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Ultra-processed foods cause weight gain and increased energy intake associated with reduced chewing frequency: A randomized, open-label, crossover study

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Abstract

Aim: To elucidate the effects of ultra-processed foods (UPFs) on body weight and *ad libitum* energy intake compared with non-UPFs.

Materials and Methods: In this randomized, open-label crossover study conducted at the University of Tokyo Hospital, overweight/obese Japanese male participants were randomly assigned (1:1) to start the study with consumption of either UPFs or non-UPFs for 1 week, followed by a 2-week washout period, before crossing over to the alternate food diet for 1 week. Individuals with diabetes, hypertension or any other medical conditions who visited a hospital regularly were excluded. The meals were designed to be matched for the total energy and macronutrient levels. The primary outcome was the difference in the body weight change between the UPF and non-UPF periods. The differences in the average daily energy intake and chewing frequency were assessed as one of the prespecified secondary outcomes.

Results: Nine eligible participants were randomly assigned to start the study with either UPFs or non-UPFs. All participants completed the study. During the UPF period, participants gained 1.1 kg more weight (95% confidence interval 0.2 to 2.0; $P = .021$) and consumed 813.5 kcal more per day (342.4 to 1284.7; $P = .0041$) compared with during the non-UPF period. Regarding the chewing frequency, the number of chews per calorie was significantly lower during the UPF period ($P = .016$).

Conclusions: Consumption of UPFs causes significant weight gain. Medical nutritional therapy focused on reducing the consumption of UPFs could be an effective strategy for preventing obesity.

KEYWORDS
appetite control, clinical trial, obesity therapy, randomized trial

Shoko Hamano, Mika Sawada and Masakazu Aihara contributed equally to this work.

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1 | INTRODUCTION

The prevalence of obesity has risen worldwide, contributing to the growing burden of chronic diseases and mortality.[1] Concurrently, the consumption of ultra-processed foods (UPFs) has also been steadily increasing on a global scale.[2] These food products are now increasingly replacing traditional diets, namely, minimally processed and freshly prepared meals.

The NOVA system provides a standardized framework for categorizing foods based on their level of processing.[3] The system classifies foods into four main groups: unprocessed or minimally processed foods, processed culinary ingredients, processed foods and UPFs. The classification defines UPFs as food products that have undergone extensive processing and typically contain multiple ingredients, including additives, preservatives and synthetic substances. These foods are designed to be hyperpalatable and convenient, are branded, have a long shelf life and often come in the form of ready-to-eat or ready-to-heat products. However, the nutritional profile of UPFs is often imbalanced compared with that of unprocessed foods. UPFs typically have high levels of refined carbohydrates, saturated fats and salt, while lacking in essential nutrients such as fibres and beneficial micronutrients.[4]

There is growing evidence to link the consumption of UPFs to health problems. Numerous observational studies have shown associations between the consumption of UPFs and an increased risk of obesity,[5] and obesity-related health problems such as type 2 diabetes,[6] cardiovascular diseases,[7] cancers[8] and all-cause mortality.[9] However, there is still little evidence establishing the causality between consumption of UPFs and obesity.

Despite these associations, the mechanisms by which UPFs contribute to weight gain are not fully understood. One important difference between the traditional foods and processed foods of the industrialized world is the greater need for mastication in the case of traditional foods. Unprocessed foods typically contain high amounts of fibre, which requires chewing and thus, they are eaten relatively slowly.[10] Previous meta-analyses have shown the effect of an increased number of chews in reducing food intake.[11] Other studies have further suggested the existence of a significant negative association between chewing frequency and body weight.[12,13] However, to date, no studies have examined the effect of consumption of UPFs on chewing frequency.

The current randomized, crossover study was conducted to elucidate the effects of consumption of UPFs on body weight, energy intake, metabolism and chewing frequency compared with the consumption of non-ultra-processed foods (non-UPFs), which constitute a major part of traditional diets.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This open-label, randomized, crossover study was conducted from August to October 2022 at the University of Tokyo Hospital, Tokyo, Japan. Eligible participants were Japanese males aged 18-39 years with a body mass index (BMI) of 25 kg/m^2 or higher who were weight-stable (less than ±5% over the previous 6 months).

The following participants were excluded: those who regularly visit hospitals or were on routine medication(s) for any reason(s), and those with diabetes, hypertension, eating disorders or other psychiatric conditions, such as depression and bipolar disorder. Those with food allergies and/or adhered to particular diets (e.g. vegetarian, pescatarian) were also excluded. Participants who met the inclusion criteria were admitted as inpatients during each of the diet periods to the Clinical Trial Ward Department (Phase 1 Unit) of the Clinical Research Support Center at the University of Tokyo Hospital.

Prior to the start of the study, a computer-generated randomization list was created using a pseudo-random number generator. The computer programs for the analyses were run by an unmasked investigator. Using this randomization list, the participants were randomly assigned (1:1) to begin the study with either consumption of UPFs (UPF period) or consumption of non-UPFs (non-UPF period) for 1 week, in numerical order of their acceptance to participate in the study. They were then crossed over to the alternate diet for 1 week after a 2-week washout period (Figure 1B). Neither the participants nor the investigators were blinded to the group assignment.

It was explained to participants that the study aimed to examine how UPFs versus non-UPFs could affect body weight and metabolism, and that this was not a study for facilitating weight loss.

This research was conducted in accordance with the guidelines of the Declaration of Helsinki, with the approval of the Research Ethics Committee of the University of Tokyo Hospital (2022048NI). The clinical study at the University of Tokyo Hospital was registered with the UMIN-Clinical Trials Registry as UMIN000049876. Written informed consent was obtained from each of the individuals who participated in this study.

2.2 | Procedures

2.2.1 | Diets

The diets were designed and analysed using Asken Diet software (Asken Corporation, Tokyo, Japan) with nutrient values derived from the Dietary Intake Standards for Japanese,[14] as determined by the Ministry of Health, Labour, and Welfare, Japan.

During each of the experimental diet periods, participants were given three meals daily in amounts equivalent to twice the estimated average energy requirement of a Japanese male adult aged 18-29 years with a BMI of 30 kg/m^2.[14] Pictures of an ideal meal size amount for one person, based on the estimated average daily energy requirement, were shown to participants before each meal (Figure S1). Additionally, they were instructed to eat as much or as little as they desired. There was a 60-minute time limit to consume each meal. The meals were designed to be matched across diets for total energy, macronutrient levels and energy density.

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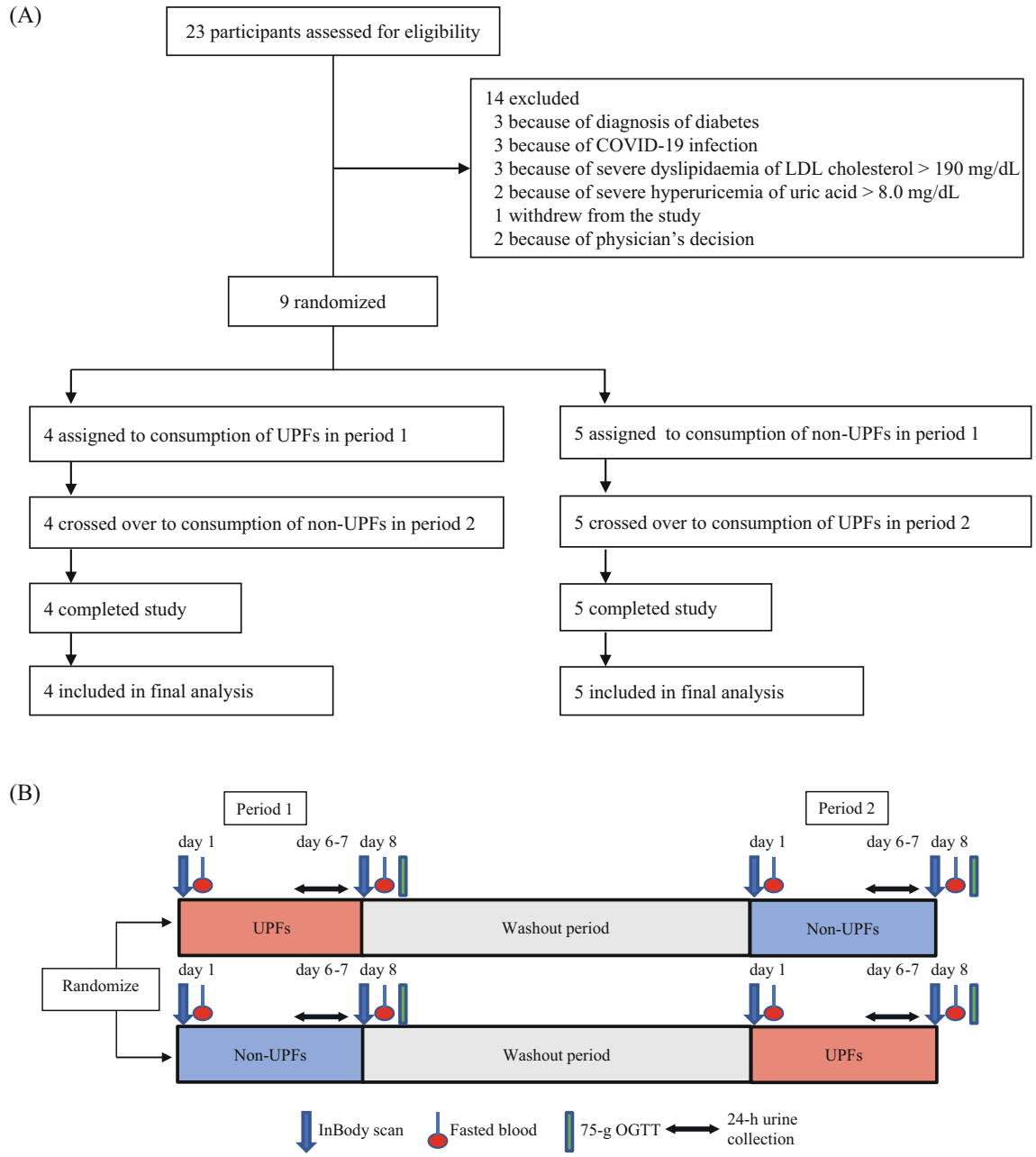


FIGURE 1 Trial flowchart (A), and Study design (B). COVID-19, coronavirus disease 2019; LDL, low-density lipoprotein; non-UPFs, non-ultra-processed foods; OGTT, oral glucose tolerance test; UPFs, ultra-processed foods.

During each of the experimental diet periods, participants had access to snacks and bottled water throughout the day. Snacks were designed to be matched across diets for total energy and macronutrient levels. The daily meals and snacks were categorized according to the NOVA classification scheme. Non-UPFs were defined as group 1-3, whereas UPFs were defined as group 4 according to the NOVA classification.

A nurse recorded the duration of each meal, then identified and weighed the remaining food to calculate the amount of food that had been consumed. The energy and nutrient intake were calculated using the nutrition software described previously.

2.2.2 | Body weight and composition

Each participant's body weight was measured daily at 07:00 AM, before breakfast. All participants wore the same pyjamas issued by the hospital; the weight of these preweighed clothes was subtracted from the scale weight during the weight measurement. Each participant's body composition was measured on the first and final days of each diet period using a Bioelectrical Impedance Analysis system (InBody 720; InBody Japan Inc., Tokyo, Japan). Participants were blinded to the results of the daily body weight and body composition measurements.

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2.2.3 | Eating rate and chewing frequency

The eating rate was calculated by dividing the measured food intake by the meal duration. During each meal, each participant wore a bites-can (Sharp Co, Osaka, Japan), a wearable masticatory counter device, to measure the chewing frequency.

2.2.4 | Fasting blood samples

Fasting blood samples were measured on the first and final days of each diet period to assess the levels of LDL and HDL cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γGTP). Appetite-related hormones, including activated ghrelin, leptin, adiponectin, activated glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), were measured on the final day of each diet period in the fasting state before breakfast.

2.2.5 | Subjective assessment of appetite

During each diet period, the participants were asked to complete surveys on appetite and their desire for specific food types before each meal; 100-point visual analogue scales (VAS) were used to assess hunger, satiety, fullness, prospective food consumption and a desire to eat something fatty, salty, sweet or savoury.[15]

2.2.6 | Physical activity monitoring

Participants were only allowed to walk within the ward during the diet periods. Physical activity was monitored by measuring the step counts per day as recorded by the built-in pedometer in Android phones.

2.3 | Outcomes

The primary outcome was the difference in body weight change during the UPF and non-UPF periods. The secondary outcomes were the differences in the average daily energy intake, changes in body composition, intake of each macronutrient, the eating rate (i.e. the number of calories consumed per minute and the grams per minute), chewing frequency (i.e. the number of chews per minute and number of chews per gram), the levels of lipid profiles, liver function variables, appetite-related hormones and the VAS ratings for appetite during each diet period.

2.4 | Statistical analysis

The sample size was determined based on the effect size of 1.3416 reported in a previous crossover study, which reported a significant difference in the weight change between the ultra-processed and unprocessed dietary intervention periods.[16] Using a paired *t*-test with a two-sided significance level of .05 and a desired statistical power of 0.80, the required sample size was calculated as being approximately 6.53 participants.

Descriptive statistics are represented as the means ± standard error. The distributional assumption of normality of the variables was assessed using the Shapiro–Wilk test. For the body weight and meal intake variables, eating rate, chewing frequency, VAS ratings and step counts, comparisons within the study arms were performed by paired *t*-tests for variables that showed normal distribution, and by Wilcoxon signed-rank tests for variables that showed non-normal distribution. For the metabolic variables, comparisons of the within-period changes between the UPF and non-UPF periods were performed by Student's *t*-tests for variables that showed normal distribution and by Mann–Whitney U tests for variables that showed non-normal distribution. Baseline and end values in each period were compared among participants using paired *t*-tests for normally distributed variables, and by Wilcoxon signed-rank tests for non-normally distributed variables. For all the analyses, the significance level was set at $\alpha = .05$. The statistical analyses were performed using JMP Pro 16 version 16.2.0.

3 | RESULTS

We screened 23 participants during 16-29 August 2022 and assigned nine eligible participants randomly to start the study with either the UPF or non-UPF period. Following randomization, four participants started the study with the UPF period for 1 week, then, after a 2-week washout period, crossed over to the non-UPF period for 1 week. The other five participants started the study with the non-UPF period then crossed over (after the 2-week washout period) to the UPF period. Daily meals and snacks during the two diet periods were matched for total energy and macronutrients (Table 1). The nine male adults (age 29.7 ± 2.1 years; mean BMI 27.4 ± 0.9 kg/m^2) were admitted as inpatients to the Clinical Trial Ward Department (Phase 1 Unit) of the Clinical Research Promotion Center at the University of Tokyo Hospital (Table 2). All nine participants completed the study (Figure 1A). No adverse events were observed during the study.

The participants gained 1.1 kg ($P = .021$) more weight at the end of the UPF period compared with the non-UPF period, and the difference was significant (Figure 2A). Body fat mass was 1.1 kg ($P = .052$) higher at the end of the UPF period than at the end of the non-UPF period, with the difference approaching statistical significance. There was no significant difference in the change in fat-free mass between the two diet periods ($P = .91$) (Figure 2B). The individual differences in body weight change were highly correlated with the differences in energy intake between the two diet periods ($r = 0.9$, $P = .0009$) (Figure S2), whereas they showed no significant correlation with baseline BMI ($r = -0.1$, $P = .71$) (data not shown).

Measurement of the daily average energy intake trend revealed significantly higher energy intake on most days during the UPF period than during the non-UPF period (Figure 2C). The average energy

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TABLE 1 Diet composition.

	Daily meals		Snacks		Daily meals and snacks	
	Non-UPF period	UPF period	Non-UPF period	UPF period	Non-UPF period	UPF period
Energy (kcal/d)	3543.0	3498.3	1796.0	1800.0	5339.0	5298.3
Carbohydrate (%)	53.6	52.1	54.0	54.2	53.7	52.7
Fat (%)	31.3	33.5	33.8	33.8	32.2	33.8
Protein (%)	15.1	14.4	12.3	12.1	14.1	13.5
Energy density (kcal/g)	1.3	1.3	0.8	3.0	1.1	1.7
Non-beverage energy density (kcal/g)	1.3	1.7	0.8	3.0	1.1	2.0
Salt (g/d)	19.9	22.1	1.1	4.1	21.0	26.2
Fibre (g/d)	40.8	36.4	36.5	6.9	77.3	43.3
Saturated fats (g/d)	30.6	36.5	14.8	22.7	45.4	59.1
Energy from non-UPFs[a] (%)	100.0	0.9	100.0	0.0	100.0	0.6
Energy from UPFs[a] (%)	0.0	99.1	0.0	100.0	0.0	99.4

Abbreviations: non-UPF, non-ultra-processed food; UPF, ultra-processed food.
[a]Energy percentages are shown as fraction of diet calories contributed from groups 1-3 as non-UPFs, and from group 4 as UPFs of the NOVA classification system.

TABLE 2 Baseline characteristics.

	Overall ($n = 9$)
Age (y)	29.7 ± 2.1
Height (cm)	173.2 ± 2.1
Body weight (kg)	82.2 ± 3.1
BMI (kg/m^2)	27.4 ± 0.9
Fat mass (kg)	23.1 ± 2.1
Body fat (%)	27.8 ± 1.8
Insulin (μU/mL)	5.6 ± 0.7
C-peptide (ng/mL)	1.3 ± 0.1
Glucose (mg/dL)	95.2 ± 9.2
HbA1c (%)	5.3 ± 0.1
HOMA-IR	1.3 ± 0.1
HOMA-β (%)	67.8 ± 10.2
Total cholesterol (mg/dL)	196 ± 7
HDL cholesterol (mg/dL)	53 ± 3
LDL cholesterol (mg/dL)	126 ± 6
Triglycerides (mg/dL)	109 ± 12
Uric acid (mg/dL)	6.7 ± 0.3
AST (IU/L)	21 ± 2
ALT (IU/L)	30 ± 4
γGTP (IU/L)	32 ± 6
UN (mg/dL)	11.0 ± 1.1
Cr (mg/dL)	0.82 ± 0.03
CRP (mg/dL)	0.1 ± 0.0

Note: Data are expressed as means ± SE.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cr, creatinine; CRP, C-reactive protein; γGTP, gamma-glutamyl transpeptidase; SE, standard error; UN, urea nitrogen.

intake was 813.5 kcal higher per day ($P = .0041$) during the UPF period than during the non-UPF period (Figure 2D).

During the UPF period, compared with the non-UPF period, there was a significant increase in energy intake at dinner ($P < .0001$) and lunch ($P = .0009$), but not at breakfast ($P = .064$) or snack times ($P = .46$) (Figure 2E). The increased energy intake observed during the UPF period was attributable to consumption of greater quantities of carbohydrates ($P = .0052$) and fats ($P = .0074$), with no significant difference observed in protein intake ($P = .26$) (Figure 2F).

Compared with the non-UPF period, the intake of water ($P = .015$), salt ($P < .0001$) and saturated fatty acids ($P = .0003$) was significantly increased during the UPF period (Figure 2G–I); however, fibre intake significantly decreased ($P = .0014$) during the UPF period (Figure 2J).

The eating rate was significantly faster during the UPF period compared with the non-UPF period, both in terms of kcal/min ($P = .0039$) and g/min ($P = .019$) (Figure 2K,L). The number of chews per calorie was significantly lower during the UPF period than during the non-UPF period ($P = .016$) (Figure 2M). The number of chews per gram tended to be lower during the UPF period than during the non-UPF period ($P = .10$) (Figure 2N).

Measurements in fasting blood samples showed a significant decrease in LDL cholesterol levels during the non-UPF period ($P = .0039$), while no significant change in LDL cholesterol was observed during the UPF period. The end values of LDL cholesterol tended to be higher after the UPF period than after the non-UPF period ($P = .074$). However, there were no significant differences in the within-period changes in LDL cholesterol between the two dietary periods ($P = .35$). While there was no significant change in blood triglyceride levels during the non-UPF period, a significant increase in triglyceride levels was observed during the UPF period ($P = .025$). The end values for triglycerides were significantly higher after the UPF

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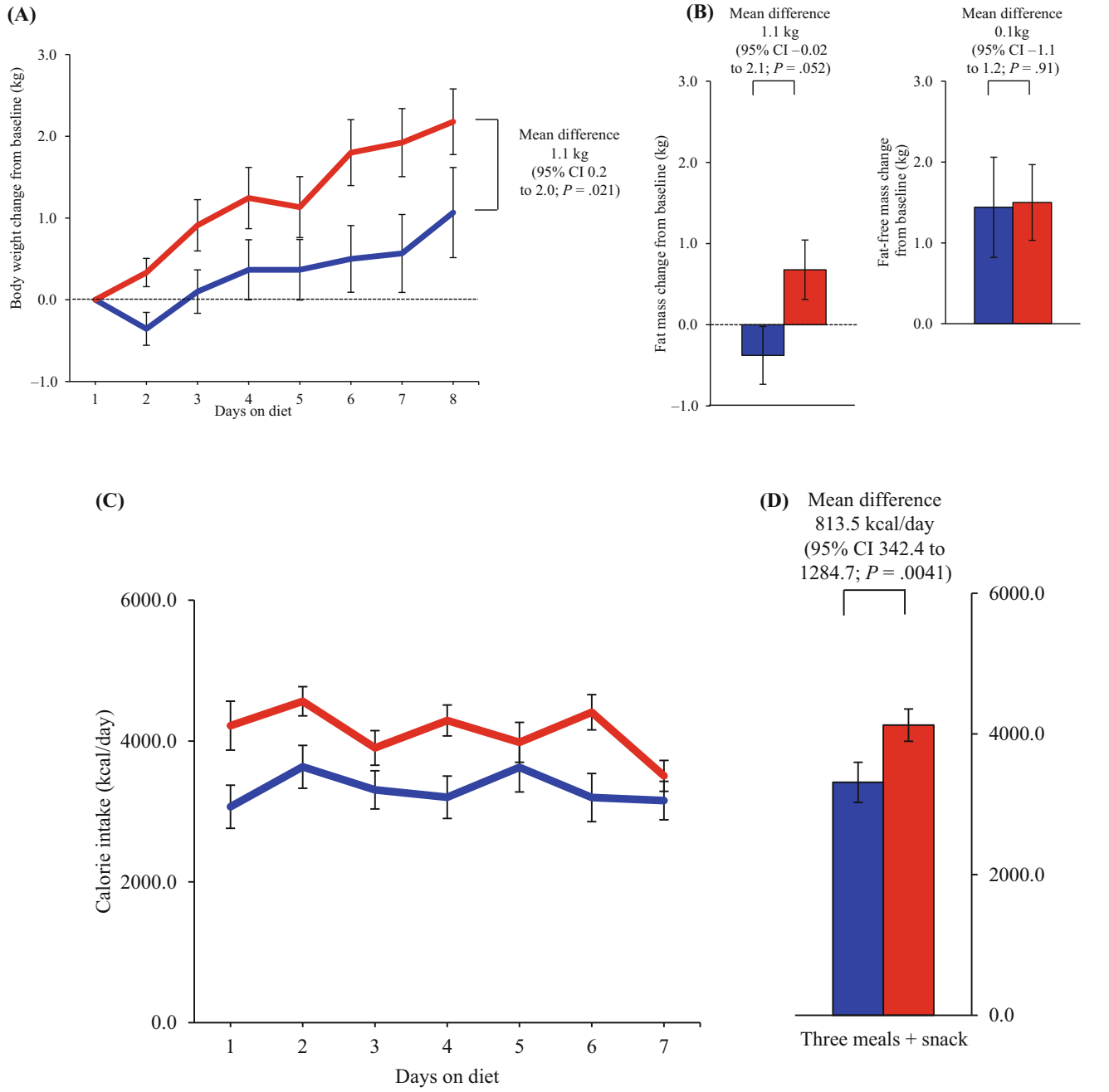


FIGURE 2 Paired analyses of the average body weight change (A), body composition change (B), daily calorie intake (C), average calorie intake (D), average calorie intake by meal (E), and intake of macronutrients (F), water (G), salt (H), saturated fatty acids (I), fibre (J), number of calories ingested per minute (K), number of grams ingested per minute (L), number of chews per calorie (M), and number of chews per gram (N). All analyses were performed using paired tests with nine participants. Wilcoxon signed-rank tests were used to compare the number of calories ingested per minute (K) and the grams ingested per minute (L). A paired *t*-test was used for all other variables. Data are expressed as means ± standard error. Blue lines and bars = non-UPFs; red lines and bars = UPFs. CI, confidence interval; non-UPFs, non-ultra-processed foods; UPFs, ultra-processed foods.

period than after the non-UPF period ($P = .011$). The within-period changes in triglycerides during the UPF period tended to be higher than those during the non-UPF period ($P = .10$) (Table 3).

In regard to the liver function variables, significant increases in the blood levels of AST ($P = .0092$), ALT ($P = .0083$) and γGTP ($P = .0080$), compared with the baseline values, were observed at the end of the UPF period, whereas no such changes in these variables were observed during the non-UPF period ($P = .69$, $P = .061$ and $P = .31$, respectively). Overall, within-period changes of AST ($P = .0068$), ALT ($P = .046$) and γGTP ($P = .015$) were significantly higher during the UPF period than during the non-UPF period (Table 3).

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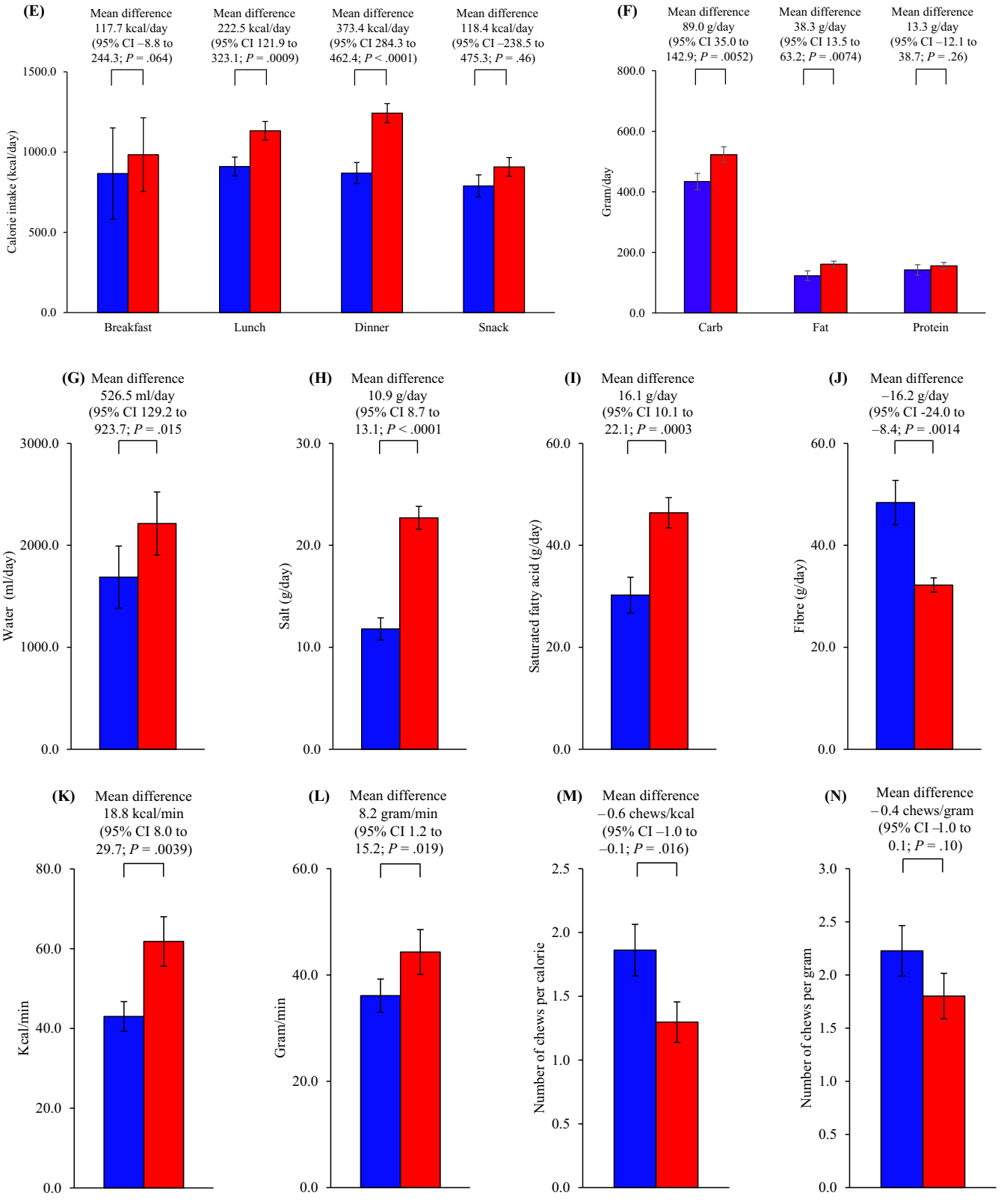


FIGURE 2 (Continued)

There were no significant differences in the blood ghrelin levels between the two diet periods ($P = .91$). Regarding the levels of appetite-suppressing hormones, both the blood leptin ($P = .044$) and adiponectin levels ($P = .0016$) were significantly higher at the end of the UPF period. The PYY levels tended to be lower at the end of the UPF period compared with at the end of the non-UPF period

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TABLE 3 Fasting blood and 24-h urine collection measurements.

	Non-UPF period			UPF period			Non-UPF period versus UPF period		
	Baseline	End	Within-period changes#	Baseline	End	Within-period changes#	Comparison of Baseline values[a]	Comparison of End values[b]	Comparison of within-period changes[c]
Active Ghrelin (pg/mL)	NA	123.7 ± 153.8	NA	NA	123.0 ± 145.3	NA	NA	−0.7 ± 7.1	NA
Leptin (ng/mL)	NA	15.6 ± 5.7	NA	NA	19.2 ± 5.9	NA	NA	3.6 ± 1.5[d]	NA
PYY (pg/mL)	NA	0.29 ± 0.09	NA	NA	0.26 ± 0.07	NA	NA	−0.03 ± 0.02	NA
Adiponectin (mg/L)	NA	6.7 ± 2.8	NA	NA	8.0 ± 2.6	NA	NA	1.2 ± 0.3[d]	NA
Active GLP-1 (pg/mL)	NA	1.7 ± 0.8	NA	NA	2.1 ± 1.0	NA	NA	0.4 ± 0.3	NA
Glucagon (pmol/L)	NA	52.3 ± 23.2	NA	NA	77.8 ± 27.9	NA	NA	25.5 ± 7.7[d]	NA
Insulin (μU/mL)	5.4 ± 1.7	8.6 ± 3.7	3.1 ± 0.9[d]	5.6 ± 1.9	8.3 ± 3.1	2.6 ± 1.0	0.2 ± 0.3	−0.3 ± 1.1	−0.5 ± 1.4
C-peptide (ng/mL)	1.3 ± 0.2	1.7 ± 0.4	0.4 ± 0.1[d]	1.3 ± 0.5	1.4 ± 0.5	0.1 ± 0.1	−0.0 ± 0.1	−0.3 ± 0.2	−0.3 ± 0.2
Glucose (mg/dL)	96.1 ± 8.7	94.6 ± 8.6	−1.4 ± 1.8	95.4 ± 8.0	91.5 ± 7.4	−3.9 ± 2.2	−0.7 ± 1.8	−3.1 ± 1.2[d]	−2.4 ± 2.8
Glycated albumin (%)	NA	12.1 ± 0.9	NA	NA	12.2 ± 1.0	NA	NA	0.1 ± 0.1	NA
HOMA-IR	1.2 ± 0.3	2.0 ± 0.8	0.8 ± 0.2[d]	1.3 ± 0.4	1.9 ± 0.7	0.6 ± 0.2	0.1 ± 0.1	−0.1 ± 0.3	−0.2 ± 0.3
HOMA-β (%)	63.8 ± 28.4	100.6 ± 44.1	36.8 ± 9.8[d]	67.2 ± 29.7	108.5 ± 44.0	41.3 ± 11.4	3.4 ± 4.5	7.8 ± 9.2	4.5 ± 15.0
Total cholesterol (mg/dL)	197 ± 22	176 ± 25	−21 ± 3[d]	196 ± 29	206 ± 24	9 ± 6	−1 ± 7	30 ± 7[d]	30 ± 7[f]
HDL cholesterol (mg/dL)	56 ± 10	47 ± 13	−9 ± 3[d]	53 ± 11	56 ± 11	4 ± 2	−3 ± 2	9 ± 2[d]	13 ± 4[f]
LDL cholesterol (mg/dL)	124 ± 20	110 ± 22	−15 ± 3[e]	130 ± 25	126 ± 22	−4 ± 7	5 ± 6	16 ± 6	11 ± 7
Triglycerides (mg/dL)	93 ± 42	124 ± 32	30 ± 15	102 ± 29	199 ± 93	96 ± 35[d]	9 ± 16	75 ± 23[d]	66 ± 38
Free fatty acids (μmol/L)	NA	248.8 ± 120.8	NA	NA	217.7 ± 51.8	NA	NA	−31.1 ± 42	NA
Uric acid (mg/dL)	6.8 ± 0.9	6.1 ± 0.9	−0.7 ± 0.2[d]	6.7 ± 0.7	6.0 ± 0.7	−0.6 ± 0.2[d]	−0.2 ± 0.1	−0.1 ± 0.2	0.1 ± 0.2
AST (IU/L)	19.6 ± 6.2	20.4 ± 4.8	0.8 ± 1.9	21.0 ± 7.5	37.4 ± 19.8	16.4 ± 4.8[e]	1.3 ± 1.7	17.0 ± 5.1[e]	15.7 ± 5.2[g]
ALT (IU/L)	27.8 ± 12.8	38.4 ± 14.6	10.6 ± 4.9	31.0 ± 13.0	70.3 ± 43.8	39.3 ± 11.3[e]	3.1 ± 3.4	31.9 ± 10.7[e]	28.8 ± 12.3[g]
γGTP (IU/L)	34.0 ± 18.3	39.0 ± 28.2	5.0 ± 4.6	32.7 ± 23.0	52.3 ± 38.1	19.6 ± 5.6[e]	−1.2 ± 4.1	13.3 ± 4.9[e]	14.6 ± 7.2[g]
UN (mg/dL)	11.7 ± 2.9	12.5 ± 2.7	0.9 ± 1.0	10.6 ± 2.5	12.1 ± 1.9	1.5 ± 0.8	−1.0 ± 0.6	−0.4 ± 0.7	0.6 ± 1.2
Cr (mg/dL)	0.82 ± 0.02	0.74 ± 0.03	−0.08 ± 0.02[d]	0.79 ± 0.03	0.73 ± 0.03	−0.07 ± 0.02[d]	−0.02 ± 0.01	−0.01 ± 0.01	0.01 ± 0.03
CRP (mg/dL)	0.8 ± 2.1	0.2 ± 0.1	−0.6 ± 0.7	0.1 ± 0.1	0.1 ± 0.1	−0.0 ± 0.0	−0.7 ± 0.7	−0.1 ± 0.1	0.6 ± 0.7
Urinary sodium (mEq/24 h)	NA	136.7 ± 14.0	NA	NA	335.7 ± 41.3	NA	NA	199.0 ± 32.6[d]	NA
Urinary potassium (mEq/24 h)	NA	87.7 ± 9.2	NA	NA	67.4 ± 8.2	NA	NA	−20.2 ± 8.8	NA
Urinary calcium (g/24 h)	NA	0.2 ± 0.0	NA	NA	0.3 ± 0.0	NA	NA	0.1 ± 0.0[e]	NA

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TABLE 3 (Continued)

	Non-UPF period			UPF period			Non-UPF period versus UPF period		
	Baseline	End	Within-period changes#	Baseline	End	Within-period changes#	Comparison of Baseline values[a]	Comparison of End values[b]	Comparison of within-period changes[c]
Urinary phosphate (g/24 h)	NA	1.1 ± 0.1	NA	NA	1.3 ± 0.1	NA	NA	0.1 ± 0.1	NA
Urinary albumin (mg/24 h)	NA	8.6 ± 2.0	NA	NA	9.6 ± 1.4	NA	NA	1.0 ± 0.8	NA

Note: Data are expressed as means ± SE. #Within-period changes were calculated by averaging the end minus baseline values for each participant.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; CRP, C-reactive protein; γGTP, gamma-glutamyl transpeptidase; GLP-1, glucagon-like peptide-1; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; NA, not applicable; non-UPF, non-ultra-processed food; PYY, peptide YY; SE, standard error; UN, urea nitrogen; UPF, ultra-processed food.
[a]Comparison of the baseline values was performed by averaging the difference of the baseline values between the UPF period and the non-UPF period (i.e. the UPF period minus the non-UPF period) for each participant.
[b]Comparison of the end values was performed by averaging the difference of the end values between the UPF period and the non-UPF period (i.e. the UPF period minus the non-UPF period) for each participant.
[c]Comparison of within-period changes was performed by the difference of the average within-period changes between the UPF period and the non-UPF period (i.e. the UPF period minus the non-UPF period).
[d]Statistical difference determined by the paired *t*-test.
[e]Statistical difference determined by the Wilcoxon signed-rank test.
[f]Statistical difference determined by the Student's *t*-test.
[g]Statistical difference determined by the Mann–Whitney U test.

($P = .054$) (Table 3). There were no significant differences in the blood levels of glycated albumin ($P = .40$), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) ($P = .63$), HOMA-β ($P = .41$) (Table 3) or the Matsuda index ($P = .31$) at the end of either diet period (data not shown).

Participants did not display any significant differences in the scores on the 100-point VAS (Figure S3). There was no significant difference in the step counts of participants between the two periods ($P = .34$) (Figure S4).

4 | DISCUSSION

We conducted a randomized controlled study to investigate the effects of consumption of UPFs compared with non-UPFs on body weight, energy intake and metabolism. Participants gained significantly more weight and consumed a significantly higher number of calories during the UPF period. The eating rate increased significantly, and the chewing frequency decreased significantly, during the UPF period. Additionally, consumption of UPFs led to unfavourable outcomes in the liver function variables compared with consumption of non-UPFs. Our findings add a causal dimension to the existing evidence regarding the associations between UPFs and obesity reported from population-based observational studies.[5,17] To the best of our knowledge, this is the first randomized crossover study to evaluate the causality between weight gain and consumption of UPFs (NOVA group 4) compared with consumption of non-UPFs (NOVA group 1-3). Furthermore, the current study is the first to propose reduced chewing frequency as a potential mechanism in the overeating of UPFs.

Several mechanisms linking the consumption of UPFs to excessive energy intake and weight gain were suggested by this study. First, the eating rate (both in terms of kcal/min and g/min) was significantly faster during the UPF period, which could be one of the reasons for overconsumption of UPFs. When in solid form, UPFs have a high energy density because of the reduced dietary fibre and water content resulting from industrial processing. When formulated as beverages, they typically contain high levels of added sugars, while lacking essential nutrients.[4] It has been reported that both the eating rate and energy density contribute to the differences in energy intake levels observed between unprocessed foods and UPFs.[18] The characteristics of UPFs, combined with a faster eating rate and the higher energy density of the foods, possibly contribute to the overconsumption of UPFs, leading to weight gain.

Second, the current study revealed a lower number of chews per calorie during the UPF period. It has been hypothesized that food processing techniques yield a softer texture of processed foods, which reduces the masticatory strain required to eat them.[19,20] Moreover, a previous clinical trial has shown a negative correlation between the number of chews per calorie and both total energy intake and waist circumference.[21] One possibility is that a decrease in chewing frequency during consumption of UPFs could potentially result in overeating and weight gain.

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Chewing thoroughly has been linked to decreased food intake through several potential mechanisms. First, it has been reported that an increased chewing frequency acts as an afferent signal for activation of the histaminergic nervous systems in the hypothalamus and prevents overeating by stimulating the satiety centre.[22] Second, experimental studies have confirmed a significant effect of chewing on subjective appetite ratings, such as hunger, fullness and a desire to eat, when participants chewed a fixed amount of food.[23–25] Third, several studies have shown that chewing 40 times before swallowing a fixed amount of food, as opposed to 15 times, resulted in elevated postprandial release of GLP-1,[26,27] glucose-dependent insulinotropic peptide[24] and cholecystokinin,[24,27] as well as a tendency towards suppressed postprandial release of ghrelin.[24] Chewing enhances the bioaccessibility of nutrients by breaking down the food matrix into smaller particles.[28] This increased bioaccessibility of nutrients stimulates the secretion of appetite-related hormones from the gastrointestinal tract, possibly leading to increased satiety and regulation of food intake through the gut–brain axis.[24] A meta-analysis suggested that thorough chewing may decrease food intake, through alterations in the gut hormone responses related to satiety.[29] To the best of our knowledge, no studies have been published that explore the relationship between chewing and PYY levels.

In the current study, the PYY level tended to be lower at the end of the UPF period. This was consistent with previous reports of significantly lower PYY levels after consumption of UPFs than after consumption of unprocessed foods.[16] Industrial processing of foods disrupts food structures in more digestible products and typically reduces the amount of dietary fibre.[4] It has been suggested that dietary fibres regulate the secretion of PYY by producing short-chain fatty acids as products of fibre fermentation.[30,31] Clinical trials have also reported that diets high in fibre cause an increase in blood PYY levels.[32,33] Moreover, a slower eating rate has been reported to increase the blood levels of PYY.[34] Thus, a lack of fibre and a faster meal-eating rate may contribute (at least partially) to lower appetite suppression following consumption of UPFs, resulting from a decrease of the blood PYY level.[31] However, there is limited scientific evidence confirming a relationship between consumption of UPFs and the blood levels of appetite-related hormones, and further research is warranted to support this contention.

The increased energy intake during the UPF period was attributable to the consumption of significantly higher quantities of carbohydrates and fats, while no significant difference was observed in protein intake. A previous randomized controlled study reported a similar profile of macronutrient intake during UPF consumption.[16] This finding suggested that the protein leverage hypothesis could explain, at least in part, the increased energy intake associated with the consumption of UPFs as an effort to maintain a consistent protein intake.[35,36]

Salt intake was significantly higher during the UPF period in the current study, and this could possibly explain overeating during the UPF period. UPFs often contain high levels of salt as a result of industrial processing.[4] A previous study showed that diets high in salt promote increased *ad libitum* energy intake.[37] Non-UPFs, especially entirely unprocessed foods, typically have low natural salt content. Despite our efforts to match the amount of salt included in each of the diets, the salt content was higher in those of UPFs. Thus, the higher salt intake associated with consumption of UPFs might have contributed to the increase in energy intake during the UPF period in the current study.

Food processing changes the nutritional content, physical structure and chemical composition (e.g. these foods may contain artificial sweeteners, additives and newly formed contaminants) of foods, potentially affecting their digestion, absorption and satiety signalling.

Although plant-based, unprocessed foods have intact fibrous cell walls that offer a substrate for fibre-degrading gut microbiota and ensure a slow bioaccessibility (release) of nutrients throughout the digestive process,[38] UPFs consist largely of acellular nutrients. Previous studies have indicated that the dense acellular nutrients in UPFs are easily digestible and influence the absorption kinetics.[38–40] This, in turn, promotes the growth of an inflammatory gut microbiota associated with leptin resistance and obesity.[41] Although existing literature proposes these possible mechanisms, we did not directly assess their impact in the current study. Future research is needed to evaluate how UPF consumption directly influences digestion and absorption.

Food processing may also impact satiety signalling.[42] UPFs are typically high energy-dense products and hypercaloric compared with unprocessed foods.[43,44] Nevertheless, human satiety mechanisms are more responsive to the volume of food rather than its caloric content.[45] UPFs, with their higher energy density, enable greater energy intake within a shorter period.[46] Experimental studies have indicated that increased eating rates can lead to increased energy intake, possibly because of delayed satiety signalling.[47] Furthermore, the intense flavouring resulting from high levels of fat, sugar and artificial additives make UPFs highly palatable, potentially overriding the endogenous satiety mechanisms.[48]

In the current study, we measured satiety using VAS and found no significant differences between the UPF and non-UPF periods (Figure S3). We attribute this to our experimental set-up, where participants were allowed to eat *ad libitum* until they reached a certain level of fullness, potentially masking any satiety differences between the groups.[11] Further investigations are warranted to clarify the biological mechanisms by which UPFs may impact satiety signalling and obesity.

Another mechanism to consider is the effect of UPFs on the metabolomics associated with obesity. Recent studies have reported the existence of an association between consumption of UPFs and altered metabolomic profiles. Specifically, consumption of UPFs is associated with decreased plasma levels of branched-chain and aromatic amino acids, and increased plasma levels of monounsaturated fatty acids, which may contribute to the accumulation of fat mass.[49] Furthermore, UPFs negatively impact the gut microbiota by reducing the levels of fibre-fermenting bacteria, which are also associated with an increased risk of obesity.[50] While we did not include metabolomic profiling in our study, further research into the mechanisms by which UPFs alter metabolic pathways is necessary to identify the biological signatures for their negative health impacts on obesity.

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A previous study reported that consumption of unprocessed foods caused weight loss, in contrast to consumption of UPFs.[16] However, in the modern world with its advanced food processing techniques, it would be challenging to sustain diets based solely on unprocessed foods. In the current study, UPFs were shown to cause significant weight gain even compared with traditional diets, which contain foods subjected to lower degrees of processing. Consequently, medical nutritional therapy, especially with an emphasis on the avoidance of UPFs, could be essential for preventing obesity.

In the current study, we found no significant weight change in participants during the control diet period (i.e. the non-UPF period). Traditional Japanese diets are based on non-UPFs and are known to promote long healthy lives.[43] Our control diet, which was based on non-UPFs, was relatively close to real-life diets. The realistic nature of the control diet could possibly have contributed to the lack of significant weight loss observed during the non-UPF period. This could also be considered one of the strengths of our study, because this indicates that UPFs cause significant weight gain even when compared with diets that are closer to real-life diets.

The current study suggested a causality between consumption of UPFs and unfavourable changes in liver function variables. A recent meta-analysis of observational studies showed an association between UPF consumption and metabolic dysfunction-associated steatotic liver disease (MASLD), with a dose–response effect.[51] High intake of saturated fatty acids in UPFs,[52] as also observed in the current study, can also cause MASLD, as well as weight gain.[53] To the best of our knowledge, this is the first randomized controlled study to report causality between UPF consumption and worsened liver function variables indicative of MASLD.

There were some limitations to this study. First, it remains unclear whether similar results would also be obtained in women, elderly or non-obese individuals, as only young overweight/obese male participants were included in the current study. Second, the intervention period was only 1 week, and the long-term consequences of consistent UPF consumption could not be elucidated. Finally, our study was limited by the small sample size. Future research using larger sample sizes will be necessary to confirm and extrapolate these findings. Nevertheless, it is noteworthy that statistically significant changes in body weight and energy intake were observed during the UPF period, even in this limited number of participants.

In conclusion, the current study provides valuable insights into the effect of consumption of UPFs on body weight. The significant increases in body weight and energy intake observed during the UPF period highlight the potential contribution of increased consumption of these foods to the increasing prevalence of obesity in the modern world. Moreover, the significant changes in the eating rate and chewing frequency of UPFs further underscore the intricate relationship between consumption of UPFs and an increase in body weight. Our study contributes to the growing evidence of the importance of dietary choices, including those based on a consideration of the degree of processing of foods, in promoting obesity prevention.

AUTHOR CONTRIBUTIONS

SH and NK wrote the manuscript. SH, MS and MA conducted the study. MS and NK contributed to the conception and design of the work. SH, MS and YS were involved in the collection and analysis of the data. RS contributed to the data acquisition and interpretation. SU provided expert advice on the statistical analysis. SH, MS, MA, YS, NK and TY contributed to the discussion of the data and interpretation of the results. All the authors edited, reviewed and approved the final version of the manuscript and agreed to be held accountable for any part of the work. NK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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