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Association Between Dietary Intake and Function in Amyotrophic Lateral Sclerosis

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Abstract

IMPORTANCE—There is growing interest in the role of nutrition in the pathogenesis and progression of amyotrophic lateral sclerosis (ALS).

OBJECTIVE—To evaluate the associations between nutrients, individually and in groups, and ALS function and respiratory function at diagnosis.

DESIGN, SETTING, AND PARTICIPANTS—A cross-sectional baseline analysis of the Amyotrophic Lateral Sclerosis Multicenter Cohort Study of Oxidative Stress study was conducted from March 14, 2008, to February 27, 2013, at 16 ALS clinics throughout the United States among 302 patients with ALS symptom duration of 18 months or less.

EXPOSURES—Nutrient intake, measured using a modified Block Food Frequency Questionnaire (FFQ).

MAIN OUTCOMES AND MEASURES—Amyotrophic lateral sclerosis function, measured using the ALS Functional Rating Scale–Revised (ALSFRS-R), and respiratory function, measured using percentage of predicted forced vital capacity (FVC).

RESULTS—Baseline data were available on 302 patients with ALS (median age, 63.2 years [interquartile range, 55.5–68.0 years]; 178 men and 124 women). Regression analysis of nutrients found that higher intakes of antioxidants and carotenes from vegetables were associated with higher ALSFRS-R scores or percentage FVC. Empirically weighted indices using the weighted

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quantile sum regression method of “good” micronutrients and “good” food groups were positively associated with ALSFRS-R scores (β [SE], 2.7 [0.69] and 2.9 [0.9], respectively) and percentage FVC (β [SE], 12.1 [2.8] and 11.5 [3.4], respectively) (all $P < .001$). Positive and significant associations with ALSFRS-R scores (β [SE], 1.5 [0.61]; $P = .02$) and percentage FVC (β [SE], 5.2 [2.2]; $P = .02$) for selected vitamins were found in exploratory analyses.

CONCLUSIONS AND RELEVANCE—Antioxidants, carotenes, fruits, and vegetables were associated with higher ALS function at baseline by regression of nutrient indices and weighted quantile sum regression analysis. We also demonstrated the usefulness of the weighted quantile sum regression method in the evaluation of diet. Those responsible for nutritional care of the patient with ALS should consider promoting fruit and vegetable intake since they are high in antioxidants and carotenes.

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disorder that causes progressive muscle atrophy, paralysis, and eventual respiratory failure. The incidence rate of ALS ranges from 1.5 to 2.5 per 100000 individuals per year, with a prevalence rate of approximately 3.9 to 8 per 100000 individuals in the United States.[1] Males are slightly more affected than females, with a ratio of approximately 1.6:1. The median survival time from onset of ALS ranges from 20 to 48 months, but 10% to 20% of patients survive longer than 10 years.[2] There is growing interest in the role of nutrition and environmental factors in the pathogenesis and progression of ALS.[3,4] There is some evidence that risk of ALS increases with increased intake of macronutrients, such as carbohydrates, glutamate, and fat, and with low intake of various micronutrients, including vitamin E, ω-3 polyunsaturated fatty acids, and carotenoids, as well as fruits and vegetables, although this risk is not consistently demonstrated in studies.[5–13] In a recent analysis of data pooled from 5 cohort studies with a total of 995 patients with ALS, the highest intake of ω-3 polyunsaturated fatty acids as compared with the lowest intake was associated with a 34%reduced risk of ALS.[14] Risk of ALS is also inversely associated with body mass index (BMI).[15]

Previous research suggests that oxidative stress is associated with the pathogenesis of ALS; there is some evidence that dietary factors may increase[5,6,16–20] or potentially decrease[5–14] oxidative stress. Previous studies have not evaluated whether nutrients or foods are associated with ALS or respiratory function soon after diagnosis. Using data from a study of ALS progression, our analysis examines associations between nutritional intake and functional performance (measured by ALS Functional Rating Scale–Revised [ALSFRS-R][21] scores) and respiratory function (measured as forced vital capacity [FVC]) at the time of study entry.

Methods

Patients diagnosed with ALS based on revised El Escorial[22] or Awaji[23] criteria less than 18 months after symptom on set were recruited into the longitudinal ALS Multicenter Cohort Study of Oxidative Stress (ALSCOSMOS) study from March 14, 2008, to February 27, 2013, at 16 clinical centers located throughout the United States. Detailed description of patients and methods were previously reported.[24] this study is a cross-sectional analysis of baseline data.

The procedures followed were in accordance with the ethical standards of each institutional review board where approval was obtained for each of the 16 clinical sites. Written consent was provided where possible and if the patient was unable to provide written consent, verbal consent with an independent witness was obtained.

Demographic and Neurological Data

Clinical assessment included height, weight, scores on the ALSFRS-Rising a 12-item questionnaire, percentage FVC, and a comprehensive neurological examination. The ALSFRS-R is the most widely used clinical outcome in ALS clinical trials[25] and has been extensively validated.[26–28]

Key Points

Question

What is the association between nutrient intake and amyotrophic lateral sclerosis function and respiratory function at diagnosis?

Findings

In this cross-sectional analysis of a multicenter cohort of 302 patients with amyotrophic lateral sclerosis, antioxidants, carotenes, fruits, and vegetables were associated with higher amyotrophic lateral sclerosis function at baseline.

Meaning

Nutritional care of the patient with amyotrophic lateral sclerosis should include promotion of foods high in antioxidants and carotenes, including fruits and vegetables.

Dietary Data

To assess diet, we used a modification of the previously validated Food Frequency Questionnaire (FFQ),[29–32] that entailed shortening the questionnaire from 127 to 85 items so that completion time would be approximately 15 minutes, similar to previously validated Fifes. Food frequency questionnaires are preferred to assess usual dietary intakes.[33] Our shortened FFQ assessed specific intake information, focusing on foods and nutrients considered to be antioxidants; vitamins A, C, and E; β-carotene; calcium; iron; zinc; and selenium. In addition to the 85 questions, there was an open-ended section on additional foods consumed, 10 summary questions, and 19 questions about supplement intake. Participants self-administered the FFQ, with caregiver assistance if needed. Nutritionquest scanned all completed FFQ forms,[34] which converted FFQ data into estimates of average daily nutrient intake using a standardized reference nutrient database and provided food-specific and food group intake data.

Given that antioxidants may be particularly important, we a priori estimated a carotene index, which was a sum of textile groupings (low, 1; moderate, 2; and high, 3) of α-carotene, β-carotene, cryptoxanthin, lute in and zeaxanthin, and limonene. The a priori antioxidant index included these nutrients as well as similar textile groupings of vitamin C, vitamin E, selenium, and quartering. We administered the survey twice to 29 patients with ALS and

there were no differences in the nutrients of interest between the results of first and second FFQ (Wilcox on signed rank test). The infraclass correlation coefficients ranged from 0.62 to 0.87 for all nutrients analyzed, except for limonene (r = 0.35).

Groups of Variables

Nutrients and food groups were grouped for further analysis based on their anticipated association with ALS function (from a review of the literature); items were primarily grouped as "good" if they had antioxidant properties or were previously associated with reduced risk of ALS[5–14] or as "bad" based on association with oxidative stress or increased risk of ALS.[5,6,16–20] Micronutrients considered potentially good were vitamin C; vitamin E; α-carotene; β-carotene; cryptoxanthin; lute in and zeaxanthin; selenium; limonene; quartering; ω-3 fatty acids; is flavones; cytokine; vitamin A; vitamin D; fiber from beans, vegetables, and fruit, and grains; and ω-6 fatty acids. Micronutrients considered potentially bad were *trans*-fat, saturated fats, ω-6 fatty acids, total sugars, high ratio of ω-6 to ω-3 fatty acids, and motioning. Macronutrients considered potentially good were food energy (calories), protein, and carbohydrates; macronutrients considered potentially bad were dietary fat and sugary beverages. Food groups considered potentially good were whole grains; milk; yogurt; solid fruits; fruit juice; legumes; eggs; fish high in ω-3 fatty acids; fish low in ω-3 fatty acids; poultry; soy foods; protein from nuts and seeds; beneficial oils (from fish, nuts, avocado, and dressing); deep yellow, orange, and dark green vegetables; other vegetables (not dark green, yellow, or orange); potatoes; and tomatoes. Food groups considered potentially bad were oils, sweets, sodas, cheese, milk, eggs, beef, pork, lamb, and lunchmeats.

In addition, exploratory analyses were performed on a series of nutrients considered potentially good (calcium, iron, potassium, thiamin, riboflavin, niacin, vitamin C, vitamin E, zinc, vitamin B_6, magnesium, retinal, vitamin D [in micrograms], vitamin K, selenium, and total glutathione) vs. nutrients considered potentially bad (phosphorous, sodium, caffeine, and foods resulting in a high glycolic index). The use of groups of nutrients and foods allows examination of nutrients that are highly correlated based on the dietary patterns of individuals. Moreover, our weighted quantile sum (WQS) regression method, described below, ensures that nutrients that are grouped incorrectly will have a smaller weight in the proposed groupings. Thus, we were able to simultaneously examine nutrients instead of relying on examining individual nutrients, which is a less optimal method and more prone to type I error.

Statistical Analysis

All statistical models used ALSFRS-R score or percentage FVC as the outcome variables. We included covariates if the association (estimated β coefficient) changed by 10% comparing models with and without the covariates. Thus, our final models included age, sex, current BMI, duration of symptoms, and caloric intake. Regression analysis was performed using the carotene index and antioxidant index as the primary exposures.

We also used WQS regression[35,36] to account for the co linearity between nutrient exposures. Briefly, nutrients and food groups were grouped a priori. For each food grouping,

WQS regression resulted in an empirically weighted sum of the quartiles of the food group components. Each WQS regression index was included in a regression model, adjusted for covariates. The corresponding weights were used to identify important components when the regression coefficient of the index was significant. The WQS regression method is robust against improper assignment of a nutrient or food type as good or bad since that nutrient or food will be assigned a negligible weight, minimizing potential error in nutrient grouping.

Results

A total of 355 patients were eligible and enrolled in ALSCOMOS, while 477 potentially eligible but nonenrolled patients were reported by the sites. Major reasons for exclusion were that the study was not discussed (253 [53%]), patients refused to participate (143 [30%]), or patients were overwhelmed with their diagnosis (38 [8%]).[24] There were no differences between those enrolled and those not enrolled on demographics (eg, age, sex, and race/ethnicity), duration of disease, El Escorial Criteria diagnostic groups, participation in clinical trials, and use of alternative treatments; however, enrolled patients were more likely to have private insurance and less likely to be covered by Medicare compared with those who were not enrolled.[24] A total of 53 patients did not have ALSFRS-R performed or FVC measured or nutrition data were not available, leaving 302 patients for this analysis. These 302 patients (178 men [58.9%]) had a median age of 63.2 years (interquartile range [IQR], 55.5–68.0 years), median BMI (calculated as weight in kilograms divided by height in meters squared) of 26 (IQR, 23.5–28.5), and median symptom duration of 0.94 year (IQR, 0.65–1.25 years). At the baseline visit, approximately half of the patients reported eating problems early in the course of the disease and occasional choking. Two hundred sixteen patients (71.5%) had a spinal onset of disease and 85 (27.7%) had bulbar onset. The median ALSFRS-R score was 37 (IQR, 33–41), reflecting modestly severe ALS, and median FVC was 82% (IQR, 66%–97%), reflecting low normal respiratory function. Higher ALSFRS-R scores and higher percentage of FVC indicate better function.

The mean (SD) daily total calorie intake was 1730 (747); mean daily intake of other nutrients is listed in Table 1. There was no significant difference in caloric intake between those who reported eating problems early in the course of the disease and occasional choking at the baseline visit (1827 calories per day) compared with those who did not report such problems (1692 calories per day).

After controlling for age, sex, duration of symptoms, current BMI, and caloric intake, the antioxidant index and carotene index were positively associated with ALSFRS-R score (β [SE], 0.182 [0.093]; $P = .05$ and β [SE], 0.303 [0.193]; $P = .03$, respectively) and with percentage FVC (β [SE], 0.773 [0.325]; $P = .02$ and β [SE], 1.08 [0.486]; $P = .03$, respectively; Table 2). There was no significant difference between the results of the antioxidant and carotene indices and ALSFRS-R score or percentage FVC based on whether patients reported eating problems early in the course of the disease and occasional choking at the baseline visit.

Regression analysis for individual nutrients and ALSFRS-R score and percentage FVC after controlling for age, sex, current BMI, duration of symptoms, and dietary caloric intake value

of individual nutrients can be found in the eTable in the Supplement. Because there are strong correlations between these individual nutrients (r = 0.40–0.96; $P < .01$), it is not possible to determine the actual nutrients with the strongest associations; therefore, WQS regression analysis was used.

Table 3 shows the direction of the β coefficient and *P* values for WQS regression analyses. Detailed results from this analysis are described below and in the Figure, which illustrates the estimated weights of each variable for the WQS regression index for each nutrient or food, with larger weights indicating a stronger contribution to the index.

Micronutrients and Macronutrients

An empirical WQS regression index of good micronutrients was positively associated with ALSFRS-R score (β [SE], 2.7 [0.69]; $P < .001$), with 91% of the weight associated with 9 of 18 nutrients (Table 3 and Figure, A). Similarly, the WQS regression for good micronutrients associated with percentage FVC was positive (β [SE], 12.1 [2.8]; $P < .001$) (Table 3); however, 80% of the weights were concentrated on 6 nutrients (lycopene, ω-3 fatty acids, ω-6 fatty acids, isoflavones, and fiber from both vegetables and grains) (Figure, A).

The empirical WQS regression indices developed for bad micronutrients were not significantly associated with either outcome variable. The empirical WQS regression indices developed for macro nutrients were not significantly associated with ALSFRS-R score or percentage FVC (Table 3).

Food Groups

An empirical WQS regression index of good food groups was positively associated with ALSFRS-R score (β [SE], 2.9 [0.9]; $P = .001$) (Table 3), with 71% of the weight associated with fruit, eggs, fish, poultry, nuts and seeds, beneficial oils, and other vegetables (Figure, B). The WQS regression index of good food groups was also positively associated with percentage FVC (β [SE], 11.5 [3.4]; $P < .001$) (Table 3), with weights similar to those for ALSFRS-R: yogurt, fruits, fish, poultry, nuts and seeds, beneficial oils, and other vegetables (Figure, B).

The empirical WQS regression index of bad food groups was negatively and significantly associated with ALSFRS-R score (β [SE], –1.6 [0.53]; $P = .002$) (Table 3). The primary component was milk, with 50% of the weight, as well as beef and pork (11%) and lunchmeats (32%) (Figure, C). There was no association with percentage FVC.

Exploratory Analyses With WQS Regression

When selected beneficial vitamins and minerals were considered, the WQS regression index had a positive and significant association with ALSFRS-R score (β [SE], 1.5 [0.61]; $P = .02$). Five vitamins held 95% of the weight (niacin, vitamin B_6, vitamin K, selenium, and glutathione). A similar WQS regression index was positive and significantly associated with percentage FVC (β [SE], 5.2 [2.2]; $P = .02$), with 85% of the weight from vitamin B_6, riboflavin, vitamin E, vitamin K, and glutathione.

Discussion

In the longitudinal ALS COSMOS study, we analyzed the cross-sectional data of dietary variables and ALS function at baseline (as ALSFRS-R score and percentage FVC). Our results indicate that greater intakes of antioxidant nutrients and foods high in carotenoids appear to be associated with better function at study entry. Weighted quantile sum regression allows for the analysis of combinations of nutrients and food groups compared with the typical evaluation of single nutrients that cannot be performed owing to strong collinearity between all nutrients. Weighted quantile sum regression determines an empirically weighted quantile sum index associating a set of nutrients with specific outcome variables, in this case ALSFRS-R score and percentage FVC. The 2 most highly weighted micronutrients associated with ALSFRS-R score were nutrients believed to be strong antioxidants: lutein and zeaxanthin (15%) and ω-3 fatty acids (18%); the dominant components associated with percentage FVC were ω-3 fatty acids (19%), ω-6 fatty acids (23%), and fiber from grains and vegetables and fruit (9% and 14%, respectively). The primary components from the analyses of the good food group were eggs (19% associated with with ALSFRS-R score), fish, poultry, beneficial oils, and vegetables. These foods supply antioxidants and are typically associated with a healthy diet. On the other hand, milk (50%) and lunch meats (32%) were highly weighted in a negative association with ALSFRS-R score, perhaps a result of the higher fat intake and the potential for these foods to promote oxidative stress.

There were some limitations in this study and only associations, not cause and effect, can be found in this cross-sectional analysis. Ideally, WQS regression is performed on 2 independent data sets—one to build the WQS regression index through bootstrap sampling, and the second to test the significance of the signal from the created index. In our analysis, the sample size of 302 was not considered large enough to split the data into a discovery data set and a validation data set. Therefore, weights were estimated in the same data used to test for significance. In addition, data were collected with an FFQ as an attempt to measure dietary habits over time, but this method may not always represent true daily diets. Although the caloric intake may be slightly underreported with the use of an FFQ,[37] the ranking of caloric and nutrient intake will be accurate. There are only limited data on which nutrients are associated with the development of ALS or are associated with progression of ALS. Our groupings of good and bad foods and nutrients were based on existing knowledge of ALS and general dietary knowledge.[5–14,16–20] However, if we incorrectly assigned a nutrient or food type to a nutrient group, it will have a very small weight in the WQS regression, minimizing the error from nutrient grouping.

A strength of this study was the relatively large sample size of patients with ALS who appear representative of all eligible patients at the ALS centers, improving generalizability. To our knowledge, this is also one of the first studies to evaluate diet in association with measures of ALS function near the time of diagnosis. The consistency of the findings using 2 different statistical methods adds strength. Although we used cross-sectional data for this analysis, we intend to include the 24-month data on both dietary intake and progression of ALS in future analyses when those data are available. Longitudinal data will be important to confirm any findings from this study as well as to evaluate the role of nutrition in the progression of ALS.

Several nutrients have been proposed to be associated with the development of ALS, although the data are largely inconsistent.[5–11,13,14,38] Fitzgerald et al[14] suggested that fatty acid composition of cell plasma membranes might modulate oxidative stress responses, excitotoxicity, and inflammation, factors hypothesized to be associated with ALS.[39] Polyunsaturated fatty acid intake may also be associated with body fat, which also appears to protect against ALS.[40,41]

We found that milk intake may have a negative affect on ALS function (assessed by ALSFRS-R score and percentage FVC) at study entry. Milk-based supplements are used for patients with ALS and were reported to lead to weight gain, improved biochemistry, and a slower decline in ALSFRS-R score based on a 4-month study of only 16 patients with ALS.[42] It will be important to see how dairy and milk intake are associated with changes in ALSFRS-R score and mortality in the longitudinal follow-up of the ALS COSMOS population.

Although previous studies have associated the intake of several healthy nutrients and foods with reduced risk of ALS,[4–13] for the first time, to our knowledge, we have shown that healthy nutrients and antioxidants are associated with better ALS function around the time of diagnosis. Therefore, nutritional care of the patient with ALS might include not only caloric management but also promotion of fruit and vegetable intake.

Conclusions

Evaluation of baseline dietary intake and severity of ALS (assessed by percentage FVC and ALSFRS-R score) indicates a consistent association between these variables and certain nutrients. Antioxidant nutrients, foods high in carotenoids and fiber, and vegetable intake are associated with better ALS function using 2 different analysis methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

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Obtained funding: Factor-Litvak, Mitsumoto.

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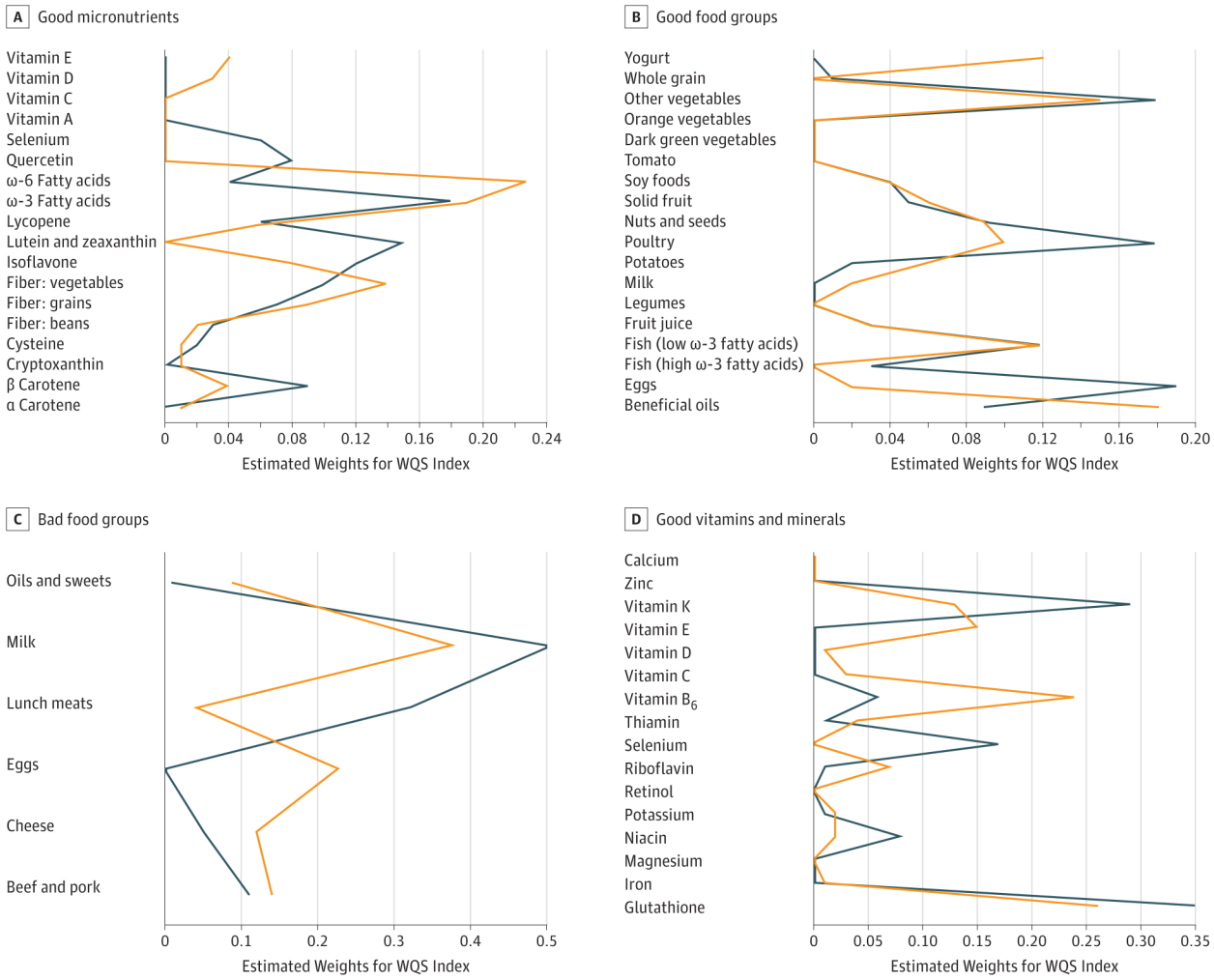

Figure. Estimated Weights for the Weighted Quantile Sum (WQS) Regression Index

A, Good micronutrients (Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised [ALSFRS-R] score, positive β coefficient; $P < .001$; percentage forced vital capacity [FVC], positive β; $P < .001$). B, Good food groups (ALSFRS-R score, positive β; $P = .001$; percentage FVC, positive β; $P = .001$). C, Bad food groups (ALSFRS-R score, negative β; $P = .002$; percentage FVC, negative β; $P = .29$). D, Good vitamins and minerals (ALSFRS-R score, positive β; $P = .02$; percentage FVC, positive β; $P = .02$). The value indicates the estimated weights of each variable for the WQS regression index for the category. Blue indicates ALSFRS-R score and orange, percentage FVC.

Table 1

Dietary Intake in Patients With ALS

Characteristic	Dietary Reference Intake[a]	Mean (SD) [Range]
Kilocalories		1730 (747) [264–5839]
Protein, g	46–56	69 (34) [11–304]
Carbohydrates, %	45–65	45 (8) [23–75]
Sweets, %	<25	14 (11) [0–69]
Fat, %	20–35	37 (6) [15–58]
Total fat, g		72 (34) [14–287]
Saturated fat, g		23 (12) [4–90]
Trans fats, g		2.5 (1.4) [0–10]
ω-3 Fatty acids, g	1.1–1.6	8.2 (2.2) [3.5–20]
ω-6 Fatty acids, g	11–17	13.4 (6.7) [2.0–47]
Dietary ω-6 fatty acid to ω-3 fatty acid ratio, g		8.2 (2.2) [3.5–20]
Dietary fiber, g	21–30	14.2 (7.4) [0–55]
Vitamin A, μg	700–900	778 (411) [79–2676]
α-Carotene, μg		385 (426) [0–4086]
β-Carotene, μg		3605 (2990) [1–25 383]
Riboflavin, mg	1.1–1.3	1.86 (0.93) [0–6]
Niacin, mg	14–16	18.9 (9.8) [3–77]
Vitamin B_6, mg	1.5–1.7	1.91 (0.96) [0–7]
Vitamin C, mg	75–90	97.8 (59.7) [11–395]
Vitamin D, μg	15–20	5.4 (3.7) [0–22]
Vitamin E, mg	15	8.1 (4.7) [1–35]
Vitamin K, μg	90–120	191 (154) [19–1222]
Cryptoxanthin, μg		139 (119) [0–565]
Lutein and zeaxanthin, μg		2945 (2805) [0–23 645]
Lycopene, μg		3986 (2814) [0–20 174]
Selenium, μg	55	85 (41) [12–332]
Quercetin, mg		5.3 (3.4) [0–19]
Isoflavones, mg		22.7 (206.4) [0–3531]
Cysteine, mg		1.0 (0.5) [0–5]
Methionine, mg		1.5 (0.8) [0–7]
Glutathione, total, mg		38.7 (20.2) [0–171]
Meat, No. servings		2.2 (1.5) [0–12]
Dairy, cups	3	1.6 (1.4) [0–9]
Vegetables, cups	2.5	2.5 (1.8) [0–14]
Fruit, cups	2	1.3 (1.1) [0–5]
Grain, No. servings		5.0 (2.6) [2–4.6]

Abbreviation: ALS, amyotrophic lateral sclerosis.

[a]Empty cells indicate no true Dietary Reference Intakes.

Table 2

Regression Analysis of Carotene and Antioxidant Indices and ALSFRS-R Score and Percentage FVC

	ALSFRS-R Score		FCV%	
Index	**β (SE)**	***P* Value**	**β (SE)**	***P* Value**
Carotene	0.303 (0.139)	.03[a]	1.08 (0.486)	.03[a]
Antioxidant	0.182 (0.093)	.05[a]	0.773 (0.325)	.02[a]

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; FVC, forced vital capacity.

[a]By regression analysis after controlling for age, sex, current body mass index, duration of symptoms, and caloric intake.

Table 3

Weighted Quartile Sum Regression

	ALSFRS-R Score		FVC%	
Characteristic	**β Coefficient**	***P* Value**	**β Coefficient**	***P* Value**
Micronutrients				
Good	Positive	<.001	Positive	<.001
Bad	Negative	.53	Negative	.39
Macronutrients				
Good	Positive	.92	Positive	.10
Bad	Negative	.50	Negative	.36
Food Groups				
Good	Positive	<.001	Positive	<.001
Bad	Negative	.002	Negative	.29
Vitamins				
Good	Positive	.02	Positive	.02
Bad	Negative	.44	Negative	.99

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; FVC, forced vital capacity.