Zhou et al. BMC Geriatrics (2025) 25:107
https://doi.org/10.1186/s12877-024-05580-3

RESEARCH

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Associations of dynapenic abdominal obesity and its components with cognitive impairment among hemodialysis patients

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Abstract

Objective Cognitive impairment (CI) is a prevalent and significant health concern among patients undergoing maintenance hemodialysis (MHD). Recent studies have highlighted the growing interest in dynapenic abdominal obesity (DAO), which combines both low muscle strength and excess abdominal fat. Despite the increasing recognition of DAO, its association with CI in MHD patients remains uncertain. The objective of this study was to investigate the relationship between DAO and CI in MHD patients.

Methods We conducted a multicenter, cross-sectional study in twenty dialysis centers, encompassing 3767 adult MHD patients. Participants were categorized into four distinct groups based on the criteria for abdominal obesity (AO), defined as waist circumference (WC) ≥ 90 cm for men and ≥ 85 cm for women, and dynapenia, characterized by handgrip strength (HGS) < 28 kg in men and < 18 kg in women. The groups were: non-dynapenic/non-abdominal obesity (NDNAO), non-dynapenic/abdominal obesity (NDAO), dynapenic/non-abdominal obesity (DNAO), and dynapenic/abdominal obesity (DAO). Cognitive function was assessed using the Mini-Mental State Examination (MMSE), with a score below 27 indicating cognitive impairment (CI). Multivariate logistic models were used to investigate the correlations between DAO and its components with the risk of CI. Smooth curve fittings were used to identify the potential nonlinear relationship between WC and the MMSE scores. The piecewise regression model was used for fitting while the log-likelihood ratio test was used to determine whether a significant inflection point existed. Additionally, we conducted a series of subgroup analyses to test the robustness of our results.

Results The multi-variable adjusted odds ratios (ORs) of CI for DNAO and DAO were 2.10 (1.68–2.62, *P* < 0.001) and 1.81 (1.40–2.33, *P* < 0.001), respectively. These findings were consistently observed across subgroup analyses, indicating robustness in our results. AO was associated with increased risk of CI in the crude model (OR 1.22, 95%CI 1.05–1.41; *P* = 0.008), however, it became a protective factor after adjusting for potential confounders (OR 0.84, 95%CI 0.71–0.98; *P* = 0.03). We identified a significant nonlinear relationship between WC, HGS, and MMSE scores (P for non-linearity < 0.05). Notably, an inflection point at 23.29 kg for HGS was determined through threshold effect analysis.

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Below a WC threshold of 101 cm, MMSE scores demonstrated a positive correlation with WC (β = 0.03, 95% CI 0.01–0.04, $P < 0.001$). However, this relationship did not achieve statistical significance for WC values above 101 cm.

Conclusions Both DAO and DNAO are associated with increased odds of CI in MHD patients, with dynapenia being the major factor contributing to the increased odds of CI, while AO appears to play a protective role against CI.

Keywords Dynapenic / abdominal obesity, Maintenance hemodialysis, Cognitive impairment, Abdominal obesity, Obesity paradox, Grip strength

Introduction

Cognitive impairment (CI), including dementia, has become a common and critical health issue in patients with end-stage kidney disease (ESKD), especially in those requiring maintenance hemodialysis (MHD) treatments. The reported prevalence of CI in MHD patients varied between 40 and 70%, which is more than three times higher than that of the age-matched general population [1–3]. Furthermore, as society ages, the prevalence of CI is increasing rapidly. CI not only imposes a significant physical, psychological, and economic burden on patients, families, and society but also results in a heightened risk of premature death among MHD patients [4]. Early diagnosis and effective treatment of CI is relatively limited currently and CI is regarded as a preventable condition with numerous modifiable risk factors. Thus, screening modifiable risk factors of CI and taking targeted interventions early is of great importance to delay its onset and progression.

MHD patients are particularly susceptible to dynapenia, characterized by reduced muscle strength, due to factors such as Protein-Energy Wasting (PEW) and the accelerated breakdown of muscle proteins induced by uremic toxins [5]. Our previous research indicated that individuals in the lowest quartile of handgrip strength (HGS) were 2.82 times more likely to have CI compared to those in the highest quartile [6].

With the improvement of living standards, the incidence of obesity and overweight has been increasing annually in both the general population and among hemodialysis patients [7]. According to a recent study, 56.4% of MHD patients exhibit abdominal obesity (AO) [8]. Dynapenic abdominal obesity (DAO), which is defined as the co-occurrence of AO and dynapenia, has obtained increasing attention in recent years. DAO has been associated with several adverse health outcomes, including an increased risk of falls, worsening disability, and cardiovascular mortality [9, 10]. Despite numerous prior studies suggesting a correlation between a greater waist circumference (WC) and an increased susceptibility to CI, the findings are inconsistent, particularly among the elderly and individuals with chronic diseases who are more likely to be influenced by the "the obesity paradox" [11–14].

The association between the concurrent presence of AO and dynapenia, namely DAO, and the risk of CI in MHD patients remains uncertain. Therefore, the aim of this study was to investigate the associations between DAO and its components with the risk of CI among MHD patients.

Methods

Study design and participants

We conducted a multicenter, cross-sectional study in twenty dialysis centers in Guizhou Province, China between June 2019 and September 2020. Patients who have been on regular hemodialysis trice per week for a minimum of three months, 18 years or older were eligible. Participants were excluded from the study if they fulfilled the following criteria: (1) visual or hearing difficulties; (2) language barriers; (3) mental disability; (4) any physical deformity; (5) receiving nutritional support therapy; (6) having an excessive volume load, such as those with ongoing heart failure. Ethical approval for this study was obtained from the Medical Ethics Committee of Guizhou Provincial People's Hospital (approval number: [2020] 208). All study subjects had provided written consent.

Covariates

A standardized questionnaire was administered by well-trained interviewers to collect participants' information. Demographic variables, such as age, sex, education level (low: < 12th grade; high: ≥ 12th grade) and histories of hypertension, diabetes, stroke, duration of hemodialysis, details of the participant's lifestyle such as history of smoking, alcohol use were collected through the questionnaire. Anthropometric measurements, including body weight, height, HGS, WC, and laboratory measurements, including hemoglobin (Hb) (g/L), serum creatinine (Scr)(μmol/L), serum albumin (ALB), uric acid (SUA)(mmol/L), C-reactive protein (CRP) (mmol/L) were collected. For laboratory measurements, blood samples were collected after fasting for 8–10 h before the initiation of hemodialysis at least once every 3 months for routine blood tests. The nearest laboratory parameters were collected from the medical records. Participants without blood tests performed within the last 3 months were excluded from the final analysis.

Anthropometric and body composition measurement
Anthropometric measurements were performed before the initiation of the usual dialysis schedule by well-trained dialysis nurses. An electronic weighing scale was used to evaluate body weight with participants barefooted and wearing light clothing. A stadiometer was used to assess the standing height of the participants. The body mass index (BMI) was determined by dividing the weight (in kilograms) by the square of the height (in meters). The HGS on non-fistula hands was measured twice with a handheld dynamometer (CAMRY EH101, Zhongshan, China) before a dialysis session and the maximum measurements were recorded. For participants with an indwelling dialysis catheter, a single trial for each hand was tested and the maximal score was used in the final analysis. WC was measured at the umbilical level with an unstretched tape meter with the participants wearing light clothing and measurements were recorded to the nearest 0.1 cm. A portable whole-body bioimpedance spectroscopy device, the body composition monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) was used to evaluate lean tissue index(LTI), and fat tissue index (FTI) before the HD session according to the manufacturer's instructions.

Assessment of cognitive impairment
The Chinese version of the Mini-Mental State Examination (MMSE) questionnaire was used to assess cognitive function by professional physicians and trained nurses. The MMSE test is a widely used screening test for the assessment of cognitive function. The total MMSE score varies from 0 to 30, with lower scores indicating poorer cognitive ability. Individuals with an MMSE score of less than 27 were considered to have CI [15].

Definition of dynapenic abdominal obesity
The simultaneous presence of AO and dynapenia was defined as DAO, as elucidated earlier. AO was defined as WC > = 90 cm in men and WC > = 85 cm in women, according to the criteria proposed for Chinese by the Chinese Diabetes Society [16]. Low muscle strength was defined as handgrip strength (HGS) < 28 kg for men and < 18 kg for women, according to the Asian Working Group for Sarcopenia (AWGS) [17]. The participants were divided into four groups based on the presence or absence of AO and dynapenia: NDNAO, NDAO, DNAO, and DAO.

Statistical analyses
The participants' characteristics were displayed as the average with standard deviations and the median (interquartile range, IQR), correspondingly, for continuous variables that were normally or non-normally distributed. For categorical variables, data were presented as numbers and proportions and analyzed with chi-square with Bonferroni correction for multiple testing. Significances between multiple groups were determined by one-way ANOVA followed by LSD or nonparametric test followed by the Kruskal-Wallis H test. Univariate and multivariate binary logistic regression analyses were conducted to evaluate the association between DAO and CI by calculating odds ratios (ORs) with 95% confidence intervals (CIs). The NDNAO group was regarded as the reference group. Variables with a P-value below 0.05 in the univariate analyses were identified as covariates for adjustment in the multivariate logistic regression analysis. Despite not meeting the statistical significance criteria in the univariate analysis, history of diabetes, smoking status, and BMI are recognized risk factors for CI in MHD patients and were consequently incorporated into the adjusted models [18]. To further examine the independent association between each DAO component (low HGS and AO) and CI, a mutually adjusted model was created by including the other DAO components as continuous variables as well as the covariates in Model 3, respectively. The smooth curve fittings were employed to ascertain the possible nonlinear correlation between WC and MMSE scores. If a non-linear relationship was observed, the piecewise regression model was used for fitting, and the log-likelihood ratio test was used to determine whether a significant inflection point existed. To test the robustness of the association between the DAO and CI, subgroup analyses based on different genders, age groups (< 45, >=45 and < 65, >=65 years), educational attainment (junior high school (low), high school or above (high), BMI levels (< 18.5, >=18.5 and < 24, and > = 24) and a history of diabetes (Yes vs. NO) and stroke (Yes vs. NO) were performed. The likelihood ratio test was conducted to evaluate the interaction among subgroups. All analyses were performed using SPSS version 23.0 and R software version 4.2.0. A two-tailed P value < 0.05 was considered to have statistical significance.

Results
Baseline characteristics
A total of 3767 HD patients were included in the final analysis. The detailed process of patient selection is shown in Fig. 1. Of the 3767 eligible participants, 60.7% (2287) were male and the mean age was 54.4 ± 15.2 years old. A comparison of the clinical characteristics between the four groups is shown in Table 1. Participants in the DAO group were older, more likely to have a history of diabetes and stroke, and had higher levels of FTI, compared to those in other groups.

Associations between the DAO category and CI
The ORs and 95% CIs of CI in different DAO category groups are shown in Table 2. As shown in crude model

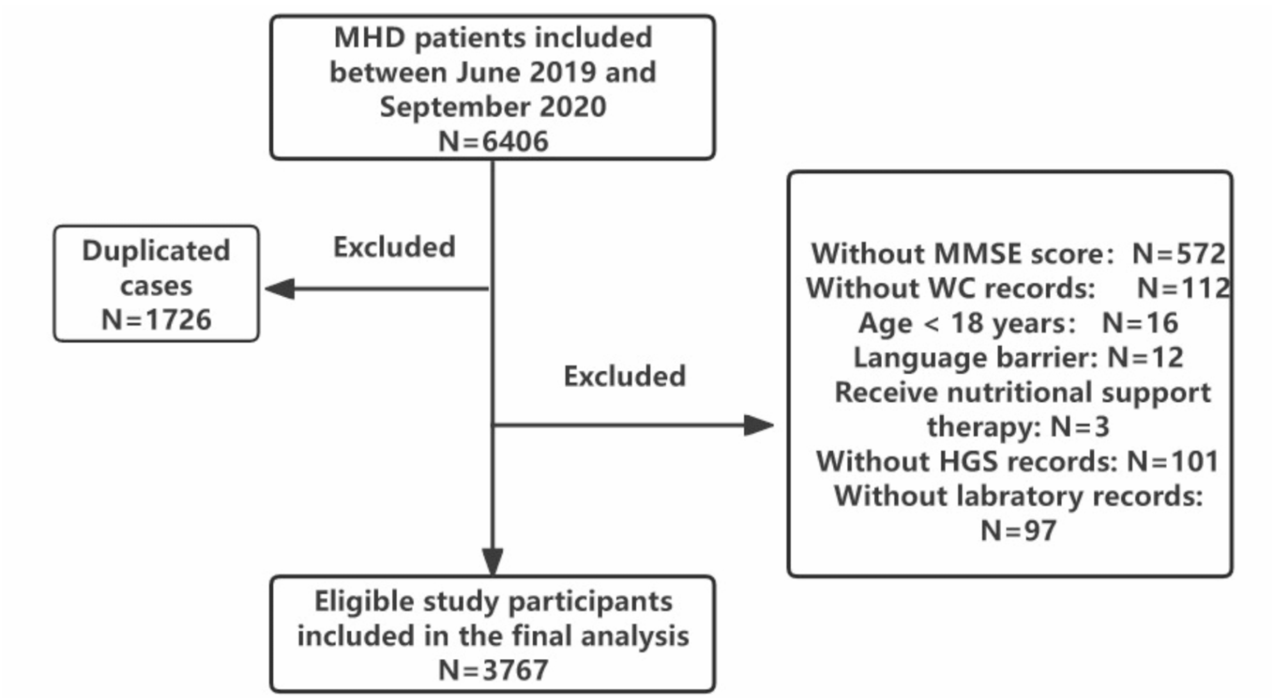

Fig. 1 Flow chart of the recruitment of subjects

1, the DNAO and DAO groups were significantly associated with CI (OR = 3.07, 95% CI 2.50–3.75 and OR = 3.47, 95% CI 2.77–4.33, respectively). Multi-adjusted models revealed a greater correlation between DNAO and CI, in contrast to the DAO group. The adjusted odds ratio (95% CI) for DNAO and DAO were 2.10 (1.68–2.62, $P < 0.001$) and 1.81 (1.40–2.33, $P < 0.001$), respectively, after adjusting for age, sex, education level, current smoking status, current alcohol consumption, dialysis vintage, history of hypertension, history of stroke, and history of diabetes. The association persisted even after adjusting for BMI, Hb, and CRP (Model 4). The NDAO group did not show any significant correlation with CI in either crude or multi-variable adjusted models.

Associations between dynapenia, abdominal obesity, and CI

As shown in Table 3, dynapenia was independently associated with CI even after adjusting for age, sex, educational status, dialysis vintage, smoking status, drinking status, and history of hypertension, diabetes, and stroke, the OR of CI was 2.12 (95% CI 1.76–2.54, $P < 0.001$). The association persisted even after further adjustment for WC in the mutually model. AO was associated with CI in the crude model (OR 1.22, 95%CI 1.05–1.41; $P = 0.008$), however, it became a protective factor after adjusting for age, sex, educational status (OR 0.84, 95%CI 0.71–0.98; $P = 0.03$) and other confounders (model 3). The protective effect of AO against CI disappeared after further adjustment for HGS in the mutually model.

Relationship between WC, HGS, and MMSE scores

Figures 2 and 3 depicted a nonlinear relationship between WC, HGS, and MMSE scores (P for non-linearity < 0.05), after adjusting for age, sex, educational levels, and dialysis vintage. Notably, a threshold effect analysis identified an inflection point at 23.29 Kg for HGS. Prior to this inflection point, a significant positive correlation was observed between HGS and MMSE scores, with a regression coefficient (β) of 0.115 (95% confidence interval [CI] 0.079–0.151). Beyond the inflection point, the association was not statistically significant, with a β (95% CI) of 0.67 (0.12, 3.85). The MMSE scores appeared to increase with WC up to a threshold of approximately 100 cm. Further analysis using threshold effect analysis confirmed the presence of a significant inflection point in the smoothed curve between WC and MMSE scores. Specifically, MMSE scores increased with WC below 101 cm, with a β of 0.025 (95% CI 0.011, 0.039, $P < 0.001$) as detailed in Table 4. In contrast, the relationship between WC and MMSE scores was not statistically significant for WC values exceeding 101 cm.

Subgroup analyses of the association between the DAO category and CI

To further assess the robustness of the relationship between the DAO category and CI across various

Table 1 Clinical characteristics of the participants

Variables	Total (*n* = 3767)	NDNAO (*n* = 943)	NDAO (*n* = 385)	DNAO (*n* = 1599)	DAO (*n* = 840)	*P* value
Male sex (*n*, %)	2287(60.7)	581(61.6)[b, d]	225(58.4)	1027(64.2)[d]	454(54)[a, c,]	< 0.001
Age (year)	53.7 ± 15.3	43.0 ± 12.6[b, c,d]	53.5 ± 12.2[a, d]	55.5 ± 15.1[a, d]	62.6 ± 12.3[a, b,c]	< 0.001
Educational status (≥ high school) (%)	1008 (26.8)	287 (30.4)[c, d]	132 (34.3)[c, d]	381 (23.8)[a, b]	208 (24.8)[a, b]	< 0.001
Currently smoking (*n*, %)	828 (22.0)	241 (25.6)[d]	96 (24.9)[d]	346 (21.6)	145 (17.3)[a]	< 0.001
Currently drinking (*n*, %)	190 (5.0)	53 (5.6)	26 (6.8)	78 (4.9)	33 (3.9)	< 0.001
History Of hypertension (*n*, %)	2789 (74.0)	703 (74.5)	283 (73.5)	1178 (73.7)	625 (74.4)	0.95
History of diabetes (n*n*,%)	1005 (26.7)	98 (10.4)[b, c,d]	126 (32.7)[a, c,d]	410 (25.6)[a, b,d]	371 (44.2)[a, b,c]	< 0.001
History of stroke (*n*,%)	287(7.6)	33(3.5)[c, d]	25(6.5)[d]	130(8.1)[a, d]	99(11.8)[a, b,c]	< 0.001
Hand grip strength (kg)	21.0 ± 8.9	29.4 ± 7.3[c, d]	29.4 ± 7.3[c, d]	16.6 ± 5.9[a, b]	16.1 ± 5.9[a, b]	< 0.001
Waist circumference (cm)	83.1 ± 11.1	76.3 ± 6.7[b, c,d]	95.8 ± 6.7[a, c]	77.5 ± 6.8[a, b,d]	95.5 ± 7.2[a, c]	< 0.001
Dialysis vintage (months)	47.0 ± 39.0	47.8 ± 37.5	48.8 ± 43.3	46.3 ± 39.5	46.5 ± 37.5	0.613
Cognitive impairment (*n*,%)	1138 (30.2)	149 (15.8)[c, d]	74 (19.2)[c, d]	584 (36.5)[a, b]	331 (39.4)[a, b]	< 0.001
Serum creatinine (μmol/L)	954.2 ± 1869.6	1105.6 ± 2435.4[c, d]	992.3 ± 320.4	910.8 ± 2153.7[a]	847.7 ± 307.2[a]	0.031
Serum uric acid (μmol/L)	432.0 ± 191.6	442.9 ± 125.4[b, c]	472.5 ± 343.6[a, c,d]	413.9 ± 133.2[a, b,d]	434.7 ± 237.5[b, c]	< 0.001
BMI	22.7 ± 3.6	21.3 ± 2.3[a, b,c]	26.4 ± 3.1[a, c,d]	20.9 ± 2.5[a, b,d]	25.8 ± 3.2[a, b,c]	< 0.001
Hemoglobin, g/L	108.4 ± 20.6	109.6 ± 20.7	109.4 ± 17.8	107.7 ± 22.0	107.8 ± 18.8	0.075
Serum albumin, g/L	40.4 ± 8.8	41.7 ± 15.4[c, d]	40.7 ± 4.2[c]	39.7 ± 5.2[a, b]	40.0 ± 4.1[a]	< 0.001
LTI, kg/m^2	15.2 ± 4.4	16.3 ± 4.4[c, d]	16.2 ± 3.2[c]	14.7 ± 4.1[a, b]	14.6 ± 4.8[a, b]	< 0.001
FTI, kg/m^2	8.0 ± 6.0	6.1 ± 6.1[b, d]	10.6 ± 5.4[a, c,d]	6.5 ± 5.3[b, d]	11.5 ± 5.6[a, b,c]	< 0.001
MMSE score	29.0 (26.0, 30.0)	30.0 (28.0, 30.0) [c, d]	29.0 (27.0, 30.0) [c, d]	28.0 (25.0, 30.0)[a, b]	28.0 (24.0, 30.0)[a, b]	< 0.001
CRP(mmol/L)	2.4(1.1,6.4)	1.8(0.7,3.4)[b, c,d]	3.4(1.6,7.3)[a, c]	2.4(1.0,6.9)[a, d]	4.1(1.8,10.1)[a, c]	< 0.001

Note: *P* values refer to comparisons among all four groups. The alphabetic footnotes a, b, c, and d represent the NDNAO, NDAO, DNAO, and DAO group, respectively, and the group with a letter represents that there was statistically significant difference between the groups

Abbreviations: NDNAO, non-abdominal obesity; NDAO, non-dynapenic abdominal obesity (NDAO); DNAO, dynapenic non-abdominal obesity; DAO, dynapenic abdominal obesity; BMI, body mass index; LTI, lean tissue index; FTI, fat tissue index;

a There is statistical difference compared with NDNAO group

b There is statistical difference compared with NDAO group

c There is statistical difference compared with DNAO group

d There is statistical difference compared with DAO group

Table 2 ORs for cognitive impairment according to the presence of Sarcopenia and obesity

Groups	Model 1	*P*	Model 2	*P*	Model 3	*P*	Model 4	*P*
Non-dynapenic non-abdominal obesity (NDNAO)	Reference		Reference		Reference		Reference	
Non-dynapenic/abdominal obesity (NDAO)	1.27 (0.93,1.73)	0.131	0.89 (0.64,1.23)	0.484	0.89 (0.65,1.24)	0.503	0.85 (0.50,1.43)	0.534
Dynapenic/non-abdominal obesity (DNAO)	3.07 (2.50,3.75)	< 0.001	2.02 (1.62,2.51)	< 0.001	2.10 (1.68,2.62)	< 0.001	2.27 (1.66,3.10)	< 0.001
Dynapenic/abdominal obesity (DAO)	3.47 (2.77,4.33)	< 0.001	1.72 (1.34,2.21)	< 0.001	1.81 (1.40,2.33)	< 0.001	2.05 (1.35,3.10)	0.001
Trend test	1.57 (1.46,1.68)	< 0.001	1.26 (1.17,1.37)	< 0.001	1.29 (1.19,1.40)	< 0.001	1.41 (1.25,1.59)	< 0.001

Model 1, crude model

Model 2, adjusted for age, sex, education, dialysis vintage

Model 3, adjusted for above + currently smoking + currently drinking + history of hypertension, diabetes and stroke

Model 4, adjusted for above + Hb + BMI + CRP

demographic and clinical subgroups, we conducted stratified analyses based on educational level, body mass index (BMI), age, sex, history of diabetes, and stroke. As shown in Fig. 4, the association between the DAO category and CI remained consistent across all examined subgroups (P for interaction > 0.05 for all), after adjusting for the same covariates as in Model 2 of Table 2. Notably, individuals in the dynapenic non-abdominal obesity (DNAO) group exhibited higher odds of CI compared to those in the DAO group in the majority of subgroup analyses, with the exception of participants without a history of diabetes.

Discussion

The primary discovery of this present study indicates that both DAO and DNAO are independently associated with an increased risk of CI among MHD patients. Dynapenia is the predominant factor contributing to the heightened risk of CI, while AO paradoxically exhibits a

Table 3 Association between low handgrip strength (dynapenia) or high waist circumference (abdominal obesity) and cognitive impairment

Models	Dynapenia		Abdominal obesity	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Model 1	2.98(2.52–3.51)	< 0.001	1.22(1.05–1.41)	0.008
Model 2	2.01(1.68–2.40)	< 0.001	0.84(0.71–0.98)	0.030
Model 3	2.12(1.76–2.54)	< 0.001	0.84(0.71–0.99)	0.035
Mutual model	2.07(1.72–2.47)	< 0.001	0.79(0.61–1.03)	0.09

Model 1, crude model

Model 2, adjusted for age, sex, education

Model 3, further adjusted for dialysis vintage, currently smoking, currently drinking, history of hypertension, diabetes and stroke

Mutual model, adjusted for above + waist circumference / hand grip strength

protective effect against CI after adjusting for potential confounders.

In concordance with previous research [19], our results suggest that lower HGS, a condition known as dynapenia, is associated with a higher risk of CI in MHD patients. The curve fitting and threshold analyses revealed that MMSE scores increased significantly with increasing HGS up to a threshold of 23.29 kg. Beyond this threshold, the relationship was no longer significant, implying a possible threshold effect. Although the exact mechanisms underlying the link between dynapenia and CI are not fully understood, several speculative mechanisms may have explanatory value. Firstly, individuals with dynapenia are more likely to suffer from poor nutritional status [20], as evidenced by our findings of significantly lower levels of Scr, SUA, LTI, ALB, and Hb levels in these patients compared to those without dynapenia. This inadequate nutrition can lead to deficiencies in vitamins and minerals, adversely impacting cognitive function [21–23]. Additionally, inflammation, a known contributor to both CI [24] and dynapenia [20], may play a role. CRP levels are markedly elevated in patients with dynapenia than in those with normal HGS in our study. This elevated inflammation could precipitate subsequent disruptions in cognitive function, potentially through neuroinflammatory pathways that impair neuronal integrity and synaptic plasticit.

An important and novel finding of this study is the paradoxical association between AO and lower odds of CI after adjusting for potential confounders. To our knowledge, this is the first report to suggest a protective effect of AO on CI in MHD patients. While several studies have demonstrated an association between central obesity and increased risk of CI [25, 26], our findings, along with others [13, 27, 28], suggest a more complex relationship. For instance, a study in community-dwelling older Japanese women showed that greater abdominal visceral fat accumulation was associated with a lower risk of CI [27]. Similarly, a retrospective cohort study in China found that older adults with higher BMI and WC experienced slower cognitive decline [13]. An autopsy study revealed that older adults with greater direct measurements of abdominal visceral fat exhibited reduced odds of CI [29]. Though many studies have linked visceral obesity to an increased risk of CI [30], their utilization of indirect measurements to quantify abdominal visceral fat lacks the same level of credibility as directly measuring the visceral fat surrounding different abdominal organs through autopsy.

The conflicting results regarding the relationship between obesity and CI could also be attributed to a nonlinear association between central obesity and cognitive function. Our study detected a nonlinear correlation between WC and MMSE scores (P for nonlinearity < 0.05) after controlling for age, sex, education, dialysis vintage, and medical histories of diabetes, hypertension, and stroke. However, we did not identify a statistically significant inflection point through threshold effect analysis, possibly due to the limited number of participants with larger WC measurements. A previous cohort study among older Australian men also described a "J" shaped relationship between obesity measures and dementia risk, with overweight men and those with a waist-to-hip ratio (WHR) ≥ 0.9 exhibiting a lower risk compared to their normal-weight and WHR < 0.9 counterparts [31]. It is well known that WHR is also a good indicator of AO. Future studies with larger cohorts and a broader range of WC measurements are warranted to confirm the nonlinear relationship between WC and CI in MHD patients.

Furthermore, the "obesity paradox" is a phenomenon that must be considered, particularly in the elderly and those undergoing MHD therapy [32, 33]. While obesity is generally associated with numerous adverse outcomes, MHD patients may derive benefits from a higher BMI and increased body fat. Kakiya et al. [34] reported that increased fat mass index was associated with decreased all-cause and non-cardiovascular mortality in MHD patients. We hypothesize that the "obesity paradox" may extend to CI in MHD patients as well. In our study, despite similar levels of lean tissue index (LTI), participants in the DNAO group had the lowest BMI, and their fat tissue index (FTI) was significantly lower than that of the DNO group. A previous study on MHD patients suggested that normal-weight patients with abdominal obesity exhibited a more proatherogenic profile and lower physical ability than overweight and obese patients with abdominal obesity [35], which is strongly correlated with CI. Additionally, low fat mass, a characteristic of PEW, is a valuable indicator of malnutrition in MHD individuals and is associated with an increased risk of CI [36, 37]. Obesity may also provide better short-term hemodynamic stability by preventing intra-dialytic hypotension, which is linked to decreased white matter, hippocampus volume, and cognitive function [38, 39]. Moreover,

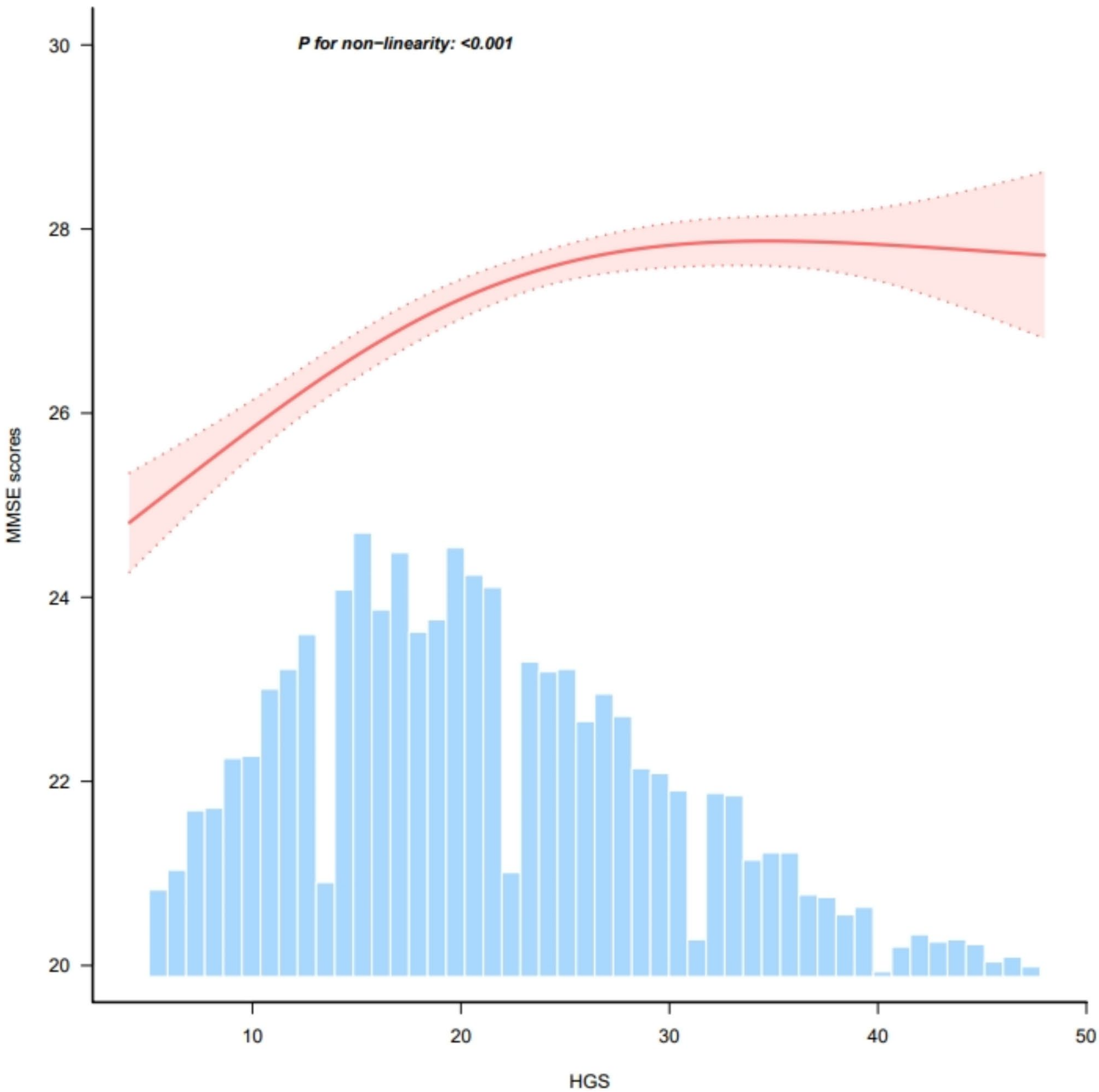

Fig. 2 Relationships between HGS and the MMSE scores

adipose tissue can secrete leptin, a hormone that protects against CI [40]. These mechanisms may partially explain the paradoxical relationship between WC and CI, as well as the higher risk of CI in the DNAO group compared to the DAO group.

Given the evidence presented, it becomes clear that although both DAO and DNAO are linked to an elevated risk of CI in MHD patients, the risk is comparatively lower in the DAO group. In mutually adjusted models, dynapenia remained significantly associated with a higher risk of CI even after adjusting for WC, while the protective effect of AO disappeared upon further adjustment for HGS, suggesting that dynapenia is the primary factor driving the increased risk of CI.

Several limitations in our study should be considered. Firstly, the cross-sectional nature of our study prevented us from making causal inferences. Secondly, though many potential confounding variables have been assessed in our study, potential unmeasured confounding variables such as depression status and physical activity may have existed and biased our study findings. Thirdly, though we found a non-linear association between WC

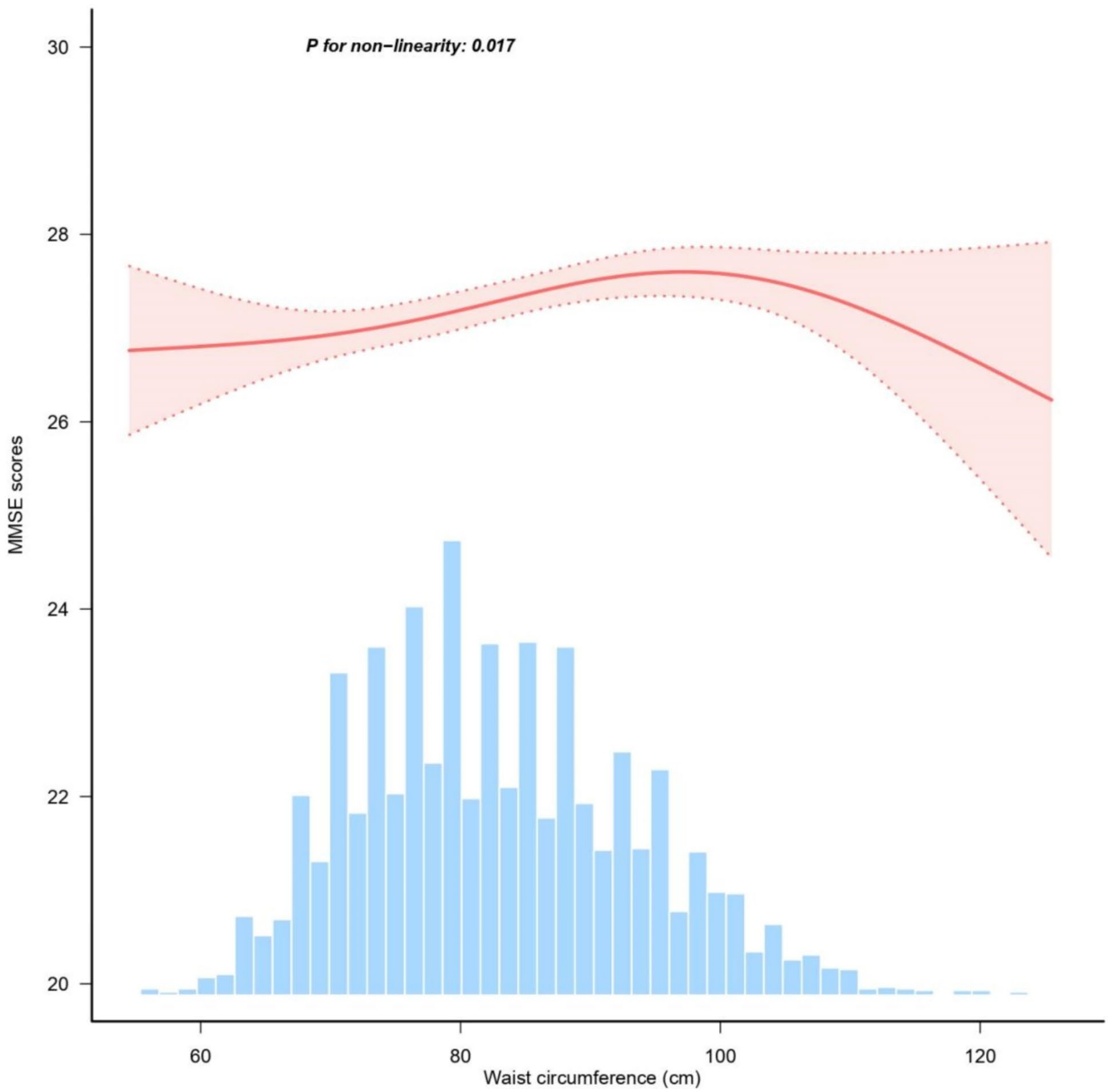

Fig. 3 Relationships between WC and the MMSE scores

Table 4 Analysis of the threshold effects of waist circumference, hand grip strength, and MMSE scores

Outcome variable	MUS (waist circumference, cm)		MUS (handgrip strength, kg)	
	β (95%CI)	*p*-value	β(95%CI)	*p*-value
Model 1: Linear regression	0.055(0.008–0.030)	0.001	0.115(0.079–0.151)	< 0.001
Model 2: Piecewise linear regression				
Inflection point K	101		23.29	
< K	0.025(0.011–0.039)	< 0.001	0.115 (0.079–0.151)	< 0.001
≥K	0.006(-0.099–0.111)	0.912	0.016 (-0.009–0.04)	0.205
Log likelihood ratio tests		0.896		< 0.001

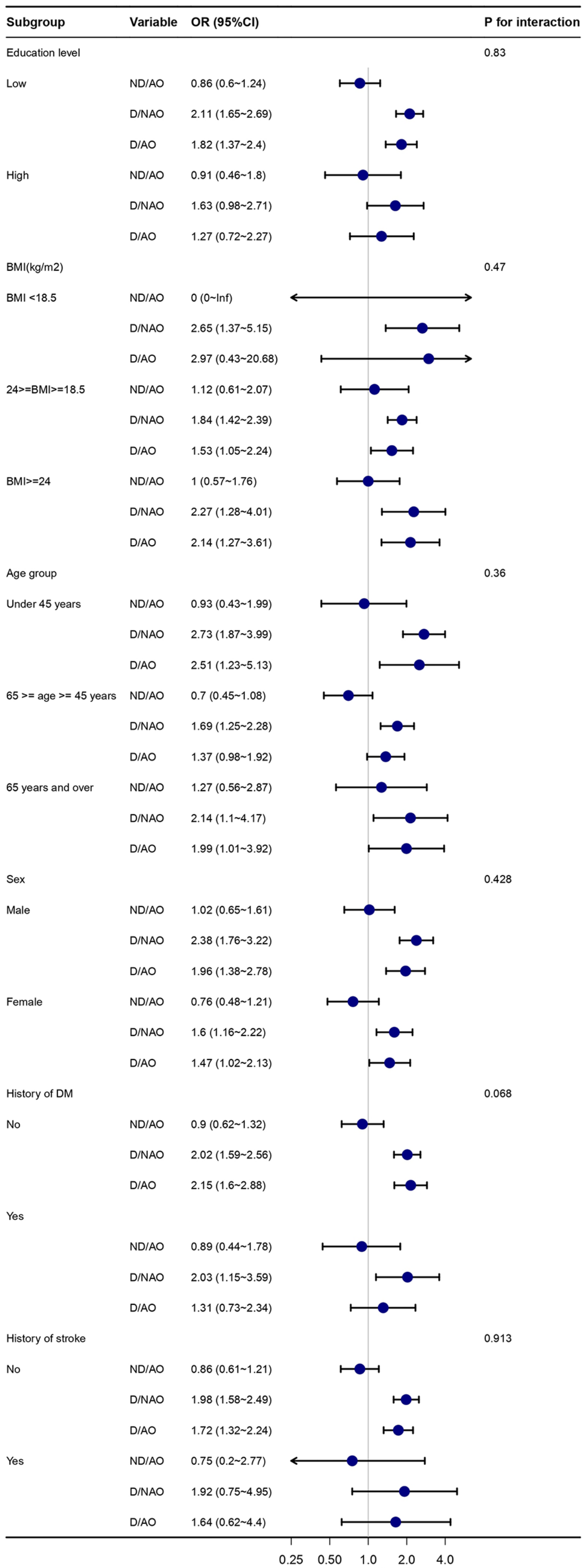

Fig. 4 Subgroup analysis

and MMSE score, we failed to find an inflection point in the threshold effect analyses. Further studies that include larger samples with a larger WC in MHD patients are needed. Fourthly, this research was focused on Chinese MHD patients, so our findings cannot be generalized to individuals from other racial or ethnic backgrounds. Fifthly, anthropometric and body composition measurements were taken before the HD session and this might have influenced data related to anthropometry and bioelectrical impedance analysis (BIA).

In conclusion, both DAO and DNAO are associated with increased odds of CI in MHD patients, with dynapenia being the major factor contributing to the increased odds of CI, while AO appears to play a protective role against CI. Interventions aimed at increasing HGS and maintaining a moderately larger WC may help reduce cognitive dysfunction in MHD patients. Further research is needed to provide recommendations for the appropriate range of WC management for CI prevention in MHD patients.

Acknowledgements
We thank all HD centers and all the patients included in the study.

Author contributions
Y Z is responsible for the general idea design and guidance of the article. CMZ, JP wrote the main manuscript text . QZP, LZ and JY are responsible for the screening and enrollment of subjects and the acquisition of the data.All authors reviewed the manuscript.

Funding
The work was supported by the National Natural Science Foundation of China (82360148), Guizhou Science & Technology Department (QKHPTRC2018-5636-2; QKHCG2023-ZD010).

Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at GuiZhou provincial people's hospital, China.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Review Committee of Guizhou Provincial People's Hospital and performed in compliance with the Declaration of Helsinki. The approval number of the Institutional Review Board was "(Scientific Research) (2019) No.29". All patients signed informed consent forms before participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors have no conflicts of interest to declare.

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Received: 22 February 2024 / Accepted: 22 November 2024
Published online: 17 February 2025

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