

Vascular Risk Factors Decrease the Risk of Cognitive Impairment in Amyotrophic Lateral Sclerosis: A Case-Control Study

Tianmi Yang

Sichuan University West China Hospital

Qianqian Wei

Sichuan University West China Hospital

Chunyu Li

Sichuan University West China Hospital

Bei Cao

Sichuan University West China Hospital

Ruwei Ou

Sichuan University West China Hospital

Yanbing Hou

Sichuan University West China Hospital

Lingyu Zhang

Sichuan University West China Hospital

Yongping Chen

Sichuan University West China Hospital

huifang Shang (✉ hfshang2002@126.com)

Sichuan University West China Hospital <https://orcid.org/0000-0003-0947-1151>

Research Article

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Abstract

Background

The disease-modifying effects of diabetes mellitus (DM), hyperlipidemia, and overweight on risk and prognosis of amyotrophic lateral sclerosis (ALS) have gained significant attention in recent years. However, whether these well-known vascular risk factors increase the cognitive burden in patients with ALS remains unclear. We aim to evaluate the association between vascular risk factors (including hypertension, DM, hyperlipidemia, overweight and smoking) and cognitive function in patients with ALS.

Methods

Patients with ALS were consecutively recruited between June 2012 and November 2019 from a tertiary referral center for ALS at the West China Hospital. Vascular risk factors were confirmed based on clinical data, while cognitive function was evaluated by the Chinese version of the Addenbrooke's Cognitive Examination-revised. Case-control design to investigate the association between vascular risk factors and cognitive impairment in ALS. With careful confounder adjustment, multivariable logistic regression analysis was performed separately (for each factor) and accumulatively (based on the sum of factors) to determine the association between cognitive impairment and vascular risk factors in ALS.

Results

Of 870 patients, 561 (64.5%) were men, the mean age at registration was 54.1 (11.3) years and 266 had cognitive impairment. No cognitive burden from vascular risk factors was found in patients with ALS. On the contrary, we first observed that DM (odds ratio [OR], 0.50; 95% confidence interval [CI], 0.25–0.98; $P=0.04$) and hyperlipidemia (OR, 0.50; 95% CI, 0.26–0.97; $P=0.04$) showed protective effects against cognitive decline in ALS, adjusted for age, sex, educational level, site of onset, Revised-ALS Functional Rating Scale score, predominant upper motor neuron phenotype, family history of ALS, and the remaining vascular risk factors. Furthermore, patients with > 2 vascular risk factors showed a significantly lower risk of cognitive impairment (OR, 0.18; 95% CI, 0.07–0.48; $P=0.001$). Sensitivity analyses of sex did not substantially reverse the risk estimates.

Conclusions

DM and hyperlipidemia decrease the risk of cognitive impairment in patients with ALS. The fitness hypothesis in ALS has been tested and expanded in our work.

Background

Amyotrophic lateral sclerosis (ALS) has been viewed as a spectrum disorder with frontotemporal dementia (FTD), in which neurodegeneration results in cognitive impairment beyond upper and lower motor neuron involvement.¹ Approximately 30–50% of patients with ALS develop varying degrees of cognitive impairment, and about 5–15% of patients with ALS meet the diagnostic criteria of ALS-FTD.^{1,2} Consistently, our previous study reported that the prevalence of cognitive impairment in patients with ALS was 30.3% and characterized by multi-cognitive domain deficit based on the Chinese version of the Addenbrooke's Cognitive Examination-revised (ACE-R).³ Cognitive impairment in ALS is associated with negative prognosis.² Determination of risk factors for cognitive impairment in ALS may provide a deeper understanding of the underlying pathophysiological mechanisms and thereby facilitate optimal clinical management.

An increasing body of evidence implicates genetic, demographic, and disease-inherent factors as possible predictors of cognitive impairment in ALS. In our previous meta-analysis, we found that *C9orf72* repeat expansion, bulbar onset, predominant upper motor neuron (PUMN) phenotype, and family history of ALS were positively correlated to cognitive impairment in ALS;⁴ however, to our knowledge, no studies to date are available concerning the effects of vascular risk factors on cognitive impairment in patients with ALS.

It has been widely investigated and consistently reported that vascular risk factors increase the risk of dementia.⁵ A history of diabetes mellitus (DM), hypertension, hyperlipidemia, overweight, and smoking are known to increase the risk of Alzheimer's disease (AD)⁵ and Parkinson's disease dementia (PDD).⁶ Interestingly, the situation was remarkably different in ALS: premorbid physical or cardiovascular fitness was observed in patients with ALS.^{7–9} Large-scale population-based case-control⁷ and cohort studies⁸ that used hospital-based data⁸ or self-reported clinical characteristics⁷ both suggested that ALS patients tended to show beneficial vascular risk profile with a low incidence of cardiovascular diseases. This fitness hypothesis was reinforced by a lower risk of cardiovascular mortality in parents of ALS for a possible common genetic predisposition between cardiovascular fitness and ALS.¹⁰ Furthermore, considerable studies have observed a protective association between specific vascular risk factors and ALS onset, as well as survival.^{7,11–17} DM decreased the risk by 32% (based on the results of the latest meta-analysis),¹¹ delayed onset by 3-4.4 years (in European^{12,13} and Asia¹⁴) and might prolong survival time in ALS,¹⁴ although the results were inconsistent.^{18,19} Moreover, solid evidences indicated that high level of blood lipids¹⁶ and body mass index (BMI)¹⁷ both improve the prognosis of ALS. However, the association between hypertension or smoking and the risk of ALS was inconsistent. Reportedly, hypertension decreased²⁰ or was not associated⁷ with the risk of ALS, whereas smoking increased or was not associated with the risk of ALS.²⁰

Based on these interesting observational findings, we wonder if vascular risk factors will contribute to cognitive impairment in ALS, similar to AD and PDD, or dramatically not. Therefore, we aim to comprehensively investigate the possible association between various vascular risk factors (including

hypertension, DM, hyperlipidemia, overweight and smoking) and cognitive impairment in ALS from an ALS-registry-based case-control study.

Methods

Participants

Patients meeting the El Escorial revised criteria for definite, probable, and possible ALS were consecutively enrolled from June 2012 to November 2019 at the ALS registration center of West China Hospital of Sichuan University. Patients were excluded if they had one of the following: (1) King's clinical stage 4 (to avoid the respiratory interference);²¹ (2) Educational level < 3 years; (3) Severe dysarthria or hand weakness or was unable to or refuse to complete the cognitive assessment for other serious medical conditions. All patients were diagnosed and evaluated by trained neurologists in a standardized manner.

Data collection for demographic and clinical characteristics

Demographic and clinical characteristics, as well as patients' medical and personal history were collected during the patient's first visit to our tertiary referral center as previously described.^{3,19} We recorded age at the symptom onset, sex, height, weight, educational level, site of onset, and disease duration. The severity of the disease was assessed by Revised-ALS Functional Rating Scale (ALSFRS-R). Progression rate was determined by (48 - ALSFRS-R total score at the first visit) / duration between onset and first visit. A positive family history was defined as family history of ALS in the first or second generations.

Classification of clinical phenotypes was based on guidelines established by Chiò et al.²² Detailed past medical history and smoking history were provided from patients and (or) caregivers.

Ascertainment of vascular risk factors

Combinations of vascular risk factors were ascertained based on patients' medical history, current treatment and laboratory tests. Hypertension was defined as a history of hypertension, systolic blood pressure (BP) \geq 140 mmHg, or diastolic BP \geq 90 mmHg. DM was defined as a history of DM or serum hemoglobin A1c \geq 6.5%. Hyperlipidemia was defined as a history of hyperlipidemia or serum total cholesterol \geq 6.2 mmol/L. The administration of antihypertensive, antidiabetic and antihyperlipidemic drugs was reviewed. BMI was calculated ($BMI = \text{weight}/\text{height}^2$, in kg/m²) and overweight was defined as $BMI > 25$ kg/m². Smoking is a well-known vascular risk factor, both past and present smoking were labeled with smoking. Cardiovascular disease included coronary heart disease and stroke.

Cognition assessment

We applied the ACE-R, a multidimensional dementia screening tool with excellent diagnostic performance^{3,23} to detect cognitive impairment in ALS. Cognitive impairment was defined as a total ACE-R score < 75 , a cut-off value established in our ALS cohort, which was 1.5 standard deviations (SD) below

the mean value for healthy controls.³ Scores of subdomains including language, memory, verbal fluency, orientation/attention and visuospatial ability were also recorded.

Mutation screening

Whole-exome sequencing was performed to identify ALS-related genes. A repeat-primed polymerase chain reaction assay was used to screen for *C9orf72* repeat expansion. Repeat lengths ≥ 30 was considered to be pathogenic.

Statistical analysis

Continuous variables were expressed as mean and SD, and categorical variables as frequency and percentage. Student's t-tests or Mann-Whitney U-tests was performed for between-group comparisons of continuous variables and χ^2 tests for categorical variables. A *P* value < 0.05 was considered statistically significant. Statistical analysis was conducted using SPSS 18.0 (SPSS Inc, Chicago, IL, USA).

Logistic regression analysis was performed separately (for each factor) and accumulatively (based on the sum of factors) to determine the association between cognitive impairment and vascular risk factors in ALS. Two multivariable logistic models were created for confounder adjustment. In the first model, we adjusted for possible predictors of cognitive impairment in ALS (which were summarized in our previous meta-analysis), including age, sex, educational level, site of onset, ALSFRS-R score, PUMN phenotype and family history of ALS. In the second model, a more rigorous adjustment was performed for the remaining vascular risk factors. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Tests for linear trend in effects across the cumulative numbers of vascular risk factors were performed by treating the sum as continuous variables.

We performed sensitivity analysis restricted to men and women separately because of sex-based differences in vascular risk factors, particularly with regard to smoking. Age-related modification on DM and the risk of ALS was noted in previous studies: a protective association was observed in older age groups, and this association was stronger with increasing age.^{15,24} Therefore, we conducted logistic analysis of variables stratified by age at ALS registration (< 50, 50–59, 60–69, and ≥ 70 years or according to quartiles) to explore the association between DM and cognitive impairment in ALS. The second adjustment model was applied to the sensitivity analysis and the age-related stratified analysis.

Results

Characteristics of patients with ALS

A total of 1814 patients with ALS were consecutively enrolled between June 2012 and November 2019, eventually, we investigated 870 eligible patients were included (Fig. 1). The mean age at registration was 54.1 (11.3) years and 64.5% of them were men. The mean disease duration was 16.5 (15.5) months. Cognitive impairment was detected in one-third of patients (30.6%), which was similar to previous reports.^{1,3} Demographic and clinical characteristics of patients with ALS with and without cognitive

impairment are summarized in Table 1. The prevalence of vascular risk factors in patients with ALS was 13.4% with hypertension, 7.7% with DM, 8.0% with hyperlipidemia, 45.6% with smoking and 12.5% with overweight. Data of comorbidities in men and women patients are shown in Fig. 1. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement²⁵ (Additional file 1).

Table 1
Demographic and clinical characteristics of patients with ALS with and without cognitive impairment

Characteristic	Cognitive normal (n = 604)	Cognitive impairment (n = 266)	P value
Age of onset, No. (%)			
≤ 45 years	180 (29.8)	42 (15.8)	< 0.001
> 45 years	424 (70.2)	224 (84.2)	
Sex, No. (%)			
Men	417 (69.0)	144 (54.1)	< 0.001
Women	187 (31.0)	122 (45.9)	
Educational level, No. (%)			
≤ 6 years	101 (16.7)	133 (50.0)	< 0.001
> 6 ~ ≤ 12 years	376 (62.3)	130 (48.9)	
>12 years	127 (21.0)	3 (1.1)	
Disease duration, No. (%)			
≤ 2 years	487 (80.6)	221 (83.1)	0.39
> 2 years	117 (19.4)	45 (16.9)	
ALSFRS-R score, No. (%)			
≤ 39	160 (26.5)	107 (40.2)	< 0.001
> 39	444 (73.5)	159 (59.8)	
Progression rate, No. (%)			
≤ 0.47	315 (52.2)	120 (45.1)	0.06
> 0.47	289 (47.8)	146 (54.9)	
Family history of ALS, No. (%)			
Yes	14 (2.3)	5 (1.9)	0.68
No	590 (97.7)	261 (98.1)	
Site of onset, No. (%)			
Bulbar	83 (13.7)	45 (16.9)	0.22

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised-ALS Functional Rating Scale; DM, diabetes mellitus; PUMN, predominant upper motor neuron.

Characteristic	Cognitive normal (n = 604)	Cognitive impairment (n = 266)	P value
Limb	521 (86.3)	221 (83.1)	
Phenotype, No. (%)			
PUMN	18 (3.0)	7 (2.6)	0.78
No PUMN	586 (97.0)	259 (97.4)	
Hypertension, No. (%)			
Yes	83 (13.7)	47 (17.7)	0.13
No	521 (86.3)	219 (82.3)	
DM, No. (%)			
Yes	51 (8.4)	17 (6.4)	0.30
No	553 (91.6)	249 (93.6)	
Hyperlipidemia, No. (%)			
Yes	54 (8.9)	17 (6.4)	0.21
No	550 (91.1)	249 (93.6)	
Smoking, No. (%)			
Yes	289 (47.8)	106 (39.8)	0.03
No	315 (52.2)	160 (60.2)	
Overweight, No. (%)			
Yes	89 (14.7)	25 (9.4)	0.03
No	515 (85.3)	241 (90.6)	
Cardiovascular disease, No. (%)			
Yes	18 (3.0)	4 (1.5)	0.20
No	586 (97.0)	262 (98.5)	

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised-ALS Functional Rating Scale; DM, diabetes mellitus; PUMN, predominant upper motor neuron.

Vascular risk factors and cognitive impairment

We observed that DM (OR, 0.50; 95% CI, 0.26–0.97; $P=0.04$) was significantly associated with a decreased risk of cognitive impairment in ALS; this association remained significant even after adjustment for all other vascular risk factors (OR, 0.50; 95% CI, 0.25–0.98; $P=0.04$) (Table 2).

Hyperlipidemia also showed an inverse association with cognitive impairment, and this association was significant in the second adjusted model (OR, 0.50; 95% CI, 0.26–0.97; $P = 0.04$). Cardiovascular disease also showed a protective effect on ALS cognition, though there was a limited sample size (cognitive impairment was detected in only 4 of 22 patients with ALS combined with cardiovascular disease). Hypertension, smoking, and overweight were not associated with cognitive impairment in ALS. Patients with > 2 vascular risk factors were significantly less likely to have cognitive impairment (OR, 0.18; 95% CI, 0.07–0.48; $P = 0.001$). Each additional increase in the accumulative number of vascular risk factors was associated with a 27.4% ($P_{\text{trend}} = 0.003$) decreased risk of cognitive impairment.

Table 2
Association between vascular risk factors and cognitive impairment in patients with ALS

	OR ^a (95% CI)	<i>P</i> value ^a	OR ^b (95% CI)	<i>P</i> value ^b		
Vascular risk factors						
Hypertension	0.87 (0.54–1.41)	0.57	1.11 (0.70–1.83)	0.69		
DM	0.50 (0.26–0.97)	0.04	0.50 (0.25–0.98)	0.04		
Hyperlipidemia	0.54 (0.28–1.03)	0.06	0.50 (0.26–0.97)	0.04		
Smoking	0.95 (0.59–1.51)	0.81	0.94 (0.58–1.50)	0.78		
Overweight	0.61 (0.36–1.04)	0.07	0.64 (0.37–1.10)	0.11		
Cardiovascular disease	0.26 (0.07–0.89)	0.03	0.24 (0.07–0.86)	0.03		
Number of vascular risk factors						
None	1 [Reference]	-	<i>P</i> trend = 0.003			
1	0.81 (0.53–1.23)	0.32				
2	0.74 (0.42–1.29)	0.28				
>2	0.18 (0.07–0.48)	0.001				
Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.						
^a Multivariable logistic model one: adjusted for age, sex, educational level, site of onset, Revised-ALS Functional Rating Scale score, predominant upper motor neuron phenotype and family history of ALS.						
^b Multivariable logistic model two: further adjusted for the remaining vascular risk factors based on the multivariable logistic model one.						

To further understand the protective role of vascular risk factors on cognition in ALS, we compared the demographic and clinical data of ALS patients with and without DM, hyperlipidemia, and cardiovascular disease (Additional file 2, 3 and 4). Sex, educational level, site of onset, phenotype, ALSFRS-R score,

progression rate, and family history of ALS were comparable between patients combined with and without DM (Additional file 2). The mean age of onset of ALS was older in patients with DM (ALS-DM) than those without DM (60.5 ± 9.5 vs. 52.5 ± 11.3 ; $P < 0.001$).

Sensitivity analysis

Consistent protective association between DM and cognition was observed only in men with ALS (OR, 0.27; 95% CI, 0.09–0.79; $P = 0.02$). Other vascular risk factors, including hypertension, hyperlipidemia, smoking, overweight, and cardiovascular disease were not associated with cognitive impairment in patients of either sex. All ORs and 95%CI for each vascular risk factor in the sensitivity analysis were listed in Table 3. Similar protective trend was observed in men ($P_{\text{trend}} = 0.002$): the accumulated protective effect on cognition was significant in men with > 2 vascular risk factors (OR, 0.12; 95% CI, 0.03–0.44; $P = 0.001$).

Table 3
Sensitivity analysis of association between vascular risk factors and cognitive impairment in ALS regarding sex

	Men		Women	
	OR ^b (95% CI)	P value ^b	OR ^b (95% CI)	P value ^b
Vascular risk factors				
Hypertension	0.85 (0.44–1.65)	0.63	1.57 (0.67–3.68)	0.30
DM	0.27 (0.09–0.79)	0.02	0.98 (0.35–2.73)	0.97
Hyperlipidemia	0.49 (0.19–1.24)	0.13	0.52 (0.19–1.41)	0.20
Smoking	0.81 (0.50–1.32)	0.39	5.42 (0.99–29.82)	0.05
Overweight	0.56 (0.27–1.13)	0.11	0.58 (0.31–1.91)	0.58
Cardiovascular disease	0.32 (0.06–1.67)	0.18	0.14 (0.02–1.18)	0.07
Number of vascular risk factors				
None	1 [Reference]	-	1 [Reference]	-
1	0.75 (0.41–1.53)	0.33	0.81 (0.42–1.58)	0.54
2	0.57 (0.27–1.20)	0.14	1.19 (0.47–3.01)	0.71
> 2	0.12 (0.03–0.44)	0.001	0.58 (0.06–5.78)	0.64
Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.				
^b Multivariable logistic model two: adjusted for age, educational level, site of onset, Revised-ALS Functional Rating Scale score, predominant upper motor neuron phenotype, family history of ALS and the remaining vascular risk factors.				

Age-related stratified analysis of DM

After adjustment for demographics and clinical characteristics and comorbidities in the second model, a U-shaped effect modification was observed on the association between DM and the risk of cognitive impairment in ALS by stratifying age at ALS registration. The OR initially decreased with increasing age to a nadir around the age of 60 years, and subsequently increased with age, although with no significance (Fig. 2a). A similar U-shaped temporal association was observed when the per quartile increased with age (Fig. 2b). ORs for each age group were listed in the Additional file 5.

Gene and cognitive impairment

Thirty-eight ALS-related genes were identified among the 509 patients who completed genetic testing, and nearly 29% ($n = 149$) of patients showed a positive mutation (data not shown). The ACE-R score did not differ between the genetic ALS patients (*SOD1*, *TARDBP*, *FUS*, *GRN*, *TBK1*, and *SQSTM1*) and non-genetic ALS patients (Additional file 6). Predictably, patients with *C9orf72* repeat expansion mutation performed worse in ACE-R tests than those without *C9orf72* mutation (67.7 ± 18.4 vs. 79.5 ± 13.0 ; $P = 0.02$).

Discussion

This ALS-registry-based case-control study is the first attempt to investigate the association between vascular risk factors and cognitive impairment in patients with ALS. Contrary to findings in AD and PDD, no cognitive burden secondary to vascular risk factors was observed in ALS; however, DM and hyperlipidemia offered protection against cognitive decline, which was unexpected but within reason. Hence, the fitness hypothesis in ALS was supported and broadened based on the decreased risk of cognitive impairment in the ALS-DM and ALS-hyperlipidemia groups.

Premorbid physical fitness in ALS was noticed by both patients and neurologists. Military personnel showed an elevated risk of ALS,²⁶ and tended to have a beneficial vascular profile. Consistent with prior findings,^{9, 14, 27, 28} we observed a low frequency of cardiovascular disease, hypertension, DM, hyperlipidemia and overweight in patients with ALS than in the general population. However, previous studies have not discussed the role of vascular risk factors on ALS cognition. Notably, the protective effect conferred by DM, hyperlipidemia, and cardiovascular disease against cognitive impairment in patients with ALS remained nearly unchanged or reached statistical significance after adjustment for age, sex, educational level, site of onset, ALSFRS-R score, PUMN phenotype, family history of ALS, and other vascular risk factors in the two multivariable logistic models used in our study. Sensitivity analyses corroborated the inverse association between DM and the risk of cognitive impairment in men. The cut sample size in women might have limited the statistical power of this study. In addition, as the cumulative total for vascular risk factors increased, the protective trend for ALS cognition was enhanced, suggesting that biological mechanisms influencing vascular condition may be related to the pathogenesis of ALS.

Two possible hypotheses could be involved for the explanation. The fitness hypothesis for ALS has been described above. A favorable cardiovascular profile may not directly affect the cognition in ALS; but it may serve as a marker for genetic predisposition and physical activity, which are more closely related to the etiology of ALS. A study showed a reduced risk of both stroke and myocardial infarction in the relatives (including grandparents, aunts, uncles, and siblings besides parents) of patients with ALS.²⁹ Additionally, a recent population-based study reported that the risk of cardiovascular mortality was low in parents of ALS.¹⁰ The evidence so far suggests that both patients with ALS and their relatives, particularly parents tend to share a favorable cardiovascular profile. Polygenic overlap between cardiovascular disease and cardiometabolic risk factors was observed in genome-wide association studies (GWAS),³⁰ and the relatively high heritability of cardiovascular disease has been acknowledged.³¹ Thus, we infer that a specific genetic background increases cardiovascular risk while decreasing the risk of ALS onset and cognitive impairment. Some recent mendelian randomization studies based on GWAS have described causal associations between DM,³² premorbid BMI,³³ and blood lipids³⁴ and ALS. However, more caution and further investigation are necessary for the new field. Besides heredity, environmental factors such as physical activity may promote cardiovascular health and increase ALS susceptibility.³⁵ Therefore, we recommend that future studies estimate the association between cardiovascular traits and ALS cognition by controlling patients' physical activity levels.

An alternative hypothesis, not mutually exclusive from the previous one related to the pathogenesis, would be that the vascular profile is a surrogate marker of energy metabolism in patients with ALS, regarding the compensatory mechanisms. Hypermetabolism, characterized by increased resting energy expenditure, was common in ALS and associated with greater functional decline and shorter survival.³⁶ Elevated levels of blood glucose in DM or of lipids in hyperlipidemia may offset the higher energy demand caused by the hypermetabolic state, thereby delaying the neurodegenerative process in ALS.^{12, 16, 36} Impressively, it has been reported that the serum retinol-binding protein 4 (RBP4) concentration is inversely associated with the risk and prognosis of ALS.³⁷ RBP4 is regarded as a novel cardiometabolic risk factor, which can induce insulin resistance and contribute to the development of DM, dyslipidemia, hypertension, cardiovascular disease, and other metabolic syndromes.³⁸ Therefore, our observations raise the possibility that a relatively unfavorable vascular profile plays a neuroprotective role in ALS through the elevated RBP4 indirectly. However, further researches are needed to elucidate the association among RBP4, cardiovascular status, and ALS.

According to the major misaccumulated protein, TAR DNA-binding protein 43 (TDP-43) inclusion is positive in over 95% ALS and approximately 45% FTD.³⁹ Progranulin deficiency from mutations of *GRN*, a common causative gene for both ALS and FTD, was shown to aggravate TDP-43 accumulation by impairing autophagy in ALS mice model.⁴⁰ On the other hand, overexpression of progranulin was shown to reduce insoluble TDP-43 levels and prolong survival in TDP-43 mice.⁴¹ In fact, progranulin is a recently recognized multifunctional adipokine which was shown to be increased and involved in obesity and DM.⁴² Hence, from the point of pathological deposit protein, DM may delay neurodegeneration in ALS by

promoting autophagy, which facilitates clearance of aggregated TDP-43 through elevated progranulin, although whether sex or age plays a role in the modification of DM on ALS remains largely unknown. A case-control study that included 100 patients with clinical diagnosed FTD reported that DM increased the risk of FTD.⁴³ However, the association between DM and FTD could not be conclusively established without pathological diagnosis, because other pathologies such as Tau and FUS, in addition to TDP-43 account for more than half cases.³⁹ Unlike ALS and FTD, AD is marked by amyloid beta deposition. A novel mechanism is proposed, that is the upregulation of β-site amyloid precursor protein cleaving enzyme 1 in DM promotes amyloidogenesis and insulin resistance and thereby contributes to AD.⁴⁴ Collectively, the distinctive pathological pathway is crucial for gaining deeper insight into the modification effect of DM on different neurodegenerative diseases.

This study has several principal limitations. First, participants who were incapable of performing neuropsychological tests were excluded from the study, which might have resulted in a selection bias. Second, the ACE-R is a cognitive screening tool, despite its superior sensitivity and specificity,^{3,23} it may not accurately detect the spectrum of deficits resulting from frontotemporal dysfunction. Future studies are warranted to investigate the role of vascular risk factors in ALS, ALS-FTD, and FTD individually. Third, neither vascular risk factor exposure nor relevant drug use misclassification or omission could be excluded due to the observational nature of our study.

Conclusions

Overall, with careful adjustment for the aforementioned variables, our findings suggest that vascular risk factors, particularly DM and hyperlipidemia are associated with cognitive benefits in patients with ALS. This neuroprotective effect adds new evidence to the fitness hypothesis and highlights the unique aspects of ALS, both in clinical heterogeneity and pathophysiological complexity. Elucidation of mechanisms behind these observed associations might open new perspectives in ALS therapeutics.

Abbreviations

ACE-R: Addenbrooke's Cognitive Examination-revised; AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; ALSFRS-R: Revised-amyotrophic lateral sclerosis functional rating scale; BMI: Body mass index; BP: Blood pressure; C9orf72: Chromosome 9 open reading frame 72; CI: Confidence interval; DM: Diabetes mellitus; FTD: Frontotemporal dementia; FUS: Fused in sarcoma; GRN: Granulin; GWAS: Genome-wide association studies; OR: Odds ratio; PDD: Parkinson's disease dementia; PUMN: Predominant upper motor neuron; RBP4: Retinol-binding protein 4; SD: Standard deviations; SOD1: Superoxide dismutase 1; SQSTM1: Sequestosome 1; TARDBP: Trans-active response DNA binding protein; TBK1: TANK binding kinase 1; TDP-43: Trans-activation response DNA-binding protein 43

Declarations

Ethics approval and consent to participate

Ethics approval for the study was approved by the institutional ethics committee of Sichuan University. Written informed consent was obtained from each participant or their primary caregiver.

Consent for publication

Not Applicable.

Availability of data and materials

Data and materials are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

HFS, TMY and QQW conceived and designed the study. QQW, BC, RWO, YBH, LYZ, YPC and TMY collected the data. QQW, TMY and RWO contributed to the statistical analysis. TMY wrote the first draft of the manuscript. TMY, HFS, CYL and QQW contributed to the writing of the final version of the manuscript. All authors read and approved the final manuscript.

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Figures

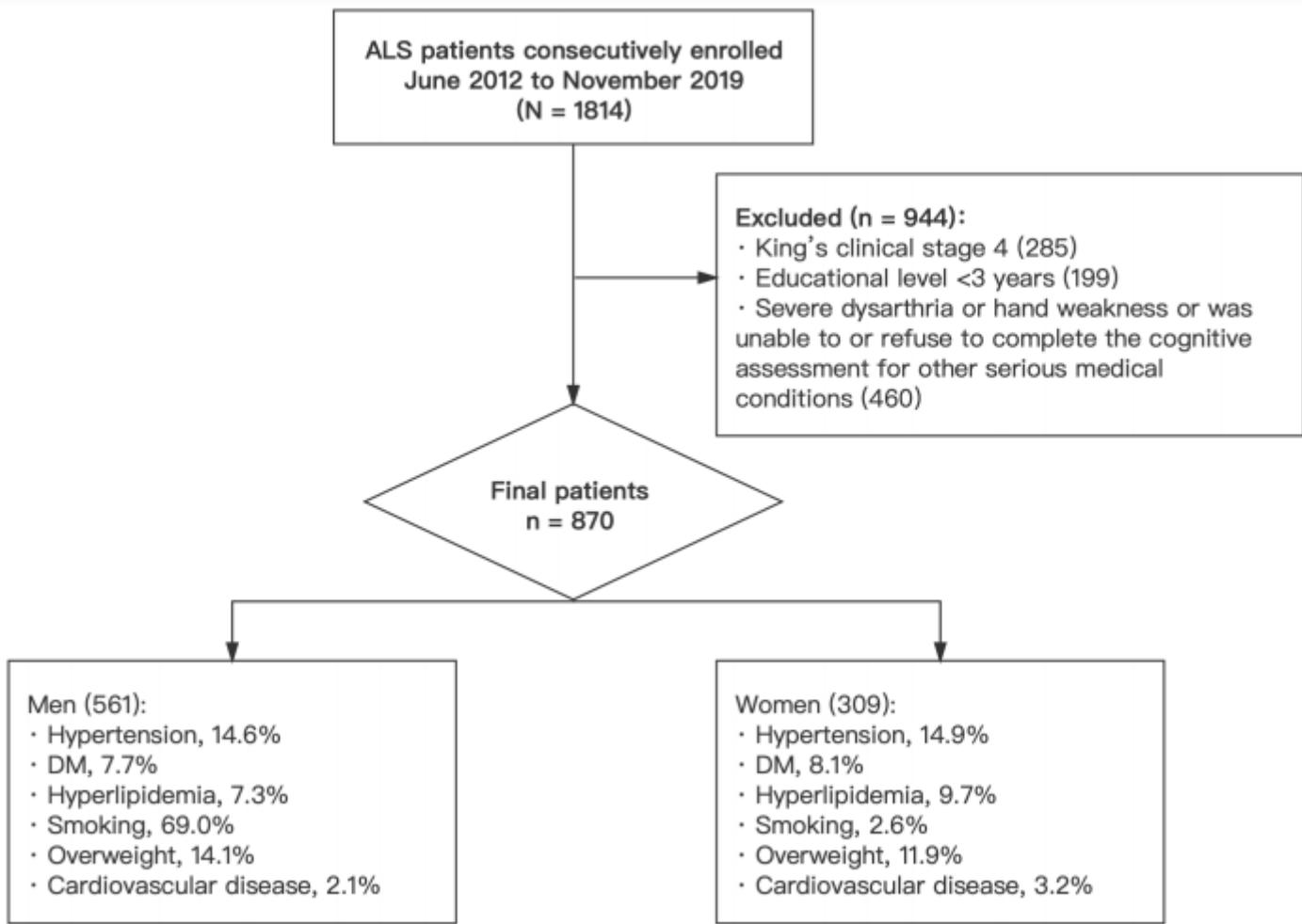


Figure 1

Flowchart showing selection of patients and data of comorbidities in men and women Abbreviations:
ALS, myotrophic lateral sclerosis; DM, diabetes mellitus.

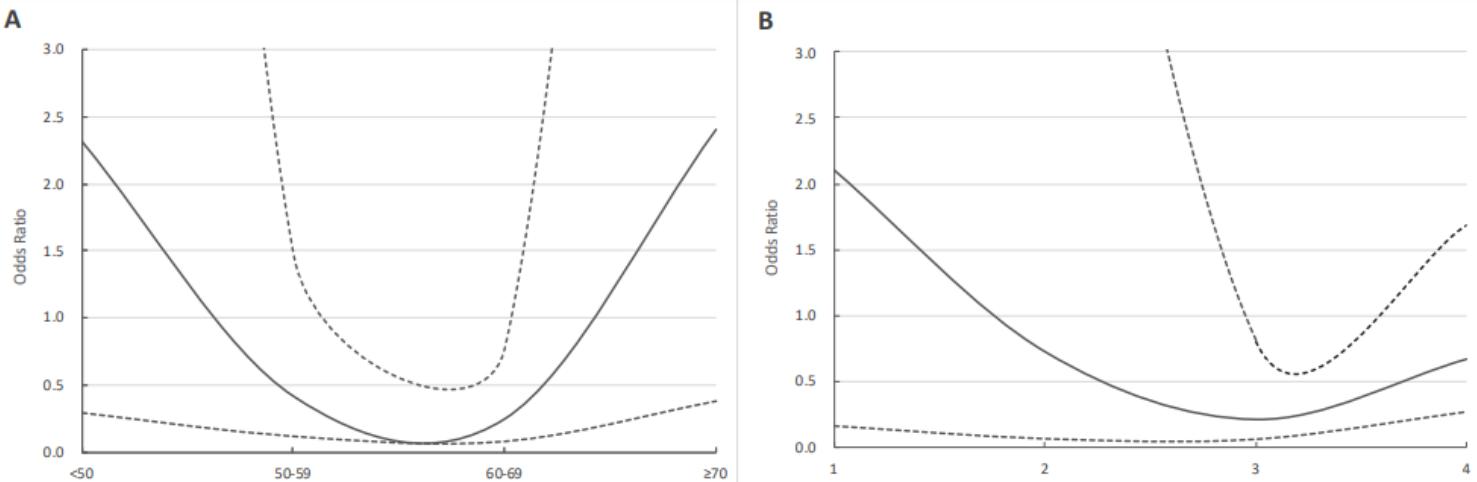


Figure 2

Temporal relationship between DM and the risk of cognitive impairment in ALS (A)Age at ALS registration was stratified by <50, 50–59, 60–69 and ≥70 years.(B)Age at ALS registration was stratified by quartiles. Abbreviations: ALS, amyotrophic lateral sclerosis; DM, diabetes mellitus.

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