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Original Contribution

Body Mass Index and Amyotrophic Lateral Sclerosis: A Study of US Military Veterans

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Amyotrophic lateral sclerosis (ALS) may be associated with low body mass index (BMI) at the time of diagnosis. However, the role of premorbid BMI in the development of ALS and survival after diagnosis remains unclear. In 2005–2010, we interviewed 467 patients with ALS from the US National Registry of Veterans with ALS and 975 frequency-matched veteran controls. In this sample, we evaluated the association of BMI and BMI change at different ages with ALS risk using unconditional logistic models and with survival after ALS diagnosis using Cox proportional hazards models. After adjustment for confounders, compared with a moderate increase in BMI between ages 25 and 40 years, stable or decreasing BMI was positively associated with ALS risk (odds ratio (OR) = 1.61, 95% confidence interval (CI): 1.20, 2.16). A 1-unit increase in BMI at age 40 years (OR = 0.95, 95% CI: 0.91, 0.98) but not at age 25 years (OR = 0.99, 95% CI: 0.95, 1.03) was inversely associated with ALS. These associations were similar for bulbar and spinal ALS but stronger for those with a delay of less than 1 year between symptom onset and diagnosis. We found no association between prediagnosis BMI and survival. A decreasing BMI from early to middle age and a low BMI in middle age may be positively associated with ALS risk.

amyotrophic lateral sclerosis; body mass index; body weight changes; United States

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; GENEVA, Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis; MSAS, minimum sufficient adjustment set; OR, odds ratio; VA, Department of Veterans Affairs.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by loss of motor neurons in the brain and spinal cord (1). The disease leads to muscle weakness in multiple regions of the body and often progresses rapidly to death. Approximately 5%–10% of patients have a family history of ALS, and mutations identified to date account for up to 70% of familial cases (2). Conversely, the etiology of sporadic ALS is largely unknown, although complex interactions between external causes and genetic susceptibility are likely to be involved (3).

Hypermetabolism, together with abnormalities in lipid and carbohydrate metabolism, is prevalent in patients with ALS (4–6). Positive prognostic factors in patients with ALS may include elevated triglyceride and cholesterol levels, high subcutaneous fat, and a high-energy diet (7–10). Lower body mass index (BMI) and faster reductions in BMI after disease onset have been independently associated with shorter ALS survival (11, 12). Whether premorbid BMI and weight change are associated with ALS prognosis is unknown.

Metabolic factors may be associated with ALS risk as well as prognosis. In 2 cohort studies, higher ALS incidence or mortality was associated with lower premorbid BMI measured up to 28 years before symptom onset (13, 14). However, the relationship between premorbid weight change and ALS risk has rarely been examined.

Early adulthood and middle age may be important time windows for neurodegeneration, as suggested for Parkinson disease (15). Therefore, we studied the association of premorbid BMI and BMI change with ALS risk and survival in a

sample of US military veterans, focusing on young adulthood (age 25 years) and middle age (age 40 years).

METHODS

Study design

The Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis (GENEVA) Study is a case-control study that enrolled cases from the National Registry of Veterans with ALS, established by the Department of Veterans Affairs (VA), and a representative sample of veteran controls (16). Using data from GENEVA, we conducted a case-control analysis to compare self-reported BMIs at specific ages in individuals who developed ALS with those of matched controls. To assess the association of BMI with ALS survival, we followed cases prospectively until death or administrative censoring. Institutional review boards at the Durham Veterans Administration Medical Center, Duke University Medical Center, and the National Institute of Environmental Health Sciences approved the study, and all participants provided informed written or oral consent.

Study participants and outcome definitions

The Durham Veterans Administration Medical Center enrolled individuals with motor neuron diseases in the VA Registry between April 1, 2003, and September 30, 2007 (17). Neurologists specializing in motor neuron diseases used information from medical records to assign a diagnosis according to a formal algorithm based on the World Federation of Neurology's revised El Escorial ALS diagnostic criteria (18). The VA Registry included patients diagnosed with ALS (definite, probable, or possible), lower motor neuron disease (suspected ALS), or primary lateral sclerosis. Patients were interviewed by telephone every 6 months to monitor disease progression (clinical interview).

GENEVA included a subset of ALS patients from the VA Registry. The present analysis excluded patients with primary lateral sclerosis (which generally does not progress to ALS) ($n = 39$), patients with lower motor neuron disease ($n = 114$), and patients with possible ALS ($n = 48$), leaving 469 cases with definite or probable ALS. One of these patients was diagnosed with a defined pathogenic mutation according to the medical records. Because prediagnosis weight before age 25 years was not ascertained, we excluded 2 participants who were less than 25 years of age at their ALS diagnosis, leaving 467 cases for analysis.

Veteran controls ($n = 975$) were identified from the Beneficiary Identification and Records Locator Subsystem database maintained by the VA (16). From an age-stratified random sample of 10,000 veterans, controls were frequency-matched to cases on age at the reference date (the date of ALS diagnosis for cases and the date of interview for controls) and on use of VA health care before the reference date. The latter factor compensates for the possibility that veterans with ALS might use VA health care more after diagnosis because of the suspicion that the condition is related to military service, while controls would lack such motivation. The study sample reflects a 77% participation rate among patients and a 63% participation rate among controls.

Clinical information—such as site of symptom onset (bulbar, if difficulties in speaking or swallowing, or spinal, if limb symptoms) and diagnostic delay (time between symptom onset and diagnosis)—was available from participants' medical records and was used to group patients with ALS. Birth and diagnosis dates were used to compute age at ALS diagnosis (years). We extracted dates of death through July 2013 from the Austin Vital Status File, which has been validated against the National Death Index (19).

Exposure and covariates

We collected information retrospectively in a structured telephone interview conducted with GENEVA participants or their proxies; proxies were interviewed for 30 ALS cases and no controls. We interviewed participants with ALS an average of 4 years after they were diagnosed. We collected information on weight at age 25 years, at age 40 years, and at the reference date, as well as information on height at age 25 years and at the reference date. We chose ages 25 and 40 years a priori to represent young adulthood and middle age.

We calculated BMI (weight (kg)/height (m)^2) at age 25 years and at the reference date from the self-reported weights and heights at those ages, respectively (20). Because information on height at age 40 years was not collected, BMI for that age was calculated using height at age 25 years and only if the participant's age at the reference date was at least 40 years. BMI values of ≤15 or ≥55 were considered unlikely and set to missing. BMI was considered as a continuous or categorical variable (lean: <20; normal weight: 20–<25; overweight: 25–<30; obese: ≥30). BMI change was defined as the difference in BMI between 2 time points and was considered as either a continuous or categorical variable (based on the interquartile range of change in BMI between ages 25 and 40 years: decrease or stable: <0.5; moderate increase: 0.5–<3.5; substantial increase: ≥3.5).

We constructed directed acyclic graphs to identify confounders and minimum sufficient adjustment sets (MSASs) for the association of BMI at different ages or BMI change with ALS risk or survival (21).

ALS risk. In addition to the matching variables, we considered other potential confounders (collected in the telephone interview) for the association between BMI measures and ALS risk. These potential confounders included sex, race/ethnicity (non-Hispanic white, other), smoking (never or ever smoked at least 1 cigarette/day before reference date), education (5–12, 13–16, 17–20, or 21–35 years), and birth date as an indicator of cohort effects. Our proposed directed acyclic graph suggested an MSAS for BMI (at any age) that included age, use of VA health care, sex, race/ethnicity, smoking, and education (see Web Figure 1, available at http://aje.oxfordjournals.org/). We also carefully considered alternative directed acyclic graphs that included more variables, such as variables related to military service.

ALS survival. Potential confounders for the association between BMI measures and ALS survival also included length of diagnostic delay (days) as a measure of disease progression, site of symptom onset, and use of riluzole (the only

drug approved for the treatment of ALS) (22). Use of riluzole was ascertained in the clinical interviews conducted through September 2009 to monitor the health status of patients. For survival, the MSAS included birth date and diagnostic delay for prediagnosis BMI, and it included age at diagnosis, diagnostic delay, riluzole use, and symptom onset site for BMI at diagnosis (Web Figure 1). We defined use of riluzole (yes, no) by using information from the clinical interview closest to the date of GENEVA enrollment.

Statistical analyses

ALS risk. We compared distributions of BMI variables and covariates between cases and controls using the χ^2 test or Wilcoxon rank-sum test, depending on the nature of the variable. We used unconditional logistic regression to estimate odds ratios and 95% confidence intervals for associations between ALS risk and BMI at different ages and BMI change between ages. We used multinomial logistic regression and likelihood ratio tests to study whether the association of BMI with ALS varied by site of symptom onset (spinal, bulbar) or diagnostic delay (short: ≤1 year; moderate: >1–≤3 years; long: >3 years). To assess whether high BMI or BMI change was associated with delayed ALS onset, we tested the association between BMI measures and age at ALS diagnosis using linear regression.

ALS survival. We employed Cox regression analysis to estimate hazard ratios and 95% confidence intervals for associations between survival and BMI measures among patients with ALS. The time scale of interest was time (days) since ALS diagnosis. Patients entered the risk set at the date of the GENEVA interview and were followed until death or July 2013, whichever came first. To properly account for left-truncation, we excluded the time interval before the completion of the GENEVA interview from the time at risk, since patients had to remain alive until the interview to be eligible. The assumption of proportional hazards was assessed using Schoenfeld residuals.

For both risk and survival, we estimated measures of association for each unit increase in BMI (or BMI change) by using continuous BMI (or BMI change). We used within-category median values to create a predictor variable for testing trends. Mutual adjustment and stratification were used to investigate the independence of the associations of BMI change across different ages and the respective attained BMI with ALS risk and survival. Analyses stratified by sex and race/ethnicity were conducted if the sample size of the subgroups was sufficiently large.

We conducted a sensitivity analysis restricted to cases diagnosed within 2 years before the GENEVA interview because long-surviving patients are potentially overrepresented in GENEVA. Similarly, to address the possibility that the presence of undiagnosed ALS could account for participants with ALS having lower BMIs than control participants at age 40 years, we conducted an analysis restricted to participants with an age at the reference date of more than 45 years, assuming that patients with ALS would be free of symptoms 5 or more years before diagnosis.

We used STATA, version 12.1 (StataCorp LP, College Station, Texas), for statistical analyses.

RESULTS

ALS risk

Compared with controls, patients with ALS were more likely to be male, non-Hispanic white, and less educated (Table 1). Cases and controls were on average 59 years of age, and 94% were aged 40 years or older at the reference date.

After adjustment for age, use of VA health care, sex, and race/ethnicity, ALS was not associated with BMI at age 25 years, but it was inversely associated with BMI both at age 40 years and at the reference date (Table 2). Further adjustment for smoking and education (the suggested MSAS) produced similar estimates. The presence of missing values for the covariates was independent of BMI ($P > 0.05$).

The correlation between BMI at age 25 years and BMI at age 40 years was 0.70. BMI change between ages 25 and 40 years was inversely associated with ALS; a stable or decreasing BMI between ages 25 and 40 years was associated with 60% higher odds of ALS compared with a moderate increase, but we saw no change in odds between substantial and moderate increases in BMI (Table 3). BMI change between age 40 years and the reference date was also inversely associated with ALS after adjustment for the MSAS plus BMI at the reference date (odds ratio (OR) = 0.94, 95% confidence interval (CI): 0.89, 0.98). The association of ALS risk with BMI change was constant across categories of BMI; similarly, the association of ALS risk with BMI was constant across categories of BMI change (data not shown).

Age at diagnosis was independent of prediagnosis BMI at age 25 years (average increase in years per 1-unit increase in BMI = 0.07, 95% CI: −0.08, 0.22) and at age 40 years (average increase = 0.08, 95% CI: −0.05, 0.21) or BMI change between ages 25 and 40 years (average increase = 0.09, 95% CI: −0.09, 0.27) after adjustment for birth date, sex, race/ethnicity, use of VA health care, smoking status, and education.

The association between BMI at age 40 years and ALS did not vary with symptom onset site, but it appeared strongest among patients with a short diagnostic delay (Tables 4 and 5). Similar patterns were noted for BMI at age 25 years and at the reference date (Web Tables 1 and 2).

The results were similar after restricting the analysis to men (for BMI at age 40 years, MSAS-adjusted OR = 0.95, 95% CI: 0.92, 0.99) and to non-Hispanic white men (for BMI at age 40 years, MSAS-adjusted OR = 0.95, 95% CI: 0.91, 0.98). The number of women and participants of other races/ethnicities was too low to analyze these subgroups separately (Table 1).

The exclusion of 273 cases that were diagnosed 2 or more years before the GENEVA interview left results largely unchanged (for BMI at age 40 years, MSAS-adjusted OR = 0.97, 95% CI: 0.93, 1.02). Therefore, these associations are not unique to long-surviving patients. Furthermore, after excluding 44 controls and 27 cases with an age at the reference date of less than 45 years, none of the cases included

Table 1. Characteristics of Veterans Included in the Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis Study, United States, 2005–2010

Characteristic	Controls (n = 975)			ALS Cases[a] (n = 467)			P Value[b]
	Median (IQR)	No.	%	Median (IQR)	No.	%	
BMI at age 25 years[c]	23.7 (21.7–25.2)			23.6 (21.7–25.5)			0.727
BMI at age 40 years	25.8 (23.8–28.0)			25.2 (23.1–27.8)			0.020
BMI at reference date	27.7 (25.2–31.0)			26.4 (23.8–29.0)			<0.001
Age at reference date, years	60 (53–68)			60 (53–67)			0.510
Years between reference date and interview	0.0 (0.0–0.0)			2.5 (1.3–4.8)			
Sex							<0.001
Male		907	93.0		456	97.6	
Female		68	7.0		11	2.4	
Race/ethnicity							0.004
Non-Hispanic white		847	86.9		430	92.1	
Other		128	13.1		37	7.9	
Use of VA health care							0.613
Never use before reference date		571	58.7		280	60.1	
Ever use before reference date		402	41.3		186	39.9	
Missing		2			1		
Education before reference date, years							<0.001
5–12		210	21.7		143	30.8	
13–16		494	51.0		227	48.8	
17–20		216	22.3		87	18.7	
21–35		49	5.1		8	1.7	
Missing		6			2		
Cigarette smoking (≥1 cigarette/day)							0.998
Never smoking before reference date		358	37.2		168	37.2	
Ever smoking before reference date		605	62.8		284	62.8	
Missing		12			15		

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; IQR, interquartile range; VA, Department of Veterans Affairs.
[a] Diagnosed as having clinically definite or clinically probable ALS.
[b] P value from Wilcoxon rank-sum test (continuous variables) or χ^2 test (categorical variables).
[c] BMI was calculated as weight (kg)/height (m)^2.

had symptom onset before age 40 years, and the MSAS-adjusted odds ratio for BMI at age 40 years remained 0.96 (95% CI: 0.92, 0.99), suggesting that the effect of symptomatic ALS on BMI is unlikely to explain the association between BMI at age 40 years and ALS.

We found no evidence for confounding due to factors related to military service after additionally adjusting for years of service, years of deployment, and role in the military (officer vs. enlisted) (data not shown).

ALS survival

After excluding 7 patients who had died before their proxies were interviewed, the median follow-up time for the patients (time between interview and death or censoring) was 2 years (interquartile range, 1–6 years). Among the 333 patients who died during follow-up (72%), the median survival from diagnosis was 4 years (interquartile range, 2–6 years).

Higher BMI at diagnosis, but not at age 40 years, was associated with longer survival (Table 6). A greater increase in BMI between age 40 years and diagnosis was also associated with longer survival (hazard ratio = 0.92, 95% CI: 0.88, 0.97; adjusted for the MSAS plus BMI at diagnosis). We found no association with ALS survival for either BMI at age 25 years (MSAS-adjusted hazard ratio = 1.00, 95% CI: 0.96, 1.04) or BMI change between ages 25 and 40 years (MSAS-adjusted hazard ratio = 1.03, 95% CI: 0.98, 1.08). The proportional hazards assumption was met for all measures of BMI except for categories of BMI at diagnosis, and we cannot exclude the possibility that the association of BMI at diagnosis with survival changes over time.

DISCUSSION

We found that individuals with a stable or decreasing BMI between ages 25 and 40 years were at significantly

Table 2. Associations of Body Mass Index at Age 25 Years, Age 40 Years, and the Reference Date With the Risk of Amyotrophic Lateral Sclerosis, Genes and Environmental Exposures in Veterans With Amyotrophic Lateral Sclerosis Study, United States, 2005–2010

Variable	Controls		ALS Cases		Model 1[a]		Model 2[b]	
	No.	%	No.	%	OR	95% CI	OR	95% CI
BMI at age 25 years[c,d]	972	100.0	454	100.0	0.99	0.95, 1.03	0.99	0.95, 1.03
Category of BMI at age 25 years								
15–<20	88	9.0	36	7.9	0.96	0.63, 1.46	0.88	0.57, 1.35
20–<25	581	59.8	265	58.4	1.00	Referent	1.00	Referent
25–<30	269	27.7	141	31.1	1.08	0.83, 1.39	1.07	0.82, 1.38
≥30.0	34	3.5	12	2.6	0.73	0.37, 1.45	0.71	0.36, 1.42
P for linear trend[e]					0.969		0.930	
Missing	3		13					
BMI at age 40 years[d]	914	100.0	421	100.0	0.95	0.91, 0.98	0.95	0.91, 0.98
Category of BMI at age 40 years								
15–<20	17	1.9	8	1.9	0.95	0.40, 2.26	0.92	0.38, 2.22
20–<25	346	37.9	177	42.0	1.00	Referent	1.00	Referent
25–<30	435	47.6	199	47.3	0.84	0.65, 1.08	0.85	0.65, 1.10
≥30.0	116	12.7	37	8.8	0.59	0.39, 0.90	0.60	0.39, 0.92
P for linear trend[e]					0.015		0.021	
Missing	7		13					
BMI at reference date[d]	974	100.0	466	100.0	0.90	0.88, 0.93	0.90	0.88, 0.93
Category of BMI at reference date								
15–<20	8	0.8	13	2.8	2.27	0.90, 5.71	2.21	0.87, 5.66
20–<25	204	21.0	152	32.6	1.00	Referent	1.00	Referent
25–<30	441	45.3	217	46.6	0.63	0.48, 0.83	0.66	0.50, 0.87
≥30.0	321	33.0	84	18.0	0.34	0.24, 0.47	0.35	0.25, 0.49
P for linear trend[e]					<0.001		<0.001	
Missing	1		1					

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] Odds ratios were adjusted for age, sex, race/ethnicity, and use of the Department of Veterans Affairs system for health care. Because of missing values in the covariates, 1 case and 2 controls were excluded from the model for BMI at age 25 years, age 40 years, and the reference date.

[b] Odds ratios were adjusted for age, sex, race/ethnicity, use of the Department of Veterans Affairs system for health care, cigarette smoking, and years of education. Because of missing values in the covariates, 17 cases and 20 controls were excluded from the model for BMI at age 25 years and the reference date, and 16 cases and 18 controls were excluded from the model for BMI at age 40 years.

[c] BMI was calculated as weight (kg)/height $(m)^2$.

[d] Odds ratio for ALS for a 1-unit increase in BMI.

[e] The within-category median BMI was assigned to each observation, and this new variable was used as a predictor variable for testing the trend.

higher risk of ALS compared with those who gained weight while aging. We also found an inverse relationship between prediagnosis BMI in middle age (40 years) and ALS risk. In addition, we found a higher BMI at ALS diagnosis and increases in BMI between age 40 years and diagnosis to be associated with longer ALS survival. However, prediagnosis BMI and BMI change before age 40 years were not associated with survival.

Low premorbid BMI has previously been suggested to be a risk factor for ALS (23). We found no association of ALS with BMI at age 25 years, but the underrepresentation of overweight and obese groups among military personnel at that age could have minimized the real association. Nevertheless, the inverse association between BMI at age 40 years and ALS is similar to that reported in a previous meta-analysis, which found a relative rate of ALS of 0.79 (95% CI: 0.73, 0.86) per 5-unit increase in premorbid BMI (14). An association of premorbid BMI and BMI change with ALS is consistent with a study by Dupuis et al. (24), which found that superoxide dismutase 1 (*SOD1*)-mutant mice had reduced adipose tissue accumulation and increased energy expenditure weeks before symptom onset. We found that the association between BMI and ALS risk was stronger for ALS with a short diagnostic delay and that individuals with low BMI had a shorter diagnostic delay. This result may be due to individuals with low BMI

Table 3. Association of Change in Body Mass Index Between Ages 25 and 40 Years With the Risk of Amyotrophic Lateral Sclerosis, Genes and Environmental Exposures in Veterans With Amyotrophic Lateral Sclerosis Study, United States, 2005–2010

Variable	Controls		ALS Cases		Model 1[a]		Model 2[b]	
	No.	%	No.	%	OR	95% CI	OR	95% CI
BMI change[c,d]	913	100.0	418	100.0	0.94	0.89, 1.00	0.94	0.89, 1.00
Category of change in BMI[e]								
Decrease or stable	188	20.6	128	30.6	1.61	1.21, 2.14	1.61	1.20, 2.16
Moderate increase	473	51.8	194	46.4	1.00	Referent	1.00	Referent
Substantial increase	252	27.6	96	23.0	1.06	0.77, 1.45	1.06	0.76, 1.47
P for linear trend[f]					0.088		0.093	
Missing	8		16					

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] Odds ratios were adjusted for age at the reference date, use of the Department of Veterans Affairs system for health care, and BMI at age 40 years; 1 case and 2 controls were excluded from the model because of missing values in the covariates.

[b] Odds ratios were adjusted for age, use of the Department of Veterans Affairs system for health care, BMI at age 40 years, cigarette smoking, and years of education; 16 cases and 18 controls were excluded from the model because of missing values in the covariates.

[c] BMI was calculated as weight (kg)/height $(m)^2$.

[d] Odds ratio for ALS for a 1-unit increase in BMI change.

[e] Based on the interquartile range of change in BMI between ages 25 and 40 years: decrease or stable: <0.5; moderate increase: 0.5–<3.5; substantial increase: ≥3.5.

[f] The within-category median BMI change was assigned to each observation, and this new variable was used as a predictor variable for testing the trend.

Table 4. Association of Body Mass Index at Age 40 Years With Amyotrophic Lateral Sclerosis According to Site of Symptom Onset, Genes and Environmental Exposures in Veterans With Amyotrophic Lateral Sclerosis Study, United States, 2005–2010

Variable	Site of ALS Symptom Onset							
	Spinal				Bulbar			
	No. of Cases	%	OR[a]	95% CI	No. of Cases	%	OR[a]	95% CI
BMI at age 40 years[b,c]	341	100.0	0.95	0.92, 0.99	60	100.0	0.93	0.85, 1.01
Category of BMI at age 40 years								
15–<20	7	2.0	1.02	0.41, 2.55	1	1.7	0.76	0.10, 6.05
20–<25	139	40.8	1.00	Referent	28	46.7	1.00	Referent
25–<30	161	47.2	0.85	0.64, 1.12	29	48.3	0.93	0.53, 1.65
≥30.0	34	10.0	0.68	0.44, 1.07	2	3.3	0.25	0.06, 1.10
P for linear trend[d]			0.107				0.140	
Missing	9				3			
P for combining spinal- and bulbar-onset ALS[e]			0.285					

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] Odds ratios for the association of BMI with bulbar or spinal ALS versus no ALS. Estimates were adjusted for age, sex, race/ethnicity, use of the Department of Veterans Affairs system for health care, cigarette smoking, and years of education; 16 cases and 18 controls were excluded from the model because of missing values in the covariates.

[b] BMI was calculated as weight (kg)/height $(m)^2$.

[c] Odds ratio for ALS for a 1-unit increase in BMI.

[d] The within-category median BMI was assigned to each observation, and this new variable was used as a predictor variable for testing the trend.

[e] *P* value from likelihood ratio tests of whether the 2 types could be combined.

Table 5. Association of Body Mass Index at Age 40 Years With Amyotrophic Lateral Sclerosis According to Diagnostic Delay, Genes and Environmental Exposures in Veterans With Amyotrophic Lateral Sclerosis Study, United States, 2005–2010

Variable	ALS Diagnostic Delay											
	Short (≤1 Year)				Moderate (>1–≤3 Years)				Long (>3 Years)			
	No. of Cases	%	OR[a]	95% CI	No. of Cases	%	OR[a]	95% CI	No. of Cases	%	OR[a]	95% CI
BMI at age 40 years[b,c]	189	100.0	0.91	0.87, 0.96	147	100.0	0.96	0.91, 1.02	70	100.0	1.01	0.95, 1.09
Category of BMI at age 40 years												
15–<20	5	2.7	1.22	0.43, 3.46	1	0.7	0.36	0.05, 2.77	2	2.9	1.60	0.34, 7.45
20–<25	87	46.0	1.00	Referent	58	39.5	1.00	Referent	23	32.9	1.00	Referent
25–<30	83	43.9	0.72	0.51, 1.02	73	49.7	0.89	0.60, 1.32	38	54.3	1.38	0.80, 2.38
≥30.0	14	7.4	0.44	0.23, 0.81	15	10.2	0.78	0.41, 1.45	7	10.0	0.92	0.38, 2.25
P for linear trend[d]			0.003				0.586				0.948	
Missing	9				2				1			
P for combining short and moderate delays[e]			0.459									
P for combining short and long delays[e]			0.094									
P for combining moderate and long delays[e]			0.388									

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] Odds ratios for the association of BMI with ALS with short, moderate, and long diagnostic delays versus no ALS. Estimates were adjusted for age, sex, race/ethnicity, use of the Department of Veterans Affairs system for health care, cigarette smoking, and years of education; 16 cases and 18 controls were excluded from the model because of missing values in the covariates.

[b] BMI was calculated as weight (kg)/height $(m)^2$.

[c] Odds ratio for ALS for a 1-unit increase in BMI.

[d] The within-category median BMI was assigned to each observation, and this new variable was used as a predictor variable for testing the trend.

[e] *P* value from likelihood ratio tests of whether the 2 outcomes could be combined.

being diagnosed sooner rather than having a faster progression rate. In fact, we did not find an association between prediagnosis BMI and ALS survival; only BMI at diagnosis and BMI change between age 40 years and diagnosis were associated with ALS survival. Other studies support the hypothesis that BMI change immediately before ALS diagnosis is both a common feature of ALS and a prognostic factor, whereas evidence that BMI at ALS diagnosis is a prognostic factor is inconsistent, possibly due to small sample sizes in some studies (12, 25–27).

Research on fat metabolism and ALS is sparse, and the mechanisms underlying hypermetabolism in ALS are currently unclear (10). However, many of the main ALS genes are related to energy metabolism to some extent. Dyslipidemia, reduced adipose tissue accumulation, and increased resting energy expenditure are typical features of the *SOD1*-mutant ALS mice in the presymptomatic phase (24, 28). Moreover, mice lacking TAR DNA-binding protein 43 (TDP-43), which is pathologically altered in ALS, had rapid loss of body fat and down-regulation of TBC1 domain family member 1 (*TBC1D1*), a gene linked to human obesity (29–31). RNA/DNA-binding fused in sarcoma (FUS), another protein important for RNA metabolism that has been linked to ALS, interacts with key proteins in energy metabolism (32). Interestingly, mutations affecting TDP-43 and FUS are uncommon in patients with ALS and co-occurring frontotemporal dementia that have higher BMI compared with patients without cognitive symptoms (33, 34). The most commonly mutated gene in ALS known to date is chromosome 9 open reading frame 72 (*C9ORF72*), which encodes a protein of still uncharacterized function (35). Nevertheless, *C9ORF72* repeat expansions in a mouse model were associated with TDP-43 pathology, decreased body weight, and hyperactivity (36).

Whether metabolic features are risk factors for ALS or rather prodromal symptoms of the disease remains unclear. ALS may have a long presymptomatic period similar to that observed for Alzheimer and Parkinson diseases (37). Although we cannot address this question, our study provides evidence that patients with ALS may have altered BMI long before the onset of motor symptoms. Availability of energy reserves in individuals with normal or high BMI might both provide protection from neurotoxic exposures and retard the development and progression of symptoms by mitigating the increased energy requirements associated with ALS. Furthermore, low BMI might be an early and maybe lifelong feature of the disease that is suggestive of an underlying disease process leading to clinically manifest ALS years later. Metabolic dysfunction, especially hyperlipidemia, is known to predict disease progression and prognosis, but a better understanding of the role and timing of metabolic changes occurring before motor symptoms is needed to determine whether the association between BMI and ALS is due to reverse causation (38, 39).

Table 6. Associations of Body Mass Index at Age 40 Years and Body Mass Index at Diagnosis Date With Survival After Amyotrophic Lateral Sclerosis Diagnosis, Genes and Environmental Exposures in Veterans With Amyotrophic Lateral Sclerosis Study, United States, 2005–2013

Variable	No. of ALS Cases	%	No. of Deaths	%	Person-Years of Follow-up	Age-Adjusted Model		Multivariable-Adjusted Model	
						HR[a]	95% CI	HR[b]	95% CI
BMI at age 40 years[c,d]	415	100.0	308	100.0	1 330.7	1.01	0.97, 1.04	1.02	0.98, 1.05
Category of BMI at age 40 years									
15–<20	7	1.7	6	1.9	30.0	1.39	0.61, 3.19	1.36	0.60, 3.12
20–<25	175	42.2	127	41.2	551.6	1.00	Referent	1.00	Referent
25–<30	196	47.2	146	47.4	639.3	0.95	0.75, 1.21	0.98	0.77, 1.25
≥30.0	37	8.9	29	9.4	109.8	1.11	0.73, 1.67	1.22	0.81, 1.85
P for linear trend[e]						0.961		0.686	
Missing	12		10						
BMI at diagnosis[d]	459	100.0	333	100.0	1 515.5	0.97	0.94, 1.00	0.98	0.95, 1.01
Category of BMI at diagnosis									
15–<20	13	2.8	12	3.6	30.7	1.64	0.89, 3.04	1.63	0.88, 3.02
20–<25	148	32.2	108	32.4	467.6	1.00	Referent	1.00	Referent
25–<30	215	46.8	160	48.1	719.6	0.87	0.68, 1.11	0.90	0.70, 1.17
≥30.0	83	18.1	53	15.9	297.7	0.70	0.50, 0.97	0.76	0.54, 1.07
P for linear trend[e]						0.008		0.035	
Missing	1		0						

Abbreviations: ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; HR, hazard ratio.

[a] Hazard ratio for death from ALS among cases (adjusted for age at diagnosis).

[b] Hazard ratio for death from ALS among cases according to BMI at age 40 years (adjusted for date of birth and diagnostic delay) or BMI at ALS diagnosis date (adjusted for age at diagnosis, diagnostic delay, riluzole use, and symptom onset site); 10 and 25 subjects were excluded from the models for BMI at age 40 years and at the diagnosis date, respectively, because of missing values in the covariates.

[c] BMI was calculated as weight (kg)/height $(m)^2$.

[d] Hazard ratio for ALS death for a 1-unit increase in BMI.

[e] The within-category median BMI was assigned to each observation, and this new variable was used as a predictor variable for testing the trend.

Our results should be interpreted cautiously because BMI fails to discriminate between very muscular individuals and overweight individuals (40). Nevertheless, both BMI and waist-to-hip ratio—but not height and hip circumference—were found to be inversely associated with ALS mortality (13).

Our study had several limitations. First, self-reporting of weight and height may have produced misclassification of BMI. Our results would overestimate the real association between BMI at age 40 years and ALS risk if persons with ALS underestimated their weight at age 40 years compared with controls, for example if current BMI affects the recall of previous BMI.

Second, controls in our study might have only imperfectly represented the underlying population giving rise to the ALS cases. Controls were on average more educated than both the general population of US military veterans and the GENEVA ALS cases (16). Adjusting for education did not, however, change the association between BMI and ALS observed in the present study. Further, because educational level is inversely associated with BMI in the US population, it is possible that controls were thinner than the general population of US veterans and that the inverse association between BMI and ALS was underestimated in our study (41).

Third, the data we used for the survival analyses were left-truncated because only patients with ALS who survived until the time of interview were included. Therefore, the proportion of patients with a long disease duration might be higher in GENEVA than in the entire population of US military veterans. The association of ALS with BMI at age 40 years, however, changed only slightly after exclusion of patients diagnosed at least 2 years before the interview.

Finally, our sample of US military veterans—which consisted mostly of non-Hispanic white men—may not represent other populations of ALS patients and healthy controls. Veterans might have had different environmental exposures than nonmilitary populations. Although exposure to toxic agents has been found to be associated with risk of ALS among military personnel, it is not very likely that the associations between BMI and ALS would be confounded by exposures specifically associated with military service, because these risk factors for ALS do not strongly affect BMI (42). If any residual confounding is present, it could arise from the imperfect adjustment for smoking and lack of detailed information on physical activity (43). However, information on smoking duration, cigarette pack-years, and participation in organized sport was available,

and there was no association of ALS risk with these factors in GENEVA (44).

Characteristics of our study population that were not a consequence of military service, such as the sex distribution or the racial/ethnic and genetic background of participants, may affect the generalizability of our results.

Sex differences in the association between BMI and ALS have previously been suggested and—although our estimates were similar in the entire sample, in men, and in non-Hispanic white men—our study lacked the statistical power to study the associations among women or other ethnic groups (13). Nevertheless, our results were consistent with published findings from different populations (12, 13).

Strengths of our study include the large sample size, medical record–confirmed ALS diagnosis, detailed information on covariates and clinical features, and information on BMI at different ages. The latter enabled us to analyze BMI and BMI change at younger ages.

In conclusion, a low BMI in middle age and a BMI that did not increase before middle age may be associated with a higher ALS risk later in life but not with ALS survival. Further investigation of ALS risk and prediagnosis metabolic features at younger ages is needed to better understand our findings.

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