# Kleckner, *et al*.,The effects of a Mediterranean Diet intervention on cancer-related fatigue among patients undergoing chemotherapy: A pilot randomized controlled trial

Supplemental Materials

# Figure S1: Blood-based lipid measures, homocysteine, and fructosamine, as well as body weight, at baseline, week 4, and week 8 for those in the control and Mediterranean Diet groups

# Figure S2: Representative raw trace from the Seahorse XFe96 extracellular flux instrument

# Table S1: The effect of a Mediterranean Diet (MedDiet) intervention on Mediterranean Diet adherence score and nutrient intake

# Table S2: Average of number of servings in each food group per day

# Table S3: Baseline associations between Mediterranean Diet adherence and cancer-related fatigue

# Table S4: Associations between Mediterranean Diet adherence and cancer-related fatigue over three time points—baseline, week 4, and week 8.

# **Figure S1.** Blood-based lipid measures, homocysteine, and fructosamine, as well as body weight, at baseline, week 4, and week 8 for those in the control (*n*=10) and Mediterranean Diet (MedDiet) groups (*n*=20 for blood-based markers and *n*=23 for body weight). ES=effect size, which denotes the effect of the intervention from baseline to week 4 or baseline to week 8. \**p*<0.05, †*p*<0.10 in an analysis of covariance (ANCOVA), for difference between groups at weeks 4 or 8, controlling for value at baseline. HDL=high-density cholesterol, LDL=low-density cholesterol, NHDLC=non-high-density lipoprotein cholesterol



# Figure S2. Representative raw trace from the Seahorse XFe96 extracellular flux instrument. Error bars depict standard deviation from 9 technical replicates.



# **Table S1.** The effect of a Mediterranean Diet (MedDiet) intervention on Mediterranean Diet adherence score (*n*=33) and nutrient intake (*n*=25). To assess between-group differences, a mixed model was constructed to estimate outcomes (e.g, MedDiet Score, energy) at 4 or 8 weeks with group, time, and group×time as fixed effects, and baseline value as an independent variable. Average between-group differences were estimated using marginal means estimates.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Control** | **MedDiet** |  |  |
| **Nutrient** | **Re-commended Daily Allowance (RDA)\*** | **Baseline (mean ± SD)** | **4 weeks (mean ± SD)** | **8 weeks (mean ± SD)** | **Baseline (mean ± SD)** | **4 weeks (mean ± SD)** | **8 weeks (mean ± SD)** | **Average Between-Group Difference in Change from Baseline (MedDiet-Control) ± SE** | ***p*-value** |
| MedDiet score† | Not determined | 4.7 ± 1.9 | 5.7 ± 3.0 | 5.2 ± 3.0 | 4.0 ± 2.7 | 6.7 ± 2.8 | 6.5 ± 2.6 | -1.7 ± 1.0 | 0.080 |
| Energy (kcal) | Not determined | 1855 ± 537 | 1744 ± 531 | 1418 ± 253 | 1716 ± 289 | 1652 ± 360 | 1701 ± 371 | 10 ± 156 | 0.949 |
| Fat (g) | Not determined | 77.3 ± 31.2 | 75.0 ± 27.2 | 63.4 ± 14.1 | 73.5 ± 11.4 | 69.8 ± 18.8 | 76.1 ± 19.7 | -0.4 ± 9.0 | 0.963 |
| Carbohydrates (g) | 130 | 224.6 ± 57.3 | 203.6 ± 66.4 | 158.1 ± 39.7 | 199.0 ± 63.8 | 190.6 ± 51.1 | 192.5 ± 50.9 | 11.8 ± 18.8 | 0.539 |
| Protein (g) | 56 (males), 46 (females) | 71.4 ± 26.9 | 69.9 ± 13.4 | 63.9 ± 11.1 | 73.3 ± 12.3 | 75.7 ± 20.6 | 72.2 ± 15.0 | -7.4 ± 5.9 | 0.227 |
| Fiber (g) | 38 (males 19-50 y), 30 (males >50 y), 25 (females 19-50 y), 21 (females >50 y) | 22.0 ± 3.9 | 17.2 ± 4.6 | 20.0 ± 5.8 | 18.5 ± 7.2 | 23.5 ± 8.8 | 22.5 ± 10.1 | 0.2 ± 5.5 | 0.977 |
| Saturated fat (g) | Not determined | 26.7 ± 13.3 | 26.2 ± 11.4 | 18.4 ± 9.5 | 24.9 ± 8.3 | 19.9 ± 5.9 | 21.9 ± 8.0 | 1.1 ± 3.2 | 0.734 |
| Monounsaturated fat (g) | Not determined | 26.8 ± 10.3 | 28.4 ± 13.3 | 24.1 ± 4.8 | 25.1 ± 5.0 | 27.4 ± 11.5 | 30.8 ± 12.7 | -4.0 ± 4.8 | 0.407 |
| Polyunsaturated fat (g) | Not determined | 16.8 ± 7.9 | 18 ± 10.5 | 17.4 ± 6.4 | 16.4 ± 3.1 | 13.7 ± 4.5 | 17.0 ± 6.7 | 2.5 ± 2.9 | 0.404 |
| Cholesterol (g) | Not determined | 227.3 ± 140.8 | 224.5 ± 119.7 | 206.0 ± 176.3 | 335.0 ± 125.9 | 256.4 ± 121.0 | 310.0 ± 129.0 | -55.7 ± 57.4 | 0.345 |
| Total Vitamin A Activity (International Units) (IU) | 900 (males), 700 (females) | 11739 ± 8863 | 6258 ± 5970 | 8985 ± 5274 | 8165 ± 5039 | 12079 ± 10157 | 9856 ± 7200 | -4315 ± 3192 | 0.180 |
| Vitamin D (calciferol) (mcg) | 15 (19-70 y), 20 (>70 y) | 29.8 ± 47.8 | 28.7 ± 55.8 | 9.8 ± 19.1 | 23.4 ± 22.3 | 11.6 ± 19.0 | 8.1 ± 15.0 | 7.8 ± 7.6 | 0.322 |
| Vitamin E (Total Alpha-Tocopherol) (mg) | 15 | 12.4 ± 5.3 | 11.1 ± 6.8 | 10.8 ± 4.2 | 10.5 ± 5.8 | 11.9 ± 9.1 | 12.5 ± 10.0 | -3.0 ± 3.0 | 0.317 |
| Vitamin C (ascorbic acid) (mg) | 90 (males), 75 (females) | 112.7 ± 67.8 | 106.5 ± 75.9 | 110.4 ± 68.4 | 69.6 ± 37 | 110.1 ± 68.3 | 106.3 ± 63.2 | -1564.9 ± 1711.4 | 0.366 |
| Thiamin (vitamin B1) (mg) | 1.2 (males), 1.1 (females) | 1.6 ± 0.5 | 1.4 ± 0.4 | 1.4 ± 0.3 | 1.5 ± 0.6 | 1.4 ± 0.6 | 1.3 ± 0.6 | 0.0 ± 0.2 | 0.994 |
| Riboflavin (vitamin B2) (mg) | 1.3 (males), 1.1 (females) | 2.1 ± 0.7 | 1.9 ± 0.9 | 1.6 ± 0.4 | 1.9 ± 0.7 | 1.7 ± 0.7 | 1.7 ± 0.7 | -0.1 ± 0.3 | 0.805 |
| Niacin (vitamin B3) (mg) | 16 (males), 14 (females) | 21.3 ± 8.2 | 19.7 ± 6.5 | 19.1 ± 5 | 22.6 ± 7 | 22.4 ± 8.1 | 21.3 ± 8.4 | -2.1 ± 2.8 | 0.463 |
| Pantothenic Acid (mg) | Not determined | 6.4 ± 2.9 | 5.2 ± 2.7 | 4.9 ± 1.3 | 6.4 ± 3.3 | 5.5 ± 3.2 | 5.5 ± 3.6 | -0.5 ± 1.2 | 0.691 |
| Vitamin B-6 (pyridoxine, pyridoxyl, & pyridoxamine) (mg) | 1.3 (19-50 y), 1.7 (males >50 y), 1.5 (females >50 y) | 1.9 ± 0.9 | 1.6 ± 0.6 | 1.5 ± 0.5 | 2.0 ± 0.9 | 2.1 ± 0.9 | 2.0 ± 1.0 | -0.4 ± 0.4 | 0.236 |
| Total Folate (mcg) | 400 | 360.0 ± 140.7 | 302.6 ± 118.6 | 353.7 ± 87.7 | 370.5 ± 157.7 | 405.3 ± 191.5 | 351.6 ± 242 | -38.5 ± 75.7 | 0.617 |
| Vitamin B-12 (cobalamin) (mcg) | 2.4 | 4.0 ± 2.5 | 6.0 ± 5.9 | 3.5 ± 2.5 | 5.7 ± 3.1 | 3.9 ± 2 | 4.7 ± 4.2 | 1.1 ± 1.5 | 0.468 |
| Calcium (mg) | 1000 (19-50 y, males 51-70 y), 1200 (females 51-70 y, >70y) | 977.0 ± 399.9 | 889.8 ± 471.1 | 658.2 ± 178.4 | 921.1 ± 478.1 | 851.7 ± 500.7 | 750.5 ± 383.6 | -56.3 ± 164.6 | 0.736 |
| Phosphorus (mg) | 700 | 1193.0 ± 395.6 | 1128.0 ± 394.8 | 1001.6 ± 251.7 | 1151.5 ± 260.7 | 1147.4 ± 288.7 | 1141.9 ± 348.9 | -101.9 ± 112.4 | 0.377 |
| Magnesium (mg) | 400 (males 19-30), 420 (males >30 y), 310 (females 19-30 y), 320 (females >30 y) | 300.0 ± 65.1 | 256.6 ± 73.3 | 261.5 ± 106 | 252.2 ± 61.8 | 330.1 ± 121.7 | 304.5 ± 144.3 | -118.0 ± 43.8 | 0.015 |
| Iron (mg) | 8 (males, females >50 y), 18 (females 19-50 y) | 12.5 ± 5.4 | 11.3 ± 3.4 | 10.4 ± 3 | 14.7 ± 6.6 | 14.1 ± 6.3 | 12.9 ± 7.8 | -1.1 ± 2.2 | 0.641 |
| Zinc (mg) | 11 (males), 8 (females) | 10.1 ± 5.1 | 8.1 ± 2.5 | 7.0 ± 2.2 | 11.0 ± 4.5 | 10.3 ± 5.3 | 10.2 ± 5.6 | -2.6 ± 1.9 | 0.187 |
| Copper (mg) | 900 | 1.1 ± 0.3 | 0.9 ± 0.2 | 0.9 ± 0.3 | 1.2 ± 0.4 | 1.4 ± 0.7 | 1.4 ± 0.9 | -0.5 ± 0.3 | 0.095 |
| Selenium (mcg) | 55 | 101.8 ± 36.6 | 103.9 ± 19.5 | 97.1 ± 30.0 | 116.4 ± 23.6 | 101.1 ± 34.0 | 124.6 ± 39.0 | -8.5 ± 15.0 | 0.577 |
| Sodium (mg) | 1500 | 2885.4 ± 1477.8 | 2841.8 ± 1290.4 | 2474.3 ± 1215.1 | 2848.5 ± 847.7 | 2502.4 ± 590.2 | 2441.7 ± 675.1 | 242.1 ± 294.0 | 0.421 |
| Potassium (mg) | 3400 (males), 2600 (females) | 2420.8 ± 736.8 | 2234.0 ± 653.5 | 2195.7 ± 661.1 | 2283.3 ± 611.2 | 2650.9 ± 1024.9 | 2614.3 ± 1170.5 | -483.1 ± 401.9 | 0.230 |

\*RDA: Recommended Daily Allowances from the National Academy of Medicine (NAM) of the National Academies (United States). These represent the estimated average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy people.

†MedDiet score: Adherence to the Mediterranean Diet using the 14-item Mediterranean Diet Assessment Tool [34], a higher score indicates higher adherence

# Table S2. Average of number of servings in each food group per day, as measured using 3-day food records. To assess between-group differences, a mixed model was constructed to estimate the number of servings at 4 or 8 weeks with group, time, and group×time as fixed effects, and the number of servings at baseline as an independent covariate. Average between-group differences were estimated using marginal means estimates.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control (*n*=7-8)** | **MedDiet (*n*=16)** |  |  |
| **Food group\*** | **Baseline****(mean± SD)** | **Week 4** **(mean± SD)** | **Week 8** **(mean± SD)** | **Baseline** **(mean± SD)** | **Week 4** **(mean± SD)** | **Week 8** **(mean± SD)** | **Average Between-Group Difference in Change from Baseline (MedDiet-Control) ± SE** | ***p*-value** |
| Fruit | 2.1 ± 1.1 | 1.6 ± 1.4 | 1.7 ± 1.6 | 1.9 ± 1.8 | 1.2 ± 1.2 | 1.4 ± 1.2 | -0.37 ± 0.56 | 0.524 |
| Vegetables | 3.0 ± 2.4 | 2.3 ± 2.5 | 3.4 ± 2.1 | 2.2 ± 1.1 | 3.5 ± 1.8 | 3.6 ± 2.6 | 0.92 ± 0.75 | 0.232 |
| Potatoes and other starchy vegetables | 0.2 ± 0.2 | 0.6 ± 0.6 | 0.3 ± 0.5 | 0.6 ± 0.7 | 0.5 ± 0.4 | 0.8 ± 0.8 | 0.16 ± 0.23 | 0.482 |
| Beans and legumes | 0.3 ± 0.8 | 0.1 ± 0.2 | 0.1 ± 0.3 | 0.2 ± 0.3 | 0.4 ± 0.4 | 0.4 ± 0.5 | 0.29 ± 0.15 | 0.076 |
| Whole grains | 0.7 ± 0.8 | 1.0 ± 1.3 | 1.0 ± 2.0 | 0.6 ± 0.7 | 1.8 ± 1.3 | 1.8 ± 1.3 | 1.08 ± 0.47 | 0.034**†** |
| Grains, some whole grain | 0.8 ± 1.7 | 0.4 ± 0.5 | 0.8 ± 1.6 | 0.6 ± 0.6 | 0.4 ± 0.5 | 0.5 ± 0.8 | -0.13 ± 0.26 | 0.622 |
| Refined grains | 3.3 ± 1.4 | 3.5 ± 2.2 | 2.8 ± 2.4 | 3.8 ± 1.7 | 2.4 ± 1.9 | 2.2 ± 1.6 | -1.40 ± 0.77 | 0.084 |
| Meat and poultry | 3.5 ± 3.0 | 3.1 ± 1.9 | 2.5 ± 1.4 | 3.1 ± 1.1 | 3.0 ± 1.4 | 2.4 ± 1.9 | 0.25 ± 0.49 | 0.606 |
| Fish | 0.1 ± 0.2 | 0.7 ± 1.1 | 0.7 ± 1.1 | 1.1 ± 1.0 | 0.9 ± 0.8 | 1.5 ± 1.3 | 0.54 ± 0.46 | 0.253 |
| Eggs | 0.3 ± 0.5 | 0.4 ± 0.3 | 0.5 ± 0.8 | 0.8 ± 0.7 | 0.7 ± 0.6 | 1.0 ± 0.7 | 0.37 ± 0.25 | 0.154 |
| Nuts | 0.9 ± 1.3 | 0.3 ± 0.5 | 0.7 ± 1.0 | 0.8 ± 0.8 | 0.9 ± 0.7 | 1.3 ± 1.6 | 0.63 ± 0.38 | 0.114 |
| Meat alternatives | 0 ± 0 | 0.1 ± 0.3 | 0.1 ± 0.3 | 0 ± 0 | 0.3 ± 0.5 | 0.1 ± 0.4 | 0.00 ± 0.10 | 0.966 |
| Dairy | 3.9 ± 2.6 | 2.7 ± 2.5 | 2.7 ± 1.9 | 3.2 ± 1.5 | 2.1 ± 1.5 | 2.4 ± 1.4 | -0.10 ± 0.74 | 0.889 |
| Oil | 1.5 ± 1.2 | 1.7 ± 1.5 | 2.3 ± 1.5 | 1.6 ± 0.7 | 3.1 ± 3.1 | 3.1 ± 2.8 | 1.02 ± 1.21 | 0.410 |
| Butter and shortening | 2.1 ± 2.9 | 1.7 ± 2.1 | 0.8 ± 1.5 | 1.2 ± 1.5 | 0.5 ± 0.7 | 1.6 ± 2.7 | 0.23 ± 0.60 | 0.708 |
| Sweets | 0.8 ± 0.5 | 0.8 ± 1.0 | 0.9 ± 1.2 | 1.0 ± 1.1 | 1.0 ± 1.5 | 1.0 ± 1.2 | -0.01 ± 0.39 | 0.975 |
| Sweetened beverages | 1.6 ± 1.9 | 0.5 ± 0.7 | 0.5 ± 0.9 | 0.5 ± 0.6 | 0.2 ± 0.6 | 0.4 ± 0.7 | -0.12 ± 0.32 | 0.705 |

\*NDSR codes: Fruits includes fruit, fruit juice, avocado, fried fruits, and fruit-based savory snacks (FRU0100-FRU0700). Vegetables includes dark green vegetables (VEG0100), deep yellow vegetables (VEG0200), tomatoes (VEG0300), other vegetables (VEG0600), fried vegetables (VEG0900), vegetable juice (VEG0500), and vegetable-based savory snacks (FMC0100). It does not include white or fried potatoes, other starchy vegetables, or legumes. Potatoes and other starchy vegetables includes white potatoes (VEG0400), fried potatoes (VEG0800), and other starchy vegetables (VEG0450). Beans and legumes includes only legumes (cooked dried beans; VEG0700). Whole grains includes whole grains, flour, and dry mixes; loaf-type bread and plain rolls; other breads; crackers; pasta; ready-to-eat cereals; cakes, cookies, pies, pastries, Danishes, doughnuts, and cobblers; snack bars; snack chips, and popcorn (all codes beginning GRW). Grains, some whole grain includes the same categories as whole grain except popcorn, but with some of the grains whole grain (all codes beginning GRS). Refined grains includes the same categories as whole grain except popcorn, plus baby food grain mixtures (all codes beginning GRR). Meat and poultry include all meat and poultry categories except the five fish categories, including beef, lamb, pork, poultry, cold cuts, sausage, meat-based savory snacks, and others (19 total). Fish includes fish and shellfish (MFF0100, MFL0100, MFF0200, MSL0100, MSF0100). Eggs includes eggs (MOF0300) and egg substitutes (MOF0400). Nuts includes nuts and seeds (MOF0500) and nut and seed butters (MOF0600). Meat alternatives includes soy-, pea protein-, and other protein-based formulations used to mimic chicken nuggets, ground beef, etc. (MOF0700). Dairy includes milk, cheese, yogurt, frozen desserts, cream, and margarine (40 categories). Oil includes oil (FOF0100) and salad dressings (FDF0100, FDR0100). Sweets includes sugar, syrup, honey, jelly, chocolate, candy, frosting, etc. (SWT0100-SWT0500, SWT0700, SWT0800, MSC1200). Sweetened beverages includes sweetened and artificially sweetened soft drinks, fruit drinks, tea, coffee, and water (all categories starting BVS and BVA), but not any unsweetened beverages.

†p<0.05

# **Table S3.** Baseline associations between Mediterranean Diet adherence and cancer-related fatigue. Linear models are adjusted for age (*n*=33). For the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), a higher score indicates less fatigue and a greater quality of life. For the Brief Fatigue Inventory and Symptom Inventory, a higher score indicates higher fatigue. \**p*<0.05

|  |  |  |
| --- | --- | --- |
| Measure | Estimate ± SE | *p*-value |
| FACIT-F: Total score | 2.92 ± 1.78 | 0.111 |
| FACIT-F: Physical well-being | 0.54 ± 0.38 | 0.163 |
| FACIT-F: Social well-being | 0.02 ± 0.22 | 0.926 |
| FACIT-F: Emotional well-being | 0.01 ± 0.31 | 0.984 |
| FACIT-F: Functional well-being | 0.46 ± 0.49 | 0.355 |
| FACIT-F: Fatigue subscale | 1.81 ± 0.87 | 0.046\* |
| FACIT-F: Trial Outcome Index | 2.82 ± 1.63 | 0.095 |
| FACIT-F: Functional Assessment of Cancer Therapy- General (FACT-G) | 1.07 ± 1.03 | 0.311 |
| Brief Fatigue Inventory: Total score | -0.38 ± 0.17 | 0.031\* |
| Brief Fatigue Inventory: Usual fatigue | -0.39 ± 0.18 | 0.040\* |
| Brief Fatigue Inventory: Worst fatigue | -0.59 ± 0.21 | 0.009\* |
| Symptom Inventory: Fatigue | -0.34 ± 0.22 | 0.130 |
| Symptom Inventory: Sleep problems | -0.12 ± 0.26 | 0.654 |
| Symptom Inventory: Drowsiness | -0.21 ± 0.21 | 0.310 |
| Symptom Inventory: How do symptoms interfere with quality of life | -0.54 ± 0.22 | 0.017\* |

# **Table S4.** Associations between Mediterranean Diet adherence and cancer-related fatigue over three time points—baseline, week 4, and week 8. The mixed model has a first-order autoregressive repeated structure (AR[1]) with random effect for participant and age and Mediterranean Diet adherence score (MedDiet) as independent variables (*n*=33). For the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), a higher score indicates less fatigue and a greater quality of life. For the Brief Fatigue Inventory and Symptom Inventory, a higher score indicates higher fatigue. \**p*<0.05

|  |  |  |
| --- | --- | --- |
| Measure | Estimate ± SE | *p*-value |
| FACIT-F: Total score | 2.360 ± 0.842 | 0.007\* |
| FACIT-F: Physical well-being | 0.545 ± 0.200 | 0.008\* |
| FACIT-F: Social well-being | 0.088 ± 0.109 | 0.419 |
| FACIT-F: Emotional well-being | 0.074 ± 0.123 | 0.545 |
| FACIT-F: Functional well-being | 0.318 ± 0.170 | 0.066 |
| FACIT-F: Fatigue subscale | 1.440 ± 0.439 | 0.002\* |
| FACIT-F: Trial Outcome Index | 2.272 ± 0.762 | 0.004\* |
| FACIT-F: Functional Assessment of Cancer Therapy- General (FACT-G) | 1.009 ± 0.431 | 0.022\* |
| Brief Fatigue Inventory: Total score | -0.303 ± 0.080 | <0.001\* |
| Brief Fatigue Inventory: Usual fatigue | -0.300 ± 0.094 | 0.002\* |
| Brief Fatigue Inventory: Worst fatigue | -0.382 ± 0.109 | 0.001\* |
| Symptom Inventory: Fatigue | -0.223 ± 0.118 | 0.063 |
| Symptom Inventory: Sleep problems | -0.111 ± 0.103 | 0.287 |
| Symptom Inventory: Drowsiness | -0.188 ± 0.110 | 0.091 |
| Symptom Inventory: How do symptoms interfere with quality of life | -0.313 ± 0.109 | 0.005\* |