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Research article

Association between sleep duration and serum neurofilament light chain levels among adults in the United States

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ABSTRACT

Background: Neurofilaments are neuron specific skeleton proteins maintaining axon transduction speed, leaked into cerebrospinal fluid and serum after axonal injury or neuron death. Sleep duration change has long related to many health issues but lack laboratory examination.
Methods: This study enrolled total 10,175 participants from 2013 to 2014 National Health and Nutrition Examination Survey and used a multi-variable linear model to analyze the relationship between sleep duration and serum neurofilament light chain (sNfL) level.
Results: There was a fixed relationship between sleep duration and sNfL level ($\beta = 0.65$, $p = 0.0280$). After adjusted for covariates, this relationship still ($\beta = 0.82$, $p = 0.0052$). Segmented regression showed that the turning point of sleep duration was 7 h 1 h decrease in sleep duration was significantly associated with −1.26 higher sNfL level (95 % CI: 2.25, −0.28; $p = 0.0115$) when sleep duration <7 h; however, 1 h increase in sleep duration was significantly associated with 3.20 higher sNfL level (95 % CI: 2.13, 4.27; $p < 0.0001$) when sleep duration >7 h. Furthermore, the stratified analysis indicated that the associations between sleep duration and sNfL level were stronger among those normal body mass index and trouble sleeping (*p*-interaction <0.0001 and 0.0003).
Conclusion: In summary, there was a J-shaped relationship between sleep duration and sNfL level in the United States of America representative group, these may suggest that extreme sleep duration can be deleterious judged by sNfL level. And still need large cohort study to determine the accurate relationship, and cluster analysis to infer the nervous disease connected with extreme sleep duration.

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1. Background

Neurofilaments (NFs) are neuron specific intermediate filaments composed by three subunits with apparent molecular weights of 68,000 Da (NfL), 145,000 Da (NF-M), and 200,000 Da (NF–H) (determined by SDS-gel electrophoresis) [1–3], one of the components of the neuron cytoskeleton, confirmed help maintaining axon structure, axon and dendritic branching and growth and axonal transport speed [2–5], by assembled into 10 nm filamentous structures [2,3,6]. Neurofilament light chain (NfL) is a member of filament proteins family [7,8], most abundant and most soluble subunit [3], widely thought could be a potential biomarker in neuro-damage events, cause robust and early levitated in both cerebrospinal fluid (CSF) and serum after neuronal cell damage such as axonal injury and axonal death [4,8–11], besides, the serum (or plasma) NfL level is correlated with CSF NfL level, implies that two measurements reflect similar physiological process [12,13], this elevation effect always before obvious neurological disease onset, and a higher level of serum NfL generally comes with worse outcome [4,9,10,12,14].

In 2005 Abdo and coworkers found out that elevated CSF NfL level can be used to differentia multiple system atrophy (MSA) from Parkinson's disease [15]; then it was confirmed a promising biomarker in nervous diseases like sporadic Creutzfeldt-Jakob disease (sCJD) [16]; amyotrophic lateral sclerosis (ALS) [17]; 2016, Bacioglu and his colleges claimed that both serum and CSF NfL level can be used in detecting neurodegenerative disease [4]; next year, Fyfe alleged that high plasma NfL level is associated with cognitive decline in Alzheimer disease (AD) [18]. The level of NfL is not only related to the outcome, but also to the responses to treatment [6,12,19,20]. Beyond these highly sensitivity, third-generation (electrochemiluminescence) and fourth generation (single molecule array) assay also enabled reliable serum NfL measurement make it easier to determine NfL level [6,12].

Sleep is an essential step for optimal health and under genetic regulation [21–23], The American Academy of Sleep Medicine and the Sleep Research Society determined that adults require ≥7 h sleep per day [24]. Healthy sleep requires adequate duration, quality, appropriate timing and regularity [25,26], sleep loss confirmed slowing information processing speed and other neurocognitive performances [27,28], short sleep duration has long been considered as risk of behavioral or problems such as anxiety, aggressive behavior, daytime sleepiness and lowered cognitive function [28,29], even some disease states like cardiovascular disease, obesity, depression, type-2 diabetes, cancer even suicidal ideation [23,25,27,30–35]. Liu confirmed that lack of non-rapid eye movement sleep increased serum and CSF NfL level in C57BL/6J mice [36], but the detailed relationship between neuro-damage and sleep duration still need further investigation. In this study we enrolled 2013–2014 residents from National Health and Nutrition Examination Survey

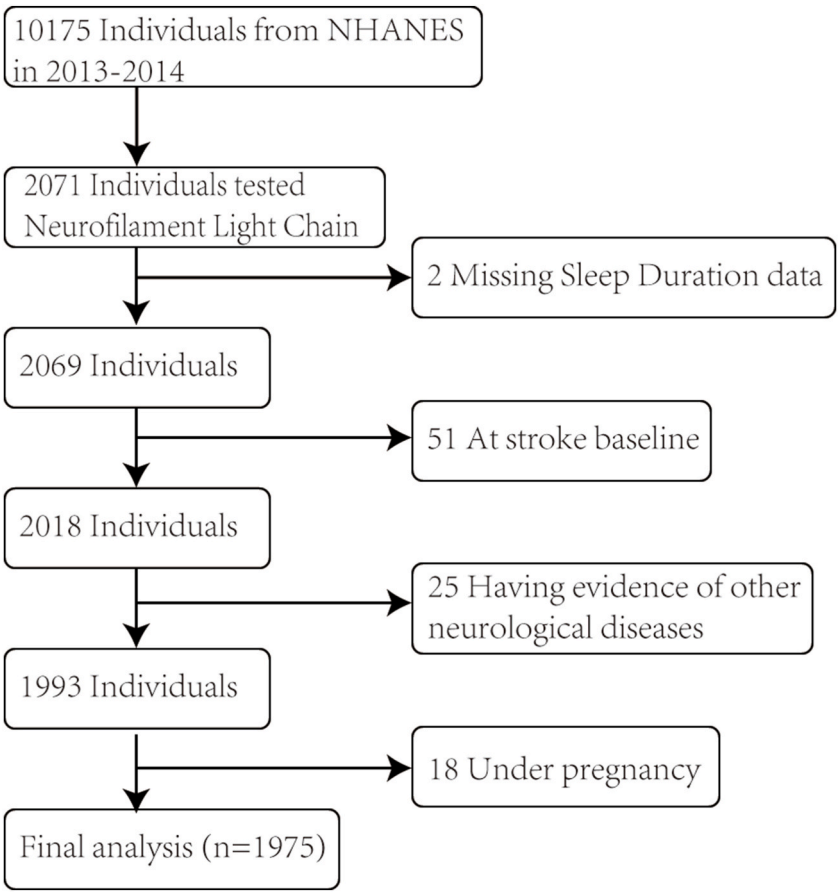

Fig. 1. Flow chart of study design and sample disposition.

(NHANES), analyzed the connection between serum NfL level and sleep time duration, tried to figure out the detailed neuro-damage progression with differential sleep time.

2. Methods

2.1. Study design and population

This study enrolled 2013–2014 respondents from NHANES (which also is where can trace the original data), a complex, multi-stage representative national survey leaded by National Center for Health Statistics (NCHS), reports mainly about the health and nutrition characteristics of non-institutionalized populations lived in the United States. Participants not only underwent questionnaires assessing demographic, socioeconomic, nutritional, health, and other domains during face-to-face interviews in their homes, but also underwent physical examinations in medical facilities to collect medical and physiological data; additional laboratory tests were performed on blood and urine samples collected in the field, and surplus or pristine serum samples were stored for future studies, were eligible. All respondents who participated in the study provided informed consent. The NCHS Ethics Review Board (ERB) approved the ethical review of the project (www.cdc.gov/nchs/nhanes/irba98.htm). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines, thus the IRB/ethics committee approval is not applicable in this submission.

The downloaded data was analyzed visually using the statistical package R (R4.2.0). In this study, a total of 10,175 participants were investigated. Serum neurofilament light chain (sNfL) analysis measurements were received in surplus or pristine serum samples (n = 2071, ages 25–75 years). After excluding missing sleep data (n = 2), baseline self-reported Stroke (n = 51), and organic brain lesions diagnosed by ICD-10 codes [37]:Transient cerebral ischemic attack (G45.9), Epilepsy and recurrent seizures (G40), Alzheimer's disease (G30.9), Multiple sclerosis (G35), Mild cognitive impairment (G31.84), Parkinson's disease (G20), Degenerative disease of nervous system (G31.9), Spastic hemiplegia (G81.1), Trigeminal neuralgia (G50.0)) (n = 25) and Pregnancy (n = 18), a total of 1975 participants were included in the final analysis (Fig. 1).

2.2. Serum neurofilament light chain

Detailed specimen collection and handling instructions are discussed in NHANES Laboratory Methods (wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSSNFL_H.htm). The method quantifies sNfL by a highly sensitive immunoassay. Using acridinium ester (AE) chemiluminescence and paramagnetic particles and may be run on an existing, high-throughput, automated platform (Attelica). Initially, the sample is incubated with AE labeled antibodies, which bind to the NfL antigen. Following this step, paramagnetic particles (PMP) coated with capture antibody are added to the sample, forming complexes of antigen bound to AE-labeled antibodies and PMP. Unbound AE-labeled antibodies are then separated and removed, following which acid and base are added to initiate chemiluminescence and light emission is measured. All steps are performed on the fully automated Attelica immunoassay system.

These assays were developed by Siemens Healthineers and use Quanterix proprietary NfL antibody for the quantitative determination of NfL concentrations in samples. Analytical measurements are performed in accordance with strict quality control/quality assurance procedures. Researchers calculated the coefficient of variation (CV) and other relevant statistics to describe the quality control (QC) samples across the spectrum of sNfL measures. The lower limit of quantification (LLOQ) was defined as the concentration at which the CV was less than or equal to 20 %. The assays range from 3.9 to 500 pg/ml. In addition to study samples, low, medium, and high concentration QC samples were run each 8-h shift as well as additional replicate samples to ensure accuracy and reliability of the derived data.

2.3. Sleep duration

Baseline sleep duration is self-reported as "How much sleep do you get (hours)?" Responses are coded as integers. There were no given categories in the face-to-face interviews. Participants were divided into 6 groups for analysis based on sleep duration ($<$6, 6, 7, 8, 9, or $\geq$10 h per night).

2.4. Assessment of covariates

Sex, age, race/ethnicity (non-Hispanic white, Black, Mexican American, or other race), poverty level ($<$2.0, $\geq$ 2.0), Education level, waist circumference and body mass index (BMI), measured objectively as part of the NHANES physical examination. The NHANES interview also assessed the following: Diabetes defined as self-reported physician diagnosis of diabetes or HbA1c $\geq$ 6.5 %. Hypertension was defined as systolic blood pressure (SBP) $\geq$140 mmHg and diastolic blood pressure (DBP) $\geq$90 mmHg, or taking medication to control blood pressure. In addition, participants' renal function was assessed by measuring eGFR using the executive summary of the KDIGO 2021 Clinical Practice Guideline [38]. The urinary albumin/creatinine ratio (ACR) was also calculated. According to the ex-tended definition of chronic kidney disease (CKD), participants with ACR $\geq$30 mg/g or eGFR $\leq$60 ml/min/1.73 m^2 had CKD. According to the NCHS classification, individuals are classified as never smokers, former smokers, and current smokers. Drinking status was categorized as never (had $<$12 drinks in life time), former (had $\geq$12 drinks in 1 year and did not drink last year, or did not drink last year but drank $\geq$12 drinks in lifetime), mild drinker ($\leq$1 drink per day for women or $\leq$2 drinks per day for men on average over the past year), moderate drinker ($\leq$3 drink per day for women or $\leq$4 drinks per day for men on aver-age over the past year), or heavier

drinker (≥4 drink per day for women or ≥5 drinks per day for men on average over the past year [39]. These covariates were chosen because they were previously used to study the relationship between sleep duration.

2.5. Statistical analyses

Data were statistically analyzed according to CDC guidelines [40], and all models also incorporated the minimization weights. The weighted chi-square test was carried out for the classified variables, and the P value of the continuous variables was calculated with the weighted linear regression model. Data are expressed as numbers of percentages of categorical variables and as means of standard deviations of continuous variables. Three multivariable regression analysis were developed to investigate the relationship between sNFL levels and sleep duration. Crude Model (unadjusted); Model I adjusted for Sex, Age, and Race/Ethnicity; Model II adjusted for Sex, Age, Race/Ethnicity, Education level, BMI, Smoking status, Drinking status, Hypertension, Diabetes, CKD, and Self-reported sleep quality. The subgroup analysis was performed by stratified multivariate regression analysis. Generalized additive model and curve fitting (Restricted cubic spline, RCS) were generalized to explore the potential nonlinear correlation, six different plot were generated in which RCS package default set.

We first used smooth curve fitting to examine whether the independent variable is partitioned into intervals. We applied segmented regression (also known as piece-wise regression) that used a separate line segment to fit each interval. Log-likelihood ratio test comparing one-line (non-segmented) model to segmented regression model was used to determine whether threshold exists. The inflection point that connecting the segments was based on the model gives maximum likelihood, and it was determined using two steps recursive method.

The step 1 was to narrow down the inflection point to a 10-percentile range of the independent variable. From 5 % to 95 % incremented by 5 %, we tested 19 segmented regression models using these 19 percentile points of independent variable as the inflection point respectively to find out which percentile points gives the model with highest likelihood. The precise inflection point was narrowed down to ±4 % percentile of the percentile points which gives highest likelihood among the 19 models, called K_{min} and K_{max} respectively. The step 2 was to determine precise inflection point between K_{min} and K_{max} using the recursive method. The specific method was to first run 3 models with inflection point equals Q1 (25 % percentile), Q2 (50 % percentile) and Q3 (75 % percentile)

Table 1
Baseline Characteristics of participants.

Characteristic	Neurofilament light chain (pg/ml)					*P*-value
	Total	Q1 < 8.10	Q2 ≥8.10 to < 12.10	Q3 ≥12.10 to < 18.70	Q4 ≥18.70	
Age (years)	44.81 ± 15.05	34.02 ± 10.01	42.67 ± 13.12	49.13 ± 14.41	54.35 ± 14.09	<0.0001
Sex (%)						0.0049
Men	49.49	43.70	49.64	50.04	55.07	
Woman	50.51	56.30	50.36	49.96	44.93	
Race/ethnicity (%)						<0.0001
Mexican American	9.71	16.18	9.21	5.96	7.06	
Non-Hispanic White	64.66	53.60	62.23	71.59	72.13	
Non-Hispanic Black	11.92	13.94	14.36	7.90	11.28	
Other race/ethnicity	13.71	16.28	14.20	14.55	9.53	
Education (%)						0.2927
Less than high school	15.37	18.21	13.85	14.86	14.39	
High school or equivalent	20.30	18.27	23.06	19.38	20.56	
College or above	64.33	63.52	63.09	65.76	65.04	
Poverty Income Ratio (%)						0.2134
<2	36.88	40.85	35.46	35.38	35.60	
≥2	63.12	59.15	64.54	64.62	64.40	
Smoke (%)						0.0003
Now	20.85	20.27	19.25	22.28	21.72	
Former	22.35	16.28	21.25	25.82	26.57	
Never	56.79	63.45	59.51	51.90	51.71	
Alcohol user (%)						0.0001
Heavy	22.47	26.40	24.32	18.78	20.20	
Mild	34.30	30.48	36.70	35.44	34.69	
Moderate	19.79	21.99	20.02	20.20	16.86	
Former	12.11	7.72	9.71	14.12	17.12	
Never	11.32	13.41	9.24	11.46	11.12	
BMI (kg/m^2)	29.41 ± 7.38	30.01 ± 7.45	28.83 ± 7.29	28.76 ± 7.04	30.04 ± 7.62	0.0036
Waist circumference (cm)	99.69 ± 16.96	99.44 ± 17.13	97.33 ± 16.64	99.13 ± 16.97	103.03 ± 16.55	<0.0001
Hypertension (%)	36.36	18.29	33.46	40.84	54.48	<0.0001
Diabetes (%)	13.86	5.97	9.11	15.64	25.60	<0.0001
CKD (%)	8.98	8.98	8.56	10.11	21.51	<0.0001
Trouble sleeping (%)	12.14	20.55	27.36	25.65	31.24	0.0017
Sleep Durations (hours)	6.89 ± 1.32	6.95 ± 1.30	6.74 ± 1.25	6.97 ± 1.25	6.90 ± 1.48	0.0331

Data are presented as mean ± SD or n (%).

within the range of K_{min} and K_{max} respectively to find out which quartile point gives the model with highest likelihood among the three models. Then we narrowed down the K_{min} and K_{max} to the range of±25 % of the corresponding quartile point. By doing so, we narrowed the range of K_{min} and K_{max} 50 % recursively each time until the specific value of the independent variable was identified, that if used as inflection point will give the segmented regression model highest likelihood.

Furthermore, the inflection point is calculated by using a two-stage linear regression model. All analyses were performed with package R (http://www.R-project.org) and EmpowerStats (http://www.empowerstats.com). $p < 0.05$ was of statistical significance.

3. Results

3.1. Baseline characteristics of study participants

In this study, the analyzed data set consisted of data from 1975 participants without neurological disorders (mean age: 44.81 ± 15.05 years; 49.49 % males). The baseline characteristics of the study population according to sNFL levels are reported in Table 1. Participants with higher sNFL levels were more likely to be older, male, non-Hispanic white, and more likely to have poor lifestyle habits like smoking and drinking, worse health status (obesity, hypertension, diabetes, chronic kidney disease), and poor sleep quality ($p < 0.01$).

4. Sleep duration associated with sNfL

We designed three multivariable regression analysis to investigate the relationship be-tween sNfL and sleep duration. The results of the multivariate regression analyses are presented in Table 2. In the crude model, the shortest (<6 h) and longest (>10 h) sleep durations were associated with higher sNfL, with the highest sNfL levels in those who slept more than 10 h per night. And this pattern was maintained in Model II after correction for adjustments including age, gender, and race/ethnicity confounders. After multivariate adjustment in Model II, including further adjustment for education lev-el, BMI, smoking status, alcohol consumption status, sleep condition, disease condition, multivariate adjusted β and 95 % confidence intervals (CIs) from lowest to highest sleep duration category (<6, 6, 7, 8, 9, or ≥10 h) with sNfL of 0.00 (reference), −2.68 (−5.32, −0.04), −2.65 (−5.26, −0.05), −2.79 (−5.45, −0.13),

Table 2
Regression coefficients (β) and 95 % confidence interval for sNfL Levels across sleep duration categories.

Outcome	Crude Model		Model I		Model II	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
Complete sample						
Sleep duration	0.65 (0.07, 1.24)	0.0280	0.48 (−0.08, 1.03)	0.0946	0.82 (0.25, 1.40)	0.0052
Sleep duration categories						
< 6 h	Reference		Reference		Reference	
6 h	−3.24 (-5.93, −0.54)	0.0216	−3.19 (−5.75, −0.63)	0.0148	−2.68 (−5.32, −0.04)	0.0464
7 h	−3.03 (-5.61, −0.45)	0.0104	−4.03 (−6.50, −1.57)	0.0014	−2.65 (−5.26, −0.05)	0.0459
8 h	−3.50 (-6.18, −0.82)	0.2608	−4.06 (−6.61, −1.51)	0.0018	−2.79 (−5.45, −0.13)	0.0398
9 h	2.33 (−1.73, 6.39)	<0.0001	1.31 (−2.56, 5.17)	0.5075	2.38 (−1.56, 6.32)	0.2366
≥10 h	11.60 (5.95, 17.25)	0.0216	11.23 (5.86, 16.60)	<0.0001	12.31 (6.54, 18.07)	<0.0001
P for trend	0.110		0.319		0.125	
Men						
Sleep duration	1.02 (0.04, 2.00)	0.0419	0.80 (−0.16, 1.75)	0.1018	1.28 (0.32, 2.25)	0.0094
Sleep duration categories						
< 6 h	Reference		Reference		Reference	
6 h	−4.06 (−8.69, 0.57)	0.0861	−4.33 (−8.82, 0.16)	0.0589	−2.73 (−7.28, 1.81)	0.2392
7 h	−4.41 (−8.78, −0.05)	0.0478	−5.73 (−9.99, −1.47)	0.0085	−3.28 (−7.68, 1.12)	0.1441
8 h	−5.13 (−9.73, −0.52)	0.0295	−5.88 (-10.36,-1.40)	0.0103	−3.40 (−7.95, 1.15)	0.1433
9 h	3.34 (−4.11, 10.80)	0.3794	0.37 (−6.87, 7.60)	0.9210	3.80 (−3.44, 11.05)	0.3040
≥10 h	16.27 (7.33, 25.21)	0.0004	16.67 (8.00, 25.33)	0.0002	17.32 (7.97, 26.66)	0.0003
P for trend	0.194		0.389		0.109	
Woman						
Sleep duration	0.28 (−0.35, 0.90)	0.3863	0.10 (−0.47, 0.68)	0.7256	0.17 (−0.46, 0.80)	0.5957
Sleep duration categories						
< 6 h	Reference		Reference		Reference	
6 h	−2.30 (−5.12, 0.53)	0.1114	−1.95 (−4.54, 0.64)	0.1401	−2.72 (−5.49, 0.05)	0.0542
7 h	−1.75 (−4.50, 1.00)	0.2126	−2.25 (−4.78, 0.27)	0.0806	−2.30 (−5.09, 0.49)	0.1062
8 h	−1.80 (−4.60, 1.00)	0.2074	−2.35 (−4.92, 0.21)	0.0728	−2.54 (−5.35, 0.27)	0.0771
9 h	2.32 (−1.72, 6.36)	0.2602	2.19 (−1.52, 5.90)	0.2481	1.45 (−2.51, 5.41)	0.4743
≥10 h	3.61 (−2.94, 10.15)	0.2803	2.80 (−3.19, 8.80)	0.3596	3.55 (−2.96, 10.07)	0.2854
P for trend	0.320		0.687		0.501	

Crude Model: no covariates were adjusted.
Model I: age, sex, and race/ethnicity were adjusted.
Model II: age, sex, race/ethnicity, education level, BMI, smoking status, alcohol consumption status, trouble sleeping, history of hypertension, diabetes and chronic kidney disease; In the subgroup analysis stratified by sex, the model is not adjusted for sex.

2.38 (−1.56, 6.32), and 12.31 (6.54, 18.07), (p for trend = 0.125). This relationship persisted. We also found that when considering men separately, for those with <6 h of sleep, elevated sNFL was observed only in crude model and model I; long sleep duration was significantly associated with elevated sNFL in all 3 models. For women, however, no significant difference in sNFL with sleep duration was observed in all models.

4.1. The detection of nonlinear relationships

Weighted restricted cubic splines were used to visually assess nonlinear relationships. We found a or J-shaped association between sNFL and sleep duration (Fig. 2 Total). Then, we used a recursive algorithm to calculated the inflection point between sNFL and sleep duration and performed two linear regression models on both sides of the inflection point to investigate the analysis confirming the non-linear relationship association between sNFL and sleep duration. (Log-likelihood $p < 0.05$) (Table 3). We found that the inflection point of sNFL in the fully adjusted model was 7 h per night. When sleep duration was less than 7 h per night, each 1-h decrease in sleep duration was associated with an adjusted increase in sNFL of 1.26 (pg/ml) ($\beta = -1.26$; 95%CI: 2.24, −0.28) . More than 7 h of sleep per night and each additional hour of sleep was associated with a 3.20 (pg/ml) adjusted increase in sNFL ($\beta = 3.20$; 95%CI: 2.13, 4.27).

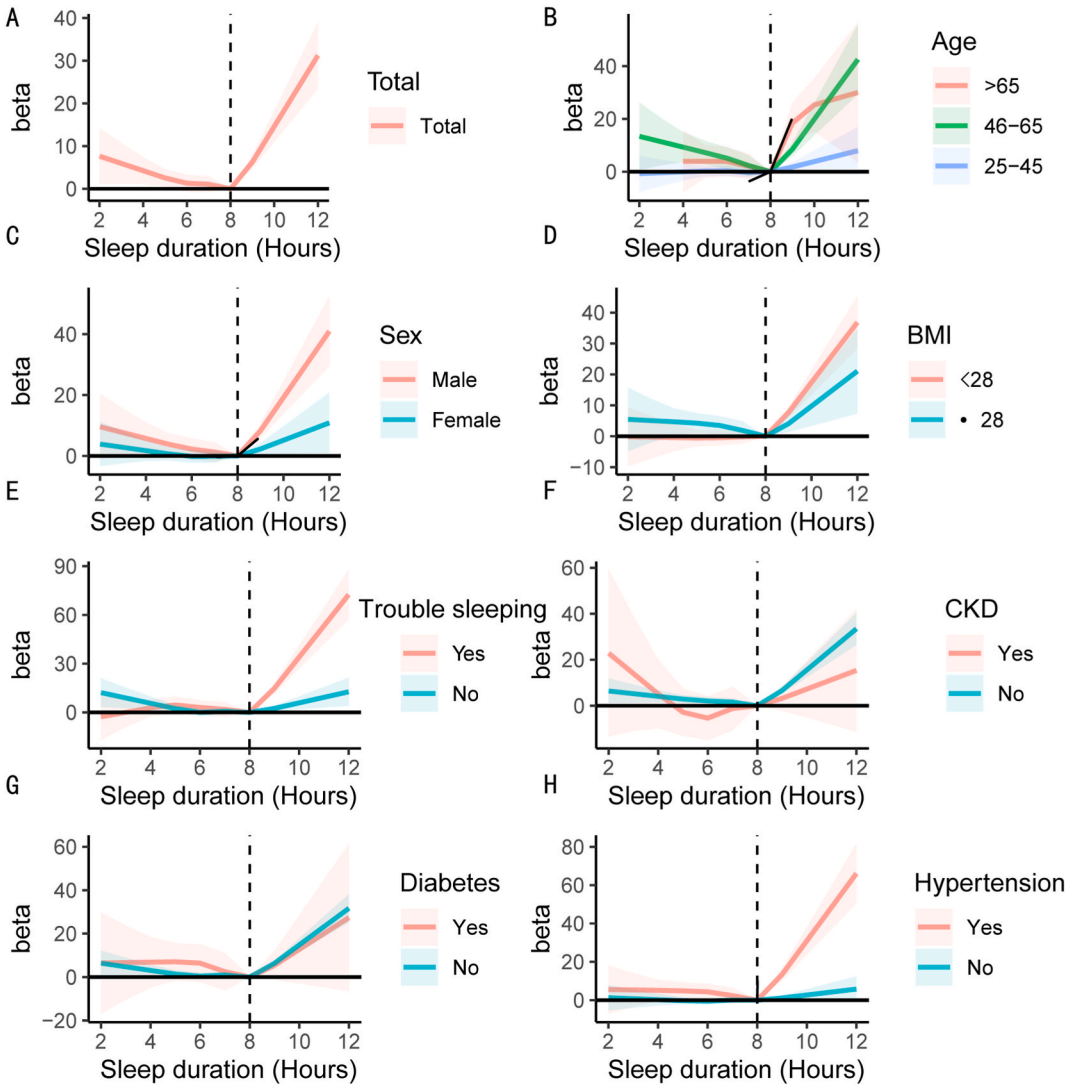

Fig. 2. Relationship between sleep duration and serum NfL level. A: Relationship between sleep duration and serum NfL level in all groups. B: Relationship between sleep duration and serum NfL level in different ages. C: Relationship between sleep duration and serum NfL level in different sexes. D: Relationship between sleep duration and serum NfL level in people with different BMIs. E: Relationship between sleep duration and serum NfL level in if suffered trouble sleeping. F: Relationship between sleep duration and serum NfL level in if suffered CKD. G: Relationship between sleep duration and serum NfL level in if suffered diabetes. H: Relationship between sleep duration and serum NfL level in if suffered hypertensions.

Table 3
Threshold Effect Analysis of sleep duration and sNfL Levels using Piece-wise Linear Regression.

	β (95 % CI) *P*-value
Crude Model	
Fitting by the standard linear model	0.65 (0.07, 1.24) 0.0280
Fitting by the two-piecewise linear model	
Inflection point	8
sleep duration <8 h	−0.87 (−1.56, −0.18) 0.0141
sleep duration >8 h	7.29 (5.53, 9.06) <0.0001
Log likelihood ratio	<0.001
Model I	
Fitting by the standard linear model	0.48 (−0.08, 1.03) 0.0946
Fitting by the two-piecewise linear model	
Inflection point	8
sleep duration <8 h	−1.05 (−1.71, −0.39) 0.0017
sleep duration >8 h	7.12 (5.44, 8.80) <0.0001
Log likelihood ratio	<0.001
Model II	
Fitting by the standard linear model	0.82 (0.25, 1.40) 0.0052
Fitting by the two-piecewise linear model	7
Inflection point	
sleep duration <7 h	−1.26 (−2.24, −0.28) 0.0115
sleep duration >7 h	3.20 (2.13, 4.27) <0.0001
Log likelihood ratio	<0.001

Crude Model: no covariates were adjusted.
Model I: age, sex, and race/ethnicity were adjusted.
Model II: age, sex, race/ethnicity, education level, BMI, smoking status, alcohol consumption status, trouble sleeping, history of hypertension, diabetes and chronic kidney disease.

4.2. Stratified analyses

As shown in Fig. 3, the subgroup analysis revealed a highly consistent pattern. In the subgroup analysis, we further explored the role of other covariates on the association between sleep duration and sNFL. The positive correlation between sleep duration and sNFL was more significant at normal body mass index (β = 2.24, 95%CI: 1.40, 3.07; P-interaction <0.0001). Subjects who reported trouble sleeping had higher sNFL levels than those who were not (β = 2.32, 95%CI: 1.33, 3.30 p for interaction = 0.0003). However, the association between sleep duration and sNFL was consistent across the following subgroups: sex, age, race, hypertension, diabetes, and chronic kidney disease (p for covariates interaction >0.05).

We further used multivariate regression models to investigate the relationship between sNfL levels and extreme sleep durations in different subgroups (Tables 4 and 5). After controlling for other variables (Table 4), remarkable elevated sNFL was observed in >10-h sleepers at normal body mass index (β = 22.01; 95%CI15.34, 28.68). Similarly, after controlling for other variables (Table 5), sNfL levels were significantly highest in the group who self-reported trouble sleeping (β = 41.78; 95%CI: 29.34, 54.22). However, this trend was not present in those who not self-reported trouble sleeping (β = 1.48,95 % CI: −5.00,7.95).

5. Discussion

During the past century human sleep duration was significantly reduced, 9 h in 1910 to 7.5 h in 1975 and 6.8 h in2005 [22,41], which raised lots of diseases incidence. Sleep restriction confirmed reduce plasma leptin and ghrelin concentration [35,42]and other negative effects such as anxiety [24], depression [43], obesity [42], diabetes [44] even cancer [23,33]. The relationship between extreme sleep duration and neurological dysfunction has long been identified [24,43,45], however, the detail measurement of neurological function or structure impairment linked with extreme sleep duration left blank remain.

Hurst and his colleges managed to locate human neurofilament gene (NEFL) at short arm of chromosome 8 in 1987 [1], which encoded a 543 amino acids primary peptide chain. Neurofilaments light chain is a member of neurofilaments family, widely expressed in central and peripheral nervous system [46], are structural scaffolding proteins in neurons and can cross-bridging and interconnecting with other components of cytoskeleton [46,47], were synthesized in cell plasma then transported by slow axonal transport into distal axon by 0.1–0.3 mm per day [2]. Usually released into CSF and serum after axonal damage or neuron death, folds over normal level [47,48], have long been identified as a promising neuro-disease biomarker [2,4,15,16,49].

In our study, we found out that there was a J shape relationship between USA adult sleep duration and serum neurofilaments level. This J shape relationship between sleep and other health state has long been discovered [23,25,31,34,42,50–53], however, there still lack nervous system data support this conception. Our effort in this study may further explain connection of extreme sleep duration and neurological dysfunction. Interestingly, our results showed that overlong sleep duration in male caused higher level sNfL than female might out of the poorer sleep in male [54]. Also, our data showed that people with normal BMI may get worsen neuro-stage, might traced back that obesity is chronical inflammatory state caused elevated sNfL level same as diabetes group [55,56].

Though in this article mainly about the relationship between sleep duration and NfL, the sleep quality has long been an important

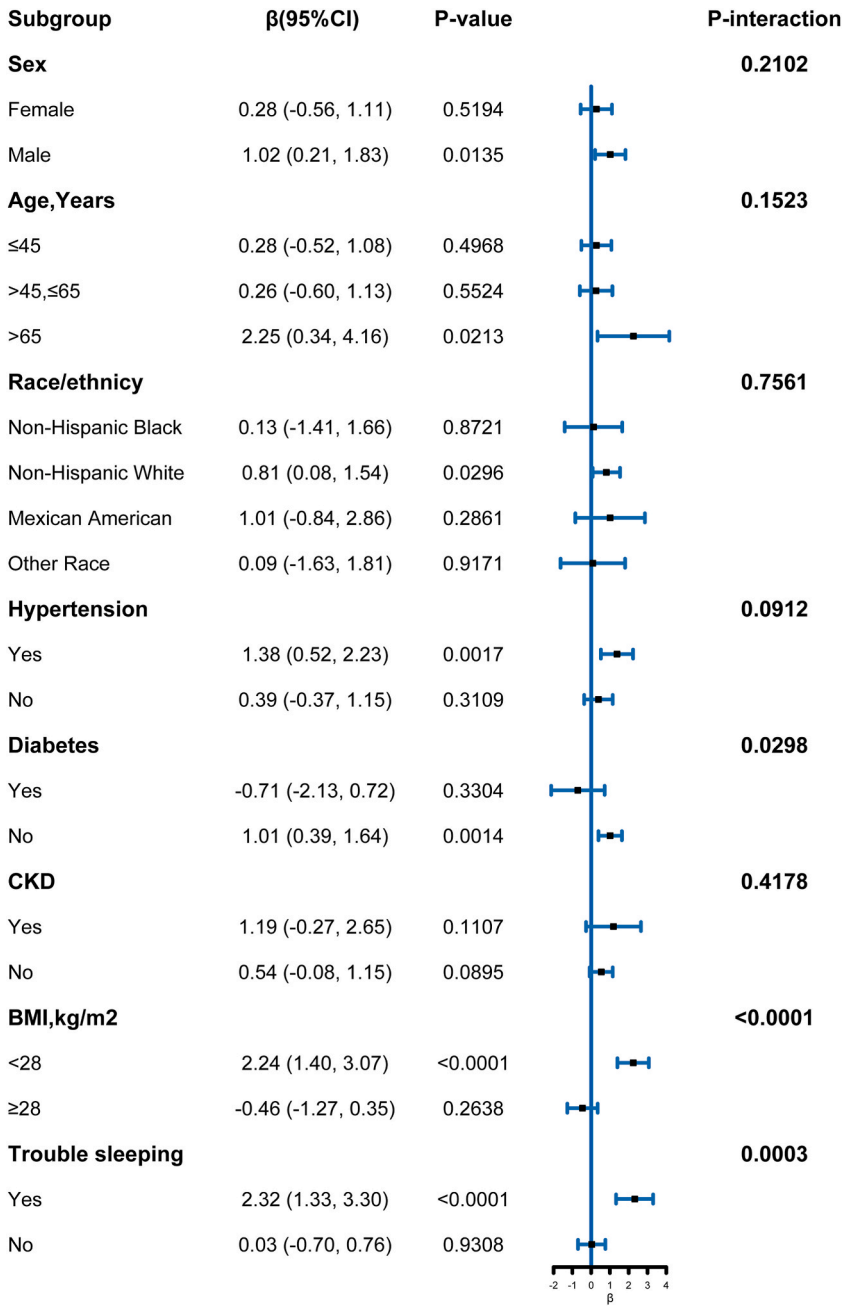

Fig. 3. Forest plots of stratified analyses of sleep duration and serum NfL level.

part [26,29], normal hormone secretion adhered a time related circadian rhythms [24,35,57], however due to the origin questionnaire design, this study lack of these parts that shall be long concerned in the following randomized designed study. In these collected data, only 1 case reported apnea-hypopnea event, which is obvious couldn't match other database [34], so this index was removed in this study.

What should be noticed is that in some brain-blood barrier (BBB) dysfunction diseases CSF NfL were also reported elevated [3], we couldn't straight jump to the conclusion that elevated serum NfL level is definitely connected with potential neuron damage, detailed study still needs further explore.

There has long been considered that sleep duration has linked to many neurodegeneration diseases [29,58,59]. Apart from some extreme status such as ABCC9 (ATP-binding cassette, sub-family C, member9) mutations [60], our result showed that sleep duration do impair neurons, but the precise pathway and link still need further exploration. Qualification in the scales always led to recall bias, also may led us to a biased result, which is only can be partially narrowed by detailed curve optimization, which is undeniable. And samples

Table 4
Regression coefficients (β) and 95 % confidence interval for sNfL Levels across sleep duration categories.

Outcome	Crude Model		Model I		Model II	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
BMI < 28 (kg/m^2)						
Sleep duration	2.24 (1.51, 2.97)	<0.0001	1.95 (1.25, 2.65)	<0.0001	2.29 (1.55, 3.04)	<0.0001
Sleep duration categories						
< 6 h	Reference		Reference		Reference	
6 h	0.54 (−2.99, 4.08)	0.7635	−0.17 (−3.54, 3.20)	0.9212	0.70 (−2.87, 4.27)	0.6998
7 h	0.65 (−2.73, 4.03)	0.7063	−1.22 (−4.46, 2.03)	0.4625	0.77 (−2.80, 4.33)	0.6726
8 h	2.05 (−1.48, 5.59)	0.2555	0.74 (−2.63, 4.12)	0.6663	2.21 (−1.43, 5.85)	0.2339
9 h	7.80 (2.87, 12.74)	0.0020	5.68 (0.98, 10.38)	0.0181	6.29 (1.37, 11.21)	0.0124
≥10 h	19.75 (13.28, 26.21)	<0.0001	18.54 (12.39, 24.69)	<0.0001	22.01 (15.34, 28.68)	<0.0001
P for trend	<0.001		<0.001		<0.001	
BMI ≥ 28 (kg/m^2)						
Sleep duration	−0.46 (−1.36, 0.44)	0.3181	−0.52 (−1.38, 0.34) 0	0.2398	−0.54 (−1.43, 0.35)	0.2325
Sleep duration categories						
< 6 h	Reference		Reference		Reference	
6 h	−4.38 (−8.39, −0.37)	0.0326	−3.77 (−7.59, 0.05)	0.0535	−4.79 (−8.71, −0.88)	0.0166
7 h	−3.85 (−7.74, 0.03) 0	0.0520	−4.04 (−7.74, −0.34)	0.0328	−4.21 (−8.05, −0.36)	0.0322
8 h	−6.35 (-10.32, −2.38)	0.0018	−6.28 (-10.07, −2.49)	0.0012	−6.18 (-10.08, −2.28)	0.0020
9 h	−0.46 (−7.09, 6.16) 0	0.8911	−0.61 (−6.93, 5.71)	0.8507	−1.41 (−7.78, 4.95)	0.6637
≥10 h	4.14 (−6.08, 14.35) 0	0.4277	4.45 (−5.29, 14.20)	0.3707	−0.56 (−10.84, 9.72)	0.9143
P for trend	0.039		0.146		0.116	

Crude Model: no covariates were adjusted.
Model I: age, sex, and race/ethnicity were adjusted.
Model II: age, sex, race/ethnicity, education level, smoking status, alcohol consumption status, trouble sleeping, history of hypertension, diabetes and chronic kidney disease.

Table 5
Regression coefficients (β) and 95 % confidence interval for sNfL Levels across sleep duration categories.

Outcome	Crude Model		Model I		Model II	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
History of trouble sleeping						
Sleep duration	2.32 (1.17, 3.46)	<0.0001	1.67 (0.55, 2.78)	0.0036	1.91 (0.71, 3.11)	0.0020
Sleep duration categories						
< 6 h	Reference		Reference		Reference	
6 h	−0.75 (−5.57, 4.07)	0.7593	−1.08 (−5.69, 3.53)	0.6472	−0.83 (−5.67, 4.01)	0.7368
7 h	−2.35 (−7.37, 2.68)	0.3606	−4.98 (−9.85, −0.10)	0.0461	−2.99 (−8.18, 2.21)	0.2604
8 h	−1.33 (−6.65, 3.98)	0.6232	−2.98 (−8.10, 2.14)	0.2543	−3.85 (−9.21, 1.51)	0.1603
9 h	7.57 (−0.40, 15.54)	0.0633	2.47 (−5.27, 10.20)	0.5326	3.45 (−4.70, 11.60)	0.4076
≥10 h	39.99 (27.86, 52.12)	<0.0001	36.91 (25.29, 48.54)	<0.0001	41.78 (29.34, 54.22)	<0.0001
P for trend	0.003		0.065		0.064	
No history of trouble sleeping						
Sleep duration	0.03 (−0.65, 0.72)	0.9266	−0.09 (−0.75, 0.56)	0.7812	0.25 (−0.42, 0.92)	0.4623
Sleep duration categories						
< 6 h	Reference		Reference		Reference	
6 h	−4.37 (−7.69, −1.06)	0.0098	−4.65 (−7.80, −1.50)	0.0039	−3.38 (−6.59, −0.18)	0.0385
7 h	−3.23 (−6.37, −0.09)	0.044	−4.35 (−7.36, −1.35)	0.0046	−2.78 (−5.86, 0.30)	0.0767
8 h	−4.07 (−7.29, −0.84)	0.0137	−4.95 (−8.03, −1.86)	0.0017	−2.85 (−5.99, 0.30)	0.0761
9 h	0.14 (−4.59, 4.87) 0	0.9531	−0.01 (−4.53, 4.51)	0.9972	1.83 (−2.73, 6.38)	0.4314
≥10 h	1.87 (−4.45, 8.19) 0	0.5623	1.73 (−4.29, 7.75)	0.5732	1.48 (−5.00, 7.95)	0.6554
P for trend	0.822		0.890		0.478	

Crude Model: no covariates were adjusted.
Model I: age, sex, and race/ethnicity were adjusted.
Model II: age, sex, race/ethnicity, education level, BMI, smoking status, alcohol consumption status, history of hypertension, diabetes and chronic kidney disease.

were extracted from NHANEs may not precisely represent population data.

6. Conclusion

The relationship between American sNfL level and sleep duration is J shaped, judged from a national representative database. Suggest extreme sleep duration could be deleterious to nervous system (overlong duration can be more obvious than too short). Also, there was an obvious elevate effect in people with normal BMI than higher BMI may indicated that people with higher BMI may

suffered from invisible nervous damage.

Ethics declarations

Informed consent was not required for this study because this study just analysis second handed data, and the original data collection was approved by NCHS ERB.

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Data availability

All the original data can be founded at NHANES website, and data generated during this manuscription would be available on reasonable request.

CRediT authorship contribution statement

Jiaxing Liang: Writing – review & editing, Writing – original draft, Conceptualization. **Tengchi Ma:** Visualization, Methodology, Data curation. **Youlei Li:** Writing – review & editing. **Ruixin Sun:** Writing – review & editing. **Shuaishuai Zhao:** Writing – review & editing. **Yuzhe Shen:** Writing – review & editing. **Hui Gao:** Writing – review & editing. **Yunhang Jing:** Writing – review & editing. **Xinyue Bai:** Writing – review & editing. **Mengze He:** Writing – review & editing. **Qingyan Wang:** Writing – review & editing. **Huilin Xi:** Writing – review & editing. **Rui Shi:** Writing – review & editing. **Yanling Yang:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

ABCC9	ATP-binding cassette, sub-family C, member 9
ACR	albumin/creatinine ratio
AD	Alzheimer disease
AE	acridinium ester
ALS	amyotrophic lateral sclerosis
BBB	brain-blood barrier
BMI	body mass index
CIs	confidence intervals
CKD	chronic kidney disease
CSF	cerebrospinal fluid
CV	coefficient of variation
DBP	diastolic blood pressure
ERB	Ethics Review Board
LLOQ	lower limit of quantification
MS	multiple sclerosis
MSA	multiple system atrophy
NCHS	National Center for Health Statistics
NEFL	neurofilament gene
NF	neurofilament
NfL	neurofilament light chain
NHANES	National Health and Nutrition Examination Survey
PMP	paramagnetic particles
QC	quality control

SBP systolic blood pressure
SCA3 spinocerebellar ataxia type 3
sCJD sporadic Creutzfeldt-Jakob disease
sNfL serum neurofilament light chain
STROBE Strengthening the Reporting of Observational Studies in Epidemiology

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