Unraveling the Mechanisms of Ultra-processed Foods

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National Institutes of Health

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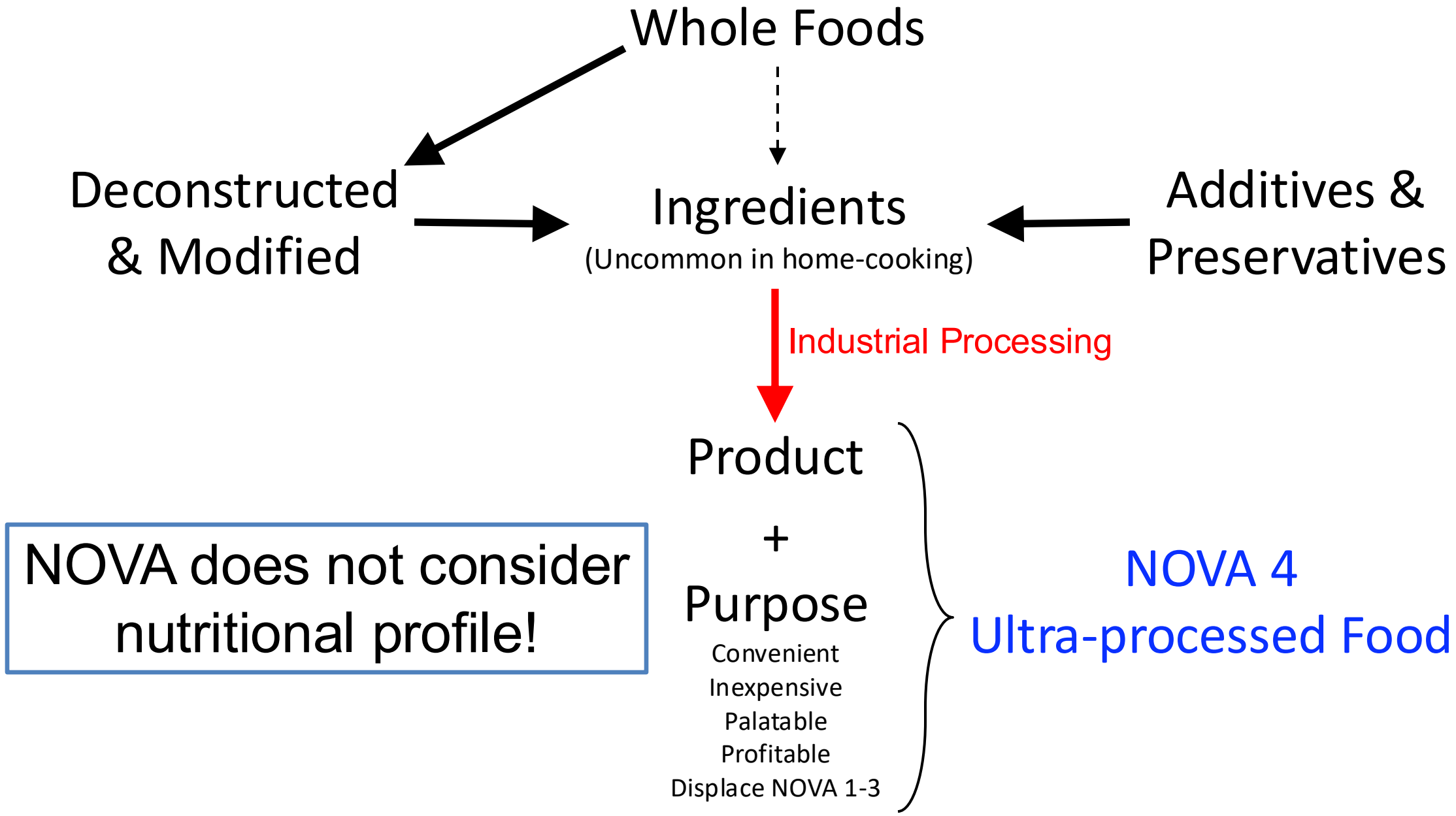
NOVA groups	Examples
1) Unprocessed or minimally processed foods Edible parts of plants and animals after separation from nature or preserved by minimal processes (no substances added)	   
2) Processed culinary ingredients Substances extracted from foods or nature and used to prepare, cook and season Group 1 foods	   
3) Processed foods Group 1 foods modified with the addition of Group 2 ingredients aiming food preservation and/or enhancement of its sensory qualities	   
4) Ultra-processed foods Formulations of several ingredients that include original or chemically modified food substances obtained with the fractioning of whole foods and additives used to make the final product palatable or hyper-palatable. The aim is to make convenient, tasteful and low-cost products liable to replace all other NOVA food groups	



G Scrinis & C Monteiro *Nat. Food* 3, 671–673 (2022)

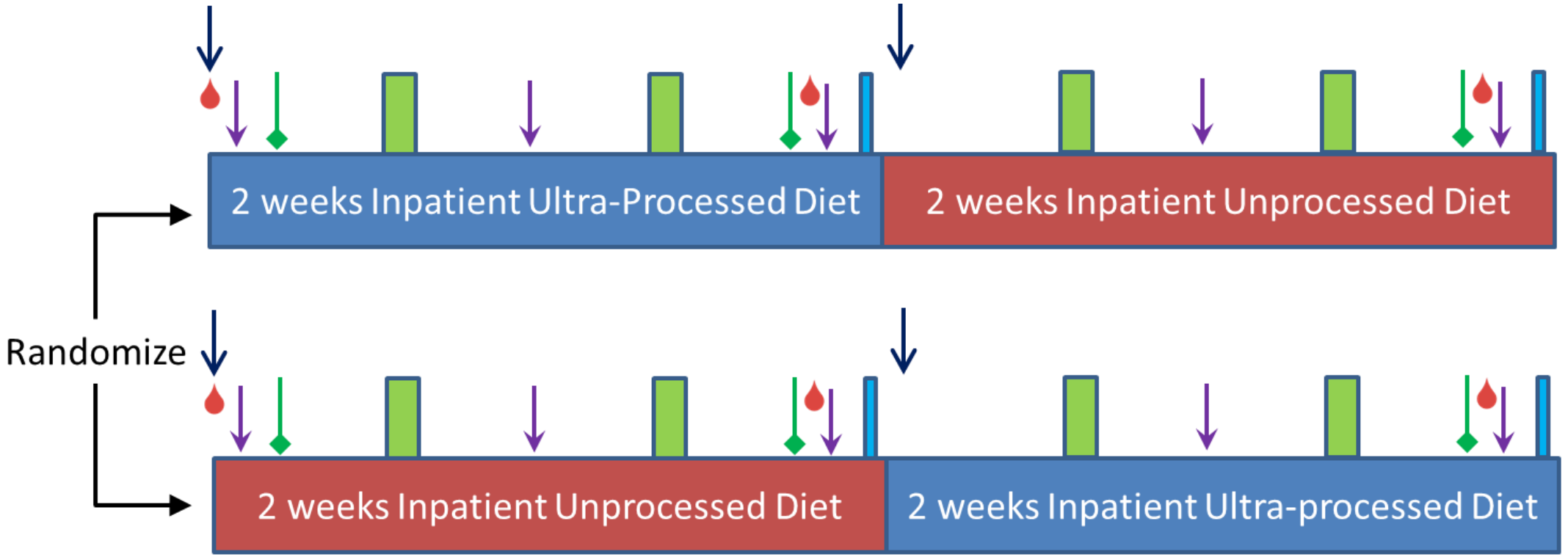
Public Health Researchers Say UPFs are Bad News!

(even after adjusting for nutritional profile)

"The observational data shows that there's a pretty clear association between ultra-processed food and a lot of bad health outcomes. Before FDA can do anything with that, we're going to need a lot more research."

FDA Commissioner Robert Califf, Jan 31, 2024

Ultra-processed vs Unprocessed Ad Libitum Diet Study

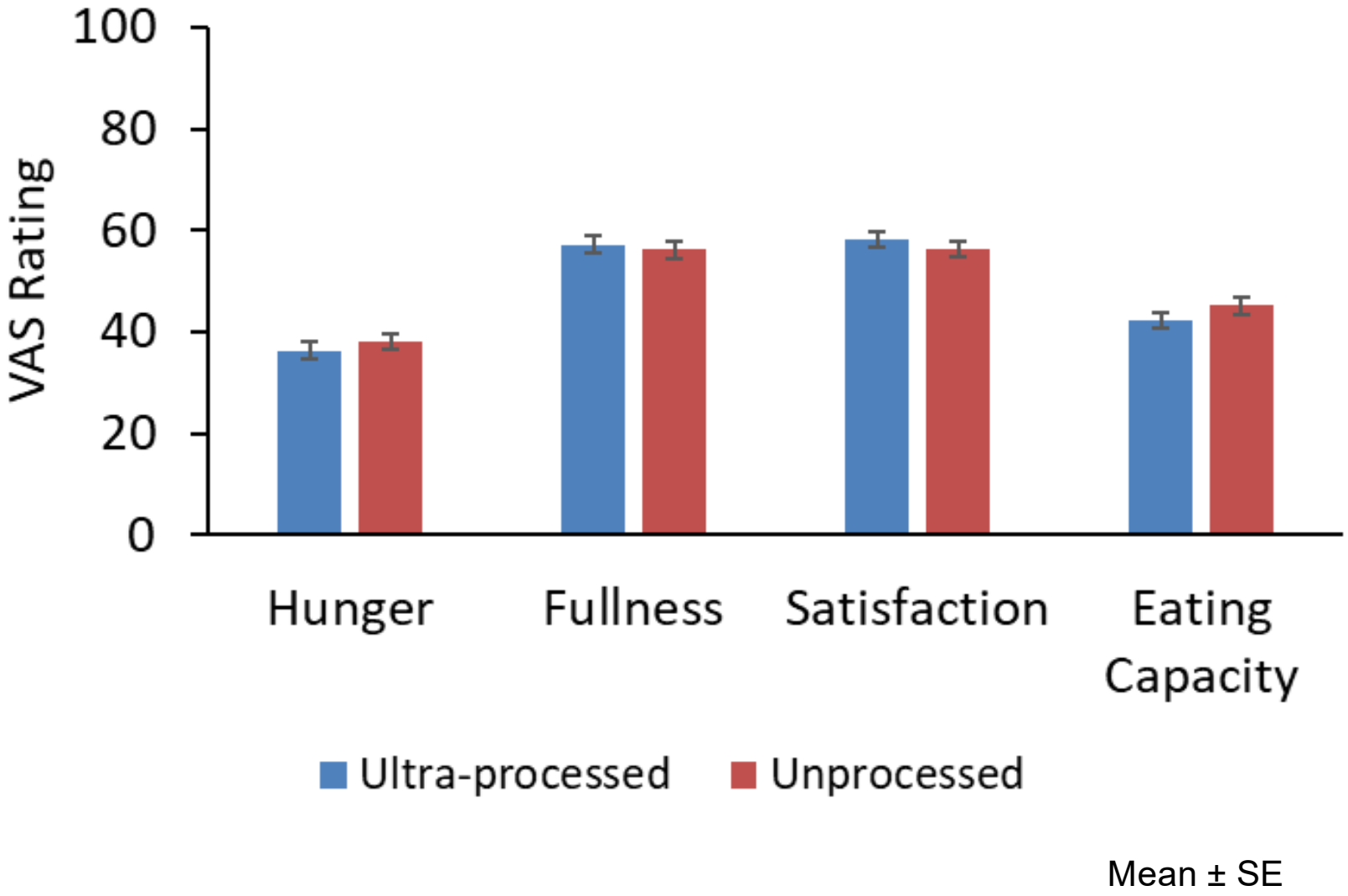


Diets matched for Presented Calories, Fat, Carbs, Sugar, Sodium, Fiber, Glycemic Load

DLW | Fasted Blood | DXA | MRI MRS | 24hr Chamber | OGTT

KD Hall et al. *Cell Metabolism* 30:1-11 (2019).

No Differences in Self-Reported Appetite Measures

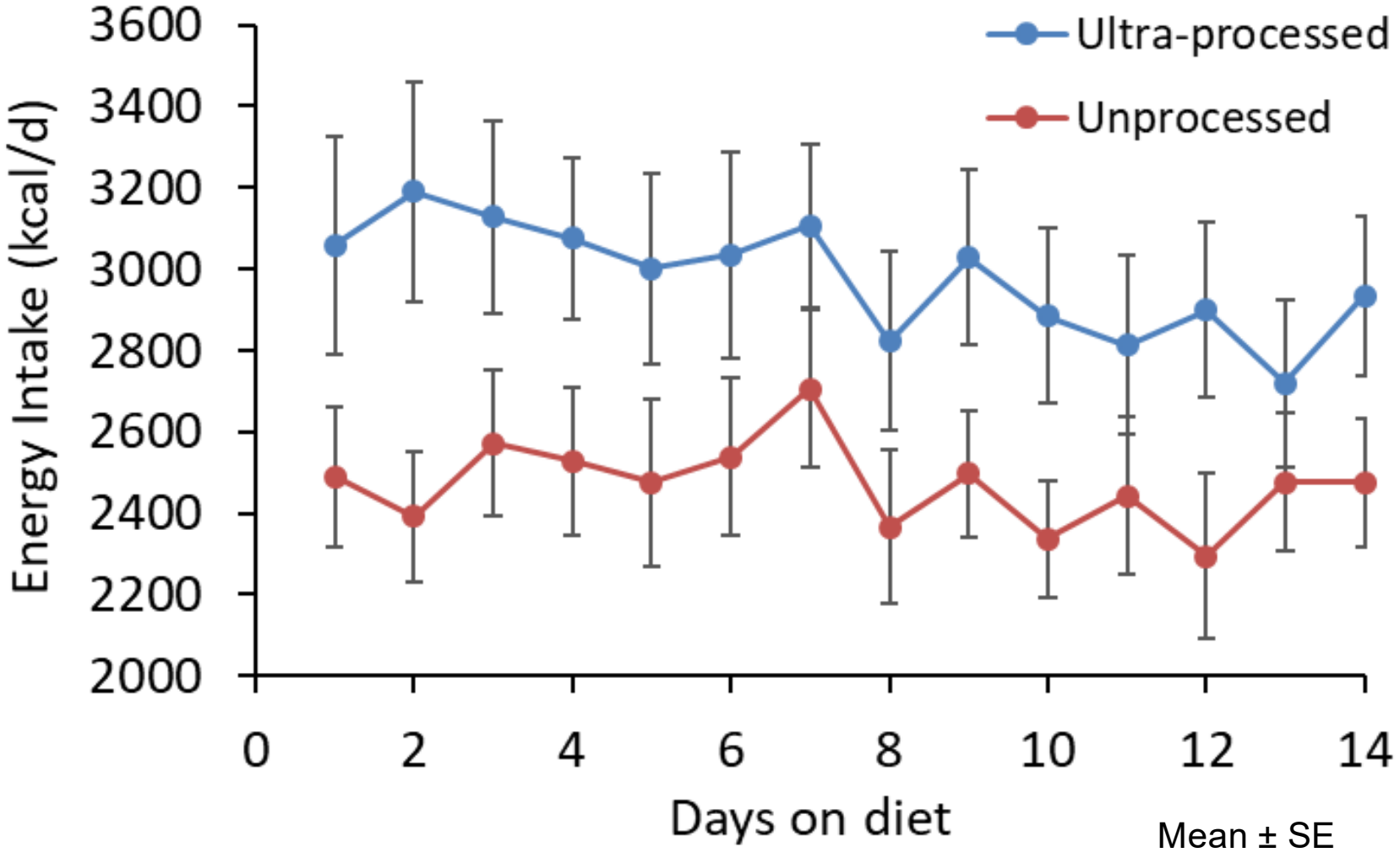


Mean ± SE

KD Hall et al. *Cell Metabolism* 30:1-11 (2019).

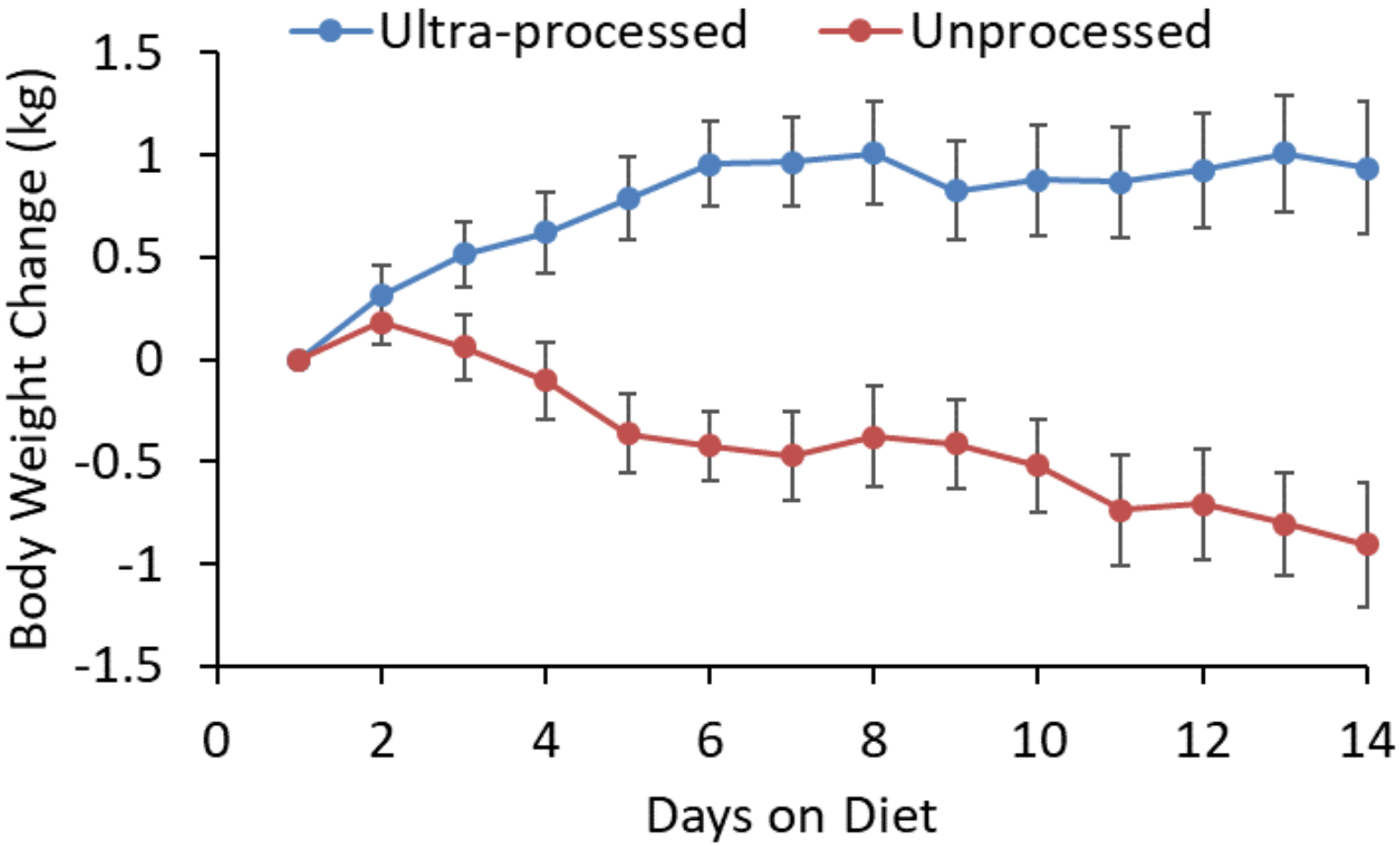
Ultra-processed Diet Caused Increased Intake

$\Delta EI = 508 \pm 106$ kcal/d; P=0.0001



KD Hall et al. *Cell Metabolism* 30:1-11 (2019).

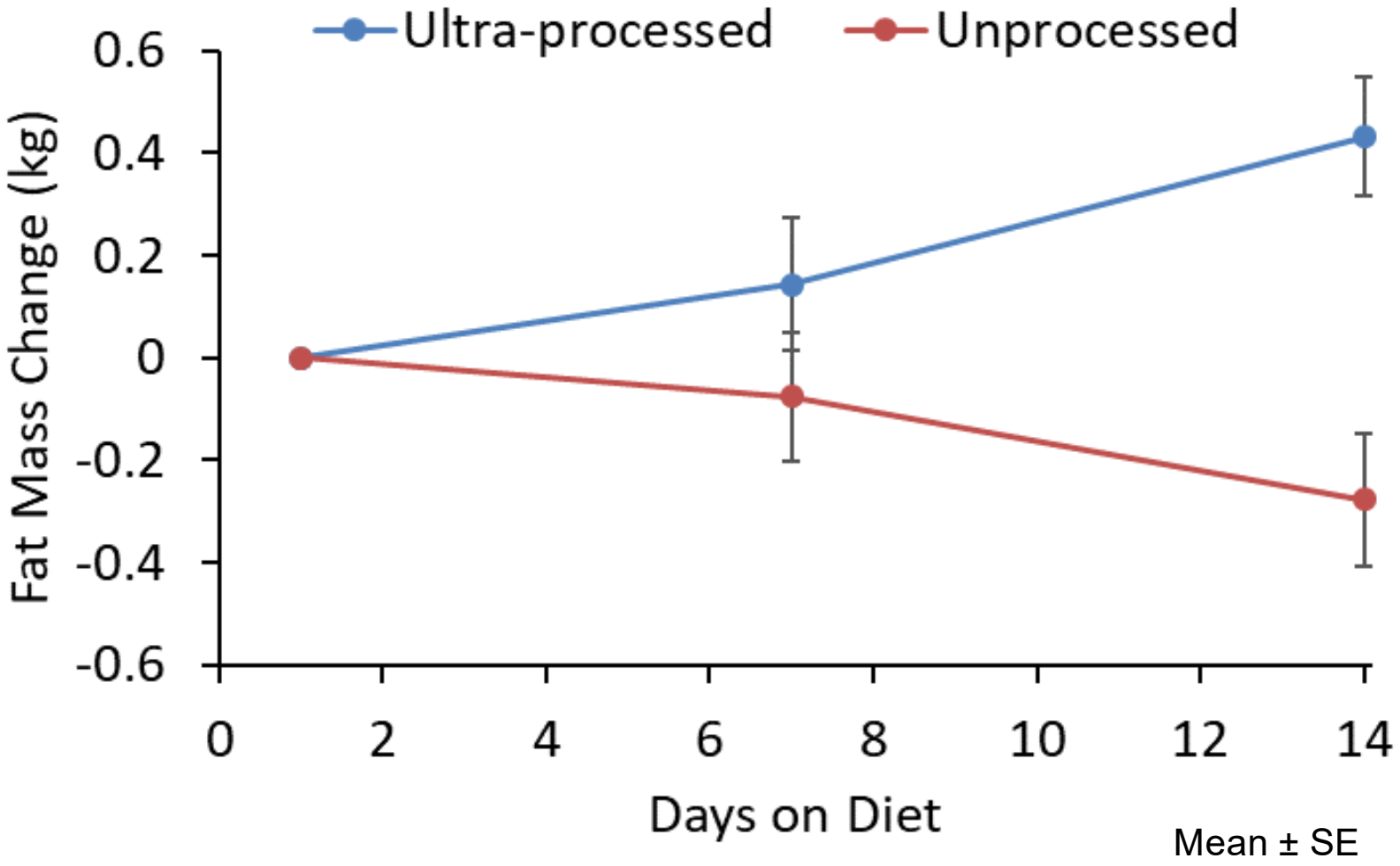
Ultra-processed Diet Caused Weight Gain



Mean ± SE

KD Hall et al. *Cell Metabolism* 30:1-11 (2019).

Ultra-processed Diet Caused Body Fat Gain



KD Hall et al. *Cell Metabolism* 30:1-11 (2019).

Mechanisms of Excess Intake with Ultra-processed Diets?

The New York Times

Are Ultraprocessed Foods Addictive?

By Alice Callahan

March 6, 2025

THE WALL STREET JOURNAL.

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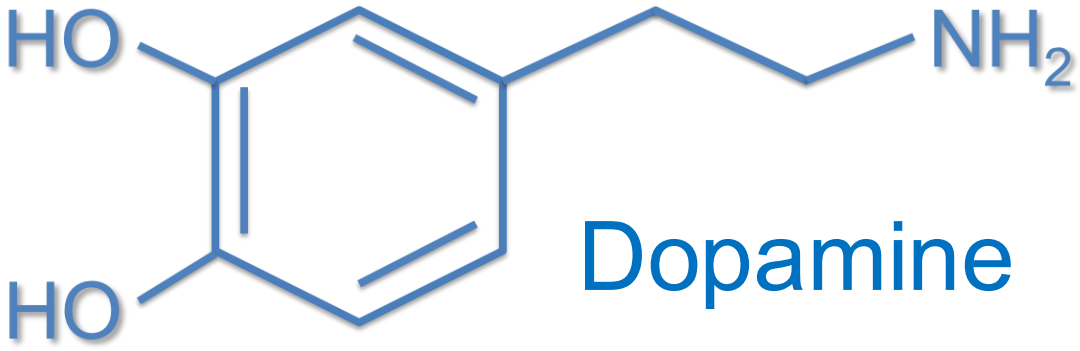


Dopamine

HEALTH | WELLNESS

The New Science on What Ultra-Processed Food Does to Your Brain

Studies are finding links between these foods and changes in the way we learn, remember and feel

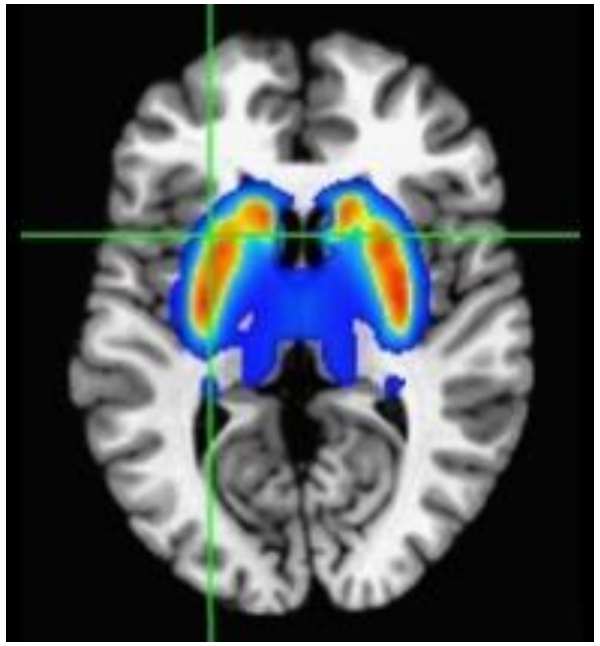
Social, clinical, and policy implications of ultra-processed food addiction

Conceptualising ultra-processed foods high in carbohydrates and fats as addictive substances can contribute to efforts to improve health, argue **Ashley Gearhardt and colleagues**

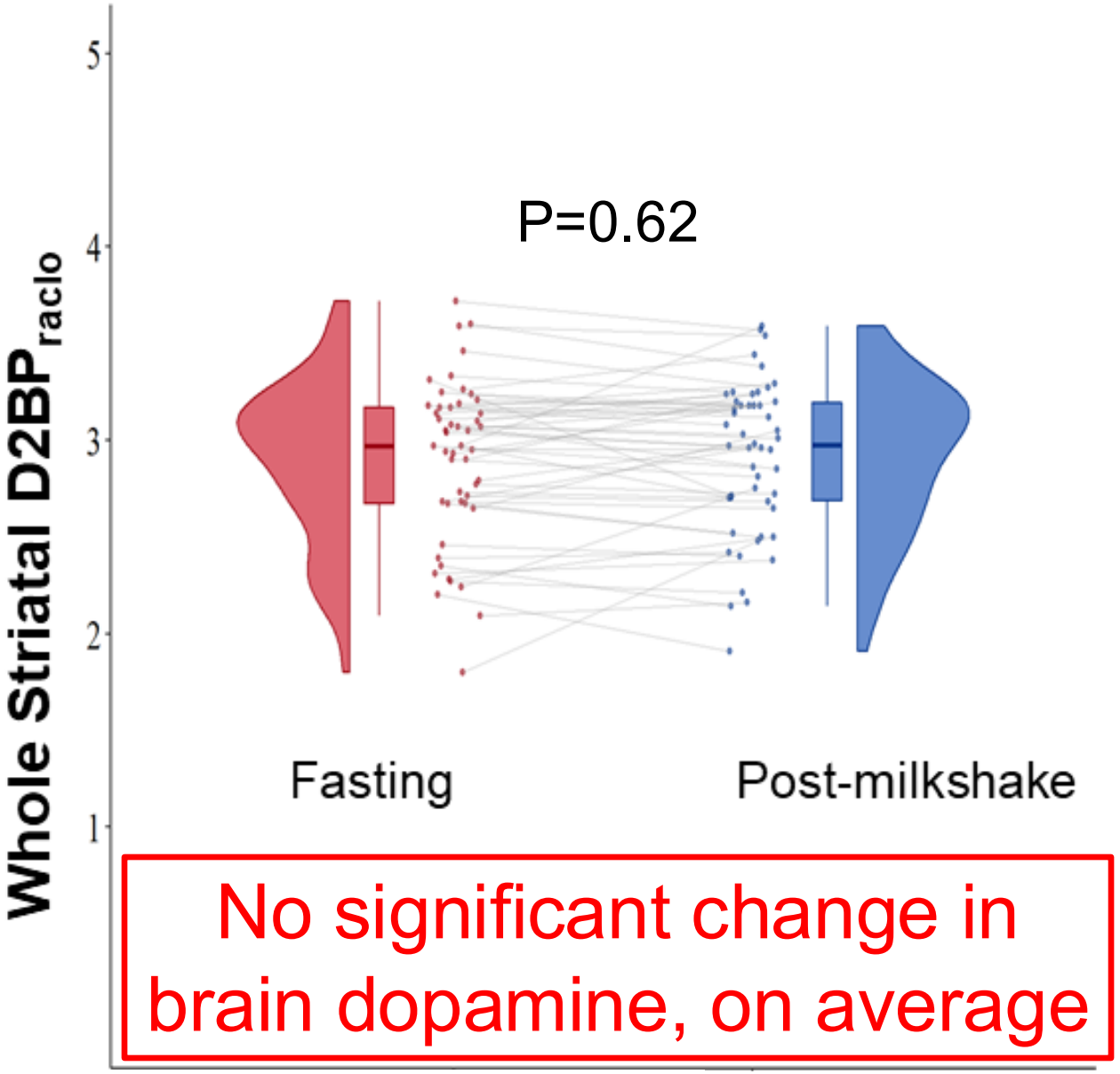
Refined carbohydrates or fats evoke similar levels of extracellular dopamine in the brain striatum to those seen with addictive substances

Gearhardt et al. *BMJ* 383:e075354 (2023)

Postingestive Dopamine Response to Ultra-processed Food?



N = 50
BMI = 20-45 kg/m^2
PET ^{11}C-raclopride
Pre & Post
420 kcal
Ultra-processed
milkshake
High in fat & sugar



No significant change in brain dopamine, on average

VL Darcey et al. Cell Metabolism 37: 616–628 (2025).

Obesity Symposium
EPIDEMIOLOGY/GENETICS

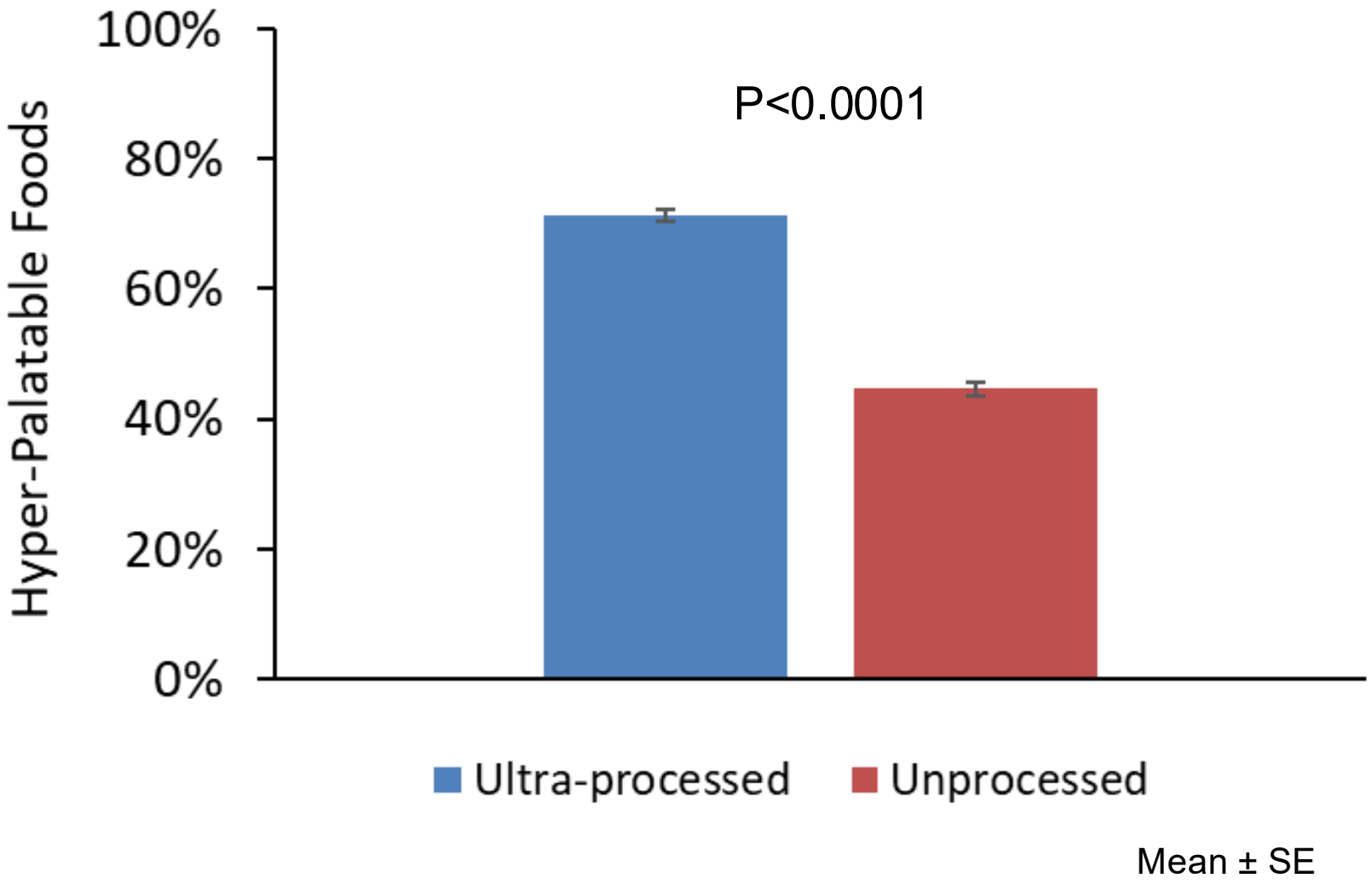
Hyper-Palatable Foods: Development of a Quantitative Definition and Application to the US Food System Database

Tera L. Fazzino [1,2], *Kaitlyn Rohde*[1,2], *and Debra K. Sullivan*[3]

Results: HPF from the literature aligned with three clusters: (1) fat and sodium (>25% kcal from fat, ≥0.30% sodium by weight), (2) fat and simple sugars (>20% kcal from fat, >20% kcal from sugar), and (3) carbohydrates and sodium (>40% kcal from carbohydrates, ≥0.20% sodium by weight). In the FNDDS, 62% (4,795/7,757) of foods met HPF criteria. The HPF criteria identified a variety of foods, including some labeled reduced or low fat and vegetables cooked in creams, sauces, or fats.

TL Fazzino et al. *Obesity 27*:1761-1768 (2019).

More Hyper-Palatable Foods in the Ultra-processed Meals



TL Fazzino et al. *Nature Food* 4:144-147 (2023).

	Ultra-Processed Diet	Unprocessed Diet
Three Daily Meals		
Energy (kcal/day)	3,905	3,871
Carbohydrate (%)	49.2	46.3
Fat (%)	34.7	35.0
Protein (%)	16.1	18.7
Energy density (kcal/g)	1.024	1.028
Non-beverage energy density (kcal/g)	1.957	1.057
Sodium (mg/1,000 kcal)	1,997	1,981
Fiber (g/1,000 kcal)	21.3	20.7
Sugars (g/1,000 kcal)	34.6	32.7
Saturated fat (g/1,000 kcal)	13.1	7.6
Omega-3 fatty acids (g/1,000 kcal)	0.7	1.4
Omega-6 fatty acids (g/1,000 kcal)	7.6	7.2
Energy from unprocessed (%)[a]	6.4	83.3
Energy from ultra-processed (%)[a]	83.5	0

What Mediated the Ultra-processed vs Unprocessed Effect?

Hyper-palatable Foods

TL Fazzino et al.
Obesity 27:1761-1768 (2019)

Non-beverage Energy Density

L Johnson et al.
Obes Rev 10:681–692 (2009)

Table 2 | Mediation analyses (N=20; 1635 Meals)

Ultraprocessed versus unprocessed diet study			
Mediator	**Estimate**	**Standard error**	***P* value**
%HPF			
NDE	69.8	13.6	<0.0001
NIE	50.3	6.3	<0.0001
% Mediated	41.9	6.5	<0.0001
ED			
NDE	65.9	19.8	0.001
NIE	54.1	15.3	0.0004
% Mediated	45.1	13.6	0.001

TL Fazzino et al. *Nature Food* 4:144-147 (2023).

New Study Ongoing: ClinicalTrials.gov NCT05290064

Compare *ad libitum* energy intake between 4 test diets provided for one week each in a randomized, counterbalanced sequence. All test diets are matched for macronutrients, fiber, sugar, and sodium:

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1. Minimally processed diet low in non-beverage energy density & low in hyper-palatable foods (MPF ll)

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2. Ultra-processed diet high in non-beverage energy density & high in hyper-palatable foods (UPF hh)

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3. Ultra-processed diet high in non-beverage energy density & low in hyper-palatable foods (UPF hl)
4. Ultra-processed diet low in non-beverage energy density & low in hyper-palatable foods (UPF ll)

Average Composition of the 7-day Menus

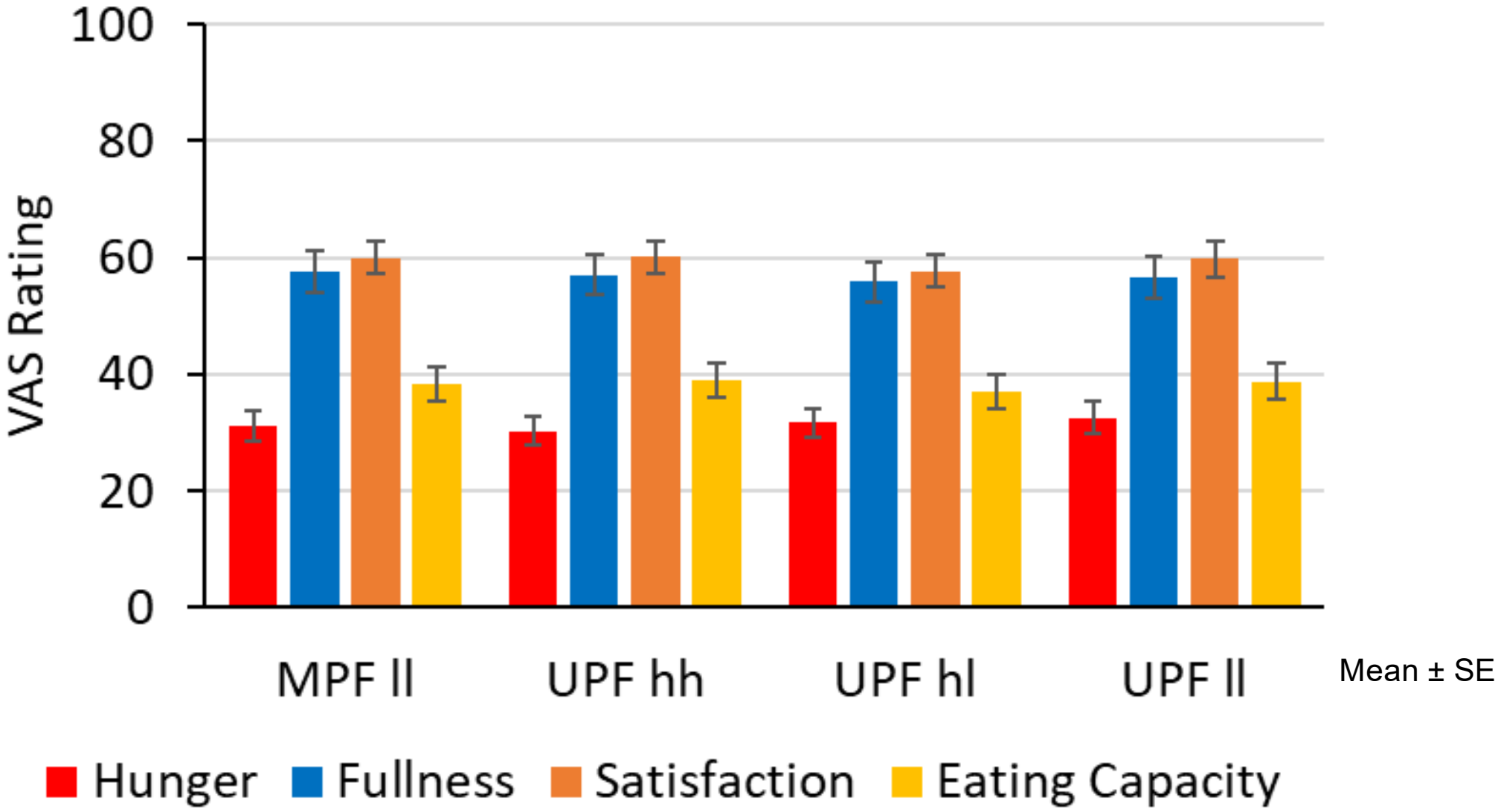
	MPF ll	UPF hh	UPF hl	UPF ll
Three Daily Meals				
Ultra-Processed Foods (% of energy)	0	88	80	81
Hyperpalatable foods (% of energy)	53	74	56	55
Non-beverage Energy Density (kcal/g)	0.99	1.95	1.90	1.01
Energy Density (kcal/g)	0.98	0.97	1.15	0.99
Carbohydrate (% of energy)	46	47	46	45
Fat (% of energy)	35	35	35	35
Protein (% of energy)	19	18	19	20
Sodium (mg/1000 kcal)	2247	1945	1891	2373
Fiber (g/1000 kcal)	21	21	21	18
Sugars (g/1000 kcal)	34	32	34	32

Baseline Participant Characteristics

	Mean ± SD (min, max)
Males/ Females	11/7
Age (y)	33.6 ± 10.4 (19, 52)
Height (cm)	172.8 ± 8.0 (158, 185)
Body Weight (kg)	86.9 ± 18.1 (61.7, 119.1)
BMI (kg/m^2)	29.0 ± 5.4 (20.8, 41.8)
Fat Mass (kg)	29.2 ± 15.6 (6.8, 66.1)
% Body Fat	32.4 ± 12.8 (10.2, 55.5)

Unpublished Interim Analysis (N=18/36): ClinicalTrials.gov NCT05290064

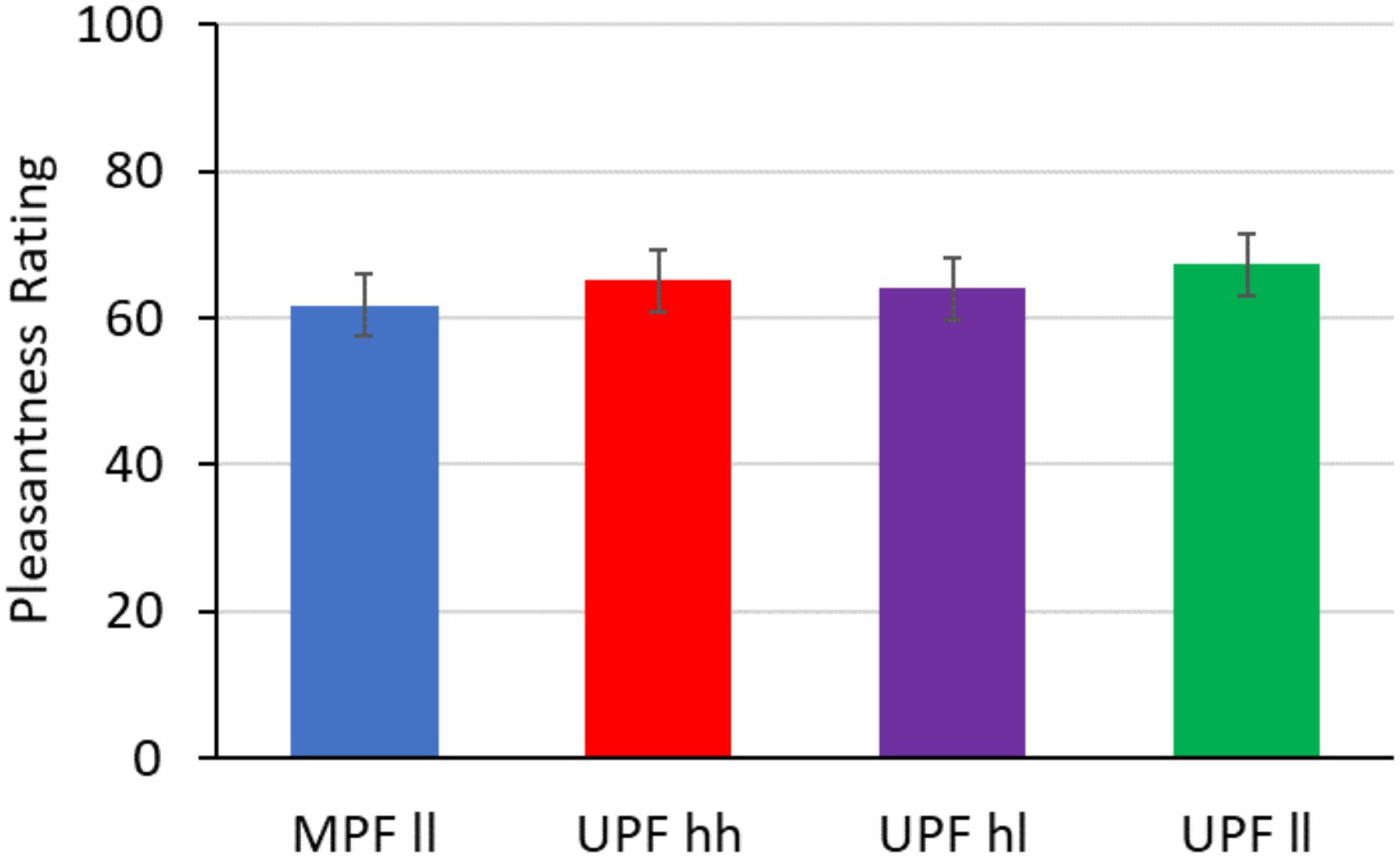
No Significant Differences in Appetite Ratings



Mean ± SE

Unpublished Interim Analysis (N=18/36): ClinicalTrials.gov NCT05290064

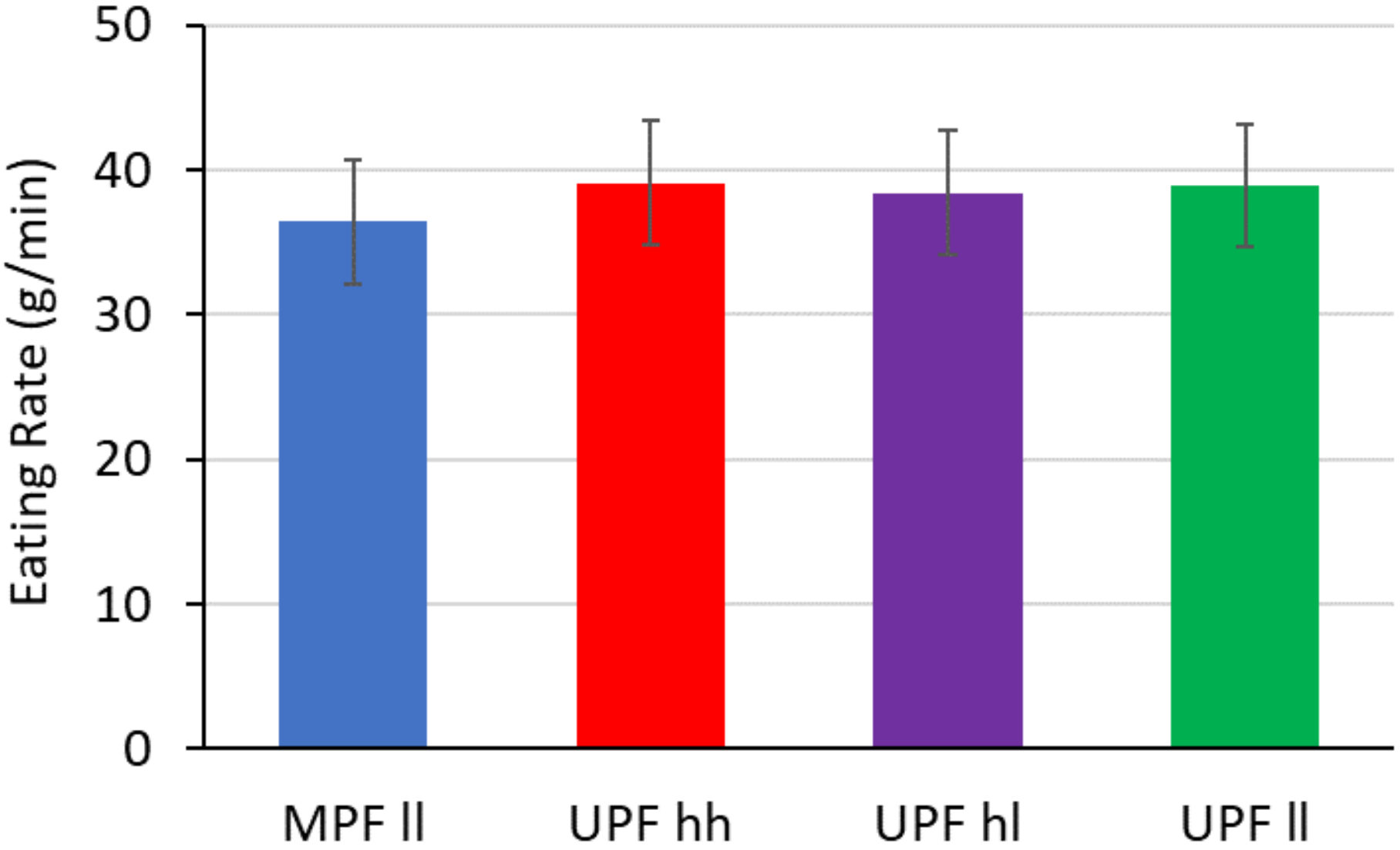
No Significant Differences in Meal Pleasantness Ratings



Mean ± SE

Unpublished Interim Analysis (N=18/36): ClinicalTrials.gov NCT05290064

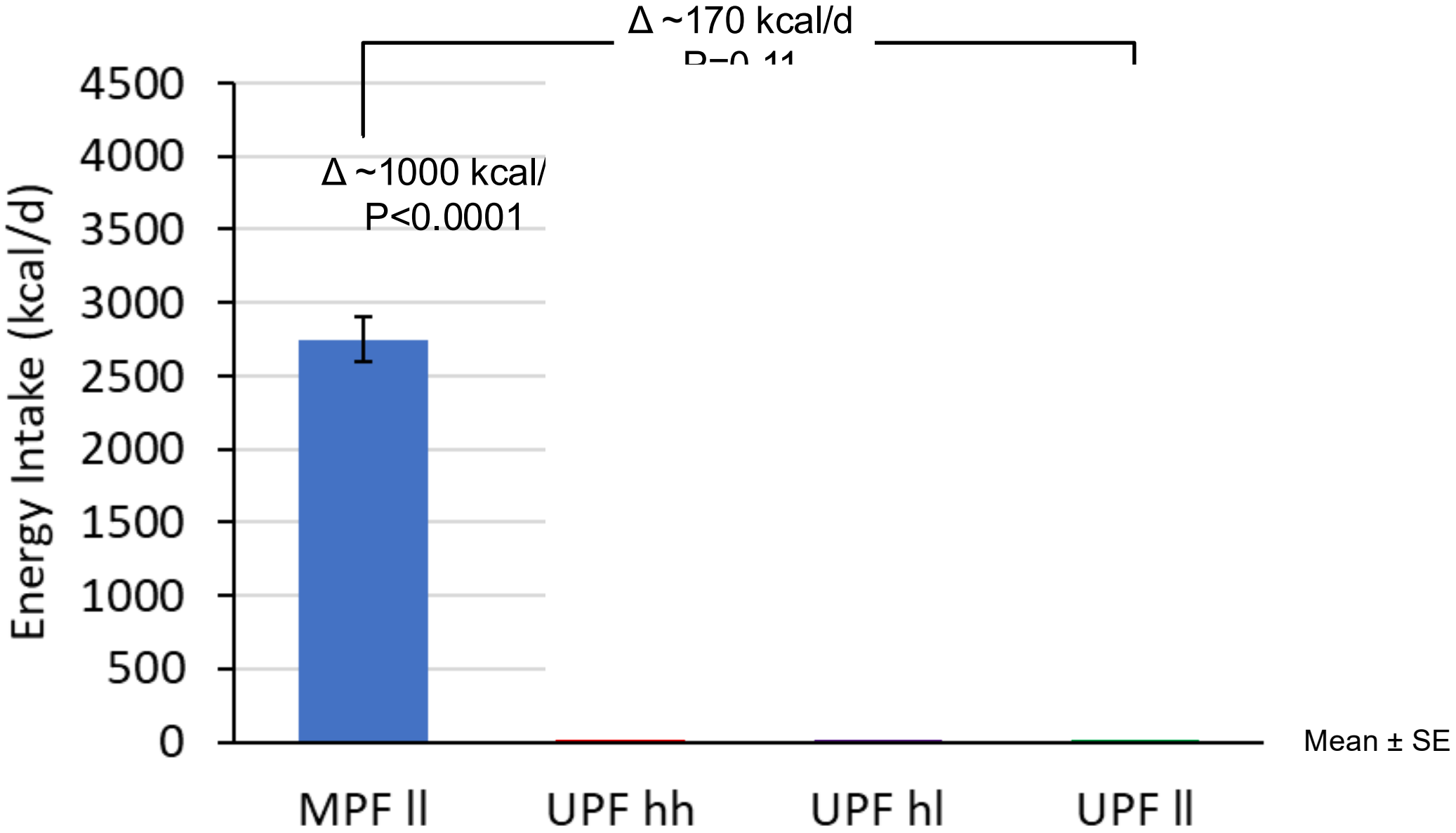
No Significant Differences in Meal Eating Rate



Mean ± SE

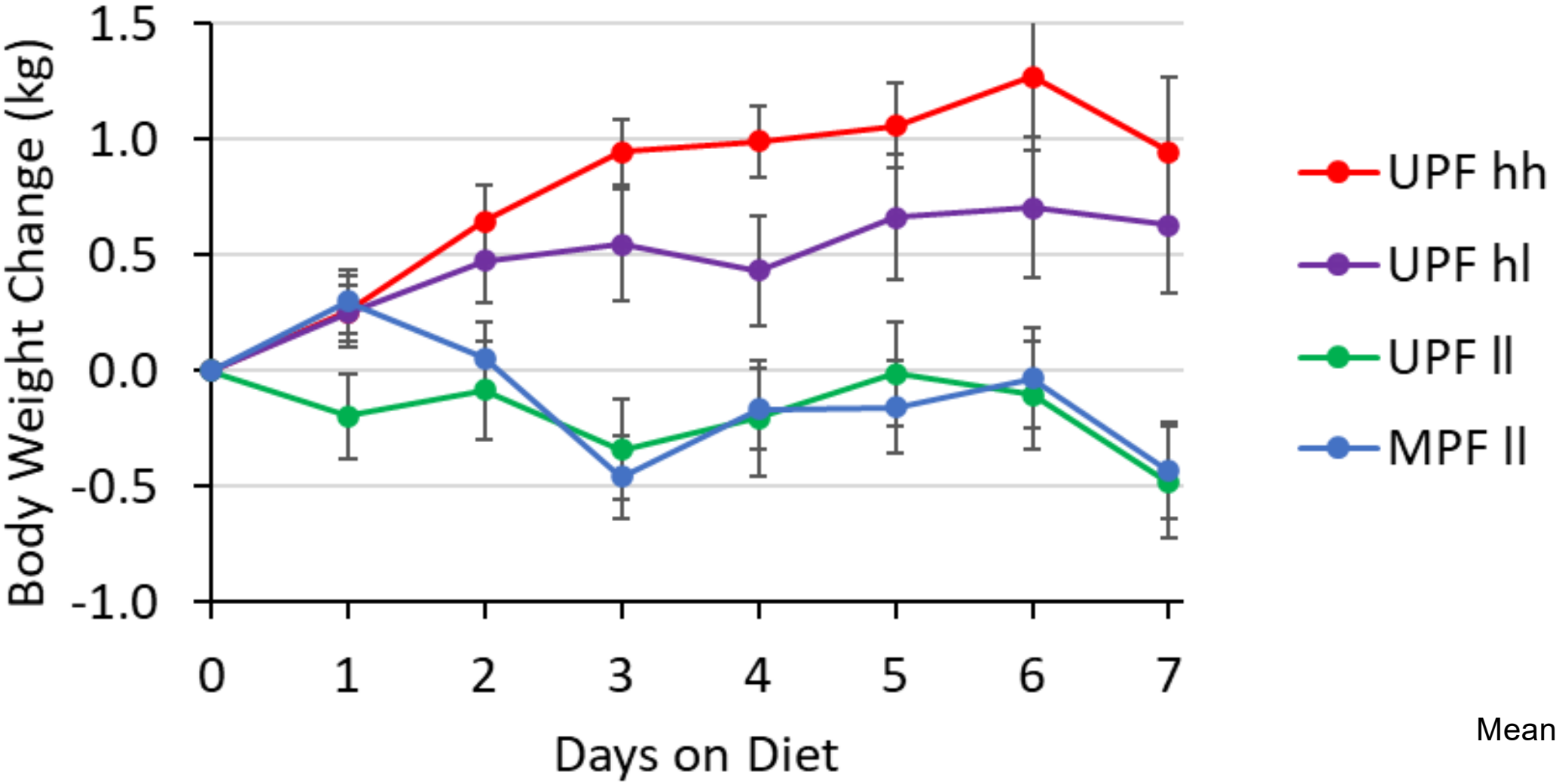
Unpublished Interim Analysis (N=18/36): ClinicalTrials.gov NCT05290064

Primary Outcome: Ad Libitum Energy Intake Differences



Unpublished Interim Analysis (N=18/36): ClinicalTrials.gov NCT05290064

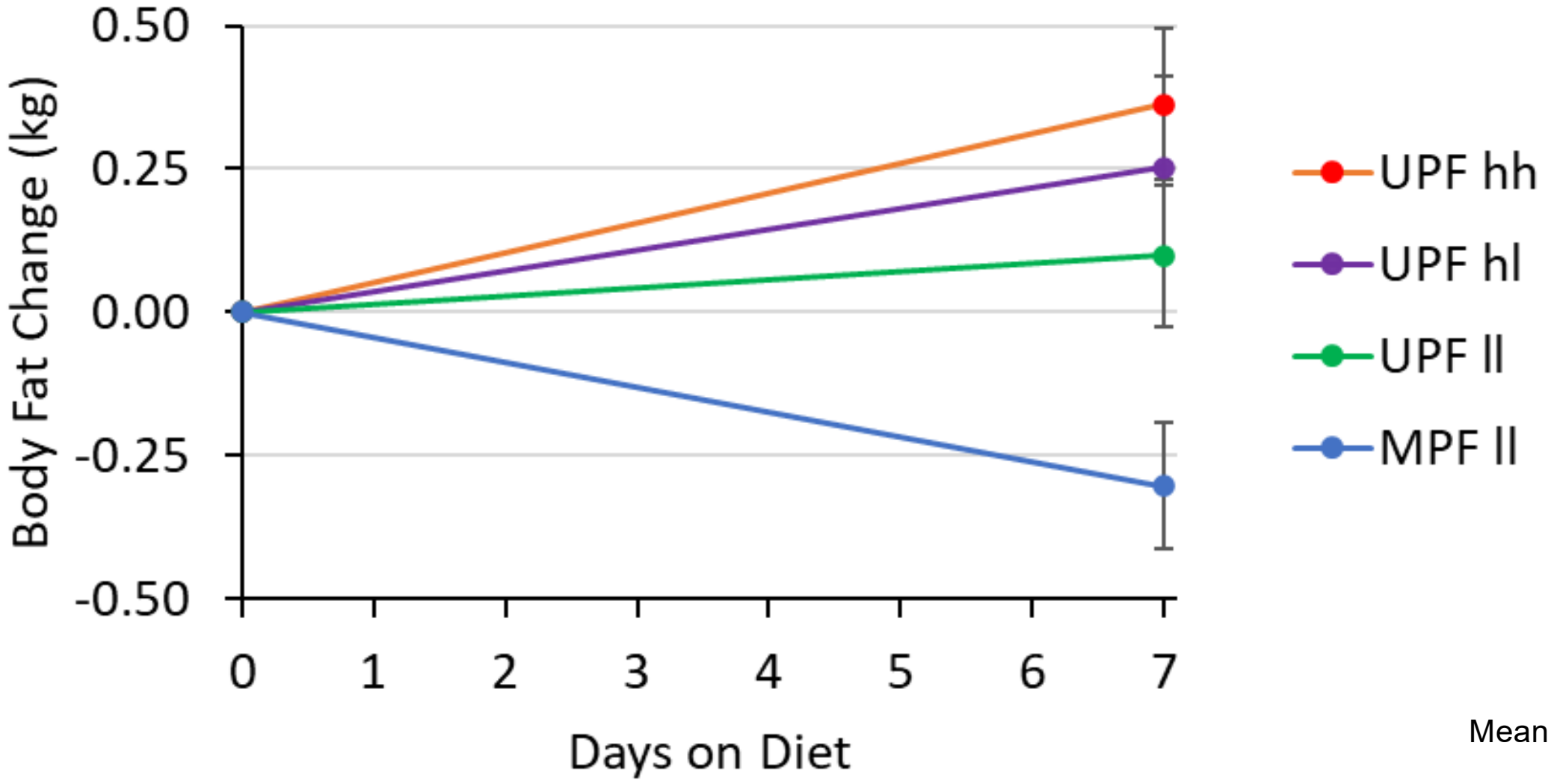
Weight Changes Correspond to Energy Intake Differences



Mean ± SE

Unpublished Interim Analysis (N=18/36): ClinicalTrials.gov NCT05290064

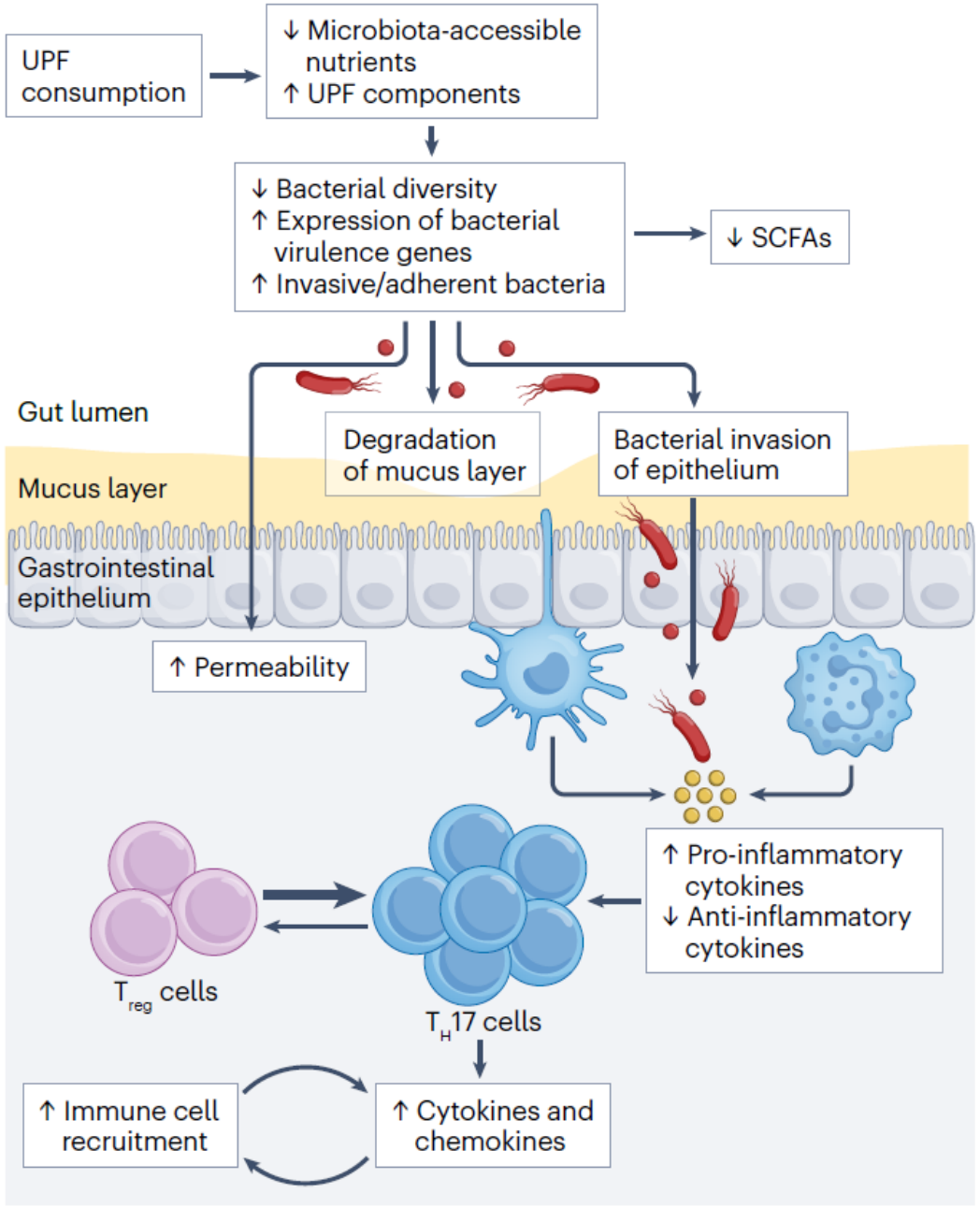
Only the Minimally Processed Diet Led to Body Fat Loss



Mean ± SE

Unpublished Interim Analysis (N=18/36): ClinicalTrials.gov NCT05290064

Ultra-processed Food Mechanisms: Beyond Obesity



Ultra-processed foods: increasing the risk of inflammation and immune dysregulation?

Katherine A. Maki, Michael N. Sack & Kevin D. Hall

Ultra-processed foods (UPFs) are industrially formulated products that contain synthetic ingredients but minimal whole-food components. Diets high in UPFs are associated with increased risk of immune dysregulation-linked diseases such as inflammatory bowel disease and potentially autoimmune disease. Several putative mechanisms have been proposed to explain this association, and these need urgent research attention.

KA Maki et al. *Nat Rev Immunol* 24:453-4 (2024).

Special Thanks

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Volunteer Study Participants

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many people
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