BMJ Open

Association between serum neurofilament light chain levels and grip strength among US adults: a cross-sectional study using National Health and Nutrition Examination Survey data from 2013 to 2014

Diliyaer Dilixiati ,[1] Kaisaierjiang Kadier ,[2] Bingzhang Qiao,[1] Weijie Zhang,[1] Daniyaer Nuerdebieke,[1] Abudureheman Zebibula,[1] Ying Yang,[3] Mulati Rexiati[1]

To cite: Dilixiati D, Kadier K, Qiao B, *et al*. Association between serum neurofilament light chain levels and grip strength among US adults: a cross-sectional study using National Health and Nutrition Examination Survey data from 2013 to 2014. *BMJ Open* 2025;**15**:e084766. doi:10.1136/bmjopen-2024-084766

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-084766).

DD and KK contributed equally.

Received 27 January 2024
Accepted 15 January 2025

Check for updates

© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to
Ying Yang;
yy15022944632@163.com, Dr Abudureheman Zebibula;
11618010@zju.edu.cn and Mulati Rexiati;
muratrixat@126.com

ABSTRACT

Objective We aimed to investigate the relationship between serum neurofilament light chain (NfL) and grip strength using data from the 2013–2014 US National Health and Nutrition Examination Survey (NHANES).

Design Secondary analysis of cross-sectional, population-based data.

Setting NHANES sample, 2013–2014.

Participants We studied 1925 participants aged 20–75 years.

Outcome measures and analysis We applied a multivariable generalised linear regression model, adjusted for several potential confounders, and restrictive cubic spline models to evaluate the association between serum NfL and grip strength. Subgroup analyses were conducted using stratified multivariable linear regression analysis.

Results We included 1925 participants (average age: 44.8±0.44 years) from the NHANES database. Participants with higher serum NfL levels had a significantly higher prevalence of medical conditions (hypertension, diabetes, cardiovascular disorder, chronic kidney disease (CKD) and cancer) compared with those with lower NfL levels (all p<0.001). After adjusting for confounding factors, there was a negative association between serum NfL and grip strength (β=−2.07; 95% CI −3.47, −0.67; p=0.007). In addition, significant interactions were found between NfL and grip strength stratified by age, physical activity and CKD (p value for interaction=0.002, 0.023 and 0.006). The results of the restricted cubic splines (RCS) analysis showed no evidence against a linear association of serum NfL levels with grip strength. (p for non-linearity=0.334).

Conclusion Our study demonstrates a strong, negative and linear correlation between elevated serum NfL levels and grip strength. Notably, our findings indicate that individuals aged between 60 and 75 years, those with physical inactivity and those with CKD exhibit a more pronounced reduction in grip strength with increasing serum NfL levels.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study employed a complex, multistage probability sampling approach to obtain a representative sample of the national population, and the high quality and large scale of the National Health and Nutrition Examination Survey (NHANES) database ensured the reliability of our results.
⇒ Subgroup analyses and restricted cubic splines were employed to further investigate potential interactions and non-linear associations.
⇒ Serum neurofilament light chain levels and grip strength were assessed using objective clinical data collected according to standardised protocols.
⇒ Due to the cross-sectional design of the NHANES database, the results of this study do not provide sufficient evidence to establish causal relationships.
⇒ The use of self-reported questionnaires and the potential for residual confounding among covariates may have biased the study results.

INTRODUCTION

Epidemiological investigations have shown that loss of muscle mass and strength is very common in the population, especially among the elderly, thereby highlighting it as a significant public health challenge in the current ageing society.[1] Skeletal muscle is essential for performing daily activities and work, with optimal muscle strength and function being critical prerequisites for overall health and physical performance. Grip strength, an indispensable biomarker for older adults, is a reliable measure of muscle strength and is considered feasible for assessing in a large sample.[2] Current epidemiological studies highlight several known determinants of low grip strength, including advanced age, decreased physical activity, impaired motor

and cognitive function and the development of underlying diseases.[3]

Neurofilament is a heteropolymeric protein composed of several components, including neurofilament heavy chain, neurofilament medium chain, neurofilament light chain (NfL), alpha-internexin and peripherin. These proteins are most abundantly found in mature myelinated axons.[4] NfL is a fundamental scaffolding protein that makes up the neuronal cytoskeleton, providing essential mechanical support and playing a crucial role in the regulation of axonal diameter.[5] After axonal damage, NfL is released into the brain's interstitial fluid, from which it enters the cerebrospinal fluid (CSF) and ultimately reaches the bloodstream.[6] Loss of axons in both the central and peripheral nervous systems has been linked to several diseases, such as amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's dementia, stroke, frontotemporal dementia, Parkinson's disease and disorders of the peripheral nervous system.[7] In addition to the role of disease, age is a significant physiological factor in determining NfL levels. In healthy individuals, there is a positive correlation between NfL and age, with NfL levels increasing by 2.2% per age group. Moreover, NfL levels show an increased rise with age beyond 60 years, accompanied by significant interindividual variability within a given age cohort.[5] With the advent of new technologies such as single-molecule array, the detection of proteins in CSF in blood has been promoted, and more and more neurological biomarkers are emerging. Recent studies have shown that NfL can serve as a biomarker for predicting the severity of chronic neurodegenerative diseases, monitoring treatment progress and determining prognosis.[8]

To date, only a single cross-sectional study has investigated the relationship between plasma NfL levels and the prodromal phase of sarcopenia, characterised by declines in grip strength, as well as the full manifestation of sarcopenia. However, the study, being a preliminary exploration, included only 300 individuals and did not encompass younger subjects.[9] Thus, whether the relationship between serum NfL and grip strength exists in young as well as large sample populations has not been studied clearly. This relationship has significant implications for public health and prevention and thus warrants further investigation. For these reasons, we aimed to investigate the relationship between serum NfL and grip strength using data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES).

METHODS

Study population and data collection

The participants for this secondary analysis were from the NHANES database 2013–2014 cycle because only this cycle contained serum NfL information.[10] The NHANES uses stratified, multistage, clustered probability sampling design, granting it the ability to be a sample that fits the US population's stratification.[10] Each participant of the NHANES study provided written informed consent. In addition, this study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting cross-sectional studies.[11] In the 2013–2014 cycle of NHANES, 10 175 participants completed the survey, of whom 5262 were aged 20–75 years. Individuals with missing data on NfL (n=3191) and grip strength (n=146) were excluded. Ultimately, 1925 participants participated in our study, as shown in figure 1.

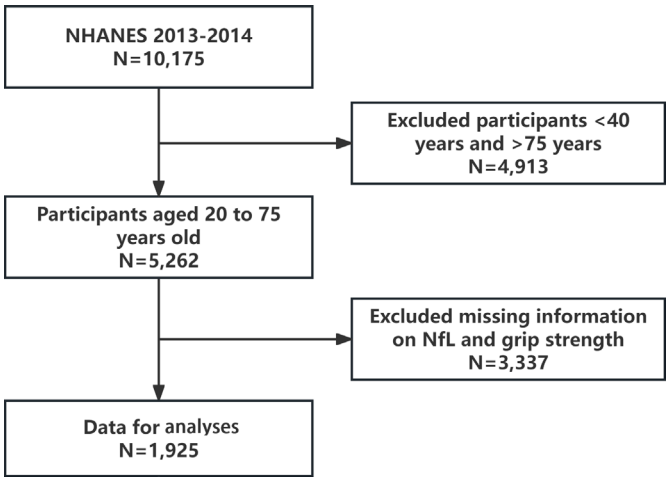

Figure 1 Flow chart of eligible NHANES participants included in the analysis. NfL, neurofilament light chain; NHANES, National Health and Nutrition Examination Survey.

Serum NfL measurement

As part of the NHANES protocol, blood samples were collected from all participants in our survey. Serum was extracted from unused residual blood samples collected from the NHANES participants aged 20–75 years, who had consented to further testing for future studies. Specifically, we extracted serum from half of the NHANES 2013–2014 samples. Already stored serum samples were also considered eligible for analysis. Serum NfL was measured by a novel high-throughput acridinate immunoassay developed by Siemens Healthcare on the Atellica platform. First, samples were incubated with acridinium ester (AE)-labelled antibodies, which in turn bound to the NfL antigen. Paramagnetic particles encapsulated with capture antibodies were added to the sample to form antigenic complexes. After the incubation period, unbound AE-labelled antibodies were separated and removed. Acid and base buffers were then added to initiate chemiluminescence, and the resulting light emission was measured. The detection range of this method was 3.9–500 pg/mL and has the advantages of high quantum yield, rapid kinetics, high repeatability, hydrophilicity, hydrolysability and stability. A detailed description of the serum NfL quantification procedure and analytical methods can be found on the official website (http://www.cdc.gov/nchs/nhanes.htm).

Grip strength assessment

We used a dynamometer to measure the combined grip strength in kilograms, following standard protocols. An experienced examiner explained and demonstrated the operation to the participant before the test was performed. The examiner adjusted the dynamometer according to the subject's hand condition and asked them to try to hold the dynamometer for trial use. Participants were instructed to exert their maximal grip strength using the dynamometer while in a standing position. After completing three trials with the first hand, participants repeated the test with their other hand, with a 60 s rest period between each trial. Combined grip strength is the sum of the maximum grip reading for each hand.

Covariates

Taking into account previous studies[12–14] into the relationship between serum NfL and grip strength (kg), alongside relevant clinical implications, we considered the following covariates: age, sex, race and ethnicity, body mass index (BMI) (kg/m^2), smoking status, alcohol consumption status, physical activity, education level, poverty income ratio (PIR), sedentary behaviour (min/day), hypertension, diabetes, cardiovascular disorder (CVD), chronic kidney disease (CKD) and cancer. Detailed information is described in online supplemental material.

Statistical analysis

Sample weights were used in the statistical analysis process to recover population-level data across the USA, which was performed according to the Centers for Disease Control and Prevention's NHANES guidance files. Continuous variables were compared using one-way analysis of variance and presented as weighted mean±SD, while categorical variables were tested using Rao-Scott χ^2 test and presented as weighted percentages (95% CI). Serum NfL was divided into tertiles based on weighted sample distribution. In addition, we performed multivariable generalised linear regression analysis to evaluate the relationship between grip strength as the outcome variable and serum NfL level as the independent variable. Beta coefficients and 95% CIs were calculated. Model 1 was a crude model. Model 2 was adjusted for age, sex and race and ethnicity. In model 3, we additionally adjusted for BMI, smoking status, alcohol consumption status, physical activity, education level, PIR, sedentary behaviour, hypertension, diabetes mellitus, CVD, CKD and cancer. Serum NfL levels were analysed using log-transformed continuous variables and tertiles.

Subgroup analyses were conducted using stratified multivariable regression analysis, with stratification based on age, sex, BMI, race and ethnicity, smoking status, alcohol consumption status, physical activity, sedentary behaviour, diabetes mellitus, CVD, hypertension and CKD. Multiplicative interactions were assessed using likelihood ratio tests. Furthermore, non-linear relationships between NfL and grip strength in the fully adjusted model were explored using restricted cubic splines (RCS) with three knots at the 10th, 50th and 90th percentiles.

In this study, we used the MissForest package in R software to address missing covariates.[15] The model has been proven to effectively handle both categorical and continuous variables, and it maintains strong performance even when dealing with missing covariate data, as shown in online supplemental table S1. Sensitivity analyses were conducted with the following criteria: (1) only participants with complete covariate data were included; and (2) age, BMI, PIR, physical activity and sedentary behaviour were included in the model as continuous variables. All statistical analyses were computed with R software (V.4.1.3).

Patient and public involvement

None.

RESULTS

Baseline characteristics

The sample for the present study included 1925 participants, representing 201 877 463 non-institutionalised adults (20–75 years) in the USA. Participant characteristics are shown in table 1 by tertiles of NfL levels. The average age of the participants was 45.7 years, with 48.7% being male. The subjects had a mean grip strength of 73.94±0.70 kg. Most participants were between 20 and 59 years of age (79.0%). Majority of these individuals were non-Hispanic white (66.5%), with 11.9% non-Hispanic black, and had a middle or high PIR (75.8%) and were at least high school graduates (85.0%). In this study, serum NfL was significantly associated with age, BMI (kg/m^2), race, PIR, smoking status, alcohol consumption status and physical activity. In addition, compared with the lower serum NfL level group (T1), the higher NfL level groups (T2 and T3) exhibited a higher prevalence of medical conditions, including hypertension, diabetes, CVD, CKD and cancer (all p<0.001). Notably, subjects' grip strength was 75.69±0.99 kg, 75.50±1.26 kg and 70.30±0.95 kg in the serum NfL tertiles, respectively. This suggests that grip strength decreases as serum NfL increases. Online supplemental table S1 presents data on the number and percentage of missing values for each covariate. For covariates not listed in the table, no missing information was recorded.

Serum NfL levels and grip strength

Table 2 displays the relationships between serum NfL levels and grip strength as observed in the linear regression analysis. The association between serum NfL as a continuous covariate and grip strength was negative in model 1 (β=−3.14; 95% CI −4.92, −1.36; p=0.002), model 2 (β=−2.79; 95% CI −4.27, −1.31; p=0.003) and model 3 (β=−2.07; 95% CI −3.47, −0.67; p=0.007). Furthermore, in model 3, when comparing the second and third tertiles of serum NfL with the lowest tertile, the beta values were −0.06 (95% CI −2.08, 1.95) and −2.80 (95% CI

Table 1 Baseline characteristics of the study population in NHANES 2013–2014

Characteristics	Overall (N=2071)	T1 (2.8–9.5) (n=643)	T2 (9.5–16.1) (n=645)	T3 (16.1–497.6) (n=637)	P value
Age					<0.0001
20–39	40.22 (35.10, 45.34)	67.50 (63.60, 71.41)	32.13 (26.33, 37.93)	19.20 (15.19, 23.22)	
40–59	38.76 (33.94, 43.58)	30.85 (26.92, 34.78)	46.28 (41.03, 51.53)	39.16 (35.10, 43.23)	
60–75	21.03 (17.64, 24.41)	1.65 (0.53, 2.76)	21.59 (15.90, 27.28)	41.63 (37.90, 45.37)	
Sex					0.059
Male	48.89 (42.72, 55.06)	44.18 (40.93, 47.42)	51.48 (47.13, 55.83)	51.21 (47.11, 55.31)	
Female	51.11 (46.56, 55.66)	55.82 (52.58, 59.07)	48.52 (44.17, 52.87)	48.79 (44.69, 52.89)	
BMI (kg/m^2)					0.028
<30	62.07 (55.37, 68.76)	58.24 (53.31, 63.17)	67.98 (63.14, 72.82)	59.78 (55.84, 63.71)	
≥30	37.93 (33.31, 42.56)	41.76 (36.83, 46.69)	32.02 (27.18, 36.86)	40.22 (36.29, 44.16)	
Race/ethnicity					0.001
Non-Hispanic white	66.05 (53.35, 78.76)	55.79 (47.78, 63.80)	69.34 (61.02, 77.66)	73.69 (66.23, 81.15)	
Non-Hispanic black	11.93 (9.06, 14.80)	14.11 (9.35, 18.86)	10.89 (7.74, 14.03)	10.69 (8.07, 13.32)	
Mexican American	9.03 (6.31, 11.76)	13.97 (10.57, 17.36)	7.27 (3.27, 11.27)	5.56 (2.24, 8.87)	
Other Hispanic	5.76 (2.85, 8.67)	7.22 (3.07, 11.37)	5.48 (2.92, 8.05)	4.47 (0.43, 8.52)	
Other race/ethnicity	7.22 (5.53, 8.91)	8.92 (5.77, 12.06)	7.02 (4.47, 9.58)	5.59 (3.27, 7.91)	
Education level					0.673
Less than high school	15.00 (12.00, 18.00)	16.60 (13.54, 19.67)	14.43 (10.40, 18.45)	13.87 (7.90, 19.85)	
High school graduate	20.34 (17.26, 23.41)	20.26 (14.70, 25.81)	19.05 (14.87, 23.23)	21.83 (17.46, 26.21)	
Above high school	64.66 (54.14, 75.19)	63.14 (57.61, 68.67)	66.52 (59.29, 73.75)	64.29 (57.27, 71.31)	
PIR					0.002
<1.3	24.23 (18.37, 30.09)	24.61 (20.34, 28.88)	24.81 (17.23, 32.39)	23.18 (13.87, 32.49)	
1.3–3.5	34.81 (31.59, 38.03)	42.15 (36.78, 47.52)	27.68 (23.83, 31.52)	34.59 (30.88, 38.30)	
≥3.5	40.96 (31.09, 50.83)	33.24 (27.05, 39.43)	47.51 (39.13, 55.90)	42.23 (33.16, 51.29)	
Smoking status					0.020
Now	20.96 (16.85, 25.08)	18.95 (16.20, 21.69)	22.81 (15.68, 29.94)	21.14 (14.50, 27.78)	
Former	22.48 (18.04, 26.92)	17.15 (14.20, 20.11)	23.59 (19.87, 27.32)	27.09 (20.62, 33.56)	
Never	56.56 (48.75, 64.37)	63.90 (60.48, 67.32)	53.60 (47.41, 59.78)	51.77 (44.91, 58.62)	
Alcohol consumption status					0.002
Heavy	42.99 (37.74, 48.25)	51.87 (47.38, 56.37)	38.42 (34.32, 42.52)	38.29 (32.71, 43.87)	
Mild	33.52 (26.77, 40.27)	28.87 (24.47, 33.27)	37.93 (31.33, 44.52)	33.78 (24.31, 43.24)	
Former	12.20 (10.37, 14.04)	7.48 (4.93, 10.03)	13.15 (10.05, 16.25)	16.34 (12.33, 20.34)	
Never	11.28 (6.85, 15.72)	11.78 (7.78, 15.78)	10.50 (5.53, 15.47)	11.60 (6.52, 16.67)	
Physical activity					0.032
Inactive	22.34 (19.10, 25.58)	19.44 (16.19, 22.68)	20.15 (16.73, 3.58)	27.92 (23.47, 32.38)	
Low active	16.46 (13.94, 18.99)	16.10 (12.73, 19.46)	15.35 (11.45, 9.26)	18.08 (14.81, 21.35)	
Highly active	16.64 (14.67, 18.61)	17.34 (14.57, 20.12)	16.07 (12.94, 19.21)	16.49 (13.26, 19.71)	
Extremely highly active	44.56 (38.96, 50.15)	47.13 (44.06, 50.19)	48.42 (43.02, 53.82)	37.51 (32.59, 42.43)	
Sedentary behaviour (min/day)					0.219
<480	52.15 (47.79, 56.50)	55.08 (50.87, 59.29)	51.57 (45.96, 57.18)	49.57 (44.80, 54.34)	
≥480	47.85 (40.32, 55.39)	44.92 (40.71, 49.13)	48.43 (42.82, 54.04)	50.43 (45.66, 55.20)	
Hypertension	45.27 (39.81, 50.74)	27.96 (22.76, 33.16)	48.19 (42.41, 53.97)	61.04 (55.34, 66.74)	<0.0001
Diabetes	10.76 (9.39, 12.13)	4.11 (2.85, 5.37)	10.47 (7.92, 13.02)	18.36 (14.71, 22.01)	<0.0001

Continued

Table 1 Continued

Characteristics	Overall (N=2071)	T1 (2.8–9.5) (n=643)	T2 (9.5–16.1) (n=645)	T3 (16.1–497.6) (n=637)	P value
CVD	6.76 (4.74, 8.77)	0.80 (0.07, 1.53)	6.89 (4.88, 8.89)	13.14 (8.11, 18.16)	<0.0001
CKD	12.36 (10.51, 14.22)	9.05 (6.28, 11.83)	8.27 (5.57, 10.98)	20.48 (17.57, 23.38)	<0.0001
Cancer	8.84 (7.09, 10.58)	4.99 (3.33, 6.64)	8.45 (5.89, 11.02)	13.47 (10.27, 16.67)	<0.001
Grip strength (kg)	73.94 ± 0.70	75.69 ± 0.99	75.50 ± 1.26	70.30 ± 0.95	0.003

Values are weighted mean±SD or weighted % (95% CI).
P values are weighted.
BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disorder; NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; T, tertile.

–5.45, –0.15), respectively. The results of the RCS analysis showed no evidence against a linear association of serum NfL levels with grip strength (p value for non-linearity=0.334) (figure 2).

Subgroup analyses

The findings of the subgroup analyses, which considered different variables such as age, sex, BMI, race and ethnicity, smoking and alcohol consumption status, physical activity, sedentary behaviour, hypertension, diabetes, and CVD and CKD status, are displayed in figure 3 and online supplemental table S2. Significant interactions were found between serum NfL levels and grip strength stratified by age, physical activity and CKD (p value for interaction=0.002, 0.023 and 0.006, respectively). These findings suggest that grip strength continues to decrease with rising serum NfL in older adults (aged 60–75 years), unlike in younger and middle-aged adults (aged 20–59 years). Moreover, a robust correlation between serum NfL and grip strength was observed in inactive individuals and those with CKD, underscoring the potential clinical relevance of our results.

Sensitivity analyses

In our sensitivity analyses, we aimed to ensure the robustness of our findings by excluding participants with missing covariates. This approach resulted in a final sample size of 1654 participants. Within this refined data set, we included age, BMI, PIR, physical activity and sedentary behaviour as continuous variables in our model. The results from these analyses were consistent with the main findings of our study, demonstrating the robustness and reliability of our conclusions (online supplemental table S3). By conducting these sensitivity analyses, we have further validated the stability of our statistical models and the generalisability of our findings across a reduced but more complete data set.

DISCUSSION

In this large nationwide study, we analysed data from the NHANES (2013–2014) database, which included 1925 participants aged 20–75 years old. Our study revealed a significant negative linear correlation between serum NfL levels and grip strength in the general US population. This association persisted even after adjusting for a range of covariates, including demographic characteristics, lifestyle factors and medical history. In addition, there was a significant interaction between elevated serum NfL and reduced grip strength stratified by age, physical activity and CKD. In age-stratified analyses, our study revealed a positive association between elevated serum NfL levels and an increased risk of reduced grip strength in the elderly (aged 60–75 years), as well as among inactive individuals and those with CKD.

Pratt and colleagues have recently delved into the correlation between plasma NfL concentrations and

Table 2 Weighted linear regression coefficients (b) and 95% confidence intervals for the association between serum neurofilament light chain levels and grip strength in NHANES 2013–2014

Exposure	Model 1	Model 2	Model 3
Continuous	–3.14 (–4.92, –1.36), p=0.002	–2.79 (–4.27, –1.31), p=0.003	–2.07 (–3.47, –0.67), p=0.007
Tertiles			
T1	Reference	Reference	Reference
T2	–0.19 (–2.52, 2.14), p=0.864	–0.44 (–2.87, 2.00), p=0.675	–0.06 (–2.08, 1.95), p=0.947
T3	–5.40 (–8.14, –2.65), p<0.001	–3.73 (–6.53, –0.93), p=0.017	–2.80 (–5.45, –0.15), p=0.040

Model 1: without any adjustment; model 2: adjusted for age, sex and race and ethnicity; model 3: adjusted for age, sex, race and ethnicity, body mass index, smoking status, alcohol consumption status, activities, education level, poverty income ratio, sedentary behaviour, hypertension, diabetes mellitus, cardiovascular disorder, chronic kidney disease and cancer.
NHANES, National Health and Nutrition Examination Survey.

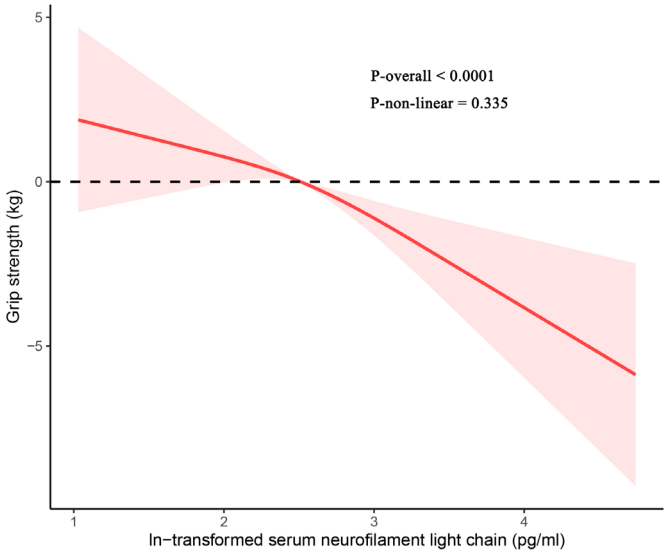

Figure 2 Restricted cubic spline of the association between serum neurofilament light chain levels and grip strength (adjusted for age, sex, race and ethnicity, body mass index, smoking status, alcohol consumption status, activities, education level, poverty income ratio, sedentary behaviour, hypertension, diabetes mellitus, cardiovascular disorder, chronic kidney disease and cancer).

muscle mass and strength in middle-aged and elderly individuals.[9] Elevated plasma levels of NfL were observed in individuals classified as presarcopenic, as indicated by low grip strength or low skeletal muscle index, in comparison to control subjects. This observation reached statistical significance (p=0.001 and p=0.006, respectively), as reported in the study.[9] In contrast to the aforementioned study, our investigation expands the study population by means of nationally representative sample data, incorporates a broader age range (20–75 years) and explores serum NfL levels rather than plasma. Furthermore, our research delves into the interactions between subgroups, thus revealing the potential use of NfL as a viable biomarker for sarcopenia.

To the best of our knowledge, this is the first study to evaluate the association between serum NfL levels and grip strength in both older and younger adults. While the reason for the association between the two variables remains unclear at present, there are several potential mechanisms that could account for it. NfLs can be released into extracellular fluid, CSF and peripheral blood, correlating with the extent of axonal injury. This can help identify a range of diseases that may potentially result in axonal damage.[16] Neurodegenerative diseases such as amyotrophic lateral sclerosis, Alzheimer's dementia and parkinsonism are associated with axon loss in both the central and peripheral nervous systems.[17] Patients with neurodegenerative diseases exhibit altered variability, intensity and frequency of corticospinal activation, leading to impaired motor unit recruitment and subsequent reduction in grip strength.[18] Thus, comorbidity factors were the primary cause of the negative linear association between NfL and grip strength.

Second, higher NfL levels are believed to indicate motor neuron damage in circuits associated with sarcopenia,[19] which has been shown to lead to a decrease in grip strength. Saak *et al*[20] explored the correlation between myodystrophy, myotonic dystrophy or mitochondrial disease genes, neuronal injuries and serum NfL levels, and established that NfL levels can serve as a useful biomarker for detecting and monitoring neuronal injuries caused by myopathy, even among patients without clinically significant central nervous system involvement. Moreover, a prospective study based on this theory monitored patients with early Parkinson's disease—excluding those who had developed Parkinsonian gait—over a period of up to 8 years and collected serum samples. The findings revealed that serum NfL levels were an independent risk factor for the development of Parkinson's gait.[21] Likewise, the diffusion tensor MRI results at 6-month follow-up after stroke indicated a positive correlation between NfL levels and secondary neurodegeneration of major white matter tracts within the infarcted hemisphere.[22] Notably, Mollenhauer *et al*'s study showed that patients with Parkinson's disease had lower serum NfL levels compared with diseases with more severe damage to the myelin tracts (multiple nodular sclerosis, Alzheimer's disease, etc).[23] On one hand, the aggregation of alpha-synuclein in patients with Parkinson's disease tends to occur mainly in neurons with less myelinated axons. On the other hand, patients with Parkinson's typically experience a relatively slow rate of neuronal cell death.[23] Finally, inflammatory response is another potential possibility. In a study of hospitalised COVID-19 patients, it was found that patients with mild pneumonia showed a positive correlation between serum NfL levels, serum C reactive protein and plasma D-dimer at the time of admission.[24] Moreover, heightened inflammation and oxidative stress have been implicated in the pathogenesis of vascular and Alzheimer's disease, as well as decreased muscle function, weakness and sarcopenia.[25] Inflammatory factors can promote accelerated muscle protein breakdown by inhibiting muscle protein synthesis and expression of muscle growth factors, ultimately leading to decreased muscle strength.[26]

Disanto *et al*'s study investigated the sex and age distribution of serum NfL concentrations in healthy subjects and found no significant sex-related differences.[27] However, there was a positive correlation observed between age and serum NfL levels, with a 2.2% increase in serum NfL for every year of age.[27] Chronic neurodegenerative diseases are defined by gradual and persistent neuronal degeneration, and NfL levels have been observed to steadily increase over time to reflect this progression. The age-related increase in NfL levels is hypothesised to have two primary causes: first, a natural decline in physiological CSF turnover rate as age increases, and second the gradual onset of axonal injury over time that characterises many neurodegenerative conditions.[28] According to a recent study, elevated baseline serum NfL levels have been found to be significantly associated with global

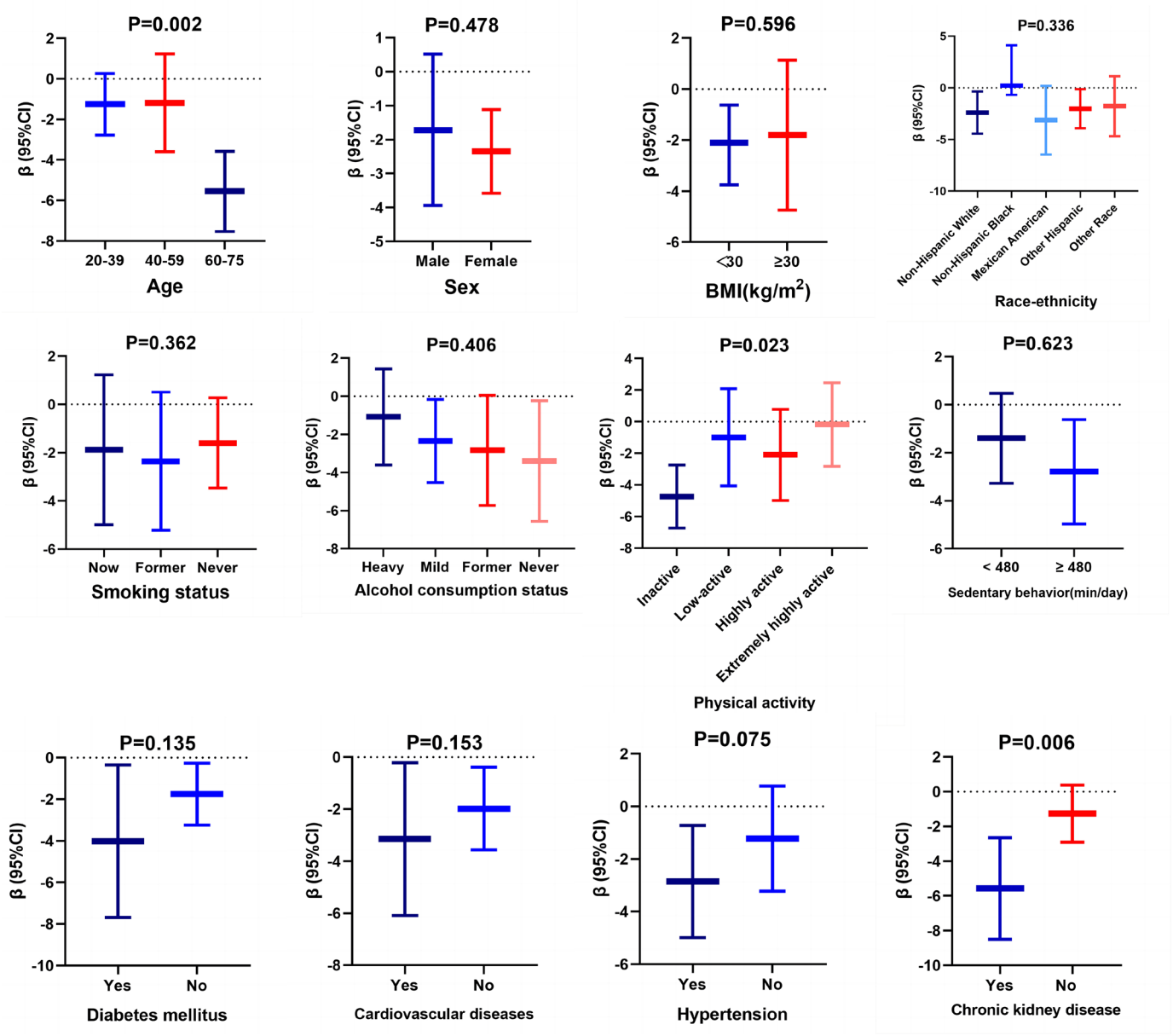

Figure 3 Multiple linear regression associations between serum neurofilament light chain levels and grip strength by subgroup analysis. BMI, body mass index.

brain atrophy detected via MRI over the next 2–5 years.[29] A prospective study of 102 elderly (65 years and older) residents tested for gait speed, grip strength and muscle mass using dual X-ray absorptiometry showed that sarcopenia is independently associated with parietal atrophy.[30]As cortical atrophy is a widespread phenomenon among the elderly, individuals who experience brain atrophy due to disease or ageing show heightened serum NfL levels concomitant with declines in systemic muscle strength. Cognitive decline, as a characteristic of the elderly population, has also been found to be significantly associated with reductions in grip strength and overall muscle strength.[31] These mechanisms effectively account for the emergence of significant age subgroup interactions, with a stronger association observed in older populations. However, it is worth noting that the association between NfL and age does not appear to be significant in specific disease populations, such as those affected by stroke.[32]

The interaction of CKD subgroups was also captured in our subgroup analysis. In a study of the factors influencing serum NfL levels in a cohort of individuals experiencing normal ageing, renal function was identified as a significant factor affecting NfL concentrations.[33] This association was believed to be due to the correlation between NfL and serum creatinine concentrations, as well as with the renal clearance process. Another study that delved into the relationship between renal function and serum NfL in patients with diabetes further explored that serum NfL and serum creatinine levels were found to be positively correlated in healthy elderly and patients with diabetes after adjusting for age, sex and BMI.[34] An alternative explanation was given by Ladang and colleagues

that damage to neurons releases not only NfL molecules, but also NfL fragments.[35] Additionally, they suggested that metabolism of NfL molecules can also produce NfL fragments, and these fragments were usually removed by normal glomerular filtration, but can accumulate when glomerular filtration was decreased due to lesions.[35] In contrast to previous studies (patients with CKD or kidney failure excluded), we further assessed participants for CKD based on serum creatinine and urine protein concentrations. Our study found that the association between serum NfL and nerve injury was more significant in individuals with CKD.

An important advantage of NfL over other biomarkers in neuro-related research is its high specificity for damage and death of neural cells, making it a valuable tool in the assessment of neuronal injury. In fact, previous related studies have focused on the analysis of CSF samples due to the higher content of NfL in CSF compared with serum. However, obtaining CSF samples can be challenging and poses a risk of injury or infection to subjects. Previous studies have established a significant positive correlation between levels of NfL in blood and those in CSF.[36] Moreover, Altmann *et al*'s study assessed the stability and efficacy of serum NfL and found that serum NfL concentrations remained stable in untreated blood samples stored at room temperature for up to 7 days.[37] In summary, based on these studies, our findings suggest that serum NfL is a highly suitable marker for assessing grip strength and can reflect the severity of neurological injuries.

Interestingly, a recent study of stroke survivors in the late phase after stroke reached different conclusions. The study reported no association between NfL levels and residual function or deterioration. Instead, elevated NfL levels were associated with improvement in balance (OR 2.34; 95% CI 1.35, 4.27), gait (OR 2.27; 95% CI 1.25, 4.32) and cognitive ability (OR 7.54; 95% CI 1.52, 45.66), indicating that higher levels of plasma NfL in late stroke survivors could be a positive predictor of functional improvement after stroke.[38] As our study had a cross-sectional design, we were unable to predict the relationship between serum NfL and future disease development in a population with sarcopenia, and more studies are still needed to validate the longitudinal link between serum NfL and disease development.

This study also has some limitations to report. First and foremost, although grip strength is recognised as one of the most critical measures of muscle strength, current definitions of muscle strength and muscle mass have been questioned. Our findings can only serve as a basis for inference rather than a direct relationship between serum NfL and muscle strength, muscle mass or sarcopenia-related diseases. Second, due to limitations in our database, we did not investigate the association between serum NfL and muscle mass, focusing instead on muscle strength. Therefore, our findings are limited to one aspect of individuals with sarcopenia or related disorders. Moreover, although we included potential covariates in the fully adjusted model, it remains possible that other unmeasured confounding factors may have been present. In addition, due to the design of cross-sectional studies, we could not obtain a definitive causality conclusion, and future longitudinal studies with large samples are needed to support our findings. Although the NHANES database uses representative data from the US population, it is important to consider the potential impact of selection bias given the limitations in the sample size. Finally, due to the extensive number of interaction analyses performed, which could lead to chance findings, the associations between serum NfL levels and grip strength across different age, physical activity and CKD strata in this study should be interpreted with caution.

CONCLUSIONS

This national population-based study indicated that serum NfL is negatively and linearly correlated with grip strength. Additionally, the interaction suggested that serum NfL levels in those aged 60–75 years, those physically inactive and those with CKD are associated with more significant grip strength reduction. However, further high-quality prospective cohort studies are needed to verify the causal relationship between elevated serum NfL levels and reduced grip strength.

Author affiliations
[1]Department of Urology, Xinjiang Medical University Affiliated First Hospital, Urumqi, Xinjiang, China
[2]Department of Cardiology, Xinjiang Medical University Affiliated First Hospital, Urumqi, Xinjiang, China
[3]State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Contributors DD, KK, AZ, YY and MR conceptualised the study. BQ, WZ and DN contributed to the analysis and interpretation of data. DD and KK wrote the manuscript. AZ, YY and MR revised the manuscript. All authors contributed to the article and approved the submitted version. AZ acted as guarantor.

Funding This research was supported by the Natural Science Foundation of Xinjiang Uygur Autonomous Region (Project No. 2022D01C763); the Foundation of the Open Project Program of the State Key Laboratory of the Construction of the Causation and Prevention of Central Asia's High-incidence Diseases (Project No. SKL-HIDCA-2022-22).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the National Center for Health Statistics Research Ethics Review Board (continuation of Protocol #2011-17). The study was conducted in accordance with the principles of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Publicly available data sets were analysed in this study. These data can be found at https://wwwn.cdc.gov/nchs/nhanes/.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and

responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Diliyaer Dilixiati http://orcid.org/0000-0002-7603-9126
Kaisaierjiang Kadier http://orcid.org/0000-0002-1178-4854

REFERENCES

1 Ethgen O, Beaudart C, Buckinx F, *et al*. The Future Prevalence of Sarcopenia in Europe: A Claim for Public Health Action. *Calcif Tissue Int* 2017;100:229–34.
2 Bohannon RW. Grip Strength: An Indispensable Biomarker For Older Adults. *Clin Interv Aging* 2019;14:1681–91.
3 Roberts HC, Denison HJ, Martin HJ, *et al*. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011;40:423–9.
4 Aamodt WW, Waligorska T, Shen J, *et al*. Neurofilament Light Chain as a Biomarker for Cognitive Decline in Parkinson Disease. *Mov Disord* 2021;36:2945–50.
5 Khalil M, Pirpamer L, Hofer E, *et al*. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. *Nat Commun* 2020;11:812.
6 Yuan A, Rao MV, *et al*. Neurofilaments and Neurofilament Proteins in Health and Disease. *Cold Spring Harb Perspect Biol* 2017;9:a018309.
7 Sleigh JN, Rossor AM, Fellows AD, *et al*. Axonal transport and neurological disease. *Nat Rev Neurol* 2019;15:691–703.
8 Dashti E, Mirazimi F, S. M. A, *et al*. Neurofilament light chain as a biomarker for diagnosis of multiple sclerosis. *EXCLI J* 2021;20:1308–25.
9 Pratt J, De Vito G, Segurado R, *et al*. Plasma neurofilament light levels associate with muscle mass and strength in middle-aged and older adults: findings from GenoFit. *J Cachexia Sarcopenia Muscle* 2022;13:1811–20.
10 Centers for disease control and prevention, national center for health statistics. national health and nutrition examination survey. Available: www.cdc.gov/nchs/nhanes/about_nhanes.html [Accessed 20 Dec 2024].
11 von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *Int J Surg* 2014;12:1495–9.
12 Fitzgerald KC, Sotirchos ES, Smith MD, *et al*. Contributors to Serum NfL Levels in People without Neurologic Disease. *Ann Neurol* 2022;92:688–98.
13 Ciardullo S, Muraca E, Bianconi E, *et al*. Diabetes Mellitus is Associated With Higher Serum Neurofilament Light Chain Levels in the General US Population. *J Clin Endocrinol Metab* 2023;108:361–7.
14 Prokopidis K, Giannos P, Ispoglou T, *et al*. Handgrip strength is associated with learning and verbal fluency in older men without dementia: insights from the NHANES. *Geroscience* 2023;45:1049–58.
15 Stekhoven DJ, Bühlmann P. MissForest—non-parametric missing value imputation for mixed-type data. *Bioinformatics* 2012;28:112–8.
16 Petzold A. Neurofilament phosphoforms: Surrogate markers for axonal injury, degeneration and loss. *J Neurol Sci* 2005;233:183–98.
17 Conforti L, Gilley J, Coleman MP. Wallerian degeneration: an emerging axon death pathway linking injury and disease. *Nat Rev Neurosci* 2014;15:394–409.
18 Roberts HC, Syddall HE, Butchart JW, *et al*. The Association of Grip Strength With Severity and Duration of Parkinson's. *Neurorehabil Neural Repair* 2015;29:889–96.
19 Krenovsky J-P, Bötzel K, Ceballos-Baumann A, *et al*. Interrelation between Sarcopenia and the Number of Motor Neurons in Patients with Parkinsonian Syndromes. *Gerontology* 2020;66:409–15.
20 Saak A, Benkert P, Akgün K, *et al*. Serum Neurofilament Light Chain: A Marker of Nervous System Damage in Myopathies. *Front Neurosci* 2021;15:791670.
21 Kim R, Jeon B. Serum neurofilament light chain predicts future freezing of gait in Parkinson's disease. *Parkinsonism & Related Disorders* 2021;91:102–4.
22 Tiedt S, Duering M, Barro C, *et al*. Serum neurofilament light. *Neurology (ECronicon)* 2018;91.
23 Mollenhauer B, Dakna M, Kruse N, *et al*. Validation of Serum Neurofilament Light Chain as a Biomarker of Parkinson's Disease Progression. *Mov Disord* 2020;35:1999–2008.
24 Verde F, Milone I, Bulgarelli I, *et al*. Serum neurofilament light chain levels in Covid-19 patients without major neurological manifestations. *J Neurol* 2022;269:5691–701.
25 Duchowny KA, Ackley SF, Brenowitz WD, *et al*. Associations Between Handgrip Strength and Dementia Risk, Cognition, and Neuroimaging Outcomes in the UK Biobank Cohort Study. *JAMA Netw Open* 2022;5:e2218314.
26 Wu D, Gao X, Shi Y, *et al*. Association between Handgrip Strength and the Systemic Immune-Inflammation Index: A Nationwide Study, NHANES 2011-2014. *Int J Environ Res Public Health* 2022;19:13616.
27 Disanto G, Barro C, Benkert P, *et al*. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. *Ann Neurol* 2017;81:857–70.
28 Idland A-V, Sala-Llonch R, Borza T, *et al*. CSF neurofilament light levels predict hippocampal atrophy in cognitively healthy older adults. *Neurobiol Aging* 2017;49:138–44.
29 Srpova B, Uher T, Hrnciarova T, *et al*. Serum neurofilament light chain reflects inflammation-driven neurodegeneration and predicts delayed brain volume loss in early stage of multiple sclerosis. *Mult Scler* 2021;27:52–60.
30 Hsu Y-H, Liang C-K, Chou M-Y, *et al*. Sarcopenia is independently associated with parietal atrophy in older adults. *Exp Gerontol* 2021;151:111402.
31 Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. *Curr Opin Clin Nutr Metab Care* 2012;15:12–22.
32 Rahmig J, Akgün K, Simon E, *et al*. Serum neurofilament light chain levels are associated with stroke severity and functional outcome in patients undergoing endovascular therapy for large vessel occlusion. *J Neurol Sci* 2021;429:118063.
33 Koini M, Pirpamer L, Hofer E, *et al*. Factors influencing serum neurofilament light chain levels in normal aging. *Aging (Albany NY)* 2021;13:25729–38.
34 Akamine S, Marutani N, Kanayama D, *et al*. Renal function is associated with blood neurofilament light chain level in older adults. *Sci Rep* 2020;10:20350.
35 Ladang A, Kovacs S, Lengelé L, *et al*. Neurofilament light chain concentration in an aging population. *Aging Clin Exp Res* 2022;34:331–9.
36 Teunissen CE, Khalil M. Neurofilaments as biomarkers in multiple sclerosis. *Mult Scler* 2012;18:552–6.
37 Altmann P, Ponleitner M, Rommer PS, *et al*. Seven day pre-analytical stability of serum and plasma neurofilament light chain. *Sci Rep* 2021;11:11034.
38 Stokowska A, Bunketorp Käll L, Blomstrand C, *et al*. Plasma neurofilament light chain levels predict improvement in late phase after stroke. *Euro J of Neurology* 2021;28:2218–28.