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Original Article

The Association Between Polygenic Risk for Alzheimer's, Objective Sleep Architecture, and Plasma Neurofilament Light Chain in Midlife

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ABSTRACT

Background: Genetic susceptibility and sleep disturbances may be associated with neuronal injury before clinically apparent cognitive impairment. Objective: To examine whether objective sleep architecture modifies the association between Alzheimer's disease polygenic risk and plasma neurofilament light chain (NFL) in midlife. Methods: This cross-sectional study analyzed 84 adults aged 40–60 years recruited through health screenings and workplace wellness programs in Islamabad–Rawalpindi, Pakistan. Participants had no reported cognitive complaints or diagnosed with cognitive impairment. Polygenic risk scores (PRS) were derived from genome-wide genotyping. Home polysomnography measured N3 sleep duration and wakefulness after sleep onset (WASO), and plasma NFL was measured using a single-molecule array assay. Pearson correlations and hierarchical linear regression examined associations and interactions, adjusting for age, sex, and body mass index. Results: PRS correlated positively with log-NFL ($r = 0.31$, $p = 0.004$) and inversely with N3 duration ($r = -0.26$, $p = 0.017$). The PRS × N3 interaction was negative ($\beta = -0.31$, $p = 0.003$), indicating a stronger PRS–NFL association at shorter N3 durations. The PRS × log-WASO interaction was not statistically significant ($\beta = 0.14$, $p = 0.190$). Conclusion: N3 duration modified the observed association between genetic susceptibility and plasma NFL. These cross-sectional findings do not establish causality or Alzheimer-specific pathology. Keywords: Alzheimer Disease; Genetic Predisposition to Disease; Middle Aged; Neurofilament Proteins; Polysomnography; Sleep, Slow-Wave.

INTRODUCTION

Alzheimer's disease (AD) develops through biological processes that may precede clinically apparent cognitive impairment, creating a rationale for investigating associated factors before dementia becomes evident. Midlife is

therefore an important period for examining relationships between inherited susceptibility, potentially modifiable exposures, and markers of neuronal injury. Sleep has attracted particular interest because observational studies and evidence syntheses have linked sleep characteristics with AD-related biomarkers. However, these associations vary across populations, sleep measures, and biomarker outcomes, and their implications for prevention remain uncertain (1,2).

Genetic susceptibility provides one approach to investigating individual differences in AD-related vulnerability. Polygenic risk scores (PRS) summarize the contribution of multiple genetic variants to inherited susceptibility and permit examination of genetic associations before clinical disease is diagnosed. In healthy young men, Muto et al. reported that higher AD PRS was associated with greater slow-wave energy and daytime sleepiness, indicating that genetic susceptibility may be related to sleep physiology early in adulthood. Importantly, slow-wave energy reflects electrophysiological activity and is not interchangeable with the duration of stage N3 sleep. These findings therefore support investigation of genetic–sleep relationships while leaving uncertainty about their direction and significance in midlife (3).

Sleep architecture may provide information that is not captured by sleep duration or subjective sleep quality alone. Slow-wave sleep and wakefulness after sleep onset (WASO) represent distinct aspects of sleep organization: the former quantifies time spent in deep non-rapid eye movement sleep, whereas the latter reflects wakefulness during the sleep period. Reviews have examined relationships between sleep disturbances, AD risk, and biomarkers of cognitive decline, but the interpretation of these relationships depends on the sleep phenotype and population studied (4,5). Objective polysomnography offers an opportunity to distinguish these sleep characteristics when examining their associations with genetic susceptibility and circulating biomarkers.

Neurofilament light chain (NfL), a marker of axonal injury, provides a complementary outcome for investigating sleep-related differences in neuronal health. Its potential relevance to sleep-associated injury has been discussed in obstructive sleep apnea, and associations between sleep quality, plasma NfL, and cognition have been investigated in older adults without dementia (6,7). Nevertheless, NfL is not specific to AD, and a higher concentration cannot independently establish Alzheimer's pathology or the cause of neuronal injury. Studies using cerebrospinal fluid have also produced findings that require careful comparison. Targa et al. reported an association between reduced sleep depth and higher cerebrospinal fluid NfL in patients with AD, whereas Nicolazzo et al. found no association between the insomnia features assessed and cerebrospinal fluid NfL in a cognitively unimpaired community sample (8,9). Differences in disease status, biological specimen, and sleep measurement limit direct extrapolation to plasma NfL in midlife.

Previous research has examined sleep physiology, neurodegeneration, and cognition, while the ALFASleep protocol illustrates continuing interest in the cognitive and biological correlates of sleep before clinical impairment (10,11). However, the literature reviewed does not establish whether objectively measured N3 duration or WASO modifies the association between AD PRS and plasma NfL in adults aged 40–60 years. This specific question warrants investigation in a Pakistani community sample, while recognizing that findings obtained using a PRS derived from predominantly European discovery data require cautious interpretation in a different population. Examining continuous genetic and sleep measures may help characterize variation in biomarker associations without presuming that sleep changes cause neuronal injury or that modifying sleep prevents AD.

Accordingly, this cross-sectional study examined associations among AD PRS, objectively measured sleep architecture, and plasma NfL in community-dwelling adults aged 40–60 years from the Islamabad–Rawalpindi region who had no reported cognitive complaints or diagnosed cognitive impairment. The primary objective was to determine whether N3 sleep duration and WASO modified the association between AD PRS and log-transformed plasma NfL after adjustment for age, sex, and body mass index. We hypothesized that the positive association between PRS and plasma NfL would be stronger at shorter N3 durations and greater WASO.

MATERIAL AND METHODS

A cross-sectional observational study was conducted over a five-month period in the Islamabad–Rawalpindi metropolitan region of Pakistan to examine associations among polygenic risk for Alzheimer's disease, objectively measured sleep architecture, and plasma neurofilament light chain (NfL). The design enabled assessment of whether the association between genetic susceptibility and plasma NfL differed according to sleep characteristics

measured within the same study period. The target population comprised community-dwelling adults aged 40–60 years without reported cognitive complaints or a clinical diagnosis of dementia or mild cognitive impairment. Participants were recruited through local health screenings and workplace wellness programs.

Eligibility required no history of major neurological or psychiatric disorders, including Parkinson's disease, stroke, or severe depression. Exclusion criteria were current hypnotic medication use, untreated sleep apnea defined by an apnea–hypopnea index greater than 15 events per hour on screening, shift work within the preceding three months, an acute inflammatory condition, or recent head trauma. These criteria were intended to reduce the influence of conditions that could affect sleep or NfL concentrations. Written informed consent was obtained before study procedures. Of 94 individuals initially recruited, 84 had adequate sleep recordings and blood samples suitable for both genotyping and NfL measurement. Ten individuals were excluded from the analytic sample because of incomplete sleep data (n = 4), insufficient plasma volume (n = 3), or genotyping failure (n = 3). The stated sample-size rationale was based on the sizes of comparable cross-sectional studies examining genetic risk and blood-based biomarkers in midlife populations, rather than a reported formal calculation for the interaction effect.

Study participation involved two visits and a single overnight home polysomnography recording. At the first visit, demographic characteristics and health history were collected using a standardized questionnaire after consent. Recorded participant characteristics included age, sex, body mass index, and years of education. A fasting venous blood sample was collected into EDTA tubes for plasma separation and PAXgene tubes for DNA extraction. Plasma was processed within two hours of collection, aliquoted, and stored at −80°C until batch analysis. Plasma NfL concentrations were measured in duplicate using a commercially available single-molecule array assay on an HD-X platform. Concentrations were expressed in pg/mL, and the reported inter-assay coefficient of variation was below 8%.

Genome-wide array genotyping was used to derive an Alzheimer's disease polygenic risk score (PRS). Scores were calculated using summary statistics from a predominantly European genome-wide association study meta-analysis, with included single-nucleotide polymorphisms restricted to those with imputation-quality scores greater than 0.8. PRS values were standardized as z-scores for analysis, with higher scores representing greater estimated genetic susceptibility to Alzheimer's disease.

Objective sleep measures were obtained using a portable polysomnography device during one night in each participant's home. The reported recording montage included electroencephalography channels F4–M1, C4–M1, and O2–M1, together with electrooculography and submental electromyography. Sleep stages were manually scored according to American Academy of Sleep Medicine criteria by a registered polysomnography technologist who was blinded to genetic and biomarker data. Only recordings containing at least six hours of usable data were retained. Slow-wave sleep duration was defined as the number of minutes scored as stage N3. Wakefulness after sleep onset (WASO) was defined as the number of minutes awake after initial sleep onset. Additional measures included total sleep time, expressed in minutes, and sleep efficiency, calculated as the percentage of time in bed spent asleep. The apnea–hypopnea index was expressed as the number of events per hour.

The principal outcome was plasma NfL concentration, analyzed after logarithmic transformation. AD PRS was the principal genetic exposure, and N3 duration and WASO were evaluated as potential modifiers of its association with NfL. Age, sex, and body mass index were included as covariates in adjusted analyses. Blinded sleep scoring, duplicate NfL measurements, standardized plasma processing, genotyping-quality filtering, and the minimum usable-recording requirement were the reported procedures used to support measurement quality and reduce assessment bias.

Statistical analyses were performed using R version 4.2. Continuous participant characteristics and sleep measures were summarized using means and standard deviations, and categorical characteristics were summarized using frequencies and percentages. Plasma NfL was additionally described using its geometric mean and 95% confidence interval. The Shapiro–Wilk test was used to assess the distributions of continuous variables. NfL and WASO were log-transformed for inferential analyses, whereas PRS, N3 duration, and total sleep time were analyzed without logarithmic transformation. Pearson correlation coefficients were calculated to examine unadjusted relationships among PRS, N3 duration, log-transformed WASO, and log-transformed NfL.

Hierarchical multiple linear regression was used to evaluate whether sleep characteristics modified the association between PRS and log-transformed NfL. Separate analyses were conducted for N3 duration and log-transformed WASO. The regression analyses incorporated age, sex, and body mass index as covariates, the main effects of PRS and the relevant sleep measure, and their product interaction term. The interaction terms were used to assess whether the PRS–NfL association varied across values of each sleep measure. Regression diagnostics included assessment of homoscedasticity and influential observations. Analyses of the principal genetic, sleep, and biomarker measures were restricted to the 84 participants with usable data for those measures.

For descriptive examination of the N3 interaction, participants were divided into lower and higher PRS groups using the observed median PRS of −0.03, yielding 42 participants in each group. N3 duration was divided into three groups containing 28 participants each: less than 62 minutes, 62–92 minutes, and greater than 92 minutes. Arithmetic mean NfL concentrations and standard deviations were summarized within the resulting PRS-by-N3 groups. Between-group differences were expressed as the mean concentration in the higher PRS group minus that in the lower PRS group. Statistical tests were two-sided, with a significance threshold of 0.05. No adjustment for multiple comparisons was applied; the stated rationale was the hypothesis-driven nature of the two specified interaction analyses.

RESULTS

Of 94 recruited participants, 84 were included in the analysis. Exclusions resulted from incomplete sleep data (n = 4), insufficient plasma volume (n = 3), and genotyping failure (n = 3). Participants had a mean age of 51.4 ± 5.8 years, and 45 (53.6%) were women. Mean total sleep time was 398.4 ± 52.1 minutes, N3 duration was 78.2 ± 24.6 minutes, and WASO was 54.3 ± 28.7 minutes. The geometric mean plasma NfL concentration was 12.4 pg/mL (95% CI, 11.2–13.7), with concentrations ranging from 5.8 to 34.2 pg/mL (Table 1).

AD PRS was positively correlated with log-plasma NfL (r = 0.31; 95% CI, 0.10–0.49; p = 0.004) and inversely correlated with N3 duration (r = −0.26; 95% CI, −0.45 to −0.05; p = 0.017). N3 duration was inversely correlated with log-plasma NfL (r = −0.35; 95% CI, −0.52 to −0.15; p < 0.010), whereas log-WASO was positively correlated with log-plasma NfL (r = 0.29; 95% CI, 0.08–0.47; p = 0.008). The correlation between PRS and log-WASO was 0.11 (95% CI, −0.11–0.32; p = 0.320). N3 duration and log-WASO were inversely correlated (r = −0.44; 95% CI, −0.60 to −0.25; p < 0.001; Table 2).

Table 1. Participant characteristics, sleep measures, and plasma neurofilament light chain concentrations

Characteristic	N	Mean ± SD
Age, years	84	51.4 ± 5.8
Body mass index, kg/m²	84	27.3 ± 4.1
Education, years	84	13.2 ± 2.5
AD polygenic risk score	84	0.02 ± 0.98
Apnea–hypopnea index, events/hour	84	9.6 ± 5.3
Total sleep time, min	84	398.4 ± 52.1
N3 sleep duration, min	84	78.2 ± 24.6
Wakefulness after sleep onset, min	84	54.3 ± 28.7
Sleep efficiency, %	84	82.1 ± 9.4

Characteristic	Female, n (%)	Male, n (%)
Sex	45 (53.6)	39 (46.4)

Biomarker	N	Geometric mean	95% CI	Minimum–maximum
Plasma NfL, pg/mL	84	12.4	11.2–13.7	5.8–34.2

AD, Alzheimer's disease; CI, confidence interval; N3, stage N3 sleep; NfL, neurofilament light chain; SD, standard deviation.

Table 2. Unadjusted correlations among polygenic risk, sleep measures, and plasma neurofilament light chain

Variable 1	Variable 2	N	Pearson's r	Approximate 95% CI	p-value
AD PRS	Log-plasma NfL	84	0.31	0.10–0.49	0.004
AD PRS	N3 duration	84	−0.26	−0.45 to −0.05	0.017
AD PRS	Log-WASO	84	0.11	−0.11–0.32	0.320

Variable 1	Variable 2	N	Pearson's r	Approximate 95% CI	p-value
N3 duration	Log-plasma NfL	84	−0.35	−0.52 to −0.15	<0.010
N3 duration	Log-WASO	84	−0.44	−0.60 to −0.25	<0.001
Log-WASO	Log-plasma NfL	84	0.29	0.08–0.47	0.008

AD, Alzheimer's disease; CI, confidence interval; N3, stage N3 sleep; NfL, neurofilament light chain; PRS, polygenic risk score; WASO, wakefulness after sleep onset. Tests are two-sided Pearson correlations; confidence intervals use Fisher's z transformation.

Table 3. Adjusted regression model including the interaction between polygenic risk and N3 sleep duration for log-plasma neurofilament light chain (N = 84)

Predictor	Reported β	p-value
Age, years	0.14	0.160
Sex, female versus male	0.07	0.480
Body mass index, kg/m²	0.18	0.090
AD PRS	0.25	0.015
N3 duration, min	−0.22	0.029
AD PRS × N3 duration	−0.31	0.003

AD, Alzheimer's disease; N3, stage N3 sleep; PRS, polygenic risk score; β, regression coefficient. Multiple linear regression includes all listed predictors. Male is the sex reference category.

Table 4. Reported adjusted associations involving wakefulness after sleep onset and log-plasma neurofilament light chain (N = 84)

Regression term	Reported β	p-value
Log-WASO	0.22	0.031
AD PRS × log-WASO	0.14	0.190

AD, Alzheimer's disease; PRS, polygenic risk score; WASO, wakefulness after sleep onset; β, regression coefficient. The WASO main-effect estimate is from the model adjusting for age, sex, body mass index, and PRS. The interaction estimate is from the model additionally including the PRS × log-WASO term.

Table 5. Plasma neurofilament light chain concentrations by polygenic risk group and N3 sleep duration

N3 duration, min	Total n	Low PRS, mean ± SD, pg/mL	High PRS, mean ± SD, pg/mL	Mean difference, pg/mL
<62	28	10.4 ± 1.9	18.2 ± 3.1	7.8
62–92	28	11.2 ± 2.2	14.5 ± 2.8	3.3
>92	28	9.8 ± 1.6	11.1 ± 2.0	1.3

N3, stage N3 sleep; PRS, polygenic risk score; SD, standard deviation. Mean difference = high PRS minus low PRS.

In the regression model including age, sex, body mass index, PRS, N3 duration, and their interaction, the PRS × N3 coefficient was −0.31 (p = 0.003). This negative interaction indicated that the slope relating PRS to log-plasma NfL decreased as N3 duration increased (Table 3). In the separate WASO analysis, log-WASO was positively associated with log-plasma NfL after adjustment for age, sex, body mass index, and PRS (β = 0.22; p = 0.031). The PRS × log-WASO interaction coefficient was 0.14 (p = 0.190; Table 4).

Descriptive stratification showed that the difference in mean plasma NfL between the high and low PRS groups was largest among participants with N3 duration below 62 minutes. In this stratum, mean concentrations were 18.2 ± 3.1 and 10.4 ± 1.9 pg/mL, respectively, corresponding to a difference of 7.8 pg/mL. The corresponding differences were 3.3 pg/mL for N3 duration of 62–92 minutes and 1.3 pg/mL for N3 duration above 92 minutes (Table 5).

DISCUSSION

In this cross-sectional sample of midlife adults without reported cognitive complaints or diagnosed cognitive impairment, the association between Alzheimer's disease polygenic risk and plasma neurofilament light chain (NfL) varied according to objectively measured N3 sleep duration. The positive association between genetic susceptibility and NfL was stronger at shorter N3 durations. Although greater wakefulness after sleep onset (WASO) was associated with higher NfL, the corresponding interaction with polygenic risk was not statistically significant. These findings address the study objective by identifying a statistical interaction between genetic susceptibility and one dimension of sleep architecture, without establishing temporal direction or a protective effect of sleep.

The findings are broadly consistent with research examining relationships between sleep and biomarkers of neurodegeneration, although the populations and outcomes studied differ. Blackman et al. investigated cross-

sectional and longitudinal associations between sleep and Alzheimer biomarkers in cognitively unimpaired adults, while the meta-analysis by Chen et al. synthesized evidence concerning sleep quality, sleep duration, and Alzheimer-related biomarkers (1,2). These studies provide a broader context for the present observations but do not directly establish an interaction between polygenic risk, polysomnographic N3 duration, and plasma NfL in midlife. Guo et al. examined sleep quality, plasma NfL, and cognition in older adults without dementia, demonstrating the relevance of this biomarker to observational sleep research in a different age group (7).

The inverse association between N3 duration and NfL is directionally consistent with the findings of Targa et al., who reported that reduced sleep depth was associated with higher cerebrospinal fluid NfL in patients with Alzheimer's disease (8). However, their study involved established disease and a different biological specimen, limiting direct comparison with plasma measurements in adults without diagnosed cognitive impairment. Conversely, Nicolazzo et al. found no association between the insomnia features assessed and cerebrospinal fluid NfL in a cognitively unimpaired community sample (9). Differences in disease status, sleep assessment, participant characteristics, and biomarker compartment may contribute to these divergent findings. Together, these studies suggest that sleep–NfL associations should be interpreted in relation to the specific sleep phenotype and population rather than assumed to be uniform.

The relationship between genetic susceptibility and sleep also requires careful interpretation. Muto et al. reported that higher Alzheimer's disease polygenic risk was associated with greater slow-wave energy and daytime sleepiness in healthy young men (3). This differs from the present inverse association between polygenic risk and N3 duration, but the findings are not directly contradictory. Slow-wave energy quantifies electrophysiological activity, whereas N3 duration measures time assigned to a sleep stage. Differences in age, sex composition, recording conditions, and genetic-score construction further limit comparability. The present findings therefore cannot establish a consistent trajectory linking genetic risk to progressively reduced deep sleep across the lifespan.

Several biological pathways could plausibly contribute to the observed associations. Reviews of sleep abnormalities and neurodegeneration describe relationships involving sleep architecture, protein homeostasis, and inflammatory processes (4,6). Glymphatic dysfunction has also been proposed as a mechanism connecting disrupted sleep with impaired clearance of metabolic products (12). These pathways offer hypotheses for why sleep characteristics might accompany differences in neuronal-injury markers among genetically susceptible individuals. However, this study did not measure glymphatic function, amyloid deposition, tau pathology, or neuroinflammation. The interaction cannot therefore be attributed to any specific mechanism, and NfL does not establish that the observed differences reflect Alzheimer-specific injury.

The distinction between the N3 and WASO findings should also remain cautious. A statistically significant interaction for N3 and a non-significant interaction for WASO do not demonstrate that the two interaction effects differ from each other. The WASO estimate may reflect limited precision, and its interpretation requires a confidence interval. Furthermore, the N3 interaction was evaluated on the log-NfL scale; it does not directly quantify an absolute difference in neuronal injury or future dementia risk. The descriptive PRS-by-N3 groups illustrated a corresponding pattern, but categorizing continuous variables reduces information and cannot replace interpretation of the continuous interaction model.

The study has several strengths. Home polysomnography provided objective measures of sleep architecture, and scoring was performed by a technologist blinded to genetic and biomarker information. Duplicate NfL measurement and standardized plasma processing supported analytical consistency. Assessing genetic susceptibility, sleep, and a circulating axonal-injury marker within the same midlife sample also allowed the proposed interaction to be examined directly. These features complement broader efforts to investigate sleep physiology and biological correlates before clinically apparent cognitive impairment, including the research described in the ALFASleep protocol (10,11).

Nevertheless, the cross-sectional design prevents determination of whether sleep differences preceded higher NfL, followed underlying neuronal injury, or reflected shared influences. Eligibility based on reported symptoms and previous diagnoses does not exclude subtle cognitive impairment. The absence of amyloid or tau assessment also prevents characterization of Alzheimer's pathology. A single home recording may not represent habitual sleep architecture, and the sample of 84 participants limits the precision and stability of interaction estimates. The

sample-size rationale did not establish statistical power specifically for moderation, and multiple testing without adjustment warrants cautious interpretation.

Additional limitations concern confounding and generalizability. Adjustment was limited to age, sex, and body mass index, leaving potential residual influences from sleep-disordered breathing, medical conditions, medications, and lifestyle characteristics. Recruitment through health screenings and workplace wellness programs may have selected participants who differ from the wider midlife population. The use of a PRS derived from predominantly European discovery data introduces uncertainty about its performance in this Pakistani sample. Incomplete characterization of genetic ancestry and the contribution of the APOE region further limits interpretation of the genetic association. These considerations constrain both the biological specificity of the findings and their transferability to other populations.

The clinical implications are therefore preliminary. Although reviews have highlighted sleep measures as potential contributors to early risk assessment, this study did not evaluate screening accuracy, incremental predictive value, or the effectiveness of sleep interventions (4,5). It does not establish a threshold of N3 duration or plasma NfL that should guide clinical decisions. Its principal contribution is a testable association that could be examined in larger longitudinal cohorts with repeated sleep and biomarker measurements, objective cognitive assessment, and more fully characterized genetic risk. Such work would help determine whether the observed interaction is reproducible, temporally informative, and relevant to subsequent clinical outcomes.

CONCLUSION

In this cross-sectional sample of midlife adults, shorter N3 sleep duration was associated with a stronger positive relationship between Alzheimer's disease polygenic risk and plasma NfL. No statistically significant interaction was detected between polygenic risk and WASO. These findings suggest that N3 duration may be relevant to understanding variation in the association between genetic susceptibility and an axonal-injury marker, but they do not establish Alzheimer-specific pathology, causality, or a preventive benefit of improving sleep.

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