ALFA+ cohort participants (65.09 ± 4.56 years, 57.9% women, 65.8 APOE-ε4 carriers) followed every 3 years for 2-4 visits. (Table 1)

PSG

Polysomnography was performed at visit 2, when participants were free of sleep medication. Individuals presenting severe sleep apnea (AHI>30) were excluded.

Table 1: Demographics across sexes

	Total (n=76)	Women (n=44, 57.9%)	Men (n=32, 42.1%)	p value (ANOVA)
Age (years) - mean (SD)	65.09 (4.56)	64.88 (4.83)	65.38 (4.14)	0.645
Sex (female) - n (%)	44 (57.9)	44 (100.0)	0 (0.0)	<0.001
APOE (ε4 carrier) - n (%)	50 (65.8)	26 (59.1)	24 (75.0)	0.231
Education (years) - mean (SD)	13.76 (3.61)	12.86 (3.67)	15.0 (3.12)	0.010
AHI (events/hour) - mean (SD)	11.26 (8.07)	9.16 (6.99)	14.13 (8.55)	0.008

Continuous measures expressed as mean (standard deviation). Categorical measures expressed as count (percentage). APOE: Apolipoprotein E, AHI: Apnea-Hypopnea Index.

SWS parameters

PSG time during *lights off* was classified into sleep stages. Only deep non rapid eye movement (NREM) sleep periods (N2 and N3) were considered.

EEG signals from the frontal channels (F3 and F4) were used to compute the power spectral density at different frequency ranges:

- Slow oscillation (SO, 0.5-1Hz),
- delta (1-4Hz), and
- slow-wave activity (SWA, 0.5-4Hz)

Slow waves (SW) were detected following the YASA⁴ algorithm. Average **SW slope** and peak-to-peak (PTP) **amplitude** (Figure 1) were measured for each individual.

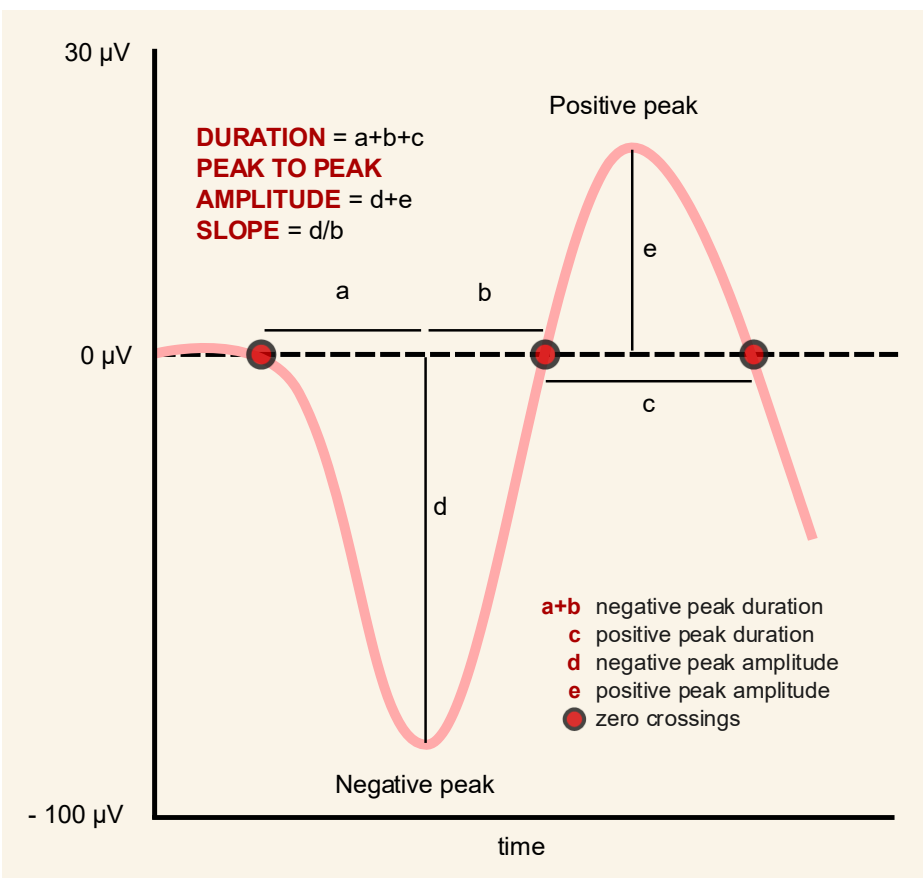


Figure 1. SW PARAMETERS. Measures of PTP amplitude and slope of the SW detected during N2 and N3.

Glymphatic function

Diffusion Tensor Image Analysis Along the Perivascular Space (DTI-ALPS)⁵ was measured as a proxy for the glymphatic function in each available visit (mean 2.8 visits, range 6.30 ± 0.59 years)

Cognitive performance

Cognitive performance was evaluated with the Preclinical Alzheimer Cognitive Composite (PACC) in each available visit (mean 3.1 visits, range 6.60 ± 0.87 years).

Statistics

Linear mixed-effects models were used to test associations between sleep metrics and DTI-ALPS and between sleep metrics and PACC.

Models were adjusted for age, sex, and APOE-ε4 status, and for education for cognitive outcomes.

Stratified analyses were performed to test sex differences in these associations.

Results

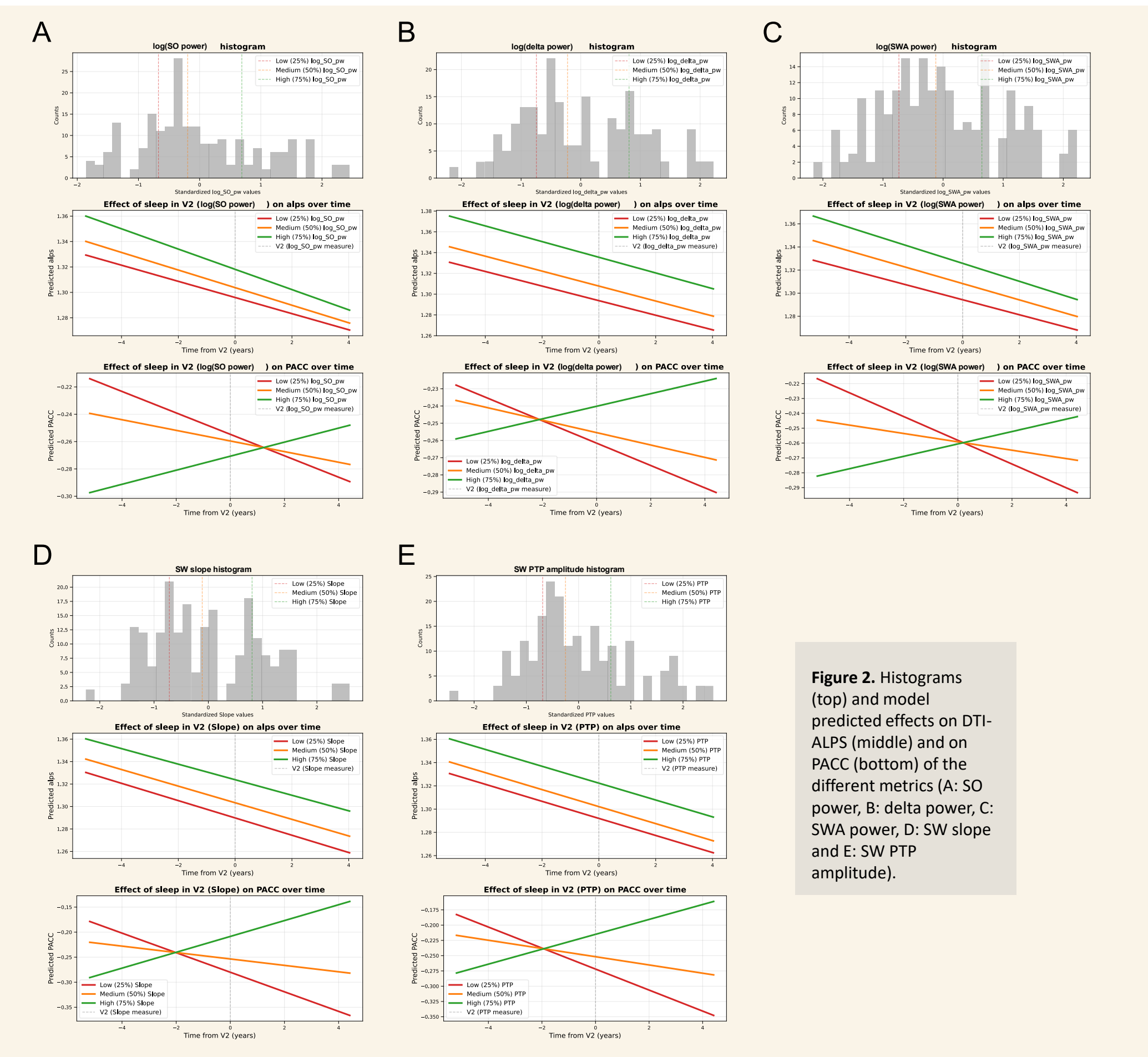


Figure 2. Histograms (top) and model predicted effects on DTI-ALPS (middle) and on PACC (bottom) of the different metrics (A: SO power, B: delta power, C: SWA power, D: SW slope and E: SW PTP amplitude).

Delta power was significantly associated with higher DTI-ALPS values, without significant effects over time.

SW slope and PTP amplitude were associated with better PACC over time.

Results were driven by men (no significant associations for the women subsample):

SO power and SW PTP amplitude were associated with higher DTI-ALPS values

power of SO, delta and SWA, and SW slope and PTP amplitude were associated with better PACC over time.

Conclusions

→ Better SWS quality associates with enhanced glymphatic function and better cognitive trajectories, particularly in men.

→ The absence of these associations in women warrants investigation, as it may contribute to understanding women's disproportionate AD burden

→ Future intervention studies targeting SWS should investigate whether SWA power, and SW slope and PTP amplitude could predict a glymphatic phenotype and cognitive trajectories in preclinical AD.

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Contact
ntort@barcelonabeta.org

www.barcelonabeta.org

