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Home-Based Virtual Culinary Nutrition Education Sessions for Amyotrophic Lateral Sclerosis Patients: Quantitative Experimental Pilot Study

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Title:

Home-Based Virtual Culinary Nutrition Education Sessions for Amyotrophic Lateral Sclerosis Patients: Quantitative Experimental Pilot Study

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Abstract:

Amyotrophic lateral sclerosis (ALS) impairs voluntary muscular activity and often results in malnutrition. The need for specialized dietary therapy for ALS-related illnesses is highlighted by recent research, but it also draws attention to the lack of targeted care and ongoing nutritional status monitoring. Technological developments like telehealth and chatbots hold potential for ALS patients' nutritional monitoring. The pilot study examined the feasibility and impact of home-based virtual culinary nutrition education sessions on nutritional knowledge, dietary intake of energy (CHO), protein (PRO) and FAT, body mass index (BMI), and functional status assessed by ALSFRS-R scores in patients with Amyotrophic Lateral Sclerosis (pALS). A total of four pALS and their caregivers were recruited from the ALS Clinic at the NSU Health Neuroscience Institute.Three, one hour culinary sessions were provided using the web-based platform zoom over a 6 week period. These sessions provide a cutting-edge strategy to manage malnutrition caused by ALS and are intended to improve the nutritional understanding and dietary behaviors of pALS. Results showed significant differences in nutrition knowledge and no significant difference in weight, BMI, ALSFRS-R scores, and dietary intake of Kcal (CHO, PRO, and FAT) demonstrating statistical importance as no significance was desired. Results were impacted by a low sample size, but demonstrate motivating outcomes for further research and emphasize the potential advantage of home-based virtual cooking instruction while highlighting the necessity for a tailored nutrition plan.

Research Question:

"Can a home-based culinary nutrition education intervention enhance nutritional intake, functional status, increase survival length after diagnosis, and improve the quality of life in people with amyotrophic lateral sclerosis?"

Background:

Amyotrophic lateral sclerosis (ALS) is a rare, progressive neurodegenerative condition that primarily affects motor neurons causing the brain to lose the ability to initiate and control voluntary muscle movements.[1] Currently, there is no cure for the disease and the average lifespan of survival after diagnosis is about 2-5 years, however some have surpassed including the late theoretical physicist Stephen Hawking.[1] Some necessary voluntary muscle movements include chewing, walking, talking, and swallowing.[1] The lack of nourishment to the motor neurons causes them to harden resulting in a slow progression of muscle weakening, wasting, atrophy, and eventually death.[1,2] Early symptoms of ALS include muscle twitches, cramps and stiffness in the arms, legs, shoulder, and tongue, slurred and nasal speech, and difficulty chewing or swallowing.[1] The progression of the loss of voluntary muscle movement control begins to affect the individual's ability to perform major tasks like moderate to high intensity exercise or traveling, to minor daily tasks like getting around the house, cooking, and maintaining energy levels while eating.[1,2] Progressive symptoms include dysphagia, dysarthria, dyspnea, hypermetabolism, and malnourishment.[1] As symptoms progress, the role of a caregiver becomes more vital to make sure pALS are receiving adequate nourishment. Due to the complex relationships between nutritional status, hypermetabolism, and many physical challenges, maintaining nutritional needs can be challenging, negatively impacting an individual's functional status and quality of life.[1,2]

To develop efficient and correct ALS management methods for pALS, it is essential to accurately analyze individual nutritional status. Current scientific research emphasizes the importance of nutritional therapies, weight management, and tailed care for ALS-related secondary disorders such as dysphagia and malnutrition. However, research also highlights the inadequacy of the typical treatment approach for these co-occurring diseases and highlights the demand for specialized and individualized therapy, as well as the need for quick routine monitoring of a patient's nutritional status to guarantee the best possible health outcomes. As of now, there is limited scientific research exploring whether an individualized, home-based virtual cooking training and nutrition education treatment for pALS may positively influence the progression of malnutrition and neuropathy, as well as the patient's functional status and quality of life.[1,2,3]

Literature Review:

Dietary difficulties often affect the prognosis and survival of pALS. According to the current literature, early nutritional evaluation and the application of technology such as telehealth or chatbots are useful tools for treating this population. Weight, BMI, and fat mass were shown to be the most important dietary markers in a study including 92 pALS. A 5% weight loss upon diagnosis tripled the chance of death. This emphasizes the need for ongoing nutritional supervision and prompt action.[5] In particular, taking into account signs like decreased physical activity and considerable weight loss, bioelectrical impedance analysis (BIA) has been proven to help forecast results and direct nutritional changes.[2] It was also discovered that individuals with a worse nutritional status at the start had a lower median survival time using the subjective global assessment (SGA) and global leadership initiative for malnutrition (GLIM) criteria. For 15 months, malnutrition as defined by SGA presented a survival risk. According to the study, nutritional state affects ALS prognosis in a significant way, and early identification and treatment can lead to better outcomes.[11]

To preserve optimal nutritional status for as long as feasible, thirty-three patients were enrolled in the trial, 12 of whom received nutritional intervention protocol monitoring, and 21 of whom received protocol monitoring first. Patients in the Protocol Group had higher BMIs and less weight loss than those in the Control Group. Fewer patients in the Protocol Group required enteral feeding at the six-month and twelve-month follow-up visits. A year after the first assessment, the mortality rate in the Protocol Group was lower than in the Control Group. These results imply that early and targeted nutritional management can postpone weight loss and prolong good nutritional status, ultimately leading to improved clinical outcomes in ALS patients.[3]

As technology developed, the impact of chatbots on improving communication between patients, caregivers, and physicians for dietary monitoring increased. Patients used a conversational interface to record their dietary intake twice a week and obtain nutritional advice monthly. 96% of participants finished the three-month follow-up and 77% finished the six-month follow-up. While the control group continued to lose weight, the chatbot group's weight stabilized. A Telehealth approach with frequent monitoring can stop additional weight loss and allow for early dietary strategy modification.[4] To better understand how the use of technology in nutritional counseling affects these patients' ability to maintain their weight, researchers conducted a randomized clinical trial. 88 patients in the trial were randomized to receive one of three dietary interventions: conventional care, RD counseling, or RD counseling assisted by a mHealth app. The secondary outcomes of calorie intake, ALSFRS-R score, and quality of life (QOL) were evaluated in addition to the primary objective of weight. Although patients using the mobile health app initially consumed more calories, the research discovered that after six

months, there was no discernible difference in long-term calorie intake or weight control between the three groups. [10]

In phase 2 clinical research, 24 individuals were randomly assigned to receive an isocaloric control diet, a high-carbohydrate hypercaloric diet, or a high-fat hypercaloric diet to determine the tolerance of hypercaloric diets in ALS patients receiving enteral nutrition. Less adverse events and serious adverse events were reported in the high-carbohydrate group, indicating that this nutritional strategy may be more bearable for pALS.[7] Another investigation looked at the impact of high- calorie food supplements (HCSs) on weight gain, tolerance, and safety in pALS. 64 ALS patients participated in this randomized controlled study in which they were given different HCSs. The results showed that although some supplements caused gastrointestinal adverse effects and appetite reduction, all three HCSs tested increased body weight successfully. [8]

Results from a study on the effects of milk whey protein supplementation on pALS showed that the supplement blend of 70% whey protein isolate (WPI): 30% modified starch (MS) enhanced various nutritional and functional indices in pALS. This shows that dietary therapy may be advantageous for pALS.[9] Additionally, pALS often experience malnutrition as a result of their inability to eat enough nutrients, which may result in mineral shortages such as Vitamin B12 deficiency. The research looked at the consequences of giving pALS very large doses of methylcobalamin to treat these deficits. According to the study, individuals who were diagnosed within a year of the trial observed dose-dependent advantages in event-free survival and a possible delay in disease development, even though there were no significant changes for the overall patient group.[12]

The literature review demonstrates a need for personalized patient care and a gap in scientific research and development of individualized nutrition intervention and nutrition education for pALS.

Methods:

Due to the lack of current research, a quantitative experimental single arm pilot study was performed. After Institutional review boards (IRB) approval, participants were recruited by Dr. Andrea Charvet, PhD, RDN, LDN at the Amyotrophic Lateral Sclerosis (ALS) multidisciplinary Clinic at the Nova Southeastern University (NSU) Health Neuroscience Institute. Participants were required to be current patients of the multidisciplinary clinic undergoing treatment and satisfy the inclusion criteria. If the inclusion criteria was met, the ALS patients and their caregivers were invited to participate in the study by Dr. Charvet at one of their in-person appointments at the clinic with the interdisciplinary team. If interested, the ALS patients and their caregivers were asked to complete a consent form at the same appointment, verifying

intervention participation. This appointment was then counted as their pre-intervention, in-person initial clinic visit. The initial clinic visit also included additional measurements that would be analyzed before and after the intervention including the patient's body weight, BMI, and ALSFRS-R score. A total of five participants and five caregivers expressed interest and completed a consent form, but due to health complications, one participant had to be excluded from the study prior to initiating the intervention.

The inclusion criteria includes participants who are18 years or older and have access to and are able to manage a personal computer or smartphone with internet connection with or without the presence of a caregiver. Participants must meet at least 75% of their dietary intake by mouth or no more than 25% via feeding tube. Participants are allowed to continue their medication regimen as prescribed by their physician and may either eat and prepare their foods without assistance or receive assistance from a caregiver. All five participants met 100% dietary intake by mouth and none required tube feeding at the start of the study.

The exclusion criteria includes participants with severe cognitive decline impacting their ability to provide consent or those who cannot commit to being at the clinic for the treatment. Participants with limited access to the internet, computer, or smart device as well as can not maintain at least an 60% attendance for the home-based virtual culinary nutrition education sessions will be excluded.

The independent variable of the study is home-based virtual culinary nutrition education sessions. Participants will participate in three, sixty-minute virtual culinary nutrition education sessions in a 6-week time span. Each session will be conducted via the internet using the web-based platform Zoom completed on a computer or smart device and caregivers are encouraged to attend with the participants. The layout of each session included nutrition education for the first 15 minutes and a 35 - 45 minute culinary demonstration; questions encouraged throughout each session. A variety of handouts designed for each session were provided via email as well as each recorded session available as a private resource to each of the pALS. Each recipe demonstrated was designed to manage malnutrition, improve energy preservation and facilitate safe chewing and swallowing. Communication was performed via NSU email and over the phone. An identification number was used to identify and protect participants.

Session one nutrition education focused on macronutrients and micronutrients. The recipe demonstration included a standardized smoothie recipe called the *Everything Smoothie,* designed to be caloric and protein dense, provide proper texture modifications for dysphagia, require little food preparation, and less energy to consume. Handouts included macronutrients and micronutrients education, a copy of the standardized smoothie recipe, and additional smoothie recipe tips and substitutions. Session two nutrition education focused on the anti-inflammatory herbs to strengthen your immune system, and tips on food preparation and cooking. The recipe

demonstration included how to prepare and cook the standardized recipe *Turkey Meatloaf*. Handouts include herb benefits and phytonutrients, food preparation and cooking tips, and a copy of the standardized turkey meatloaf recipe. Session three nutrition education focused on preserving energy, nutrient dense snack ideas, and ALS specific meals. The recipe demonstration included how to prepare and cook the standardized recipe *High Calorie and Protein Banana Bread*. Handouts include high calorie, high protein snack ideas, a copy of the standardized banana bread recipe, and a list of ALS specific meal suggestions for breakfast, lunch, and dinner.

The dependent variables include a nutrition knowledge questionnaire, ALS Functional Rating Scale-Revised (ALSFRS-R) scores, body weight, BMI, and dietary intake of calories (Kcal), carbohydrates (CHO), protein (PRO), and fat (FAT) calculated from a 24-hour dietary recall. Variables were measured before and after the intervention at the in-person ALS clinic visits. The nutrition knowledge questionnaire included 10 questions and was created on Microsoft 365- online survey poll quizzes. The ALSFRS-R score is a metric that enables the quantitative assessment of patients with Amyotrophic Lateral Sclerosis' functional state to assess functional status. Body weight and BMI were measured to analyze weight loss. A 24 hour dietary recall is a measurement of a participant's dietary intake within the last 24-hours and was used to calculate Kcal, CHO, PRO, and FAT intake.

The pre-intervention, password protected data from the initial clinic visit, was provided via NSU email from the study's faculty advisor to the PI. After the initial visit, participants were contacted within one week via the telephone to collect dietary intake using a 24-hour recall. Through the 24 hour dietary recall, total Kcal, CHO, PRO, and FAT was calculated using website and application MyFitnessPal. Intervention dates and times were also coordinated via phone. Two of the four participants were unable to speak on the phone, due to advanced ALS progression, so all verbal communication was done through the participant's caregiver. Half of the participants were called by the PI and the other half by the CI. The 24- hour dietary recall and macronutrient calculations were repeated post intervention. All collected pre and post intervention data was then inputted into an excel sheet. Participants were de-identified with identification numbers for protection.

All data analysis was found using JMP 16.00 and 4.4.4. A Bivariate Statistical table was used for pre and post intervention values. The purpose of a bivariate table is to show the relationship between the frequency distribution of the categories of the dependent variables given the occurrence of the independent variable values.[13] To determine if there were statistically significant changes ($P < 0.05$) between the pre- and post-intervention data, a Mann-Whitney U Test was used.[14] To further graphically depict the distribution and variations in the data, boxplot figures were used. Data analysis was provided by the free, data analysis services provided at Nova Southeastern University for Graduate Students.

Results:

BMI & Weight ((Table 1; Figure 1 & 2)

Table 1 provides descriptive data for baseline factors including age and BMI. The individuals' starting average weight was 153 pounds (SD = 9.68) and their starting BMI was 24.1 (SD = 0.780). Following the intervention, there was a non-significant decrease in the individuals' weight and BMI. The mean BMI dropped to 23.3 (SD = 1.23; P = 0.248) and the mean weight dropped to 148 pounds (SD = 10.5; P = 0.467).

Nutrition Knowledge (Table 1; Figure 3)

After the session, there were noticeable gains in the participants' understanding of nutrition. With a significant p-value of 0.017, the average score on the nutrition questionnaire rose from 6.00 (SD = 0.816) to 8.25 (SD = 0.500). This suggests that the participants' comprehension of nutritional concepts was successfully improved, most likely as a result of the virtual culinary education sessions.

Dietary Intake (Table 1; Figure 4, 5, & 6)

The 24-hour dietary recall data showed increases in the consumption of macronutrients and total calories. The average daily caloric intake increased to 2070 calories (SD = 314; P = 0.248) from 1790 calories (SD = 215). In a similar vein, but not statistically significant, mean protein consumption rose from 98.5 grams (SD = 32.2) to 124 grams (SD = 29.1; P = 0.309). Although not statistically significant, the consumption of lipids and carbs increased as well (P = 0.248 and 0.772, respectively).

ALS Functional Rating Scale (ALSFRS-R) (Table 1; Figure 7)

With a p-value of 0.110, the ALSFRS-R scores showed a small reduction, going from an average of 33.5 (SD = 3.51) to 28.8 (SD = 3.77). Since the intervention was not intended to stop the disease's development, this non-significant decline was expected. The study's setting deemed the little decline in functional status to be inconsequential.

Table 1. Bivariate Statistics Table

	Pre (N=4)	Post (N=4)	P-Value
Weight			0.467
Mean (SD)	153 (9.68)	148 (10.5)	
Median [Min, Max]	155 [140, 162]	147 [137, 161]	
BMI			0.248
Mean (SD)	24.1 (0.780)	23.3 (1.23)	
Median [Min, Max]	24.3 [23.0, 24.7]	23.7 [21.5, 24.3]	
Nutrition Questionnaire			0.017
Mean (SD)	6.00 (0.816)	8.25 (0.500)	
Median [Min, Max]	6.00 [5.00, 7.00]	8.00 [8.00, 9.00]	
24hr recall calories			0.248
Mean (SD)	1790 (215)	2070 (314)	
Median [Min, Max]	1790 [1540, 2060]	2010 [1760, 2500]	
24hr recall protein			0.309
Mean (SD)	98.5 (32.2)	124 (29.1)	
Median [Min, Max]	98.5 [60.0, 137]	123 [90.0, 161]	

24hr recall carbohydrates			0.772
Mean (SD)	211 (32.0)	216 (31.3)	
Median [Min, Max]	219 [166, 240]	214 [183, 252]	
24hr recall fat			0.248
Mean (SD)	60.8 (18.6)	80.3 (32.2)	
Median [Min, Max]	56.5 [44.0, 86.0]	71.0 [53.0, 126]	
Alsfrsr scores			0.110
Mean (SD)	33.5 (3.51)	28.8 (3.77)	
Median [Min, Max]	33.5 [30.0, 37.0]	29.0 [24.0, 33.0]	

* $P < 0.005$ was considered statistically significant

Figure 1.

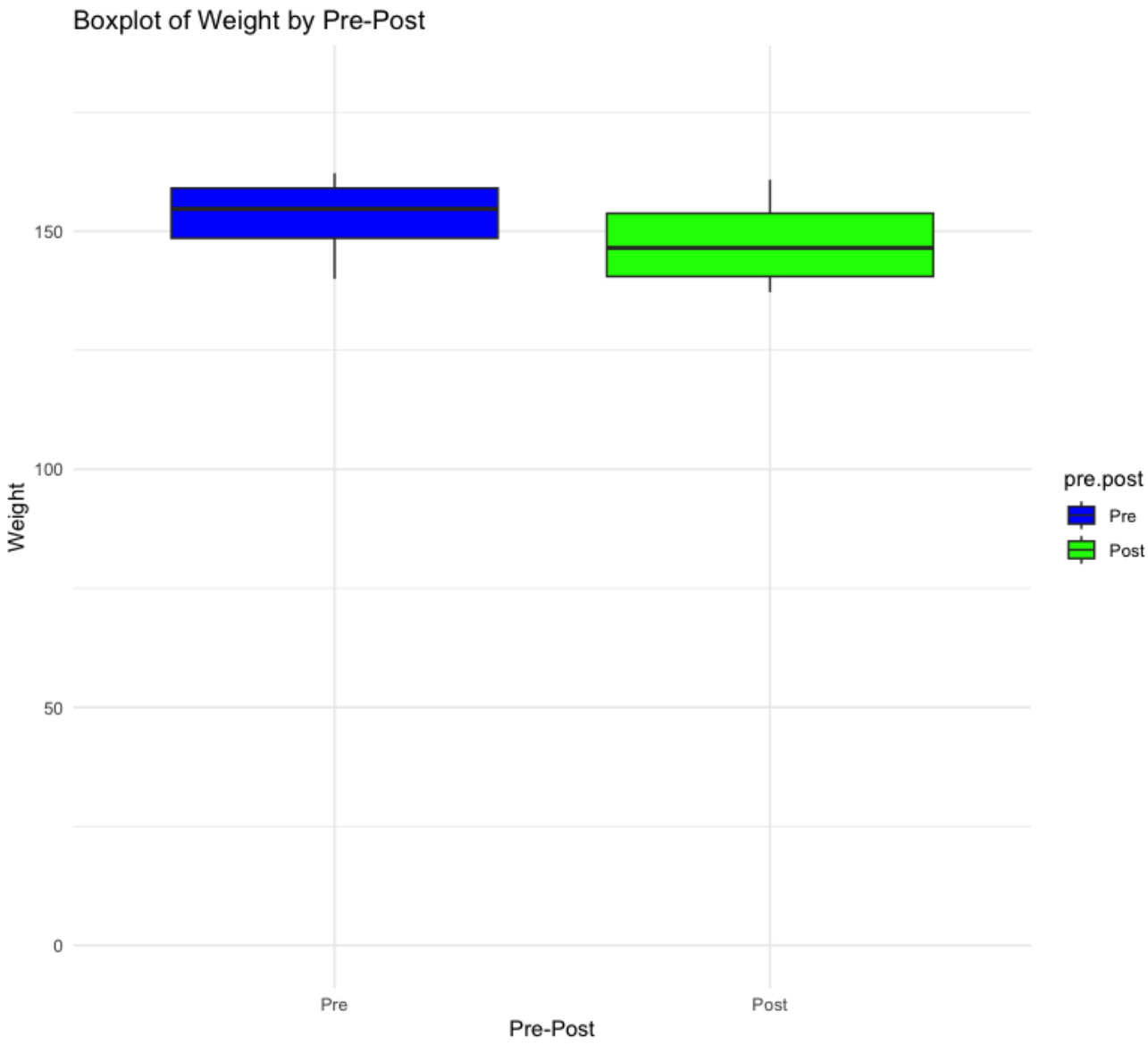

Boxplot of Weight by Pre-Post
150
100
50
0
Weight
Pre
Post
Pre-Post
pre.post
Pre
Post

Figure 2.

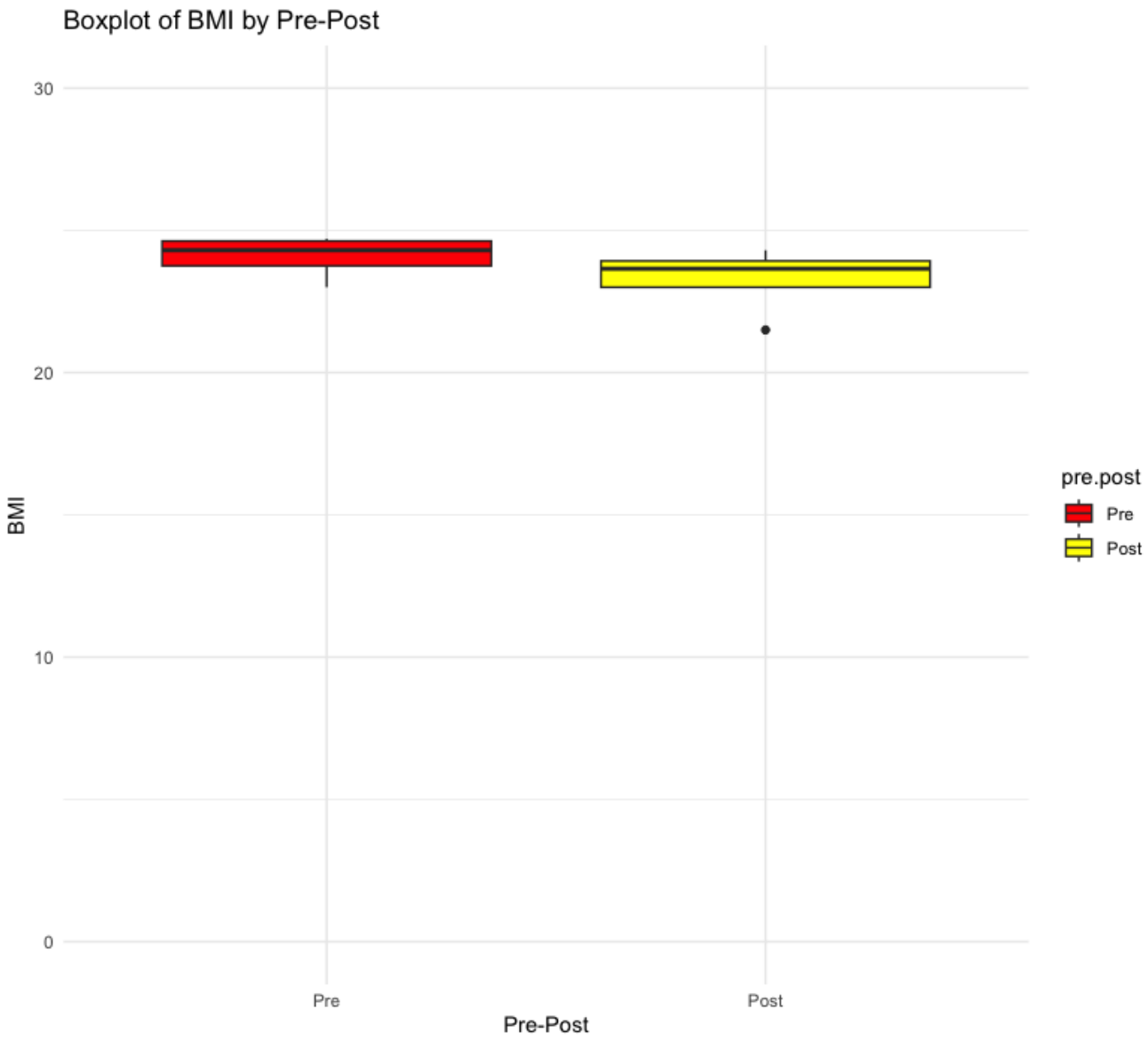

Boxplot of BMI by Pre-Post
30
20
10
0
BMI
Pre
Post
Pre-Post
pre.post
Pre
Post

Figure 3.

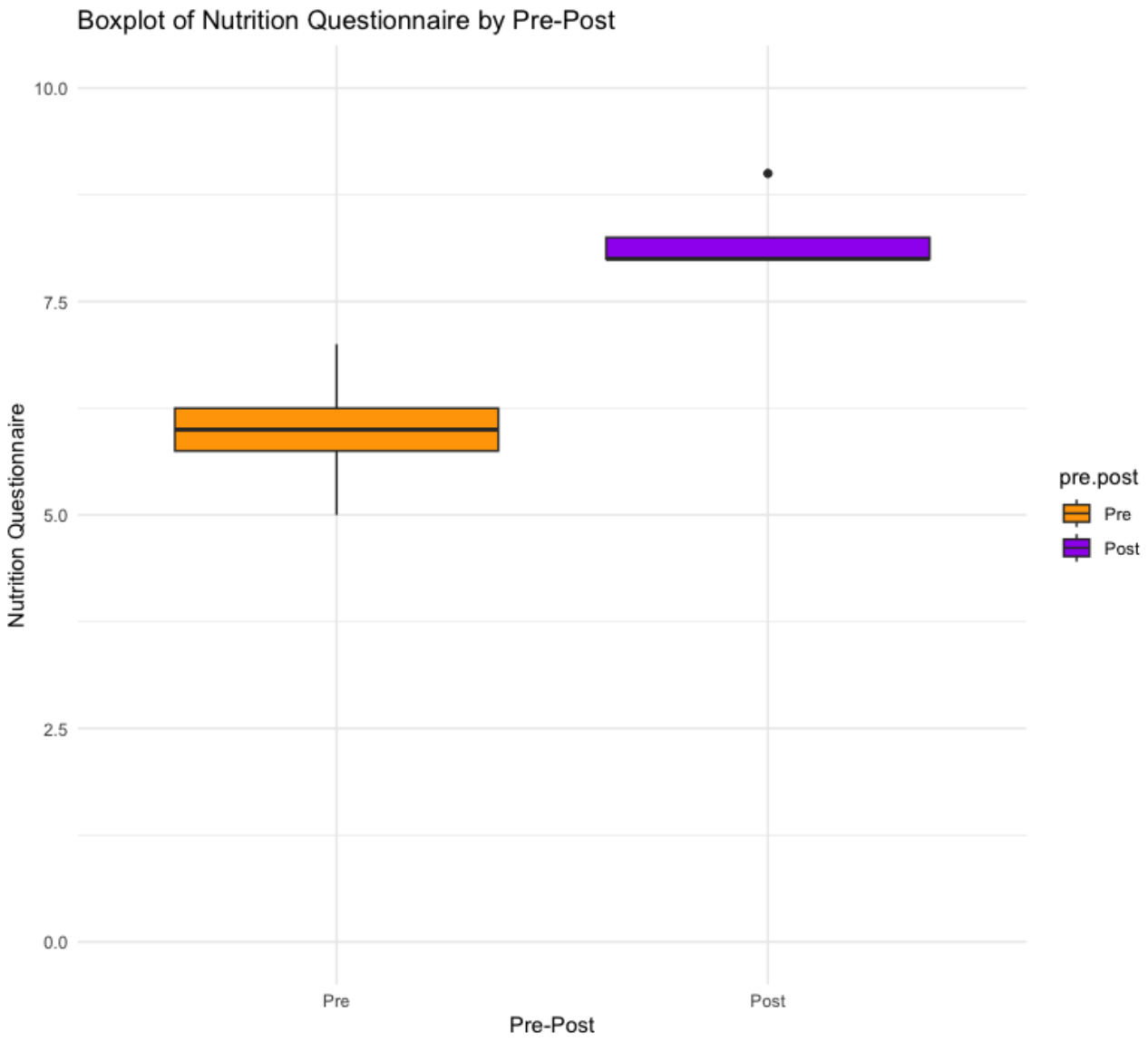

Boxplot of Nutrition Questionnaire by Pre-Post
10.0
7.5
5.0
2.5
0.0
Nutrition Questionnaire
Pre
Post
Pre-Post
pre.post
Pre
Post

Figure 4.

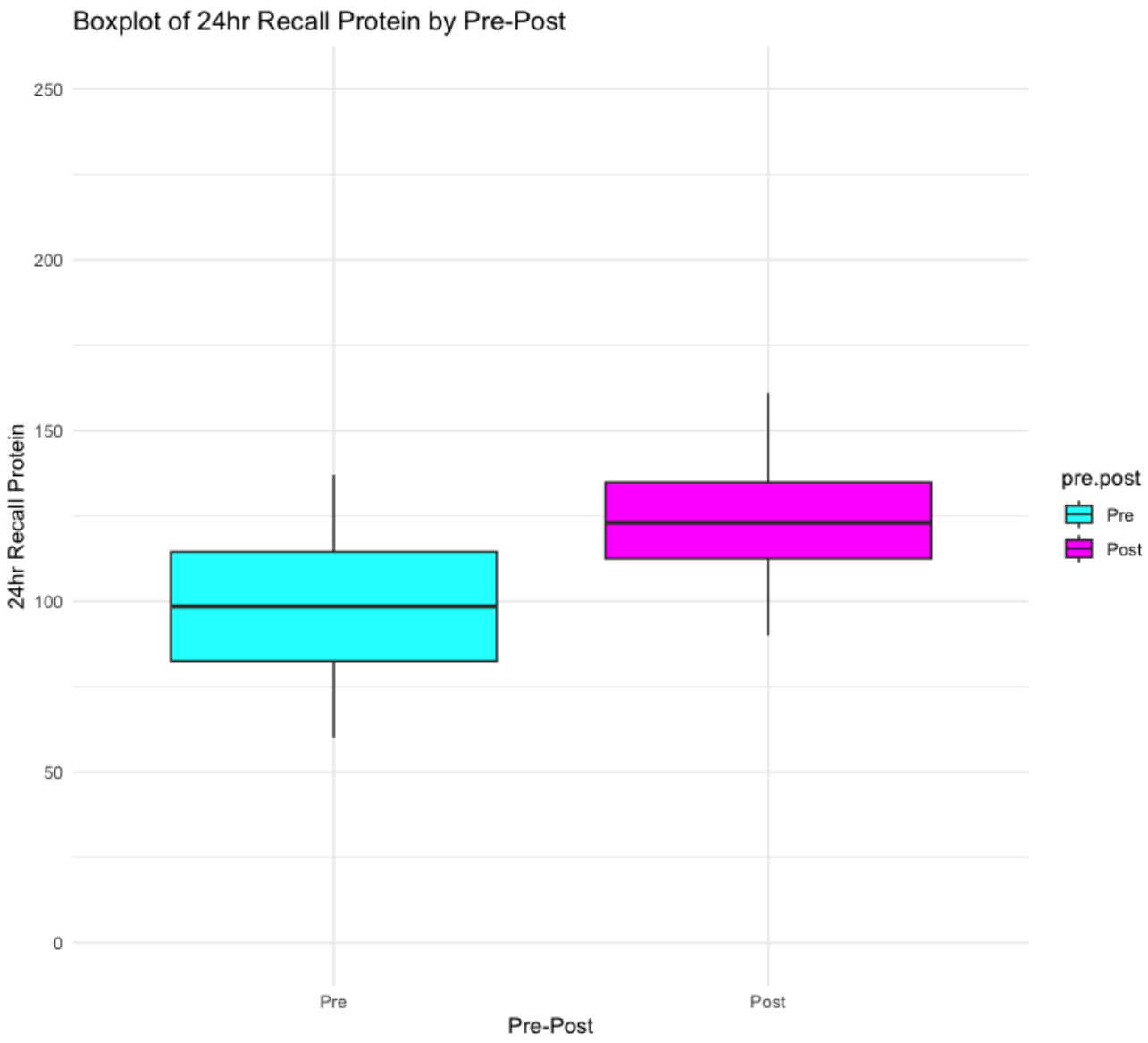

Boxplot of 24hr Recall Protein by Pre-Post
250
200
150
100
50
0
24hr Recall Protein
Pre
Post
Pre-Post
pre.post
Pre
Post

Figure 5.

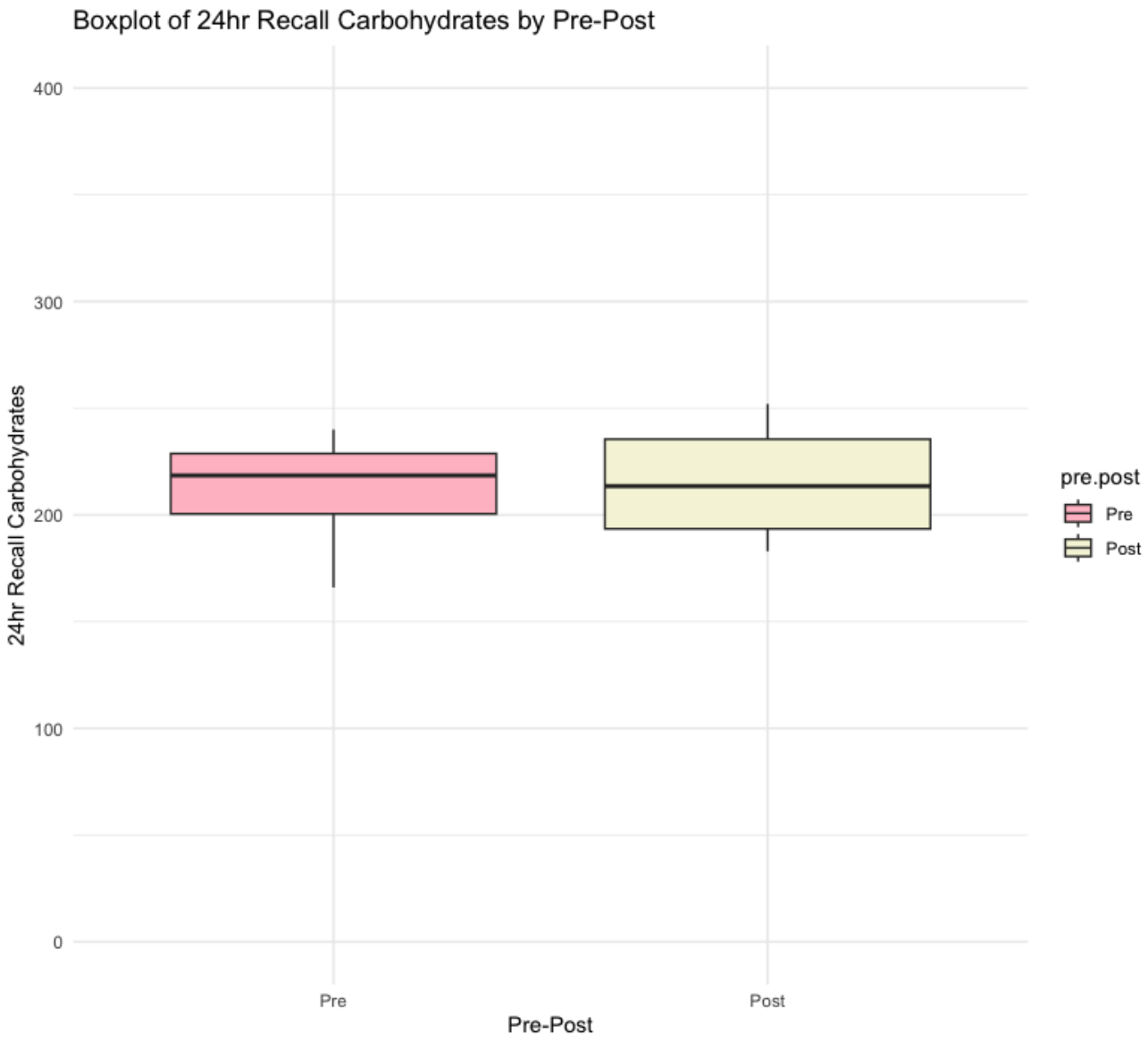

Boxplot of 24hr Recall Carbohydrates by Pre-Post
400
300
200
100
0
24hr Recall Carbohydrates
Pre
Post
Pre-Post
pre.post
Pre
Post

Figure 6.

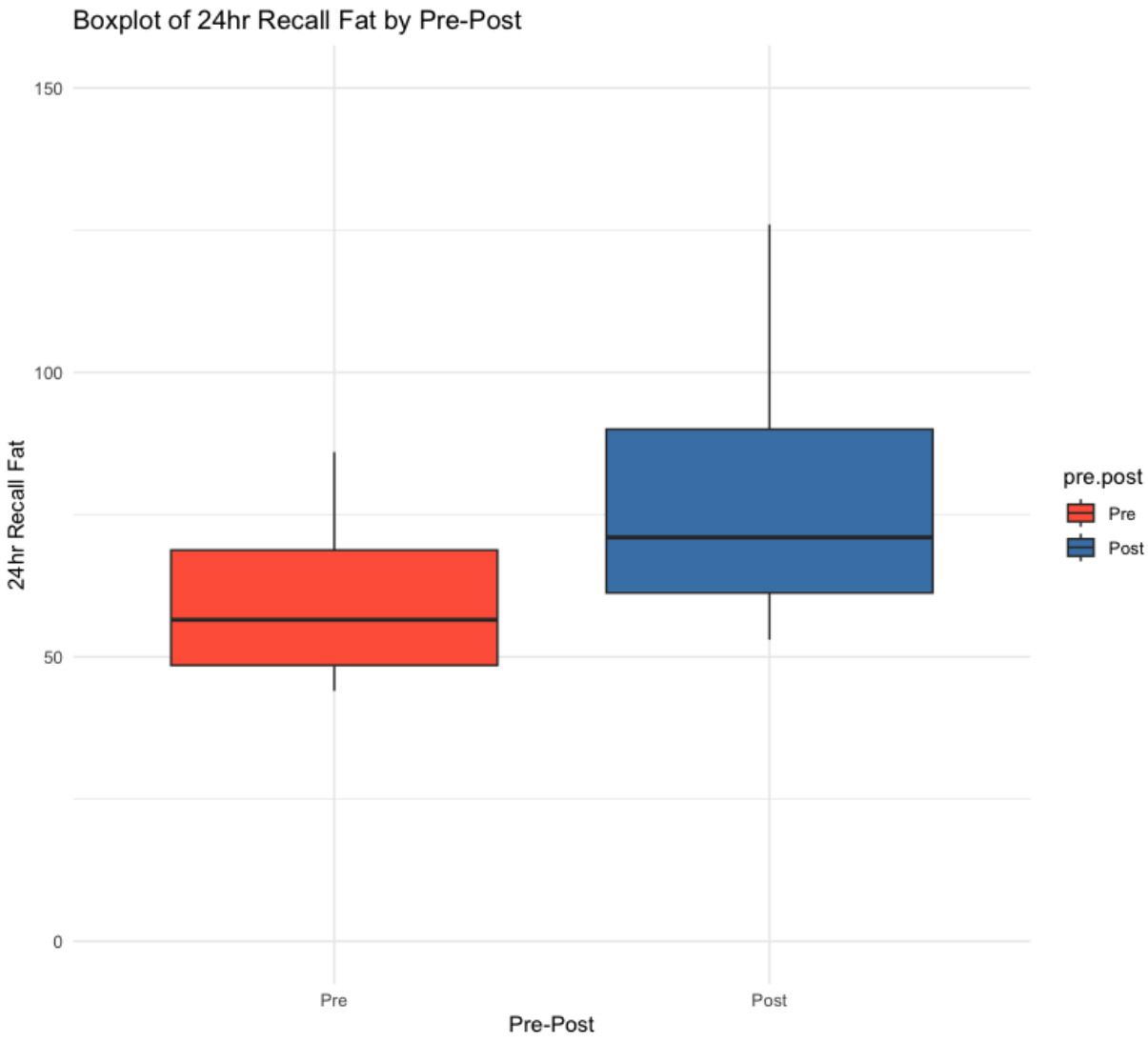
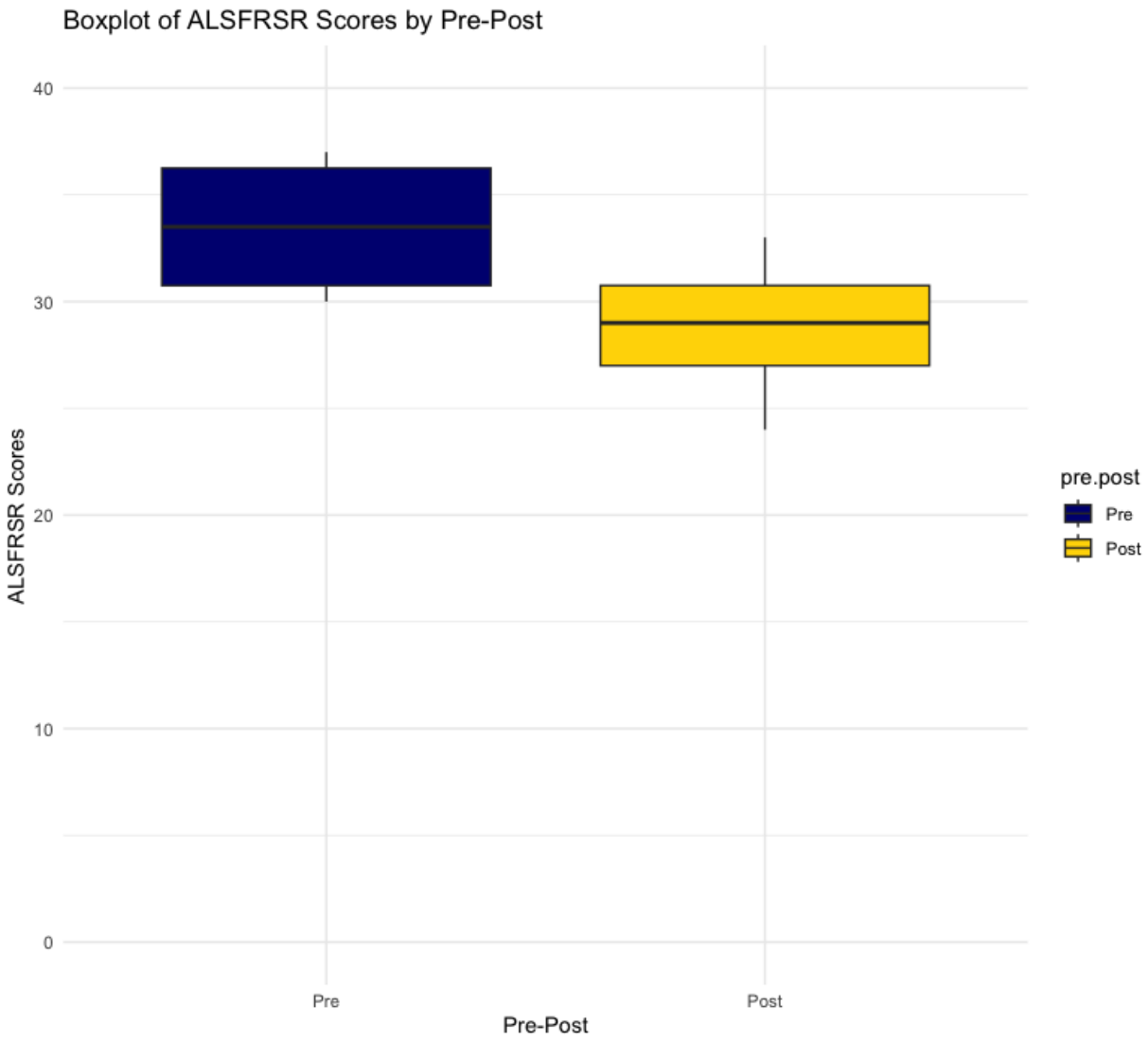

Boxplot of 24hr Recall Fat by Pre-Post
150
100
50
0
24hr Recall Fat
Pre
Post
Pre-Post
pre.post
Pre
Post

Figure 7.


Boxplot of ALSFRSR Scores by Pre-Post
40
30
20
10
0
ALSFRSR Scores
Pre
Post
Pre-Post
pre.post
Pre
Post

Discussion:

Due to the constraints of the research, it was predicted that there would be no statistically significant changes in body weight and BMI post-intervention; yet, this shows stability in these measurements. This result is noteworthy in light of the progressive nature of ALS, where it might be difficult to maintain weight owing to deteriorating physical capabilities and difficulties with eating. Although direct causality cannot be shown without a bigger sample size and controlled settings, the stability of weight and BMI may suggest indirectly how beneficial the culinary instruction is in preserving nutritional status.

It's interesting to note the Nutrition Knowledge Questionnaire scores show a considerable gain in nutrition knowledge, indicating the success of the teaching sessions. Patients' comprehension of dietary concepts may be significantly improved by focused educational interventions, as shown by the rise in mean score from 6.00 pre-intervention to 8.25 post-intervention ($P = 0.017$). This advancement is crucial because increased understanding of nutrition may enable patients and caregivers to make wise food decisions, which are especially crucial when treating long-term illnesses like ALS.

A good trend in nutritional intake is also shown by the 24-hour dietary recall findings, which show increases in calories and macronutrients. These improvements are promising because they point to a possible slowdown of the course of malnutrition in the ALS group, even if they were not statistically significant. Increasing protein and calorie intake is essential for managing ALS in order to prevent muscular atrophy and preserve energy.

It was expected that there would be a non-significant drop in ALSFRS-R scores after the intervention, although cautious interpretation is advised. Since ALS is a degenerative illness, a stable or little reduction in functional status may be seen as a rather positive result in the near run. It is important to recognize that in the absence of a control group, it becomes difficult to differentiate between the observed alterations and the inherent course of the illness.

To improve the robustness of the results, future research should try to overcome the limitations identified in this pilot study by increasing the sample size and include a control group. Furthermore, longer intervention and follow-up periods may provide more conclusive proof of the nutritional education's long-term advantages for ALS patients.

Conclusion:

The small sample size limits the study's ability to show statistical significance, but there may be other trends, such as functional status and nutrition knowledge. The study showed motivating results and potential success in utilizing nutrition education and culinary classes as a potential inclusion in ALS treatment and maintenance. Subsequent investigations need to try to tackle these constraints while furthermore examining the possible advantages of analogous therapies in enhancing outcomes for those afflicted with ALS. Larger studies are needed with longer time frame for intervention

Limitations:

Pilot studies have inherent limitations, and the complex nature of ALS makes applying therapeutic approaches difficult. To protect their privacy, Zoom participants had to turn off their cameras during sessions. Nevertheless, this limitation made it more difficult for researchers to evaluate participant presence and participation visually. Moreover, there are a lot of limitations when doing research via surveys. A major obstacle is participant authenticity since it might be difficult to get sincere answers, which could jeopardize the validity and dependability of the study.

Furthermore, getting patients' agreement to participate in research is difficult because of the continuous physical deterioration linked to ALS. The limited sample size and brief intervention period (usually two to three months) restrict the individuals' capacity to make major dietary changes, which limits the results' applicability to a larger population. Caregivers' inconsistent availability made it difficult to include all them in study; other participants did not have full-time caregivers. To ensure fair caregiver participation and evaluate their influence on results, a more extensive and thorough research design is required.

There are also questions about how accurate calorie estimates are and how trustworthy caregivers' information—like 24-hour recalls—is. To tackle these issues, considerable thought and different methods of gathering data are needed. Therefore, more continuous thought and creative solutions are needed to properly handle these complex problems.

Implication for Future Practice:

This pilot study's findings imply that virtual culinary nutrition education might help ALS patients become more knowledgeable about nutrition and perhaps stabilize their dietary intake.. These results underline the need for further investigation to completely comprehend how dietary treatments affect the course of the illness and quality of life in individuals with ALS.

Proposed next steps: The intervention should be carried out first, then set up for an interview for three months thereafter. Participants will have plenty of time to incorporate the newfound information about nutrition into their everyday routines and lives. After the participants have had enough time to put their new abilities to use, we will gather data on weight, BMI, ALSFRS-R scores, and 24-hour dietary recall in order to fully evaluate the success of the intervention. Results from this research should be more precise and trustworthy

References:

1. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;27(10):1918-1929. doi:10.1111/ene.14393
2. Roubeau V, Blasco H, Maillot F, Corcia P, Praline J. Nutritional assessment of amyotrophic lateral sclerosis in routine practice: value of weighing and bioelectrical impedance analysis. Muscle Nerve. 2015 Apr;51(4):479-84. doi: 10.1002/mus.24419. Epub 2015 Feb 24. PMID: 25130859.
3. Morassutti I, Giometto M, Baruffi C, Marcon ML, Michieletto S, Giometto B, Spinella N, Paccagnella A. Nutritional intervention for amyotrophic lateral sclerosis. Minerva Gastroenterol Dietol. 2012 Sep;58(3):253-60. PMID: 22971635.
4. De Marchi F, Serioli M, Collo A, Belotti EG, Alloatti F, Biroli G, Bolioli A, Cantello R, Riso S, Mazzini L. A Telehealth Intervention for Nutritional Counseling in Amyotrophic Lateral Sclerosis Patients. J Clin Med. 2022 Jul 23;11(15):4286. doi: 10.3390/jcm11154286. PMID: 35893377; PMCID: PMC9331838.
5. Marin B, Desport JC, Kajeu P, Jesus P, Nicolaud B, Nicol M, Preux PM, Couratier P. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. J Neurol Neurosurg Psychiatry. 2011 Jun;82(6):628-34. doi: 10.1136/jnnp.2010.211474. Epub 2010 Nov 19. PMID: 21097551.
6. Blackford K, Jancey J, Lee AH, James A, Howat P, Waddell T. Effects of a home-based intervention on diet and physical activity behaviours for rural adults with or at risk of metabolic syndrome: a randomised controlled trial. Int J Behav Nutr Phys Act. 2016; 13:13. Published 2016 Feb 1. doi:10.1186/s12966-016-0337-2
7. Wills AM, Hubbard J, Macklin EA, et al. Hypercaloric enteral nutrition in patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled phase 2 trial. Lancet. 2014;383(9934):2065-2072. doi:10.1016/S0140-6736(14)60222-1
8. Dorst J, Doenz J, Kandler K, et al. Fat-rich versus carbohydrate-rich nutrition in ALS: a randomized controlled study. J Neurol Neurosurg Psychiatry. 2022;93(3):298-302. doi:10.1136/jnnp-2021-328331
9. Silva LB, Mourão LF, Silva AA, et al. Effect of nutritional supplementation with milk whey proteins in amyotrophic lateral sclerosis patients. Arq Neuropsiquiatr. 2010;68(2):263-268. doi:10.1590/s0004-282x2010000200021
10. Wills AM, Garry J, Hubbard J, et al. Nutritional counseling with or without mobile health technology: a randomized open-label standard-of-care-controlled trial in ALS. BMC Neurol. 2019;19(1):104. Published 2019 May 29. doi:10.1186/s12883-019-1330-6
11. López-Gómez JJ, Ballesteros-Pomar MD, Torres-Torres B, De la Maza BP, Penacho-Lázaro MÁ, Palacio-Mures JM, Abreu-Padín C, López-Guzmán A, De Luis-Román DA. Malnutrition at diagnosis in amyotrophic lateral sclerosis (als) and its influence on survival: Using glim criteria. Clin Nutr. 2021 Jan;40(1):237-244. doi: 10.1016/j.clnu.2020.05.014. Epub 2020 May 21. PMID: 32507583
12. Ultra-high dose methylcobalamin (E0302) prolongs survival of ALS: Report of 7 years randomised double-blind, phase 3 clinical trial (ClinicalTrials.gov NCT00444613)

(P7.060) Ryuji Kaji, Shigeki Kuzuhara, Yasuo Iwasaki, Koichi Okamoto, Masanori Nakagawa, Takashi Imai, Takao Takase, Hiroki Shimizu, Kunio TashiroNeurology Apr 2015, 84 (14 Supplement) P7.060

13. Department of Sociology. Bivariate Tables and cross-tabulation. Bivariate Tables - Sociology 3112 - Department of Sociology - The University of Utah. 2024. Accessed April 1, 2024. https://soc.utah.edu/sociology3112/bivariate-tables.php.
14. Fay MP, Proschan MA. Wilcoxon-Mann-Whitney or t-test? On assumptions for hypothesis tests and multiple interpretations of decision rules. *Stat Surv*. 2010;4:1-39. doi:10.1214/09-SS051