

Diet and ALS: Does what PALS eat matter?

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Disclosures

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Learning objectives

- Critically review the evidence behind nutritional composition and disease progression in ALS

Background

- Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's disease is a fatal neurodegenerative disease of motor neurons
- Progressive muscle dysfunction that deprives independence and meaningful interaction with the outside world
- Rate of progression varies among patients and during the course of disease



Weight loss is common and associated with faster progression

- Weight loss during the course of the disease predicts faster functional decline and shorter survival (Moglia et al, 2019)
- Cohort study from Italy (n=620)
- Median survival 2 yrs vs 4 yrs in weight loss vs gain groups

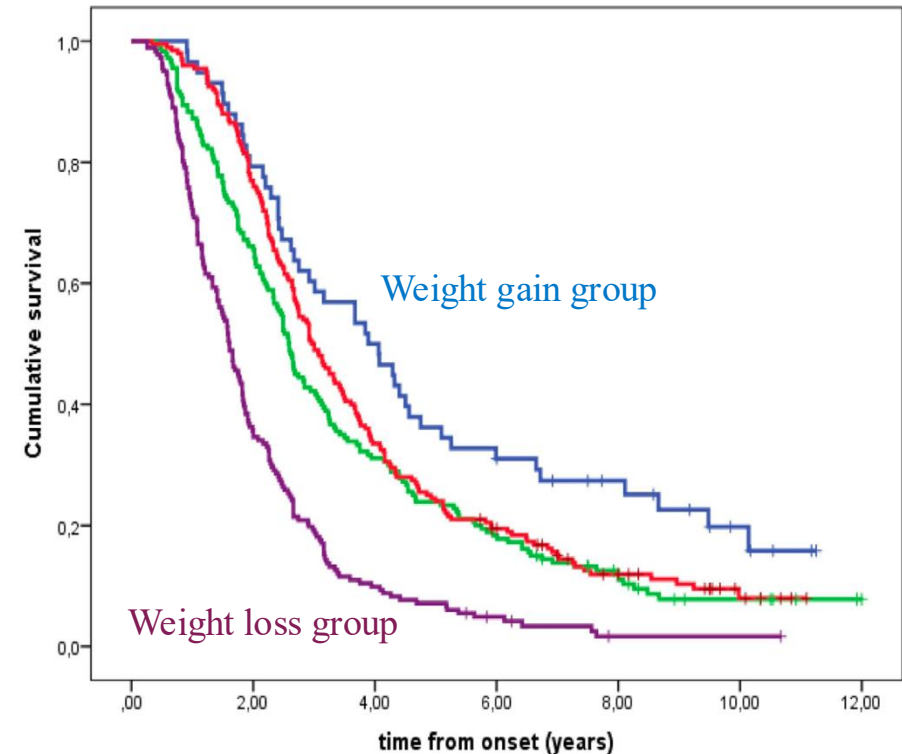
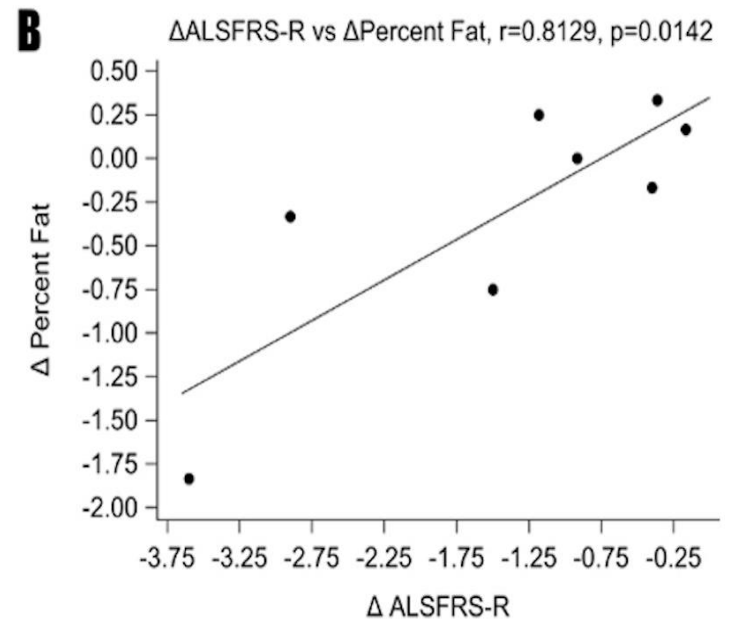
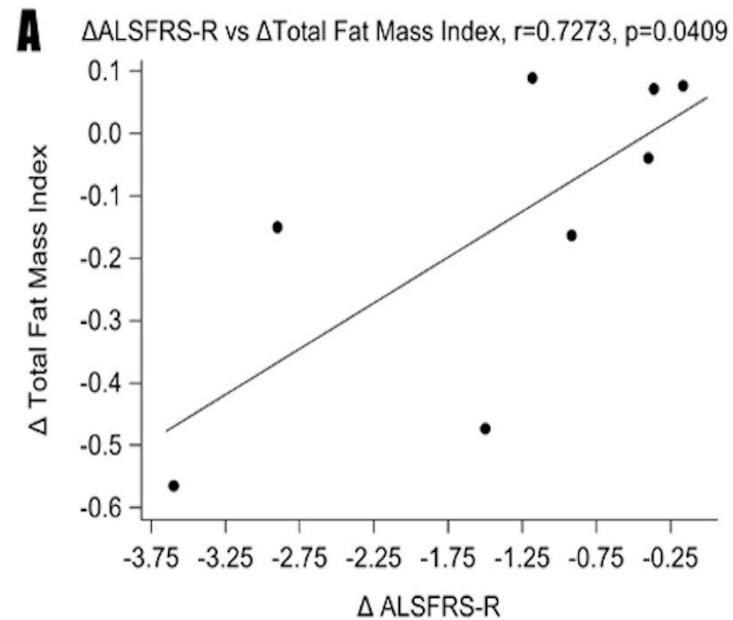
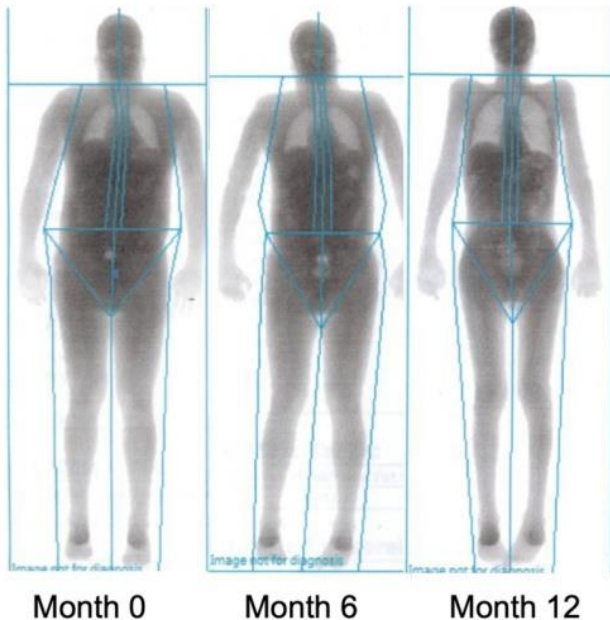


Figure 3 Survival curves according to mean monthly weight loss (blue, weight increase; red, unchanged weight; green, mean monthly weight loss 0.01% to 0.99%; purple, mean monthly weight loss $\geq 1\%$ ($p < 0.0001$)). Ticks indicate censored patients.

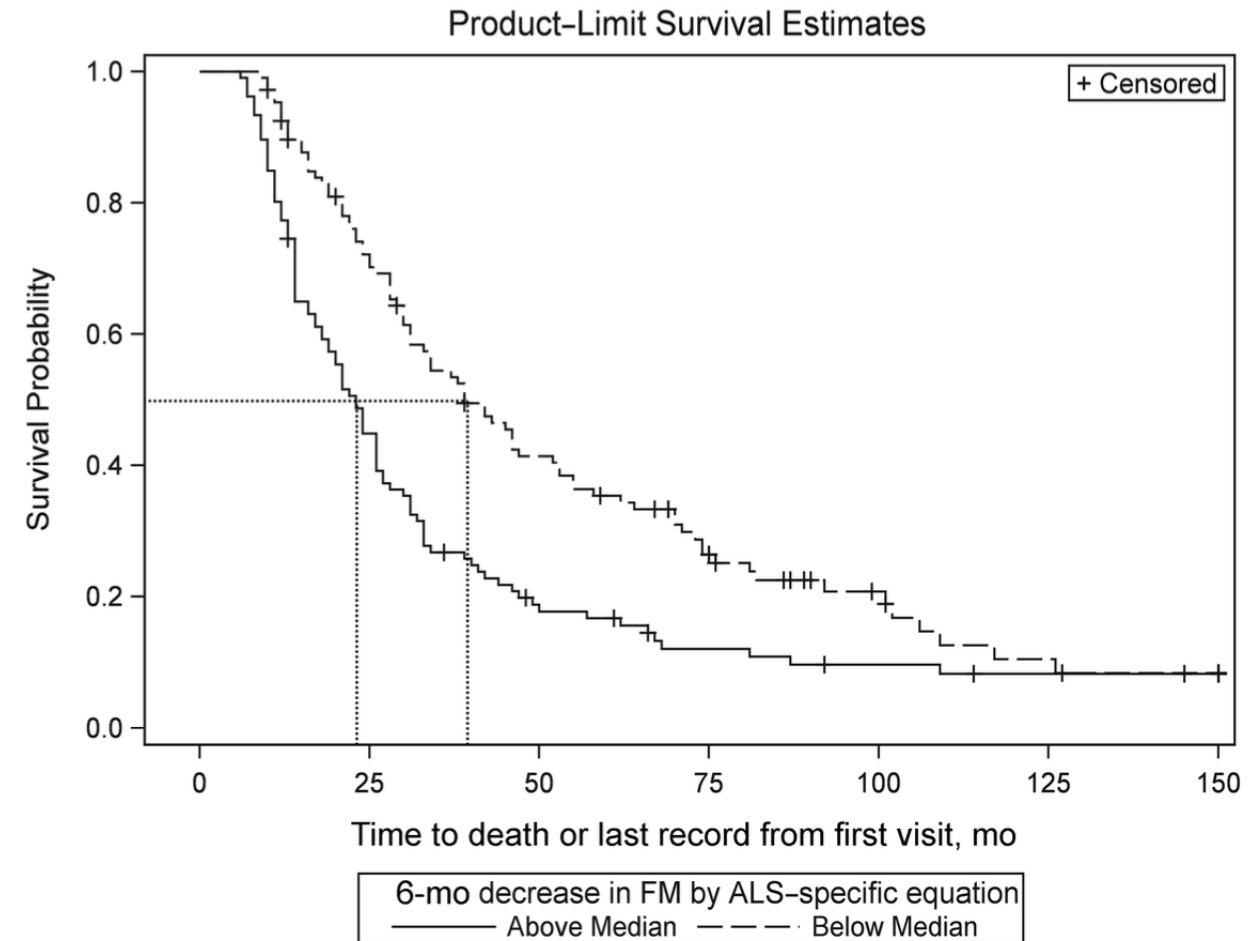
Fat mass vs lean mass loss

- Longitudinal follow up study with DXA at 0, 6, 12 months (Lee et al, 2021)
- Lean mass loss was universal while fat mass loss occurred in fast progressors
- **Fat mass loss** was associated with faster functional decline



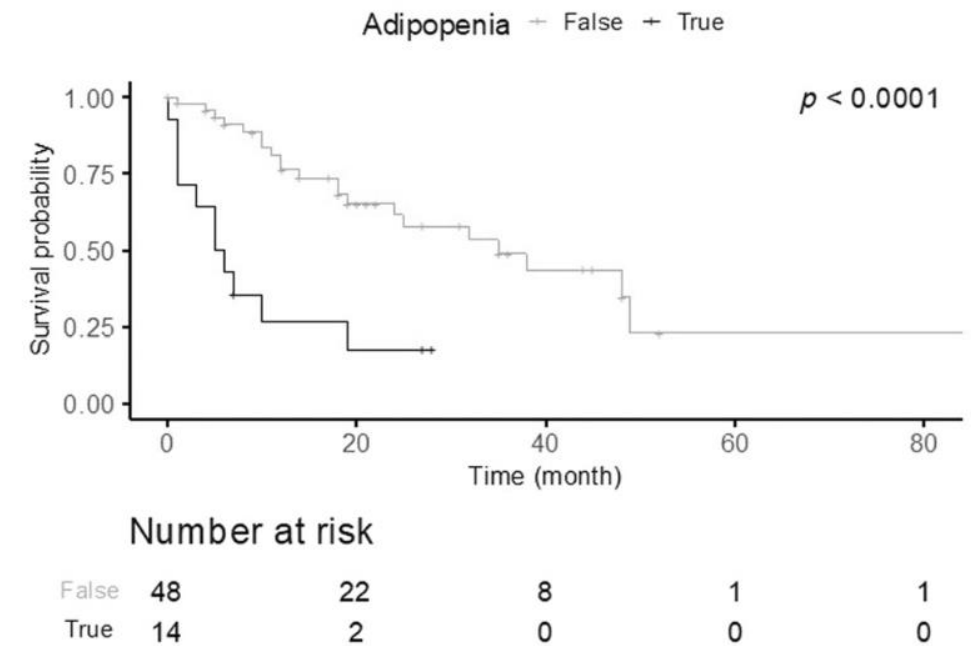
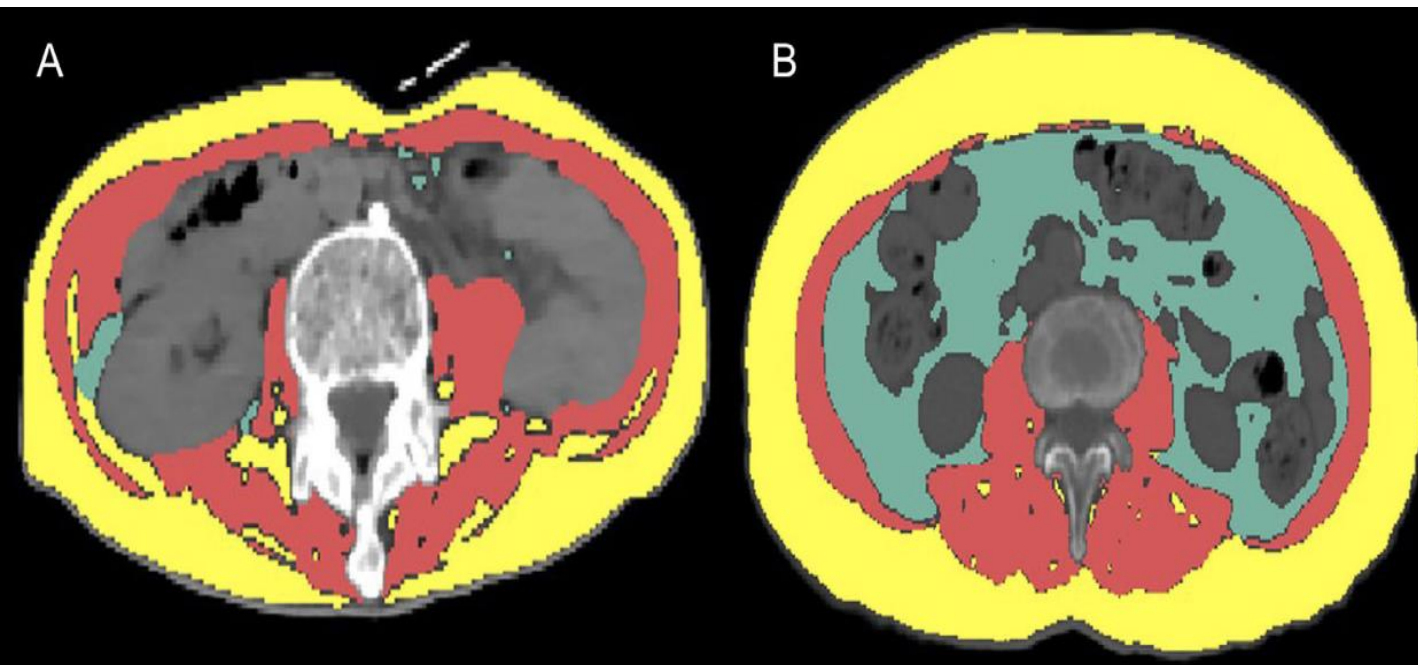
Fat mass vs lean mass loss

- Tandan et al 2022, cohort study
- Fat mass at baseline predicted survival while baseline lean mass did not
- 6-month decrease in fat mass predicted 16-months shorter survival
- Bulbar onset patients had lower fat mass



Visceral Fat mass and Survival

- Retrospective study of ALS patients with abdominal CT scan (Choi et al, 2023, n=80)
- ALS patients with low visceral fat mass (A) had 30 months shorter survival compared to those with higher fat mass (B).



Nutritional intervention trials (2005 – 2022)

	Investigators	Trial design	Intervention groups	Enrolled N	Primary outcome	Secondary outcome	Comments
Milk whey protein and modified starch in ALS	Silva et al 2010	Randomized, double-blind, 4 months	Treatment (70%WPI:30%MS), control (maltodextrin)	16	Both supplements well tolerated	ALSFRS declined in control group but not in treatment group	Small N, baseline characteristic not matched, 90% male
Hypercaloric enteral nutrition in ALS	Wills et al 2014	Randomized double-blind, placebo-ctrl, 4 months	HC/HC, HF/HC, control	24	Hypercaloric enteral nutrition is safe	Better survival in HC/HC group compared to Controls	Phase 2 study, small N, only TF
High-caloric nutrition in ALS	Ludolph et al 2020	Randomized, double-blind, placebo-ctrl, 18 months	HCFD, placebo	201	No difference in survival between groups	In subgroup of fast progressing patients, prolonged survival in HCFD group	Fatty supplement of 405kcal, no difference in weight or functional decline
Fat-rich vs carb rich nutrition in ALS	Dorst et al 2021	Randomized controlled study, 4 weeks	HCFS, UHCFS, UHCCS, control	64	All interventions well tolerated. UHCFS group had GI issues	All intervention groups had weight gain	Short intervention
High-caloric nutrition in ALS after gastrostomy	Wang et al 2022	Randomized, 6 months	Ensure, control	40	Nutritional parameter improved in intervention group	Better survival in ensure group	Questionable study quality
High dose vitamin E therapy in ALS	Graf et al 2005	Randomized, double-blinded, placebo-ctrl, 18 months	Alpha-tocopheral, placebo	160	No survival difference	No difference in functional decline	
CoQ10 for ALS	Kaufmann et al 2009	Randomized, double-blinded, placebo-ctrl, 9. months	CoQ10, placebo	150	ALSFRS change over 9 months shows futility (no go for phase 3)	CoQ10 was well tolerated	Adaptive phase 2 design
Ultra-high dose methylcobalamine in ALS	Oki et al 2022	Randomized, double-blinded, placebo-ctrl, 4 months	Vitamin B12 IM, placebo	130	Slower functional decline in B12 group	Vitamin B12 well tolerated	The survival prolongation effect also presented

Milk Whey protein and modified starch

- Silva et al 2010, studied in Brazil
- Randomized, double-blinded controlled trial, 4 months duration
- 16 patients (14 males), definite ALS
- 2 groups 1:1 randomization, supplements of milk whey protein (30% of daily requirement of 1.2g/kg body weight) + modified starch vs maltodextrin (amount?)
- Weight increased in treatment group (62.2 ->63.4kg) and decreased in control group (65.8 to 64.3kg), difference not significant
- Baseline patient characteristics?
- Quality concern

Table 3. ALSFRS-R: Level of significance among the first and second time of control and supplemented groups.

	Control group*			Treatment group*		
	0	4	p-value	0	4	p-value
ALSFRS-R	27.0 ± 3.8 ^a	23.6 ± 4.4 ^b	0.03	29.1 ± 2.4	27.0 ± 3.5	0.17

ALSFRS-R: score of Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised at first (0) and second times (4 months), respectively. Values correspond to means ± standard error of three determinations. Values not sharing similar letters in the same line are different ($p < 0.05$) by the Tukey test.

Hypercaloric enteral nutrition

- Wills et al 2015, in the US
- Randomized, double-blinded, placebo-controlled
- 24 participants with g-tube, 3 groups HC/HC, HF/HC, Control
- HC/HC group had longer survival compared to control
- No significant survival benefit in the HF/HC group
- Small sample size
- 150% of the estimated caloric intake required to gain weight

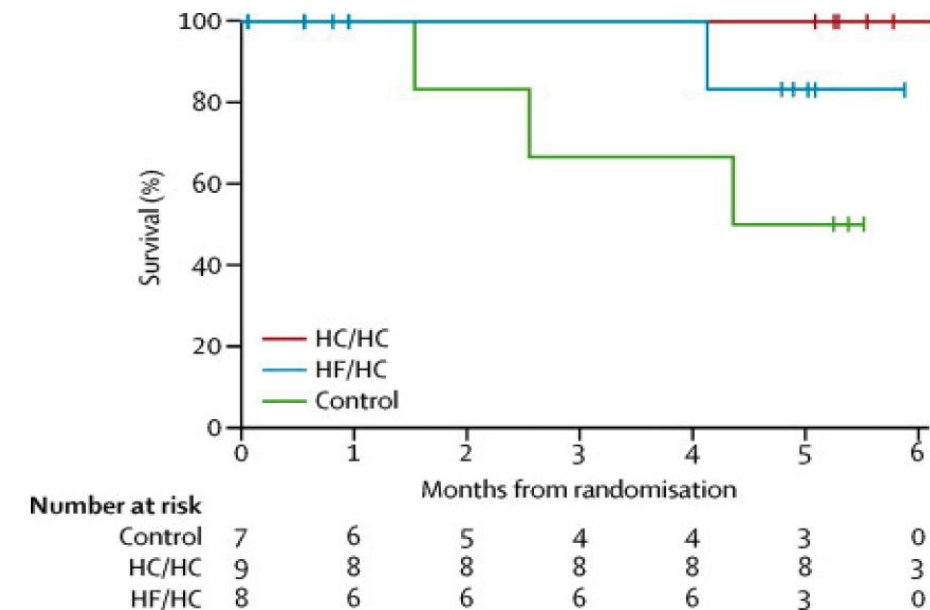


Figure 2. Kaplan-Meier curves for overall survival. HC/HC= high-carbohydrate/hypercaloric diet; HF/HC= high-fat/hypercaloric diet; Cntl= control diet. The log-rank test for the difference across all treatments was $p=0.06$. The log-rank test for the difference in survival between the HC/HC and control arms was $p=0.03$.

High-Caloric (high-fat) Nutrition

- Ludolph et al 2020, Europe
- Randomized, Double-blinded, Placebo-controlled
- 201 patients, 1:1 HCFD vs placebo
- High-fat supplement (405kcal)
- No significant survival benefit in High-fat supplement group
- Suggested survival benefit only in fast fast-progressing subgroup

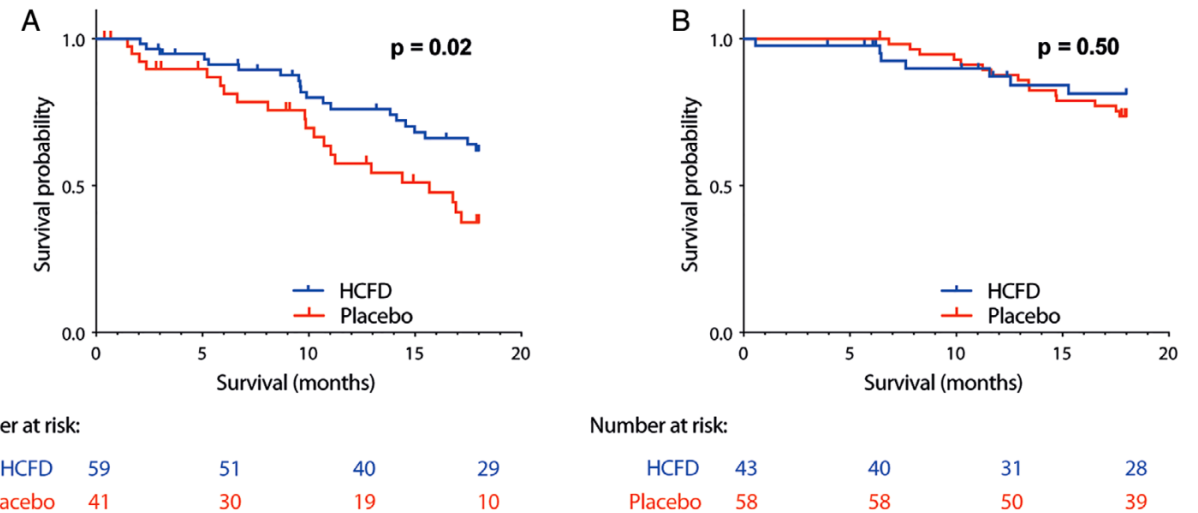


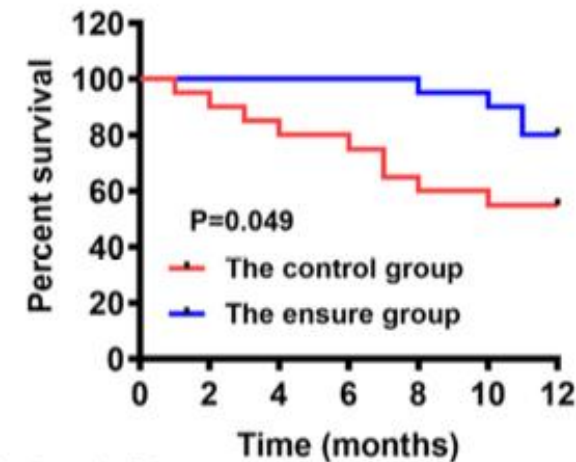
FIGURE 3: Survival in fast-progressing and slow-progressing patients. Kaplan–Meier survival curves for overall survival are shown. p = unadjusted log-rank p value. Survival after 18 months (intervention period) is shown in the subgroups of fast-progressing patients (patients with a decline in Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised [ALSFERS-R] score of >0.62 per month [median]; A) and slow-progressing patients (patients with a decline in ALSFRS-R score of ≤ 0.62 per month [median]; B), post hoc analysis (2-sided p value). HCFD = high-caloric fatty diet.

Fat-rich versus carbohydrate-rich nutrition

- Dorst et al 2021, Europe
- Randomized, controlled study
- 64 patients in 4 groups: high-fat (405kcal); ultra high-fat(810kcal); ultra high carb(900kcal); control
- GI side effects were common in ultra high-fat group while loss of appetite most common in ultra high carb group
- All supplements are suited for weight gain
- Short follow-up (4 weeks)

High-caloric nutrition in ALS after gastrostomy

- Wang et al 2022, China
- Randomized, controlled trial, duration 6 months
- 40 ALS patients with a G-tube
- 1:1 Ensure Complete twice daily vs control (fluid to semifluid to general food?)
- Ensure the group had longer survival compared to control group
- Study methods not completely clear, quality concern



NO. of patients at risk	
The control group	20 19 17 16 13 12 11
The ensure group	20 20 20 20 20 19 16

Figure 5. Cumulative survival estimate to death from intervention of 40 amyotrophic lateral sclerosis (ALS) patients.

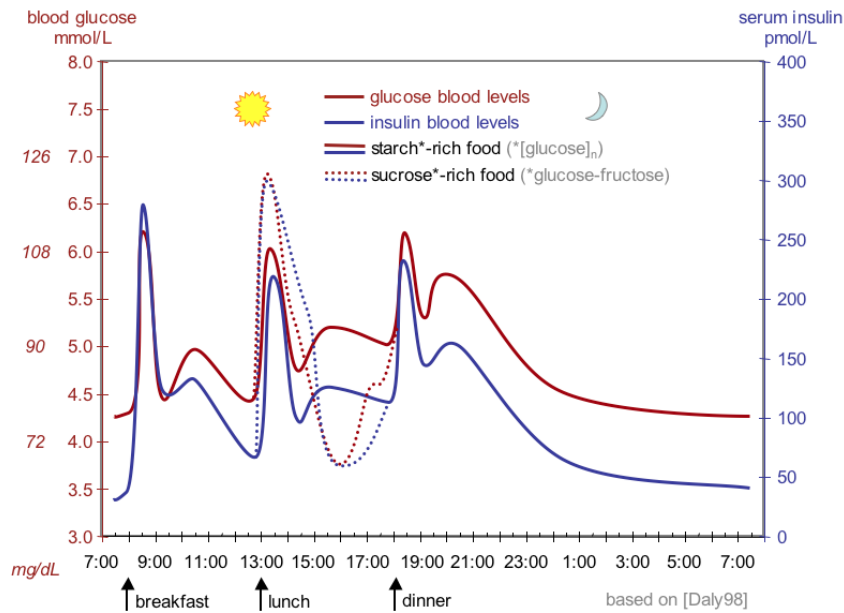
What have we learned?

- Nutritional interventions are well tolerated and might improve survival outcomes in ALS
- Conclusive evidence has not been established, especially for functional benefits
- Unclear which macronutrient should be in focus, what matters?
- Complexity in trial design due to the intervention altering dietary habits

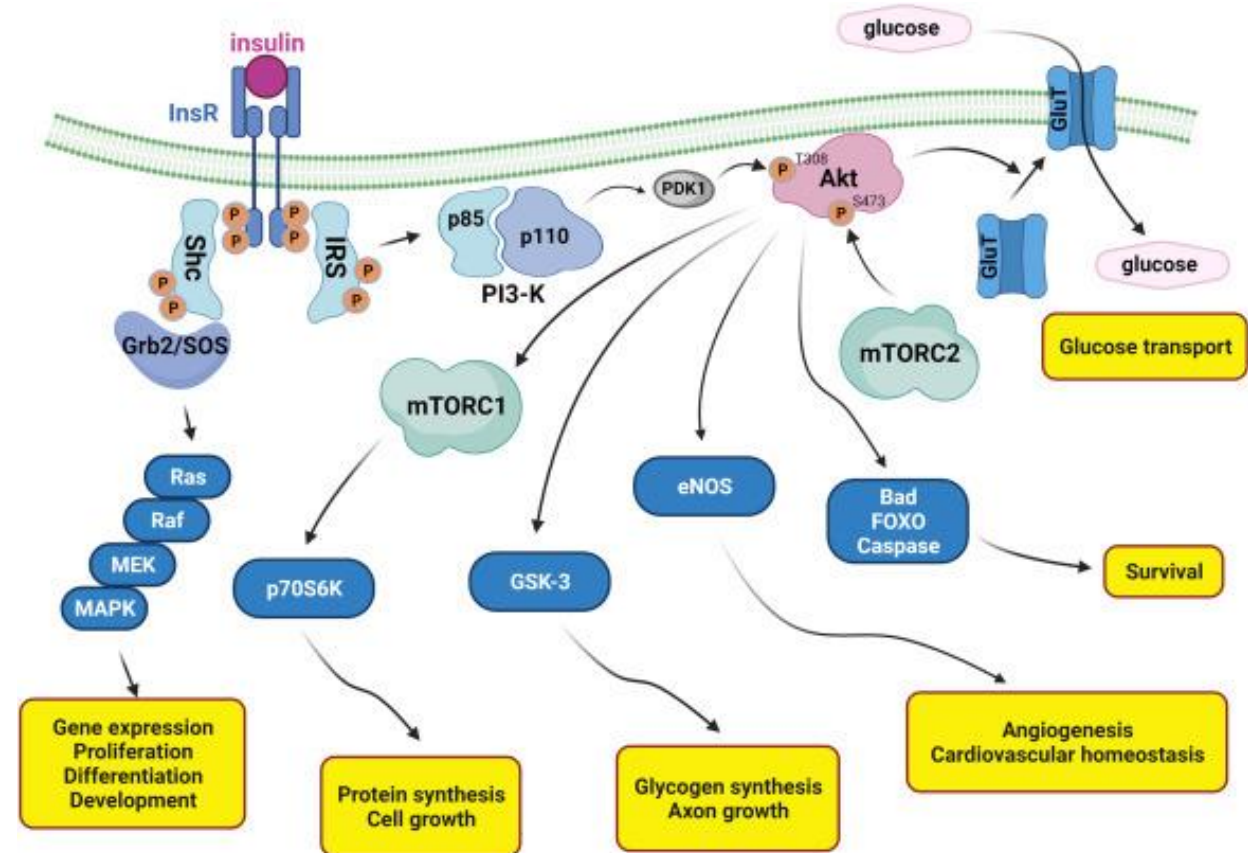
Should we focus on calorie?

- The measure of energy, 1 kcal, estimates the amount of energy required to raise the temperature of 1kg of water by 1 degree Celsius at 1 atmospheric pressure
- Wilbur O. Atwater in the late 1860s started experiments with food consumption and energy generation through metabolic chamber, bomb calorimetry and feces collection
- Calories don't reflect factors such as absorption rate, metabolic modifications, cell uptake, and hierarchical utilization.
- The same number of calories from carbohydrates, protein, and fat might have distinctive consequences
- Our body doesn't burn nutrients but instead turns them into ATPs or uses as building blocks
- How more calories can help PALS is unclear and difficult to study

Catabolic vs Anabolic states

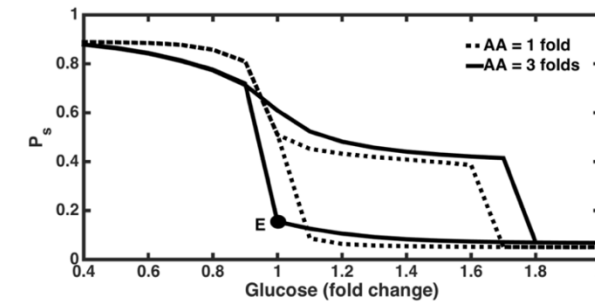
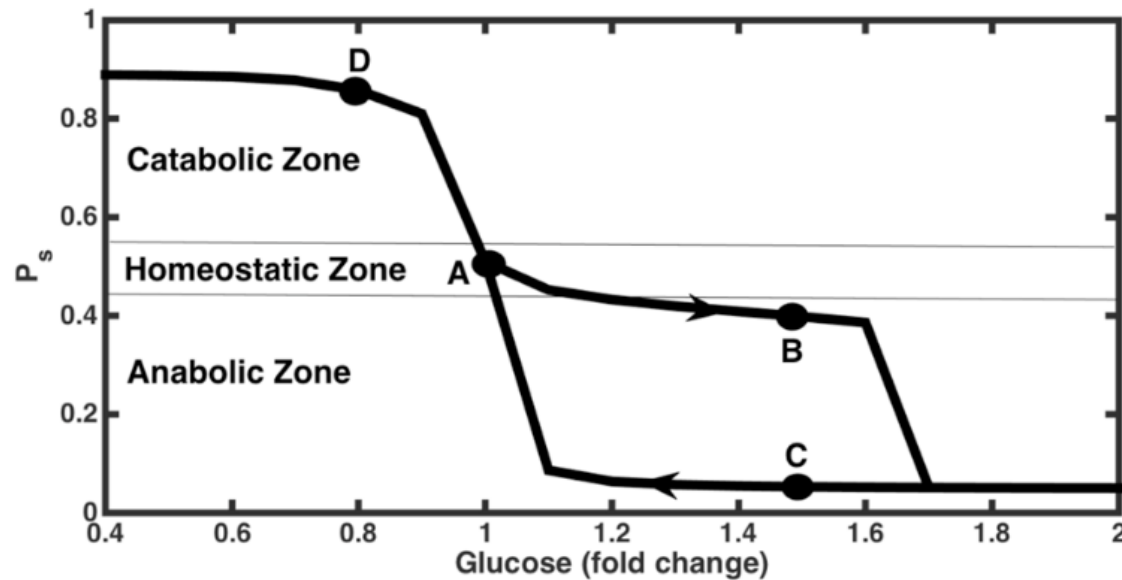


- The rise of glucose triggers insulin secretion, a key anabolic hormone (Suckale et al, 2008)

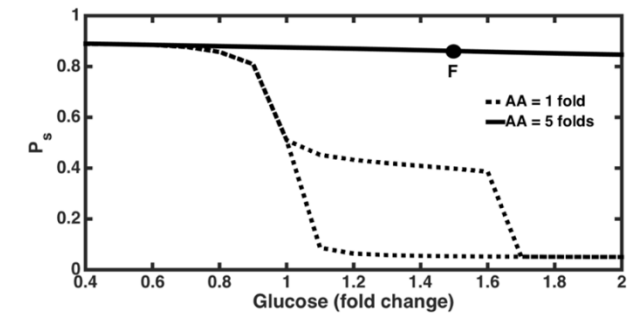


Catabolic vs Anabolic states

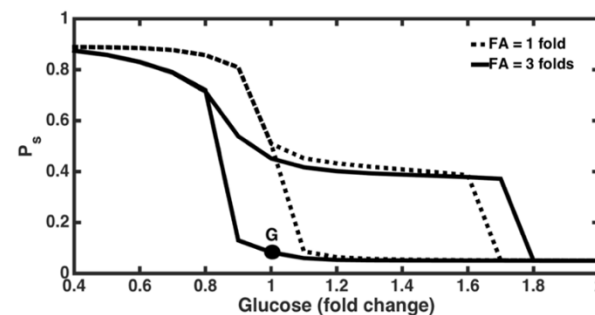
- To enter anabolic zone, glucose level needs to reach 1.7x of the baseline level (~160 mg/dL in non-diabetic person) (Somvanshi et al, 2019)



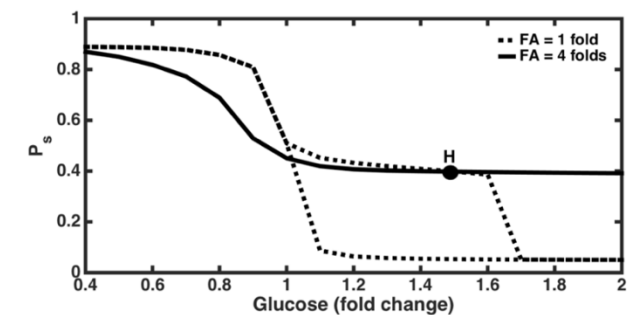
(i)



(ii)





(iii)



(iv)

Higher Glycemic Index and Glycemic Load Diet Is Associated with Slower Disease Progression in Amyotrophic Lateral Sclerosis

Ikjae Lee, MD, MSc  ¹, Hiroshi Mitsumoto, MD,¹ Seonjoo Lee, PhD,^{2,3} Edward Kasarskis, MD, PhD,⁴ Michael Rosenbaum, MD,⁵ Pam Factor-Litvak, PhD,⁶ and Jeri W. Nieves, PhD⁶

Objective: High-caloric diets may slow the progression of amyotrophic lateral sclerosis; however, key macronutrients have not been identified. We examined whether dietary macronutrients are associated with the rate of progression and length of survival among the prospective cohort study participants.

Methods: Participants with a confirmed diagnosis of sporadic amyotrophic lateral sclerosis enrolled in the Multicenter Cohort Study of Oxidative Stress were included ($n = 304$). We evaluated baseline macronutrient intake assessed by food frequency questionnaire in relation to change in revised amyotrophic lateral sclerosis functional rating scale total-score, and tracheostomy-free survival using linear regression and Cox proportional hazard models. Baseline age, sex, disease duration, diagnostic certainty, body mass index, bulbar onset, revised amyotrophic lateral sclerosis functional rating scale total-score, and forced vital capacity were included as covariates.

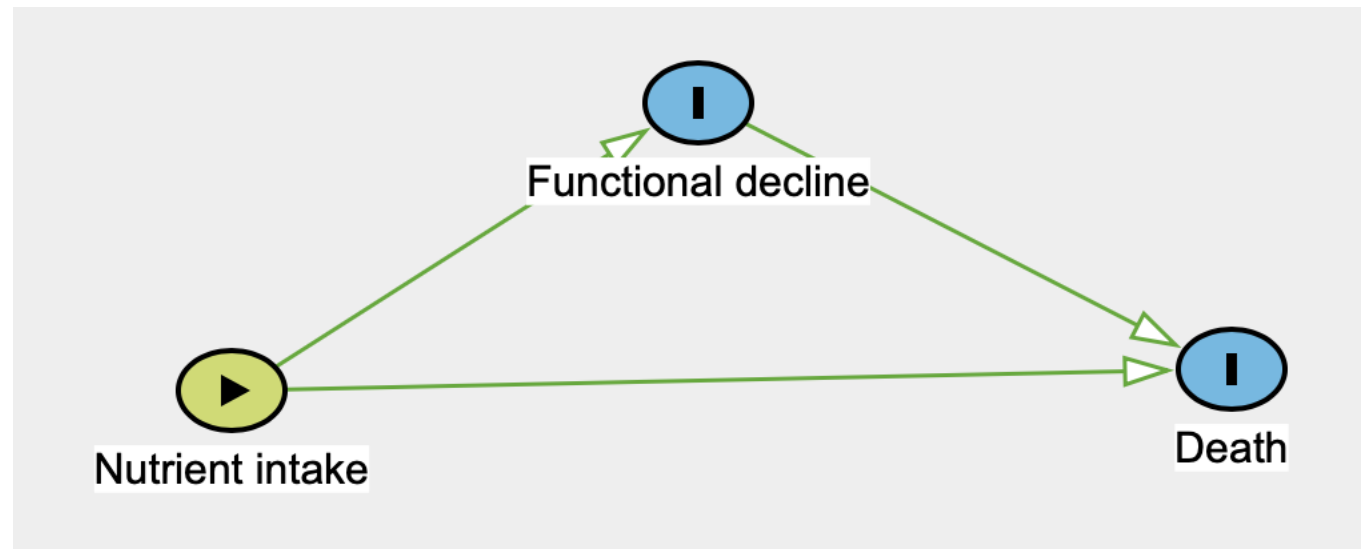
Results: Baseline higher glycemic index and load were associated with less decline of revised amyotrophic lateral sclerosis functional rating scale total score at 3-month follow-up ($\beta = -0.13$, 95% CI $-0.2, -0.01$, $p = 0.03$) and ($\beta = -0.01$, 95% CI $-0.03, -0.0007$, $p = 0.04$), respectively. Glycemic index second-quartile, third-quartile, and fourth-quartile groups were associated with less decline at 3 months by 1.9 (95% CI $-3.3, -0.5$, $p = 0.008$), 2.0 (95% CI $-3.3, -0.6$, $p = 0.006$), and 1.6 (95% CI $-3.0, -0.2$, $p = 0.03$) points compared with the first-quartile group; the glycemic load fourth-quartile group had 1.4 points less decline compared with the first-quartile group (95% CI $-2.8, 0.1$, $p = 0.07$). Higher glycemic index was associated with a trend toward longer tracheostomy-free survival (HR 0.97, 95% CI 0.93, 1.00, $p = 0.07$).

Interpretation: Higher dietary glycemic index and load are associated with slower disease progression in amyotrophic lateral sclerosis.

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Study Hypothesis:

Specific macronutrient intake is associated with functional decline and survival in ALS



Study Design and Rationale



- ALS COSMOS: a Multi-center Prospective Cohort Study of Sporadic ALS patients
- Longitudinal Assessments of Functions (24 months) and Survival
- Baseline/Follow-up Dietary Habits assessed with a Food Frequency Questionnaire
- We examined whether dietary macronutrient intake (calories, fat, carbohydrate, protein, fiber, GI and GL) is associated with disease progression and length of tracheostomy-free survival

Macronutrient Intake and Functional Decline

	Estimate *	95% Confidence Interval	p-value
Total Calories (100kcal)	-0.06	-0.1, 0.06	0.07
Caloric Deficits (100kcal)	-0.04	-0.1, 0.03	0.3
Total Fat (10g)	-0.1	-0.3, 0.04	0.14
Total Protein (10g)	-0.1	-0.3, 0.07	0.2
Total Fiber (10g)	0.07	-0.6, 0.8	0.8
Total Carbohydrate (10g)	-0.05	-0.1, 0.005	0.07
Glycemic Index	-0.2	-0.30, -0.07	0.001
Glycemic Load	-0.016	-0.02, -0.002	0.01

*Adjusted with age and sex

Macronutrient Intake and Functional Decline

	Estimate *	95% Confidence Interval	p-value
Total Calories (100kcal)	-0.06	-0.1, 0.01	0.1
Total Fat (10g)	-0.1	-0.3, 0.04	0.2
Total Carbohydrate (10g)	-0.04	-0.1, 0.01	0.1
Glycemic Index	-0.13	-0.2, -0.01	0.03
Glycemic Load	-0.01	-0.03, -0.0007	0.04

*Adjusted with age, sex, race, disease duration, definite ALS, bulbar onset, riluzole intake, baseline BMI, ALSFRS-r and FVC

Macronutrient Intake and Functional Decline

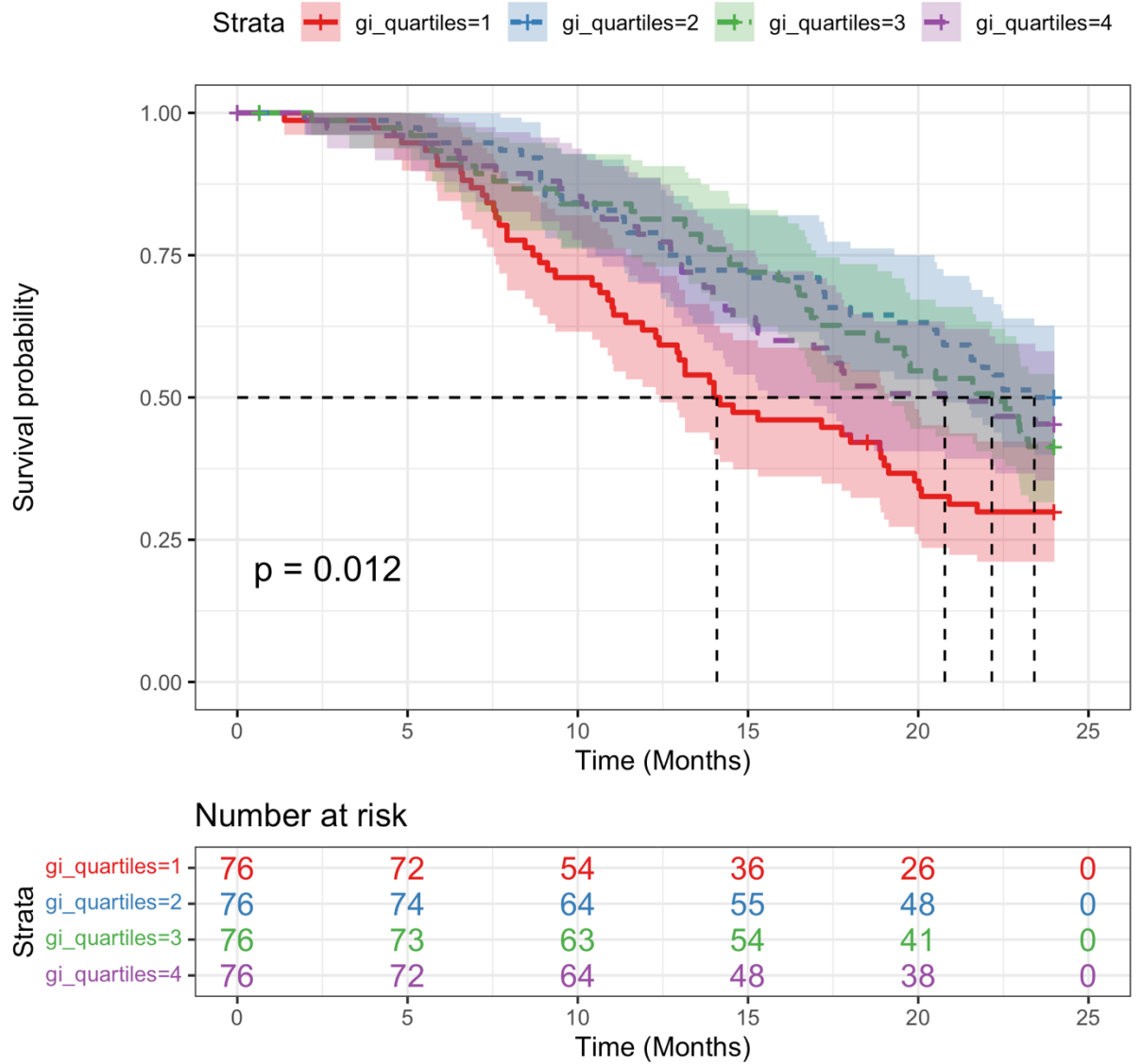
Estimate (95% CI), p-value	Q1*	Q2	Q3	Q4
Total Calories	-	-1.1 (-2.6, 0.3), 0.1	-2.0 (-3.5, -0.6), 0.01	-1.2 (-2.7, 0.3), 0.1
Total Fat	-	-1.2 (-2.6, 0.3), 0.1	-1.4 (-2.9, 0.06), 0.06	-1.4 (-2.9, 0.1), 0.07
Total Carbohydrate	-	0.7 (-0.7, 2.2), 0.3	-0.4 (-1.8, 1.1), 0.6	-0.8 (-2.3, 0.7), 0.3
Glycemic Index	-	-1.9 (-3.3, -0.5), 0.008	-2.0 (-3.3, -0.6), 0.006	-1.6 (-3.0, -0.2), 0.03
Glycemic Load	-	0.9 (-0.6, 2.4), 0.2	-0.2 (-1.6, 1.2), 0.8	-1.4 (-2.8, 0.1), 0.07

*Q1: quartile 1, reference group

Survival Analysis

- Kaplan-Meier survival curve of GI quartile groups showed the separation ($p=0.012$)
- 1 unit increase of GI was associated with longer tracheostomy-free survival (HR 0.94, 95% CI [0.91, 0.98] $p<0.001$)
- In a fully adjusted Cox PH model, 1 unit increase of GI showed a trend of association with longer tracheostomy-free survival (HR 0.97, 95% CI [0.93, 1.00] $p=0.07$)

Survival comparison between GI quartile groups



What about micronutrients?

- ALS COSMOS study (Nieves et al, 2016)
- Cross-sectional analysis examining associations between nutrient intake and functions
- Antioxidants, carotenes, fruits, and vegetables were associated with higher amyotrophic lateral sclerosis function at baseline.
- Difficult to know the direction of association, higher intake leads to better function vs better function leads to higher intake?
- No association found between micronutrients and longitudinal change of ALSFRS (unpublished data)

Index	<u>ALSFRS-R Score</u>		<u>FCV%</u>	
	β (SE)	<i>P</i> Value	β (SE)	<i>P</i> 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

High-dose vitamin E

- Graf et al 2005, Germany
- Randomized, double-blinded, placebo controlled, 18 months
- Alpha-tocopherol 5000mg vs placebo (daily recommended dose 15mg)
- 160 patients in 2 groups
- No significant differences in survival or functional decline

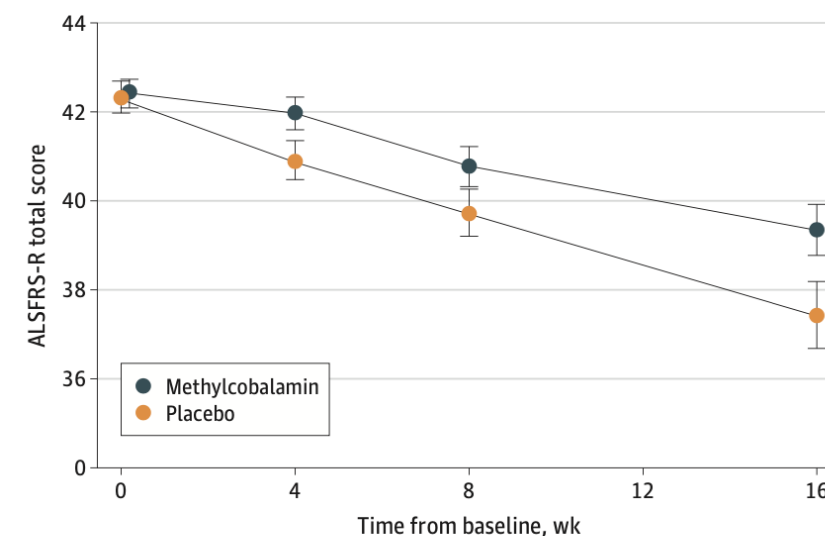
CoQ-10

- Kaufmann et al 2009, US
- Randomized, double-blinded, placebo-controlled, 9 months
- Adaptive phase 2 design to find signal for go vs no go
- 150 participants in 3 groups, low dose (1800mg), high dose (2700mg), control (daily recommended dose 100mg)
- No significant differences in ALSFRS or FVC slopes between CoQ10 at 2,700 mg/day and placebo to warrant phase 3 trial

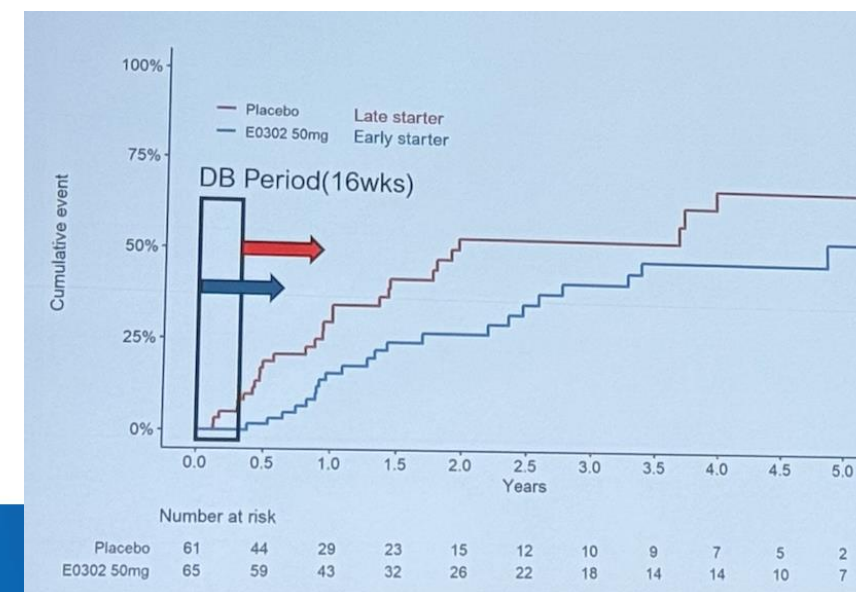
Ultra high dose methylcobalamine

- Oki et al 2022, Japan
- Randomized, double-blinded, placebo-controlled, 4 months
- 130 patients in 2 groups, IM vitamin B12 (50mg twice a week) vs placebo
- Methylcobalamine group had slower functional decline by ALSFRS
- Methylcobalamine group had longer survival (presented at the international MND symposium)

Figure 2. Primary Efficacy Outcomes



The mean and slope of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) total score in the full analysis set are shown. Data are shown as mean (SE). Error bars indicate 95% CIs.



Future directions

- Nutritional intervention trial focusing on providing high GI diet or supplement
- Mechanistic study to identify pathways through which glucose affects motor neuron survival
- Retrospective chart review study to examine the association between GLP-1 drug with disease onset and progression
- Prospective cohort study of presymptomatic variant carriers to examine whether glucose metabolism affects symptom onset

Thank you

COSMOS/ARREST
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