SUPPLEMENT

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Table S1. Eligibility criteria

Inclusion Criteria

- Any sex, any racial and ethnic groups, ages 18 and above, with 5–20 migraines/month
- Meeting the 2004 International Classification of Headache Disorders (ICHD-II) criteria for migraine, with or without aura
- Headaches present for at least two consecutive years leading up to study enrollment
- Under the care of a physician for their headaches (may be taking migraine prevention medications or abortive medications)
- Able to read and communicate in English
- Have internet access through at least one device
- Willing to be randomized to any of the study arms
- Able to understand and comply with study procedures, including keeping a headache diary
- Able to attend seven dietary counseling visits during the study
- Able to attend post-intervention visit six weeks after intervention end
- Must meet all of the above criteria within five weeks of enrollment

Exclusion Criteria

- Change in hormone or birth control use within the past six months
- Pregnancy or anticipated pregnancy, breast feeding, because of the unpredictable hormonal influences on migraine
- Marked depression, anxiety, or psychosis at time of enrollment
- Receiving active treatment for a major medical illness (Well-managed diabetes and thyroid disorders are not be excluded)
- History of significant head trauma or surgery of the head or neck within three years of screening
- Cognitive impairment that prevents understanding the protocol
- Other chronic pain syndromes requiring pain clinic management
- History of food allergy with associated rash or pulmonary symptoms such as shortness of breath or wheezing
- Stated aversion to eating seafood
- Regular exposure to fish oil or omega-3 fatty acids in the two years up to study enrollment
- Currently on a diet for the purpose of weight reduction for a period of greater than three weeks
- Previous participation in a dietary intervention investigational study
- Participation in any intervention study in past 12 months
- History suggesting substance abuse within the past five years
- Any condition that would prevent complete participation in the trial
- Suspected, potentially disabling or life-threatening conditions with headache as a major feature, such as vasculitis, intracranial mass, history of subarachnoid hemorrhage, history of central nervous system infection within the preceding five years

Description of Dietary Interventions

All three diet groups were designed to be as similar as possible with the only differences being the study-provided oil and butter formulation as well as the protein foods (high fat fish versus low fat fish or poultry) provided to achieve the fatty acid targets. Participants in all groups received the same instruction regarding oils (ie, to prepare foods at home as often as possible with only the study provided oils/butter and when grocery shopping or dining out avoid all other oils except olive oil, butter, palm oil, and coconut oil). The registered dietitian met with study participants every 2-3 weeks throughout the 16 weeks of intensive diet intervention delivering diet-specific education, counseling, and study food supplies to last until the next study visit. Participants completed a food label reading exercise with the dietitian to demonstrate competency in identifying oil ingredients of store-bought foods. The only difference in diet education was instruction for the control group to choose low fat proteins focusing on low fat poultry while the H3 and H3-L6 groups were instructed to consume high fat fish on a daily basis and limit other animal proteins. Participants in all groups were instructed to consume a small amount of ground flaxseed daily in order to standardize n-3 ALA intake between diets. The intensity of the intervention was designed to be the same across diet groups with access to the same number of education materials, number of study-provided foods and time spent with the dietitian.

Diet Intervention Education Materials: Diet Guidelines, Food List (categorizes foods into allowed, limit, avoid), Food Label Reading activity, 7-Day Meal Plan (2000, 2500 or 3000 kcal), Dining Out Guide, Cooking Guide (fish or poultry), Grocery Shopping Guides (10 local grocery stores), Diet Checklist (for self-monitoring adherence to diet guidelines), Website (diet arm specific access including all diet education materials and 75+ recipes)

Diet Guidelines

Control	H3	H3-L6
Consume foods provided by the research study on a daily basis	Consume foods provided by the research study on a daily basis	Consume foods provided by the research study on a daily basis
Replace all cooking oils, salad dressings and mayonnaise in your kitchen with those provided by the research study	Replace all cooking oils, salad dressings and mayonnaise in your kitchen with those provided by the research study	Replace all cooking oils, salad dressings and mayonnaise in your kitchen with those provided by the research study
Consume 4-8 oz of lean protein each day	**Consume at least 4 oz of fish each day**	**Consume at least 4 oz of fish each day**
Incorporate 1 ½ teaspoons of ground flaxseed into your breakfast meal daily	**Incorporate 1 ½ teaspoons of ground flaxseed into your breakfast meal daily**	**Incorporate 2 teaspoons of ground flaxseed into your breakfast meal daily**
Consume plenty of fruits and vegetables every day	Consume plenty of fruits and vegetables every day	Consume plenty of fruits and vegetables every day
Avoid processed food, fast food, and fried foods	Avoid processed food, fast food, and fried foods	Avoid processed food, fast food, and fried foods

Foods Provided to Participants

	Control	H3	H3-L6
Animal Protein			
Sockeye Salmon, wild, frozen		X	X
Tuna, Albacore, frozen		X	X
Trout, lake, frozen		X	X
Salmon, Pacific Sockeye, canned in water		X	X
Albacore Tuna, solid white, canned in water		X	X
Sardines in spring water		X	X
Chicken Breast, frozen	X		
Turkey, ground, 99% fat free	X		
Cod, frozen	X		
Chunk Light Tuna, canned in water (low EPA+DHA)	X		
Kidney Beans, canned	X		
Study provided, specially formulated oils to achieve diet targets			
Low-LA Oil Blend (75% macadamia nut oil/25% extra virgin olive oil)			X
High-LA Oil Blend (75% corn oil/25% extra virgin olive oil)	X	X	
Butter, salted			X
High-LA butter blend (50% butter/50% corn oil)	X	X	
Recipes prepared with diet arm specific oil			
Balsamic Vinaigrette	X	X	X
Muffins	X	X	X
Granola	X	X	X
Granola Bars	X	X	X
Hummus	X	X	X
Low-LA foods provided to all diet arms			
Flaxseed, whole ground (1.5 tsp or 2 tsp packets depending on diet arm)	X	X	X
Crackers, woven wheats	X	X	X
Bread, sweet wheat	X	X	X
Tortillas, flour	X	X	X
Popcorn, light	X	X	X
Vegetarian Chili (prepared recipe)	X	X	X
Blueberries, frozen	X	X	X
Mixed Fruit, frozen (pineapple, strawberry, mango)	X	X	X
Broccoli, frozen	X	X	X
Mixed Vegetables, frozen (summer squash, carrots)	X	X	X
Yogurt, low fat, vanilla	X	X	X
Mozzarella Cheese Sticks, part skim	X	X	X
Fat Free Mayonnaise	X	X	X
Shrimp	X	X	X

Example One Day Meal Plan

	Control	**H3**	**H3-L6**
Breakfast	1 Serving Smoothie, ¾ Cup Cheerios with 1 Cup Low-fat Milk	1 Serving Smoothie ¾ cup Cheerios with 1 Cup Milk	1 Serving Smoothie, ¾ cup Cheerios with 1 Cup Milk
Lunch	1 Serving Spinach Salad with Shrimp	1 Serving Spinach Salad with Shrimp	1 Serving Spinach Salad with Shrimp
Snacks	Fruit, 1 Granola Bar, 1 Mozzarella Cheese Stick	Fruit, 1 Granola Bar	Fruit, 1 Granola Bar
Dinner	4 oz Chicken with Chive Sauce, 1 Cup Broccoli Salad, 1 Cup Rice Pilaf	4.5 oz Salmon with Maple Glaze, 1 Cup Broccoli Salad, ¾ Cup Rice Pilaf	4.5 oz Salmon with Maple Glaze, 1 Cup Broccoli Salad, ¾ Cup Rice Pilaf
Dessert	½ Cup Frozen Yogurt	½ Cup Vanilla Ice Cream	½ Cup Vanilla Ice Cream

Recipe Ingredients:

Smoothie – Fruit, frozen (study provided), flaxseed meal (study provided), vanilla yogurt (study provided)

Spinach Salad - Pre-cooked shrimp (study provided), baby spinach, Navel oranges, red bell pepper, red onion, oregano, orange juice, turmeric, study oil (study provided), black pepper, salt

Granola Bar - (study provided and prepared with diet arm oil) - butter (study provided), brown sugar, honey, vanilla extract, rolled oats, raisins, Rice Krispies, pretzels

Salmon with Maple Glaze - Maple syrup**,** low-sodium Tamari or soy sauce, Dijon mustard, ginger root, honey, butter (study provided), sockeye salmon (study provided), study oil (study provided), salt, pepper

Broccoli Salad – Broccoli (fresh), cherry tomatoes, study oil (study provided), garlic clove, salt, lemon zest, lemon juice, black olives, oregano

Rice Pilaf – Vegetable broth, brown rice, yellow onion, celery, butter (study provided), salt

Chicken with Chive Sauce – Chicken breast (study provided), salt, all-purpose flour, study oil (study provided), shallots, chicken broth, reduced fat sour cream, Dijon mustard, chives

Expectation of Benefit/Credibility
INSTRUCTIONS

You have been given details about the treatments you are learning in this study. We are interested in obtaining your impressions about and reactions to the procedures presented to you thus far. Please answer the questions below by first finding the number on the scale that most accurately describes your impressions and then by filling in the oval that corresponds with that number.

1. How logical does this type of dietary intervention seem to you for helping people alleviate their headaches?

   Not logical   Very logical
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

2. How confident are you that this dietary intervention will be successful in reducing your headaches?

   Not at all confident   Very confident
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

3. How confident would you be in recommending this dietary intervention to a friend who has a problem with headaches?

   Not at all confident   Very confident
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

4. How important do you think it is that we make this dietary intervention available to others who experience headaches?

   Not at all important   Very important
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

5. How successful do you believe this dietary intervention would be in decreasing other problems involving tension, anxiety, insomnia, etc.?

   Not at all successful   Very successful
0	1	2	3	4	5	6	7	8	9
O	O	O	O	O	O	O	O	O	O

Electronic headache diary (sample)

Daily Headache Diary

Study ID: 9999

Definitions of mild, moderate and severe headaches

Mild: (a) Your pain requires less than two doses of over the counter medication per 12 hours; (b) you are able to function at an 80% level or more; (c) you have minimal nausea or sensitivity to light or sound; (d) on a scale of 1-10, with 1=minimal pain and 10=worst pain ever, your pain is a 1, 2, or 3. You may or may not experience an aura with your headache.

Moderate: (a) Your pain requires over the counter or prescription medication every 3 or 4 hours; (b) you are able to function at an 50% level or more; (c) you have mild to moderate nausea or sensitivity to light or sound; (d) on a scale of 1-10, with 1=minimal and 10 worst pain ever, your pain is a 4, 5, or 6. You may or may not experience an aura with your headache.

Severe: (a) Your pain requires maximal available pain medication every 3-4 hours; (b) your ability to function is less than 50%; (c) you have significant nausea or sensitivity to light or sound; (d) on a scale of 1-10, with 1=minimal pain and 10=worst pain ever, your pain is a 7, 8, 9 and 10. You may or may not experience an aura with your headache.

Record your diary information for: [SELECT] ▼

Time of headache	None 😊	Mild 😐	Moderate 😟	Severe 😣	Sleeping 😴
12 Midnight	⊙	⊙	⊙	⊙	⊙
1	⊙	⊙	⊙	⊙	⊙
2	⊙	⊙	⊙	⊙	⊙
3	⊙	⊙	⊙	⊙	⊙
4	⊙	⊙	⊙	⊙	⊙
5	⊙	⊙	⊙	⊙	⊙

6 AM	○	○	○	○	○
7	○	○	○	○	○
8	○	○	○	○	○
9	○	○	○	○	○
10	○	○	○	○	○
11	○	○	○	○	○
12 Noon	○	○	○	○	○
1 PM	○	○	○	○	○
2	○	○	○	○	○
3	○	○	○	○	○
4	○	○	○	○	○
5	○	○	○	○	○
6 PM	○	○	○	○	○
7	○	○	○	○	○
8	○	○	○	○	○
9	○	○	○	○	○
10	○	○	○	○	○
11 PM	○	○	○	○	○

If you had a headache, did you have an aura with it?
　　○ Yes　　○ No

Please rate your overall health today:
- ◎ Poor
- ◎ Fair
- ◎ Good
- ◎ Excellent

Medications for headache:

Name of Medicine:		Nr. of doses:	
Name of Medicine:		Nr. of doses:	
Name of Medicine:		Nr. of doses:	
Name of Medicine:		Nr. of doses:	

How stressful has your life been over the past 24 hours?
Please indicate a number from 0 to 10, with 0 meaning "not stressful at all" and 10 meaning "extremely stressful".

not stressful at all ◎ ◎ ◎ ◎ ◎ ◎ ◎ ◎ ◎ ◎ ◎ extremely stressful

Comments:

[Submit Your Diary Information for This Day]

Table S2. Headache-related medications used throughout the study

Categories	Examples of Medications
Preventive	
Anticonvulsants	Valproate, topiramate, lamotrigine, gabapentin, pregabalin, carbamazepine
Antidepressants	Duloxetine, venlafaxine, amitriptyline, nortriptyline, doxepin, clomipramine, sertraline, citalopram, fluoxetine, buproprion
Muscle relaxants	Baclofen, chlorzoxazone, cyclobenzaprine, tizanidine
Vasoactive	Beta blockers, alpha blockers, calcium channel blockers
Botulinum toxin	
Acute	
NSAIDs/Aspirin	Ibuprofen, naproxen, ketorolac, diclofenac, aspirin, celecoxib, meloxicam, piroxicam, nabumetome, etodolac, ketoprofen
Triptans	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, naratriptan
Other	Acetaminophen, tapentadol, dextromethorphan, oxycodone, hydrocodone, hydromorphone, propoxyphene, codeine, buprenorphine, butalbital, tramadol, caffeine (as medication)
Adjunctive	Anti-emetics (e.g., phenergan, ondansetron), anxiolytics (e.g., diazepam, alprazolam, lorazepam, buspirone), sleep aids/hypnotics (e.g., quetiapine, trazadone, zolpidem, eszoplicone), sinus/allergy (e.g., diphenhydramine, pseudoephedrine, loratadine), supplements (e.g., butterbur)

Table S3. Subgroup (heterogeneity) analysis by baseline chronic/episodic migraine [a]

		Episodic migraine (n=60)			Chronic migraine (n=122)		
		Control (n=18)	H3 (n=19)	H3-L6 (n=23)	Control (n=42)	H3 (n=42)	H3-L6 (n=38)
Primary Endpoints [b]							
17-HDHA in plasma, log ng/mL	**Estimate (95% CI)**	0.7 (0.2 to 1.2)	1.4 (1.1 to 1.8)	1.3 (0.9 to 1.7)	0.7 (0.4 to 0.9)	1.4 (1.1 to 1.6)	1.2 (0.9 to 1.5)
			Versus Control			*Versus Control*	
	Difference (95% CI)		0.8 (0.1 to 1.4)	0.7 (0.04 to 1.3)		0.7 (0.3 to 1.1)	0.5 (0.1 to 0.9)
	p-value		0.02	0.04		<0.001	0.008
	Cohen's d		0.47	0.40		0.69	0.50
HIT-6 score	**Estimate (95% CI)**	59.2 (55.1 to 63.3)	56.4 (52.9 to 60.0)	57.6 (54.0 to 61.2)	60.1 (58.1 to 62.1)	59.3 (57.1 to 61.5)	58.9 (56.8 to 61.0)
			Versus Control			*Versus Control*	
	Difference (95% CI)		-2.8 (-8.5 to 2.9)	-1.6 (-7.2 to 4.0)		-0.8 (-3.7 to 2.1)	-1.3 (-4.1 to 1.6)
	p-value		0.33	0.56		0.59	0.39
	Cohen's d		-0.19	-0.11		-0.10	-0.16
Secondary Endpoints [c]							
Headache hours/day	**Estimate (95% CI)**	2.2 (1.6 to 2.7)	1.6 (1.3 to 2.0)	1.7 (1.3 to 2.1)	6.2 (5.1 to 7.3)	4.6 (3.8 to 5.3)	3.9 (3.2 to 4.6)
			Versus Control			*Versus Control*	
	Difference (95% CI)		-0.5 (-1.2 to 0.2)	-0.5 (-1.1 to 0.2)		-1.6 (-2.9 to -0.4)	-2.3 (-3.5 to -1.1)
	p-value		0.15	0.18		0.009	<0.001
	Cohen's d		-0.27	-0.24		-0.45	-0.64
Headache days/month	**Estimate (95% CI)**	10.8 (8.9 to 12.6)	8.1 (6.8 to 9.4)	7.1 (6.0 to 8.3)	14.6 (13.4 to 15.7)	12.8 (11.7 to 13.9)	10.2 (9.1 to 11.2)
			Versus Control			*Versus Control*	
	Difference (95% CI)		-2.7 (-5.0 to -0.4)	-3.6 (-5.8 to -1.4)		-1.8 (-3.3 to -0.2)	-4.4 (-5.9 to -2.8)
	p-value		0.02	0.001		0.03	<0.001
	Cohen's d		-0.41	-0.59		-0.40	-1.01

[a] Chronic migraine defined as occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache. All estimates based on regression models adjusted for baseline value of the respective outcome and recruitment site. Missing data were imputed using multiple imputation procedures. P-values for the joint test of interaction coefficients equal to zero were 0.92, 0.74, 0.43, and 0.34 for 17-HDHA, HIT-6, headache hours per day, and headache days per month, respectively.

[b] ANCOVA including indicator variables for diet group.

[c] Generalized estimating equations models included continuous group-by-time interactions and were population averaged with a Poisson or negative binomial distribution.

Figure S1. Headache frequency at end of study according to baseline BMI [a]

A. Headache hours per day
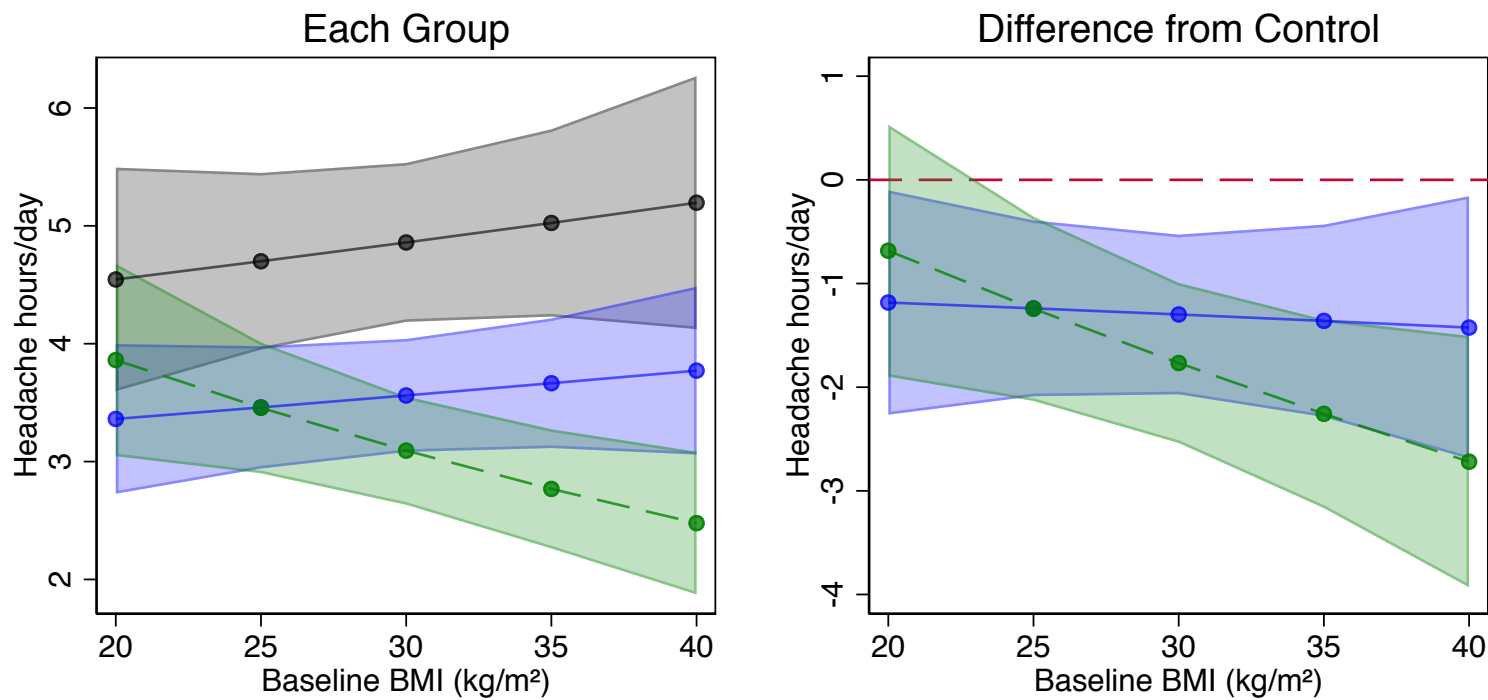
B. Headache days per month

[a] Each plot represents coefficients and 95% confidence intervals from a generalized estimating equation model which included continuous group-by-time and group-by-BMI interactions and were population averaged with a negative binomial (part A) or Poisson (part B) distribution. Missing data were imputed using multiple imputation procedures. P-values for the joint test of interaction coefficients equal to zero were 0.02 (part A) and 0.01 (part B). The addition of quadratic BMI interaction terms did not improve model fit (results not shown).

Table S4. Associations between expectation of benefit and headache endpoints [a]

		Control (n=60)	H3 (n=61)	H3-L6 (n=61)	Total (n=182)
HIT-6	**Coef (95% CI)**	0.02 (-0.21, 0.24)	0.25 (-0.08, 0.58)	-0.14 (-0.33, 0.05)	0.02 (-0.11, 0.16)
	p-value	0.86	0.14	0.13	0.76
Headache hours/day	**Coef (95% CI)**	0.02 (-0.18, 0.21)	0.00 (-0.19, 0.19)	-0.01 (-0.22, 0.19)	0.00 (-0.10, 0.11)
	p-value	0.85	1.00	0.90	0.93
Headache days/month	**Coef (95% CI)**	0.02 (-0.20, 0.24)	0.04 (-0.19, 0.28)	-0.14 (-0.33, 0.05)	-0.06 (-0.18, 0.06)
	p-value	0.86	0.73	0.15	0.33

[a] Associations determined through linear regressions of the outcome at week 16 against the credibility score and the outcome at baseline. Missing outcomes were imputed using chained equations.

Figure S2. Preventive medications reported for headache [a]
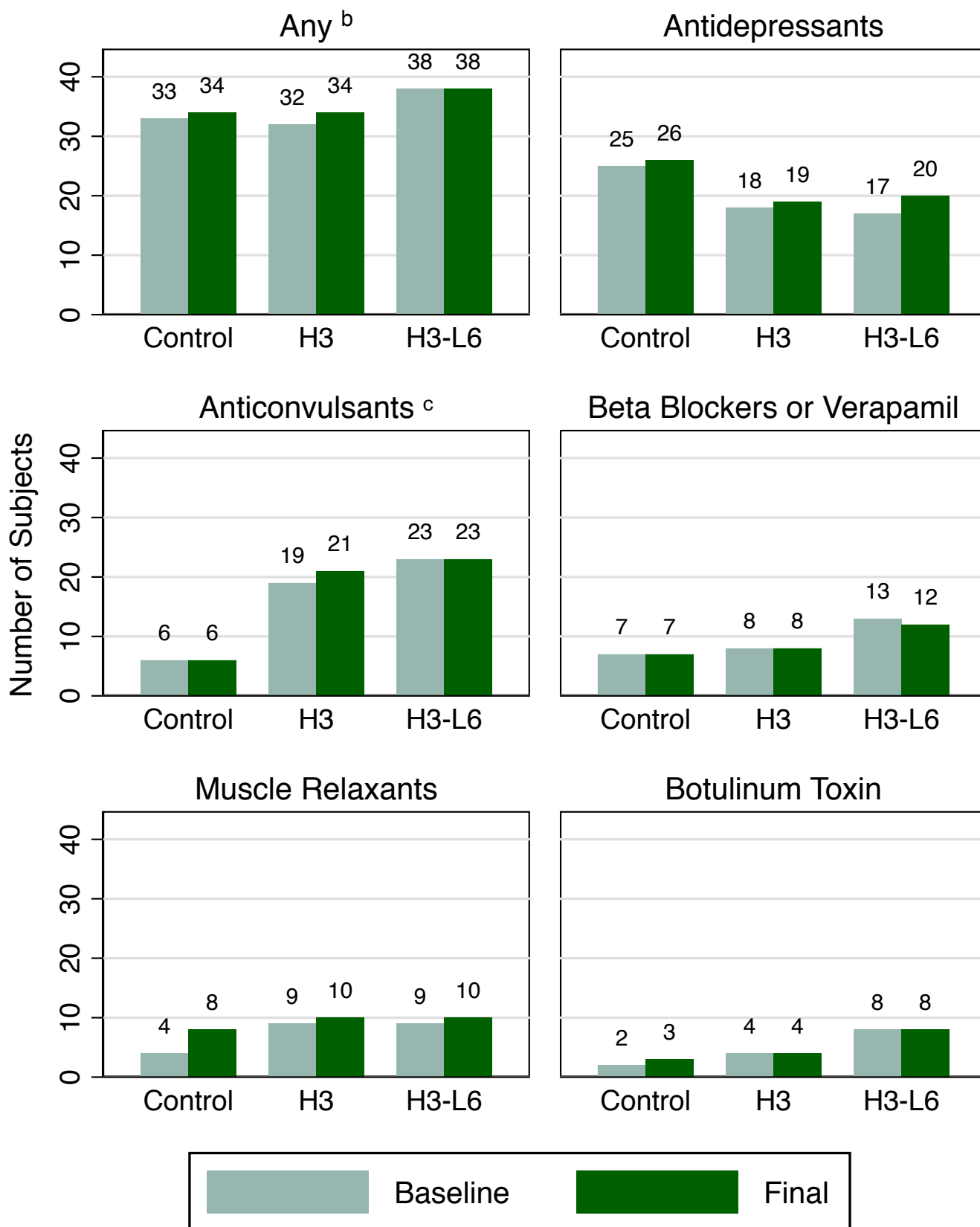
a See Table S2 for a list of medications for each class. Sample sizes for Control, H3, and H3-L6 are 60, 61, and 61, respectively.
b At baseline, chi-squared p-value = 0.52
c At baseline and week 16, p-value < 0.002.

Table S5. Sensitivity analysis—Table 2 adjusted for baseline use of anticonvulsants [a]

		Control (n=60)	H3 (n=61)	H3-L6 (n=61)
Primary Endpoints [b]				
17-HDHA in plasma, log ng/mL	**Estimate (95% CI)**	0.7 (0.4 to 0.9)	1.4 (1.2 to 1.6)	1.2 (1.0 to 1.5)
			Versus Control	
	Difference (95% CI)		0.7 (0.4 to 1.1)	0.6 (0.2 to 0.9)
	p-value		<0.001	0.003
	Cohen's d		0.79	0.61
HIT-6 score	**Estimate (95% CI)**	60.1 (58.2 to 62.1)	58.3 (56.4 to 60.2)	58.2 (56.3 to 60.1)
			Versus Control	
	Difference (95% CI)		-1.8 (-4.6 to 1.0)	-1.9 (-4.7 to 0.8)
	p-value		0.21	0.16
	Cohen's d		-0.24	-0.26
Secondary Endpoints [c]				
Headache hours/day	**Estimate (95% CI)**	5.1 (4.4 to 5.8)	3.6 (3.1 to 4.1)	3.1 (2.7 to 3.6)
			Versus Control	
	Difference (95% CI)		-1.5 (-2.3 to -0.7)	-2.0 (-2.8 to -1.2)
	p-value		<0.001	<0.001
	Cohen's d		-0.64	-0.85
Moderate-to-severe headache hours/day	**Estimate (95% CI)**	2.3 (1.9 to 2.7)	1.4 (1.1 to 1.6)	1.2 (1.0 to 1.5)
			Versus Control	
	Difference (95% CI)		-0.9 (-1.4 to -0.5)	-1.1 (-1.5 to -0.7)
	p-value		<0.001	<0.001
	Cohen's d		-0.69	-0.81
Headache days/month	**Estimate (95% CI)**	13.3 (12.3 to 14.3)	11.2 (10.3 to 12.1)	9.2 (8.4 to 10.0)
			Versus Control	
	Difference (95% CI)		-2.1 (-3.4 to -0.8)	-4.1 (-5.4 to -2.8)
	p-value		0.002	<0.001
	Cohen's d		-0.57	-1.15
Acute Pain Medications, Instances per Day [d]				
Total	**Estimate (95% CI)**	1.4 (1.0 to 1.7)	0.9 (0.7 to 1.1)	1.2 (0.9 to 1.4)
			Versus Control	
	Difference (95% CI)		-0.5 (-0.8 to -0.2)	-0.2 (-0.5 to 0.1)
	p-value		0.003	0.25
	Cohen's d		-0.45	-0.18
NSAIDs/Aspirin	**Estimate (95% CI)**	0.6 (0.4 to 0.8)	0.5 (0.3 to 0.6)	0.4 (0.3 to 0.4)
			Versus Control	
	Difference (95% CI)		-0.2 (-0.4 to 0.04)	-0.3 (-0.5 to -0.1)
	p-value		0.11	0.006
	Cohen's d		-0.24	-0.46
Triptans	**Estimate (95% CI)**	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.2)	0.2 (0.2 to 0.3)
			Versus Control	
	Difference (95% CI)		-0.1 (-0.2 to 0)	-0.05 (-0.1 to 0.1)
	p-value		0.05	0.33
	Cohen's d		-0.32	-0.16
Other	**Estimate (95% CI)**	0.5 (0.3 to 0.6)	0.3 (0.2 to 0.3)	0.5 (0.4 to 0.7)
			Versus Control	
	Difference (95% CI)		-0.2 (-0.4 to -0.05)	0.1 (-0.1 to 0.2)
	p-value		0.01	0.56
	Cohen's d		-0.42	0.09

[a] All estimates based on regression models adjusted for baseline value of the respective outcome, recruitment site, and any anticonvulsant use. Missing data were imputed using multiple imputation procedures.

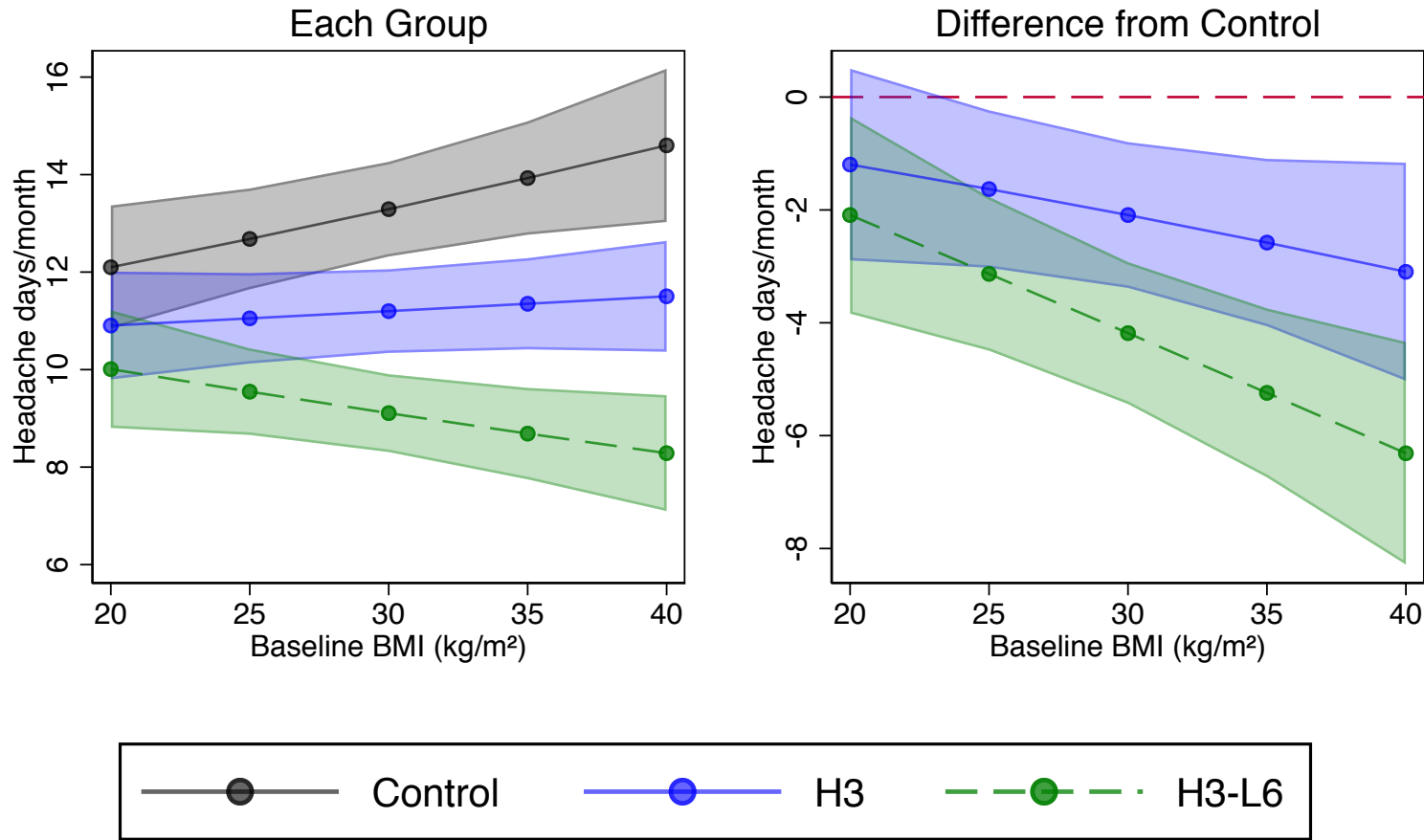[b] ANCOVA including indicator variables for diet group.

[c] Generalized estimating equation models included continuous group-by-time interactions and were population averaged with either Poisson or negative binomial distribution.

[d] See Table S2 for a list of medications. Ergotamines not included as a separate category because there was only one instance of use reported.

Table S6. Acute medication overuse at end of study (n=143) [a]

Overuse Category	Control (n=48)	H3 (n=47)	H3-L6 (n=48)	H3 vs Control [b]		H3-L6 vs Control [b]	
	n (%)	n (%)	n (%)	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
NSAIDs/Aspirin [c]	7 (15%)	7 (15%)	2 (4%)	0.78 (0.20 to 3.06)	0.73	0.10 (0.01 to 0.76)	0.03
Triptans [d]	9 (19%)	6 (13%)	5 (10%)	1.08 (0.26 to 4.54)	0.92	0.43 (0.10 to 1.93)	0.27
Other analgesics [e]	3 (6%)	5 (11%)	3 (6%)	1.55 (0.14 to 16.87)	0.72	0.38 (0.02 to 5.81)	0.49
Combination analgesics [f]	4 (8%)	2 (4%)	2 (4%)	0.21 (0.02 to 2.33)	0.20	0.12 (0.01 to 1.72)	0.12
Multiple drug classes not individually overused [g]	12 (25%)	19 (40%)	11 (23%)	2.15 (0.85 to 5.41)	0.10	0.81 (0.30 to 2.18)	0.68
Any category [h]	24 (50%)	26 (55%)	19 (40%)	1.74 (0.59 to 5.10)	0.31	0.45 (0.15 to 1.40)	0.17

[a] Post-hoc analysis including participants who completed the medication section of the electronic headache diary for at least 10 days in the last month of the study. Medication overuse endpoints based on operationalization of ICHD-3 criteria for the number of days per month of medication use. This does not indicate a diagnosis of medication overuse headache.

[b] Logistic regression of overuse endpoints adjusted for the respective baseline number of days of medication use.

[c] Consumption of NSAIDs/aspirin for ≥15 days/month.

[d] Consumption of triptans for ≥10 days/month.

[e] Consumption of acetaminophen or other non-opioid analgesics for ≥15 days/month or opioids for ≥10 days/month. Four subjects were opioid overusers at the end of study; 2 Control and 2 H3-L6.

[f] Consumption of two or more drug classes that each have an analgesic effect and/or behave as an adjuvant (e.g., aspirin/acetaminophen/caffeine) for ≥10 days/month.

[g] Consumption of triptans, non-opioid analgesics and/or opioids for a total of ≥10 days/month, but without overusing any individual class.

[h] Overuse in any of the above medication categories as well as non-opioid analgesics with no single class overused.

Table S7. Adverse events experienced at least once during the study (n=182)

	Control (n=60) Count (% [a])	H3 (n=61) Count (% [a])	H3-L6 (n=61) Count (% [a])	p-value [b]
Related or possibly related to intervention [c]				
GI complaint	0 (0%)	1 (2%)	3 (5%)	0.33
Phlebotomy or fasting blood draw	2 (3%)	3 (5%)	1 (2%)	0.70
Rash/itching	0 (0%)	1 (2%)	2 (3%)	0.77
Weight loss	0 (0%)	0 (0%)	2 (3%)	0.33
Worsening headache	1 (2%)	0 (0%)	1 (2%)	0.77
Any event	3 (5%)	5 (8%)	7 (11%)	0.47
Severity of events, related and not related to intervention [d]				
Mild (Grade 1)	24 (40%)	23 (38%)	28 (46%)	0.65
Moderate (Grade 2)	8 (13%)	5 (8%)	3 (5%)	0.24
Severe (Grade 3)	1 (2%)	0 (0%)	2 (3%)	0.55
Life threatening (Grades 4 & 5)	0 (0%)	0 (0%)	0 (0%)	1.00
Any severity	28 (47%)	23 (38%)	30 (49%)	0.42

[a] Percentages are based on the number of participants within each intervention.

[b] Fisher's exact test (two-tailed).

[c] A neurologist masked to treatment assignment determined if the adverse event was related (or possibly related) to the intervention.

[d] All events reviewed by Data and Safety Monitoring Board.

Table S8. Targeted and achieved intakes for controlled dietary variables [a]

| Diet Group | Linoleic acid (LA) (percent of energy) | | | EPA+DHA (mg per 2000 kcal) | | |
	Target	Baseline (n=181) Median (IQR)	Week 16 (n=143) Median (IQR)	Target	Baseline (n=181) Median (IQR)	Week 16 (n=143) Median (IQR)
Control	7.2	6.6 (5.4 to 9.1)	6.8 (5.1 to 9.5)	150 [c]	61 (34 to 120)	80 (29 to 174)
H3	7.2	6.5 (4.4 to 8.2)	7.1 (5.5 to 8.5)	1500 [d]	48 (27 to 74)	1484 (804 to 2367)
H3-L6	1.8 [b]	6.3 (4.7 to 8.3)	3.2 (2.7 to 4.4)	1500 [d]	44 (20 to 96)	1341 (778 to 2216)

[a] Nutrient values are based on the average of two 24-hour recalls, usually taken two weeks apart, just before randomization and the 112th day for the baseline and week 16 measures, respectively.

[b] The H3-L6 diet was designed to have linoleic acid modified as a controlled variable via isocaloric replacement of linoleic acid with monounsaturated and saturated fats (eg oleic, palmitoleic, and palmitic acids). To achieve this, the H3 and control groups were provided a blend of corn oil and extra virgin olive oil and a blend of butter and corn oil whereas the H3-L6 group was provided a blend of macadamia nut oil and extra virgin olive oil and regular butter.

[c] EPA+DHA provide an additional 10 calories per day, replaced by oleic acid in the control diet.

[d] EPA+DHA was modified as a controlled variable by substituting carefully selected fatty fish for lean fish and lean poultry, with otherwise identical interventions.

Table S9. Body weight (kg) at baseline and week 16

		Control (n=60)	H3 (n=61)	H3-L6 (n=61)
Adjusted for height				
Baseline	**Estimate (95% CI)**	81.4 (75.1 to 87.7)	80.3 (74.1 to 86.5)	81.5 (75.2 to 87.7)
Week 16 [a]	**Estimate (95% CI)**	80.0 (74.7 to 85.2)	80.1 (74.9 to 85.2)	79.6 (73.7 to 85.6)
			Versus Control	
	Difference (95% CI) [b]		0.1 (-7.0 to 7.2)	-0.3 (-8.3 to 7.6)
	p-value		0.98	0.93
Not adjusted for height				
Baseline	**Estimate (95% CI)**	82.8 (76.3 to 89.3)	80.1 (73.7 to 86.6)	80.3 (73.8 to 86.7)
Week 16 [a]	**Estimate (95% CI)**	80.5 (75.3 to 85.6)	80.0 (74.8 to 85.2)	79.2 (73.4 to 85.0)
			Versus Control	
	Difference (95% CI) [b]		-0.5 (-7.5 to 6.6)	-1.3 (-8.9 to 6.4)
	p-value		0.90	0.74

[a] Missing data were imputed using multiple imputation procedures.

[b] Based on linear regression of diet group on weight at end of study, adjusted for baseline weight.

Table S10. Diet-induced changes in erythrocyte fatty acids, % of total fatty acids (n=146)

		Values at Baseline and Week 16			Differences Between Groups at Week 16 [a]			
		Control (n=46) Median (IQR)	H3 (n=48) Median (IQR)	H3-L6 (n=52) Median (IQR)		H3 vs Control	H3-L6 vs Control	H3-L6 vs H3
Omega-3 fatty acids								
EPA+DHA	Baseline	3.6 (3.1 to 4.4)	3.7 (3.1 to 4.0)	3.5 (3.0 to 4.1)				
	Week 16	4.0 (3.3 to 4.5)	6.4 (4.8 to 7.1)	5.8 (4.6 to 7.3)	Difference	2.3	2.1	-0.23
	% Change	+10%	+74%	+64%	p-value	<0.001	<0.001	0.39
EPA (20:5n3)	Baseline	0.43 (0.31 to 0.57)	0.4 (0.34 to 0.49)	0.42 (0.33 to 0.5)				
	Week 16	0.44 (0.34 to 0.56)	0.84 (0.6 to 1.1)	0.84 (0.56 to 1.1)	Difference	0.48	0.48	-0.0021
	% Change	+4%	+109%	+103%	p-value	<0.001	<0.001	0.98
DPAn-3 (22:5n3)	Baseline	1.8 (1.6 to 2.1)	1.8 (1.7 to 1.9)	1.8 (1.6 to 2.0)				
	Week 16	1.8 (1.6 to 2.0)	1.9 (1.7 to 2.0)	1.8 (1.7 to 2.1)	Difference	0.024	0.055	0.031
	% Change	+1%	+3%	+3%	p-value	0.59	0.21	0.48
DHA (22:6n3)	Baseline	3.2 (2.8 to 3.9)	3.2 (2.7 to 3.5)	3.1 (2.7 to 3.7)				
	Week 16	3.4 (2.9 to 4.1)	5.5 (4.2 to 5.8)	5.0 (4.0 to 6.3)	Difference	1.8	1.6	-0.22
	% Change	+6%	+70%	+61%	p-value	<0.001	<0.001	0.28
ALA (18:3n3)	Baseline	0.18 (0.16 to 0.21)	0.17 (0.15 to 0.2)	0.18 (0.15 to 0.21)				
	Week 16	0.18 (0.15 to 0.2)	0.18 (0.15 to 0.21)	0.2 (0.17 to 0.22)	Difference	0.015	0.022	0.0069
	% Change	-4%	+4%	+9%	p-value	0.12	0.02	0.45
Percent n-3 in HUFA	Baseline	22 (19 to 25)	22 (20 to 24)	21 (20 to 24)				
	Week 16	23 (20 to 25)	33 (28 to 36)	30 (26 to 35)	Difference	9.7	8.4	-1.3
	% Change	+5%	+49%	+43%	p-value	<0.001	<0.001	0.20
Omega-6 fatty acids								
LA (18:2n6)	Baseline	13 (12 to 14)	13 (12 to 14)	13 (12 to 14)				
	Week 16	13 (12 to 14)	13 (12 to 14)	12 (11 to 13)	Difference	0.14	-0.73	-0.87
	% Change	-3%	-4%	-5%	p-value	0.60	0.007	0.001
GLA (18:3n6)	Baseline	0.059 (0.044 to 0.1)	0.06 (0.045 to 0.085)	0.072 (0.05 to 0.089)				
	Week 16	0.072 (0.049 to 0.095)	0.059 (0.039 to 0.078)	0.051 (0.038 to 0.069)	Difference	-0.0076	-0.019	-0.011
	% Change	+22%	-2%	-29%	p-value	0.29	0.009	0.11
EDA (20:2n6)	Baseline	0.3 (0.27 to 0.34)	0.3 (0.28 to 0.33)	0.3 (0.28 to 0.33)				
	Week 16	0.3 (0.27 to 0.34)	0.28 (0.26 to 0.32)	0.27 (0.25 to 0.29)	Difference	-0.018	-0.033	-0.016
	% Change	+1%	-7%	-11%	p-value	0.004	<0.001	0.007
DGLA (20:3n6)	Baseline	1.5 (1.4 to 2.0)	1.5 (1.4 to 1.8)	1.6 (1.3 to 1.8)				
	Week 16	1.6 (1.4 to 1.9)	1.5 (1.2 to 1.8)	1.5 (1.3 to 1.7)	Difference	-0.083	-0.08	0.0029
	% Change	+4%	-5%	-4%	p-value	0.03	0.03	0.94
AA (20:4n6)	Baseline	13 (12 to 14)	13 (12 to 14)	13 (12 to 14)				
	Week 16	13 (12 to 15)	12 (11 to 13)	13 (12 to 13)	Difference	-1.5	-1.2	0.3
	% Change	+1%	-10%	-5%	p-value	<0.001	<0.001	0.14
DTA (22:4n6)	Baseline	3.4 (3.1 to 3.9)	3.4 (3.1 to 3.7)	3.3 (3.0 to 3.8)				
	Week 16	3.6 (3.1 to 3.9)	2.5 (2.2 to 3.0)	2.7 (2.3 to 3.2)	Difference	-0.82	-0.64	0.18
	% Change	+5%	-26%	-19%	p-value	<0.001	<0.001	0.03
DPAn-6 (22:5n6)	Baseline	0.53 (0.48 to 0.67)	0.59 (0.47 to 0.69)	0.55 (0.46 to 0.63)				
	Week 16	0.57 (0.48 to 0.66)	0.38 (0.31 to 0.46)	0.4 (0.33 to 0.49)	Difference	-0.17	-0.15	0.024
	% Change	+6%	-36%	-28%	p-value	<0.001	<0.001	0.21
Percent n-6 in HUFA	Baseline	78 (75 to 81)	78 (76 to 80)	79 (76 to 80)				
	Week 16	77 (75 to 80)	67 (64 to 72)	70 (65 to 74)	Difference	-9.7	-8.4	1.3
	% Change	-1%	-14%	-11%	p-value	<0.001	<0.001	0.20
Monounsaturated fatty acids								
16:1n7	Baseline	0.36 (0.27 to 0.43)	0.29 (0.23 to 0.4)	0.32 (0.26 to 0.42)				
	Week 16	0.35 (0.29 to 0.45)	0.32 (0.26 to 0.43)	0.38 (0.29 to 0.51)	Difference	0.049	0.037	-0.013
	% Change	-1%	+12%	+18%	p-value	0.19	0.32	0.73

18:1n9	Baseline	12 (11 to 13)	13 (12 to 14)	13 (12 to 13)				
	Week 16	12 (11 to 13)	13 (12 to 14)	13 (12 to 14)	Difference	0.047	0.16	0.11
	% Change	0%	-1%	+1%	p-value	0.78	0.33	0.49
18:1n7	Baseline	1.1 (1.0 to 1.2)	1.2 (1.1 to 1.3)	1.2 (1.1 to 1.3)				
	Week 16	1.1 (1.1 to 1.2)	1.1 (1.1 to 1.3)	1.2 (1.1 to 1.3)	Difference	-0.017	0.0095	0.027
	% Change	0%	-1%	-2%	p-value	0.46	0.68	0.24
20:1n9	Baseline	0.2 (0.18 to 0.23)	0.22 (0.2 to 0.24)	0.22 (0.19 to 0.23)				
	Week 16	0.2 (0.19 to 0.22)	0.21 (0.18 to 0.23)	0.21 (0.18 to 0.25)	Difference	-0.0074	0.0042	0.012
	% Change	+1%	-5%	-4%	p-value	0.17	0.42	0.02
22:1n9	Baseline	0.057 (0.051 to 0.068)	0.066 (0.053 to 0.074)	0.062 (0.051 to 0.07)				
	Week 16	0.065 (0.048 to 0.074)	0.063 (0.056 to 0.077)	0.064 (0.054 to 0.077)	Difference	0.0009	0.0019	0.00097
	% Change	+14%	-5%	+3%	p-value	0.79	0.57	0.77
24:1n9	Baseline	4.3 (3.9 to 4.7)	4.4 (4.1 to 4.7)	4.4 (4.2 to 4.9)				
	Week 16	4.3 (4.0 to 4.8)	4.3 (4.0 to 4.9)	4.7 (4.2 to 5.0)	Difference	-0.11	0.11	0.22
	% Change	0%	-1%	+6%	p-value	0.43	0.40	0.10
Total mono-unsaturated fatty acids	Baseline	18 (18 to 19)	19 (18 to 20)	19 (18 to 20)				
	Week 16	19 (18 to 20)	19 (18 to 20)	19 (18 to 20)	Difference	-0.027	0.29	0.31
	% Change	+1%	0%	+3%	p-value	0.90	0.16	0.12
Saturated fatty acids								
14:0	Baseline	0.34 (0.25 to 0.38)	0.33 (0.28 to 0.37)	0.32 (0.26 to 0.38)				
	Week 16	0.35 (0.28 to 0.4)	0.36 (0.32 to 0.38)	0.38 (0.31 to 0.42)	Difference	0.027	0.024	-0.0031
	% Change	+3%	+7%	+19%	p-value	0.14	0.18	0.86
16:0	Baseline	24 (23 to 25)	24 (23 to 25)	24 (23 to 25)				
	Week 16	24 (23 to 25)	24 (24 to 25)	25 (24 to 25)	Difference	0.51	0.44	-0.062
	% Change	+1%	+3%	+3%	p-value	0.04	0.06	0.79
18:0	Baseline	12 (11 to 13)	12 (11 to 13)	11 (11 to 12)				
	Week 16	12 (10 to 13)	11 (10 to 13)	11 (10 to 12)	Difference	-0.17	-0.32	-0.15
	% Change	-1%	-4%	-1%	p-value	0.47	0.17	0.51
20:0	Baseline	0.41 (0.37 to 0.47)	0.42 (0.36 to 0.47)	0.44 (0.37 to 0.5)				
	Week 16	0.43 (0.37 to 0.52)	0.42 (0.39 to 0.47)	0.45 (0.41 to 0.51)	Difference	-0.015	0.013	0.028
	% Change	+4%	0%	+4%	p-value	0.35	0.42	0.08
22:0	Baseline	1.7 (1.5 to 1.8)	1.7 (1.5 to 1.8)	1.7 (1.5 to 1.8)				
	Week 16	1.6 (1.5 to 1.8)	1.6 (1.4 to 1.8)	1.7 (1.5 to 1.8)	Difference	-0.048	0.052	0.099
	% Change	-7%	-1%	0%	p-value	0.36	0.30	0.05
24:0	Baseline	5.2 (4.6 to 5.5)	4.8 (4.4 to 5.5)	4.8 (4.6 to 5.4)				
	Week 16	4.9 (4.5 to 5.2)	4.9 (4.2 to 5.4)	5.0 (4.5 to 5.6)	Difference	-0.15	0.14	0.29
	% Change	-5%	+1%	+3%	p-value	0.34	0.34	0.05
Total saturated fatty acids	Baseline	43 (43 to 44)	43 (42 to 44)	43 (42 to 44)				
	Week 16	43 (42 to 44)	43 (42 to 44)	43 (42 to 44)	Difference	0.059	0.26	0.2
	% Change	0%	+1%	0%	p-value	0.84	0.38	0.49

[a] Baseline-adjusted values are based on ANCOVA controlling for the recruitment site.

[b] All measures for 12:0 were 0.

Table S11. Diet-induced changes in immune cell fatty acids, % of total fatty acids (n=128)

		Values at Baseline and Week 16			Differences Between Groups at Week 16 [a]			
		Control (n=45) Median (IQR)	H3 (n=43) Median (IQR)	H3-L6 (n=40) Median (IQR)		H3 vs Control	H3-L6 vs Control	H3-L6 vs H3
Omega-3 fatty acids								
EPA+DHA	Baseline	1.3 (1.1 to 1.5)	1.2 (0.98 to 1.5)	1.3 (1.0 to 1.7)				
	Week 16	1.3 (1.1 to 1.6)	2.5 (1.5 to 3.2)	2.4 (1.7 to 3.4)	Difference	1.2	1.2	-0.016
	% Change	+2%	+109%	+92%	p-value	<0.001	<0.001	0.92
EPA	Baseline	0.36 (0.29 to 0.43)	0.33 (0.22 to 0.46)	0.34 (0.23 to 0.44)				
(20:5n3)	Week 16	0.34 (0.25 to 0.46)	0.67 (0.45 to 1.1)	0.75 (0.46 to 1.2)	Difference	0.4	0.45	0.056
	% Change	-3%	+99%	+124%	p-value	<0.001	<0.001	0.39
DPAn-3	Baseline	0.46 (0.23 to 0.66)	0.43 (0.26 to 0.58)	0.48 (0.24 to 0.63)				
(22:5n3)	Week 16	0.43 (0.27 to 0.65)	0.49 (0.3 to 0.77)	0.39 (0.26 to 0.66)	Difference	0.11	-0.016	-0.13
	% Change	-7%	+14%	-19%	p-value	0.07	0.79	0.04
DHA	Baseline	0.94 (0.76 to 1.2)	0.88 (0.71 to 1.1)	0.96 (0.71 to 1.2)				
(22:6n3)	Week 16	0.95 (0.73 to 1.2)	1.9 (1.2 to 2.2)	1.7 (1.2 to 2.2)	Difference	0.81	0.74	-0.064
	% Change	+1%	+114%	+74%	p-value	<0.001	<0.001	0.58
ALA	Baseline	0.49 (0.39 to 0.62)	0.5 (0.35 to 0.62)	0.57 (0.45 to 0.64)				
(18:3n3)	Week 16	0.51 (0.39 to 0.6)	0.45 (0.36 to 0.58)	0.55 (0.36 to 0.71)	Difference	-0.026	0.041	0.068
	% Change	+4%	-10%	-4%	p-value	0.47	0.27	0.07
Percent n-3	Baseline	14 (13 to 18)	14 (12 to 17)	15 (13 to 17)				
in HUFA	Week 16	16 (14 to 18)	24 (20 to 32)	23 (18 to 29)	Difference	10	8.4	-1.7
	% Change	+11%	+68%	+54%	p-value	<0.001	<0.001	0.23
Omega-6 fatty acids								
LA	Baseline	27 (23 to 29)	28 (23 to 30)	27 (25 to 29)				
(18:2n6)	Week 16	26 (22 to 29)	26 (23 to 30)	24 (23 to 27)	Difference	0.6	-1.6	-2.2
	% Change	-2%	-7%	-11%	p-value	0.49	0.08	0.02
GLA	Baseline	0.35 (0.22 to 0.54)	0.35 (0.25 to 0.41)	0.38 (0.27 to 0.49)				
(18:3n6)	Week 16	0.33 (0.22 to 0.5)	0.33 (0.25 to 0.39)	0.31 (0.22 to 0.44)	Difference	-0.034	-0.045	-0.011
	% Change	-7%	-7%	-17%	p-value	0.36	0.24	0.78
EDA	Baseline	0.27 (0.22 to 0.31)	0.24 (0.21 to 0.28)	0.25 (0.22 to 0.28)				
(20:2n6)	Week 16	0.25 (0.2 to 0.3)	0.24 (0.19 to 0.27)	0.23 (0.2 to 0.27)	Difference	-0.0077	-0.015	-0.0072
	% Change	-5%	+3%	-8%	p-value	0.62	0.35	0.65
DGLA	Baseline	1.4 (1.2 to 1.6)	1.4 (1.1 to 1.6)	1.4 (1.2 to 1.6)				
(20:3n6)	Week 16	1.4 (1.1 to 1.7)	1.2 (0.99 to 1.4)	1.3 (1.1 to 1.5)	Difference	-0.089	-0.11	-0.017
	% Change	-2%	-10%	-6%	p-value	0.15	0.09	0.79
AA	Baseline	7.5 (6.5 to 8.4)	7.0 (6.0 to 8.5)	7.6 (6.9 to 8.8)				
(20:4n6)	Week 16	7.2 (6.2 to 8.6)	6.7 (5.5 to 7.9)	7.0 (6.1 to 8.3)	Difference	-0.63	-0.26	0.37
	% Change	-5%	-5%	-8%	p-value	0.05	0.43	0.27
DTA	Baseline	0.4 (0.33 to 0.6)	0.36 (0.26 to 0.58)	0.37 (0.3 to 0.59)				
(22:4n6)	Week 16	0.35 (0.24 to 0.56)	0.3 (0.22 to 0.47)	0.34 (0.23 to 0.47)	Difference	-0.091	-0.066	0.025
	% Change	-12%	-17%	-7%	p-value	0.04	0.15	0.59
DPAn-6	Baseline	0.23 (0.14 to 0.34)	0.2 (0.17 to 0.28)	0.22 (0.16 to 0.29)				
(22:5n6)	Week 16	0.22 (0.13 to 0.28)	0.2 (0.12 to 0.25)	0.2 (0.13 to 0.24)	Difference	-0.021	-0.027	-0.0062
	% Change	-6%	-1%	-11%	p-value	0.30	0.19	0.77
Percent n-6	Baseline	86 (82 to 87)	86 (83 to 88)	85 (83 to 87)				
in HUFA	Week 16	84 (82 to 86)	76 (68 to 80)	77 (71 to 82)	Difference	-10	-8.4	1.7
	% Change	-2%	-11%	-9%	p-value	<0.001	<0.001	0.23
Monounsaturated fatty acids								
16:1n7	Baseline	1.2 (0.75 to 1.7)	0.9 (0.64 to 1.2)	1.2 (0.69 to 1.6)				
	Week 16	1.3 (0.91 to 1.8)	1.1 (0.77 to 1.5)	1.4 (0.74 to 2.0)	Difference	-0.15	0.047	0.2
	% Change	+9%	+21%	+14%	p-value	0.27	0.73	0.16

18:1n9	Baseline	17 (16 to 19)	17 (16 to 20)	17 (16 to 19)				
	Week 16	17 (16 to 20)	17 (15 to 19)	18 (16 to 20)	Difference	-1.1	0.2	1.3
	% Change	+1%	0%	+5%	p-value	0.007	0.62	0.002
18:1n7	Baseline	1.5 (1.3 to 1.6)	1.5 (1.3 to 1.7)	1.5 (1.4 to 1.6)				
	Week 16	1.5 (1.3 to 1.7)	1.5 (1.3 to 1.6)	1.6 (1.5 to 1.8)	Difference	-0.044	0.074	0.12
	% Change	+2%	-4%	+4%	p-value	0.40	0.17	0.03
20:1n9	Baseline	0.22 (0.17 to 0.31)	0.21 (0.15 to 0.3)	0.19 (0.15 to 0.27)				
	Week 16	0.19 (0.14 to 0.29)	0.21 (0.16 to 0.28)	0.19 (0.15 to 0.28)	Difference	-0.005	-0.0029	0.0021
	% Change	-12%	-2%	-3%	p-value	0.81	0.89	0.92
22:1n9	Baseline	0.12 (0.082 to 0.2)	0.11 (0.068 to 0.15)	0.1 (0.069 to 0.14)				
	Week 16	0.096 (0.063 to 0.15)	0.1 (0.076 to 0.13)	0.094 (0.07 to 0.12)	Difference	0.0053	-0.015	-0.02
	% Change	-18%	-1%	-9%	p-value	0.79	0.45	0.32
24:1n9	Baseline	1.1 (0.89 to 1.2)	1.1 (0.95 to 1.3)	1.1 (0.9 to 1.3)				
	Week 16	1.1 (0.92 to 1.2)	1.2 (1.0 to 1.4)	1.2 (0.92 to 1.3)	Difference	0.12	0.039	-0.076
	% Change	+2%	+15%	+13%	p-value	0.04	0.50	0.19
Total mono-unsaturated fatty acids	Baseline	21 (20 to 23)	21 (20 to 23)	21 (20 to 23)				
	Week 16	22 (20 to 24)	21 (19 to 23)	22 (21 to 25)	Difference	-1.1	0.38	1.5
	% Change	+4%	+1%	+5%	p-value	0.01	0.40	0.001
Saturated fatty acids								
12:0	Baseline	0.09 (0.067 to 0.16)	0.11 (0 to 0.14)	0.11 (0.068 to 0.15)				
	Week 16	0.1 (0.051 to 0.15)	0.11 (0.083 to 0.17)	0.11 (0.023 to 0.17)	Difference	0.011	0.022	0.012
	% Change	+11%	+4%	+7%	p-value	0.58	0.26	0.57
14:0	Baseline	0.73 (0.6 to 0.94)	0.72 (0.58 to 0.94)	0.78 (0.59 to 0.9)				
	Week 16	0.79 (0.61 to 0.95)	0.78 (0.6 to 0.93)	0.82 (0.64 to 1.0)	Difference	-0.05	0.029	0.078
	% Change	+8%	+9%	+6%	p-value	0.41	0.64	0.21
16:0	Baseline	25 (23 to 27)	24 (23 to 25)	25 (23 to 26)				
	Week 16	25 (24 to 27)	25 (24 to 26)	25 (24 to 27)	Difference	-0.11	0.14	0.24
	% Change	+1%	+2%	0%	p-value	0.81	0.75	0.58
18:0	Baseline	10 (8.9 to 11)	10 (9.6 to 12)	10 (9.4 to 11)				
	Week 16	9.8 (8.6 to 12)	10 (9.5 to 11)	11 (9.4 to 12)	Difference	-0.089	0.22	0.31
	% Change	-6%	-2%	+5%	p-value	0.83	0.60	0.47
20:0	Baseline	0.51 (0.36 to 0.61)	0.48 (0.36 to 0.69)	0.49 (0.32 to 0.65)				
	Week 16	0.41 (0.3 to 0.56)	0.49 (0.35 to 0.8)	0.5 (0.35 to 0.61)	Difference	0.38	-0.05	-0.43
	% Change	-19%	+1%	+2%	p-value	0.04	0.80	0.03
22:0	Baseline	1.1 (0.97 to 1.4)	1.1 (0.93 to 1.4)	1.2 (0.86 to 1.5)				
	Week 16	0.94 (0.78 to 1.3)	1.1 (0.95 to 1.4)	1.2 (0.96 to 1.5)	Difference	0.03	0.1	0.07
	% Change	-14%	-3%	+6%	p-value	0.73	0.26	0.43
24:0	Baseline	0.85 (0.73 to 1.1)	0.91 (0.74 to 1.1)	0.87 (0.66 to 1.1)				
	Week 16	0.75 (0.65 to 0.94)	0.92 (0.78 to 1.1)	0.9 (0.77 to 1.0)	Difference	0.077	0.039	-0.038
	% Change	-12%	+1%	+4%	p-value	0.15	0.48	0.49
Total saturated fatty acids	Baseline	39 (37 to 42)	39 (37 to 41)	39 (36 to 41)				
	Week 16	39 (36 to 42)	39 (37 to 42)	39 (37 to 42)	Difference	-0.066	0.35	0.42
	% Change	0%	+1%	+1%	p-value	0.93	0.62	0.56

[a] Baseline-adjusted values are based on ANCOVA controlling for the recruitment site.

Table S12. Diet-induced changes in serum oxylipins, free pool (n=144)

		Values at Baseline and Week 16			Differences Between Groups at Week 16 [a]			
		Control (n=44) Median (IQR)	H3 (n=46) Median (IQR)	H3-L6 (n=54) Median (IQR)		H3 vs Control	H3-L6 vs Control	H3-L6 vs H3
DHA derivatives								
4-HDHA	Baseline	0.19 (0.14 to 0.25)	0.16 (0.1 to 0.21)	0.15 (0.11 to 0.19)				
(ng/mL)	Week 16	0.17 (0.11 to 0.23)	0.28 (0.17 to 0.36)	0.26 (0.17 to 0.41)	Difference	0.12	0.19	0.072
	% Change	-11%	+74%	+68%	p-value	0.003	<0.001	0.06
10-HDHA	Baseline	0.094 (0.066 to 0.11)	0.084 (0.058 to 0.11)	0.078 (0.043 to 0.11)				
(ng/mL)	Week 16	0.088 (0.047 to 0.12)	0.13 (0.088 to 0.18)	0.12 (0.08 to 0.21)	Difference	0.065	0.079	0.015
	% Change	-6%	+50%	+53%	p-value	<0.001	<0.001	0.34
14-HDHA	Baseline	1.6 (1.0 to 2.4)	1.3 (0.58 to 2.8)	1.4 (0.73 to 3.0)				
(ng/mL)	Week 16	1.4 (0.72 to 2.8)	2.4 (1.3 to 6.0)	2.4 (1.4 to 7.1)	Difference	2.7	3.1	0.38
	% Change	-12%	+87%	+79%	p-value	0.008	0.002	0.69
17-HDHA	Baseline	0.42 (0.084 to 0.5)	0.4 (0.14 to 0.51)	0.41 (0.046 to 0.5)				
(ng/mL)	Week 16	0.44 (0.075 to 0.53)	0.54 (0.29 to 0.6)	0.51 (0.43 to 0.64)	Difference	0.091	0.15	0.061
	% Change	+3%	+33%	+26%	p-value	0.02	<0.001	0.11
AA derivatives								
PGE2	Baseline	79 (28 to 194)	85 (2.8 to 217)	74 (2.8 to 177)				
(pg/mL)	Week 16	52 (2.8 to 211)	112 (15 to 311)	72 (7.8 to 197)	Difference	48	36	-12
	% Change	-34%	+31%	-2%	p-value	0.23	0.35	0.75
PGE2 [b]	Baseline	520 (249 to 998)	677 (330 to 1037)	553 (94 to 894)				
(pg/mL)	Week 16	599 (206 to 1086)	646 (122 to 1064)	567 (263 to 805)	Difference	-136	-39	97
	% Change	+15%	-5%	+3%	p-value	0.10	0.62	0.22
TxB2	Baseline	11 (1.6 to 22)	12 (0.78 to 29)	7.2 (0.25 to 28)				
(ng/mL)	Week 16	5.8 (0.39 to 19)	11 (1.4 to 28)	12 (0.21 to 33)	Difference	1.3	5.6	4.3
	% Change	-47%	0%	+65%	p-value	0.83	0.36	0.47
LTB4 [b]	Baseline	88 (46 to 195)	60 (44 to 144)	89 (42 to 190)				
(pg/mL)	Week 16	106 (64 to 185)	76 (51 to 157)	86 (54 to 180)	Difference	10	0.17	-9.8
	% Change	+21%	+27%	-4%	p-value	0.72	1.00	0.71
Cysteinyl LTs [b]	Baseline	191 (156 to 225)	197 (157 to 251)	181 (150 to 254)				
(pg/mL)	Week 16	193 (167 to 220)	189 (161 to 263)	183 (142 to 247)	Difference	12	-3.1	-16
	% Change	+1%	-4%	+1%	p-value	0.54	0.87	0.42
5-HETE	Baseline	0.8 (0.55 to 1.1)	0.69 (0.54 to 1.0)	0.89 (0.53 to 1.3)				
(ng/mL)	Week 16	0.7 (0.51 to 1.1)	0.68 (0.42 to 0.96)	0.82 (0.55 to 1.1)	Difference	0.15	0.11	-0.044
	% Change	-12%	-1%	-8%	p-value	0.20	0.34	0.69
8-HETE	Baseline	0.15 (0.11 to 0.22)	0.14 (0.12 to 0.17)	0.14 (0.12 to 0.19)				
(ng/mL)	Week 16	0.14 (0.11 to 0.18)	0.14 (0.086 to 0.17)	0.15 (0.12 to 0.19)	Difference	-0.0061	0.013	0.019
	% Change	-6%	+6%	+10%	p-value	0.64	0.31	0.12
12-HETE	Baseline	18 (9.6 to 29)	19 (4.8 to 35)	15 (8.6 to 31)				
(ng/mL)	Week 16	11 (8.1 to 37)	19 (7.6 to 38)	17 (7.8 to 36)	Difference	-0.76	10	11
	% Change	-37%	0%	+15%	p-value	0.91	0.14	0.11
15-HETE	Baseline	0.85 (0.61 to 1.4)	0.82 (0.54 to 1.4)	0.71 (0.53 to 1.4)				
(ng/mL)	Week 16	0.75 (0.47 to 1.3)	0.88 (0.51 to 1.5)	0.83 (0.56 to 1.5)	Difference	0.037	0.26	0.22
	% Change	-12%	+7%	+16%	p-value	0.85	0.19	0.25
LA derivatives [c]								
9-HODE	Baseline	3.4 (2.3 to 5.0)	3.1 (2.7 to 4.2)	2.8 (2.2 to 3.7)				
(ng/mL)	Week 16	2.8 (2.1 to 3.9)	2.8 (2.2 to 4.3)	3.1 (2.4 to 3.9)	Difference	0.62	0.33	-0.29
	% Change	-17%	-11%	+9%	p-value	0.10	0.36	0.43
13-HODE	Baseline	11 (8.9 to 17)	11 (9.3 to 16)	11 (8.4 to 14)				
(ng/mL)	Week 16	11 (8.0 to 14)	11 (9.0 to 16)	11 (8.1 to 15)	Difference	1.5	0.37	-1.1
	% Change	0%	-3%	+4%	p-value	0.23	0.76	0.35

12,13-EpOME (ng/mL)	Baseline	1.2 (0.84 to 1.5)	1.1 (0.78 to 1.5)	1.0 (0.76 to 1.5)				
	Week 16	1.0 (0.71 to 1.4)	1.0 (0.73 to 1.4)	1.2 (0.89 to 1.4)	Difference	0.16	0.087	-0.076
	% Change	-14%	-11%	+12%	p-value	0.21	0.49	0.54
12,13-DiHOME (ng/mL)	Baseline	5.2 (3.4 to 8.1)	5.1 (4.2 to 6.9)	5.0 (3.5 to 6.5)				
	Week 16	3.9 (2.9 to 6.0)	4.8 (3.4 to 7.7)	4.7 (3.1 to 6.2)	Difference	1.5	0.52	-1
	% Change	-25%	-6%	-6%	p-value	0.02	0.41	0.10
11H-9,10E-LA (ng/mL)	Baseline	0.42 (0.34 to 0.54)	0.42 (0.33 to 0.57)	0.4 (0.34 to 0.46)				
	Week 16	0.39 (0.31 to 0.52)	0.4 (0.3 to 0.54)	0.38 (0.32 to 0.49)	Difference	0.011	-0.01	-0.021
	% Change	-8%	-3%	-5%	p-value	0.84	0.84	0.67
13H-9,10E-LA (ng/mL)	Baseline	0.22 (0.11 to 0.36)	0.27 (0.16 to 0.41)	0.21 (0.12 to 0.34)				
	Week 16	0.25 (0.13 to 0.4)	0.2 (0.15 to 0.42)	0.21 (0.097 to 0.34)	Difference	0.016	-0.038	-0.055
	% Change	+13%	-23%	-2%	p-value	0.70	0.34	0.17
9,10,13-TriHOME (ng/mL)	Baseline	0.91 (0.56 to 1.4)	0.78 (0.42 to 1.1)	0.82 (0.56 to 1.5)				
	Week 16	0.98 (0.73 to 1.3)	1.0 (0.58 to 1.4)	1.1 (0.74 to 1.4)	Difference	0.089	0.15	0.066
	% Change	+7%	+27%	+34%	p-value	0.46	0.18	0.56
9,12,13-TriHOME (ng/mL)	Baseline	3.1 (2.2 to 4.3)	2.8 (1.7 to 3.8)	2.9 (1.9 to 4.1)				
	Week 16	3.0 (2.3 to 4.3)	3.1 (2.2 to 4.2)	3.4 (2.4 to 4.4)	Difference	0.38	0.41	0.028
	% Change	-4%	+14%	+18%	p-value	0.32	0.27	0.94
Migraine-related neuropeptide								
CGRP [b] (pg/mL)	Baseline	3.0 (2.2 to 4.4)	2.5 (1.7 to 3.8)	2.4 (1.6 to 3.6)				
	Week 16	2.8 (1.8 to 4.0)	2.8 (1.7 to 4.3)	2.6 (1.6 to 3.8)	Difference	0.26	0.11	-0.14
	% Change	-8%	+13%	+10%	p-value	0.41	0.70	0.63

[a] Baseline-adjusted values are based on ANCOVA controlling for the recruitment site.

[b] Measured by ELISA. PGE2, n=115; LTB4, n=140; Cysteinyl LTs, n=149; CGRP, n=148.

[c] For 9H-12,13E-LA and 11H-12,13E-LA, more than half of the samples were below the limit of quantitation.

[d] Missing values for all other oxylipins were imputed with 1/2 of the minimum value in the sample at the respective time point.

Table S13. Diet-induced changes in plasma total (free plus esterified) oxylipins, ng/mL (n=150)

		Values at Baseline and Week 16				Differences Between Groups at Week 16 [a]		
		Control (n=48) Median (IQR)	H3 (n=50) Median (IQR)	H3-L6 (n=52) Median (IQR)		H3 vs Control	H3-L6 vs Control	H3-L6 vs H3
DHA derivatives								
4-HDHA	Baseline	5.5 (4.3 to 6.5)	4.8 (3.7 to 6.6)	4.8 (3.9 to 6.2)				
	Week 16	5.3 (4.1 to 6.8)	7.9 (6.3 to 12)	8.2 (5.8 to 11)	Difference	4.2	4.2	0.0092
	% Change	-3%	+65%	+70%	p-value	<0.001	<0.001	0.99
10-HDHA	Baseline	1.6 (1.1 to 1.9)	1.4 (1.0 to 1.8)	1.4 (1.0 to 1.8)				
	Week 16	1.5 (1.2 to 1.9)	2.4 (1.8 to 3.6)	2.4 (1.7 to 3.3)	Difference	1.2	1.4	0.11
	% Change	-1%	+72%	+73%	p-value	0.001	<0.001	0.76
14-HDHA	Baseline	3.8 (3.2 to 5.7)	3.4 (2.6 to 4.6)	3.8 (2.6 to 5.2)				
	Week 16	3.8 (3.0 to 5.4)	5.9 (4.6 to 9.2)	7.0 (4.6 to 9.1)	Difference	3.7	4.6	0.89
	% Change	+2%	+74%	+84%	p-value	0.006	0.001	0.49
17-HDHA	Baseline	2.8 (1.9 to 3.4)	2.4 (1.6 to 3.2)	2.6 (2.0 to 3.5)				
	Week 16	2.6 (1.6 to 3.4)	3.9 (3.1 to 5.5)	4.2 (2.7 to 6.0)	Difference	1.9	2.3	0.33
	% Change	-8%	+63%	+61%	p-value	0.001	<0.001	0.57
AA derivatives [b]								
5-HETE	Baseline	21 (15 to 24)	19 (13 to 25)	19 (17 to 26)				
	Week 16	19 (14 to 24)	15 (13 to 21)	18 (15 to 21)	Difference	-3.2	-1.4	1.8
	% Change	-10%	-17%	-8%	p-value	0.007	0.24	0.12
8-HETE	Baseline	6.9 (5.5 to 8.5)	6.5 (4.9 to 7.8)	7.0 (5.7 to 8.6)				
	Week 16	6.8 (5.3 to 8.5)	5.2 (4.4 to 6.9)	6.3 (5.3 to 7.5)	Difference	-1.5	-0.66	0.83
	% Change	-2%	-20%	-10%	p-value	0.05	0.38	0.27
12-HETE	Baseline	11 (8.7 to 16)	9.7 (7.6 to 13)	11 (9.2 to 16)				
	Week 16	11 (8.2 to 15)	9.0 (7.6 to 11)	11 (8.8 to 13)	Difference	-1.7	0.29	2.0
	% Change	+5%	-7%	-7%	p-value	0.46	0.90	0.37
15-HETE	Baseline	15 (12 to 19)	13 (11 to 17)	16 (13 to 18)				
	Week 16	15 (12 to 18)	11 (9.2 to 14)	13 (11 to 18)	Difference	-2.9	-0.84	2.1
	% Change	-3%	-16%	-14%	p-value	0.05	0.56	0.15
LA derivatives								
9-HODE	Baseline	30 (27 to 35)	29 (26 to 36)	29 (25 to 34)				
	Week 16	30 (26 to 34)	29 (25 to 32)	29 (22 to 34)	Difference	-2.8	-0.76	2.1
	% Change	-2%	-2%	0%	p-value	0.36	0.80	0.49
13-HODE	Baseline	106 (93 to 121)	103 (89 to 123)	101 (86 to 116)				
	Week 16	101 (93 to 115)	102 (90 to 115)	1.0e+02 (81 to 121)	Difference	-7.9	-2.6	5.3
	% Change	-5%	-1%	-1%	p-value	0.40	0.78	0.56
12,13-EpOME	Baseline	6.5 (5.5 to 8.0)	6.0 (4.8 to 9.2)	6.8 (6.0 to 8.1)				
	Week 16	6.5 (5.3 to 9.5)	7.3 (5.2 to 8.7)	6.9 (5.5 to 8.1)	Difference	0.4	-0.065	-0.46
	% Change	0%	+21%	+2%	p-value	0.44	0.90	0.36
12,13-DiHOME	Baseline	24 (20 to 36)	26 (19 to 37)	27 (21 to 36)				
	Week 16	24 (17 to 28)	24 (20 to 36)	26 (18 to 30)	Difference	27	1.5	-25
	% Change	-2%	-6%	-4%	p-value	0.14	0.93	0.16
9H-12,13E-LA	Baseline	86 (62 to 133)	95 (58 to 159)	115 (74 to 194)				
	Week 16	86 (60 to 117)	108 (75 to 168)	101 (75 to 148)	Difference	18	5.7	-12
	% Change	0%	+13%	-12%	p-value	0.17	0.67	0.33
11H-9,10E-LA	Baseline	132 (75 to 203)	144 (75 to 233)	184 (87 to 336)				
	Week 16	108 (78 to 165)	169 (105 to 253)	142 (83 to 201)	Difference	-169	-245	-76
	% Change	-18%	+17%	-23%	p-value	0.25	0.10	0.60

|								
11H-12,13E-LA	Baseline	65 (43 to 109)	74 (39 to 122)	105 (50 to 208)				
	Week 16	60 (43 to 97)	96 (56 to 149)	81 (55 to 138)	Difference	10	-6.4	-17
	% Change	-8%	+29%	-23%	p-value	0.66	0.78	0.47
13H-9,10E-LA	Baseline	117 (87 to 197)	148 (80 to 241)	185 (96 to 352)				
	Week 16	110 (88 to 155)	160 (106 to 278)	147 (106 to 223)	Difference	63	-4	-67
	% Change	-6%	+8%	-21%	p-value	0.10	0.92	0.07
9,10,13-TriHOME	Baseline	4.5 (4.0 to 6.0)	5.4 (4.5 to 6.5)	5.1 (3.9 to 6.7)				
	Week 16	4.6 (3.8 to 6.1)	5.0 (4.1 to 6.4)	4.9 (3.9 to 6.7)	Difference	-1.5	0.097	1.6
	% Change	+2%	-7%	-5%	p-value	0.20	0.93	0.17
9,12,13-TriHOME	Baseline	4.3 (3.6 to 5.4)	5.0 (3.9 to 6.1)	4.7 (3.5 to 6.0)				
	Week 16	4.1 (3.0 to 5.5)	4.8 (3.9 to 6.0)	4.0 (3.5 to 6.1)	Difference	-1	0.27	1.3
	% Change	-4%	-4%	-16%	p-value	0.41	0.82	0.29

[a] Baseline-adjusted values are based on ANCOVA controlling for the recruitment site.

[b] For LTB4, more than half of the samples were below the limit of quantitation.
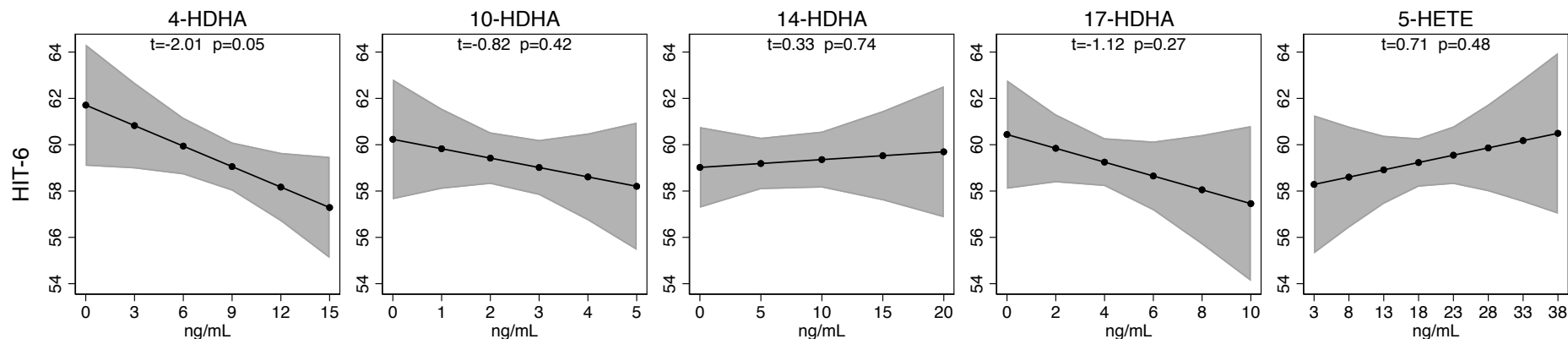
[c] Missing values for all other oxylipins were imputed with 1/2 of the minimum value in the sample at the respective time point.

Figure S3. Association of HIT-6 with precursor fatty acids and oxylipins (end of study) [a]

A. Precursor fatty acids in erythrocytes (n=133)
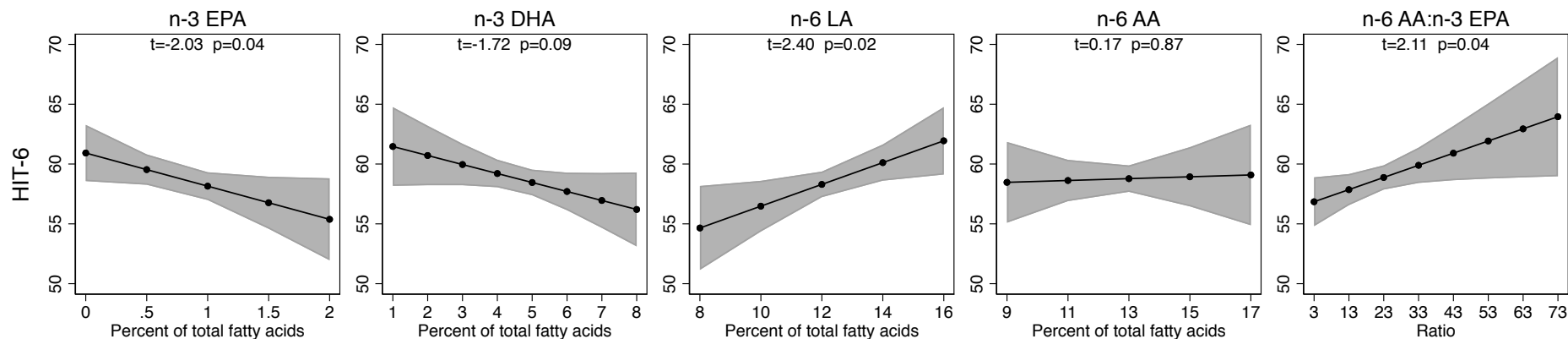
B. DHA-derived and AA-derived oxylipins in plasma (n=137)

[a] Each plot represents coefficients and 95% confidence intervals from a linear regression model of targeted fatty acids and oxylipins on HIT-6 adjusted for the following baseline variables: age, BMI, sex, headache hours per day, HIT-6, and chronic-versus-episodic migraine. Sample represents participants with data for both blood measures and headache diary at end of study.