Ultra-processed diets cause excess calorie intake and weight gain: A one-month inpatient randomized controlled trial of ad libitum food intake

KD Hall[1†], A Ayuketah[1], S Bernstein[2], R Brychta[1], H Cai[1], T Cassimatis[1], KY Chen[1], ST Chung[1], E Costa[1], A Courville[2], V Darcey[1], LA Fletcher[1], CG Forde[4], AM Gharib[1], J Guo[1], R Howard[1], PV Joseph[3], S McGehee[1], R Ouwerkerk[1], K Raisinger[2], I Rozga[1], M Stagliano[1], M Walter[1], PJ Walter[1], M Zhou[1].

[1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

[2]National Institutes of Health Clinical Center, Bethesda, MD.

[3]National Institute of Nursing Research, Bethesda, MD.

[4]Singapore Institute for Clinical Sciences, Singapore.

[†]To whom correspondence should be addressed:

Kevin D. Hall, Ph.D.

National Institute of Diabetes & Digestive & Kidney Diseases,

12A South Drive, Room 4007

Bethesda, MD 20892

kevinh@nih.gov

Phone: 301-402-8248

REVISION DATE: February 12, 2019

Summary

We investigated whether ultra-processed foods affect energy intake in 20 weight-stable adults, aged (mean±SE) 31.2±1.6 y and BMI=27±1.5 kg/m^2. Subjects were admitted to the NIH Clinical Center and randomized to receive either ultra-processed or unprocessed diets for 2 weeks immediately followed by the alternate diet for 2 weeks. Meals were designed to be matched for presented calories, energy density, macronutrients, sugar, sodium, and fiber. Subjects were instructed to consume as much or as little as desired. Energy intake was greater during the ultra-processed diet (508±106 kcal/d; p=0.0001), with increased consumption of carbohydrate (280±54 kcal/d; p<0.0001) and fat (230±53 kcal/d; p=0.0004) but not protein (-2±12 kcal/d; p=0.85). Weight changes were highly correlated with energy intake (r=0.8, p<0.0001) with participants gaining 0.8±0.3 kg (p=0.01) during the ultra-processed diet and losing 1.1±0.3 kg (p=0.001) during the unprocessed diet. Limiting consumption of ultra-processed foods may be an effective strategy for obesity prevention and treatment.

ClinicalTrials.gov Identifier NCT03407053

Introduction

The perpetual diet wars between factions promoting low-carbohydrate, keto, paleo, high-protein, low-fat, plant-based, vegan, and a seemingly endless list of other diets has led to substantial public confusion and mistrust in nutrition science. While debate rages about the relative merits and demerits of various so-called "healthy" diets, less attention is paid to the fact that otherwise diverse diet recommendations often share a common piece of advice: avoid ultra-processed foods (Katz and Meller, 2014).

Ultra-processed foods have been described as "formulations mostly of cheap industrial sources of dietary energy and nutrients plus additives, using a series of processes" and containing minimal whole foods (Monteiro et al., 2018). As an alternative to traditional approaches that focus on nutrient composition of the diet, the NOVA (not an acronym) diet classification system considers the nature, extent, and purpose of processing when categorizing foods and beverages into four groups: 1) unprocessed or minimally processed foods; 2) processed culinary ingredients; 3) processed foods; and 4) ultra-processed foods (Monteiro et al., 2018).

While the NOVA system has been criticized as being too imprecise and incomplete to form an adequate basis for making diet recommendations (Gibney et al., 2017; Jones, 2018), Brazil's national dietary guidelines use the NOVA system and recommend that ultra-processed foods should be avoided (Melo et al., 2015; Moubarac, 2015). However, several attributes of ultra-processed foods make them difficult to replace: they are inexpensive, have long shelf-life, are relatively safe from the microbiological perspective, provide important nutrients, and are highly convenient – often being either ready-to-eat or ready-to heat (Shewfelt, 2017; Weaver et al., 2014).

The growing suspicion that ultra-processed foods have contributed to the burden of chronic non-communicable disease is based on the observation that the rise in obesity and type 2 diabetes prevalence occurred in parallel with an increasingly industrialized food system (Stuckler et al., 2012) characterized by large-scale production of high-yield, inexpensive, agricultural "inputs" (primarily corn, soy, and wheat) that are refined and processed to generate an abundance of "added value" foods (Blatt, 2008; Roberts, 2008). Ultra-processed foods have become more common worldwide (Monteiro et al., 2013; Moubarac, 2015) and now constitute the majority of calories consumed in America (Martinez Steele et al., 2016).

Ultra-processed foods may facilitate overeating and the development of obesity (Poti et al., 2017) because they are typically high in calories, salt, sugar, and fat (Poti et al., 2015) and have been suggested to be engineered to have supernormal appetitive properties (Kessler, 2009; Moss, 2013; Moubarac, 2015; Schatzker, 2015). Furthermore, ultra-processed foods are theorized to disrupt gut-brain signaling and may influence food reinforcement and overall intake via mechanisms distinct from the palatability or energy density of the food (Small and DiFeliceantonio, 2019).

As compelling as such theories may be, it is important to emphasize that no causal relationship between ultra-processed food consumption and human obesity has yet been established. In fact, there has never been a randomized controlled trial demonstrating any beneficial effects of reducing ultra-processed foods or deleterious effects of increasing ultra-processed foods in the diet. Therefore, to address the causal role of ultra-processed foods on energy intake and body weight change, we conducted a randomized controlled trial examining the effects of ultra-processed versus unprocessed diets on ad libitum energy intake.

Results and Discussion

We admitted 10 male and 10 female weight-stable adults aged (mean±SE) 31.2±1.6 y with BMI=27±1.5 kg/m^2 as inpatients to the Metabolic Clinical Research Unit (MCRU) at the NIH Clinical Center where they resided for a continuous 28-day period. Subjects were randomly assigned to either the ultra-processed or unprocessed diet for 2 weeks followed immediately by the alternate diet for the final 2 weeks (Figure 1).

During each diet phase, the subjects were presented with three daily meals and were instructed to consume as much or as little as desired. Up to 60 minutes was allotted to consume each meal. Menus rotated on a 7-day schedule and were designed to be matched across diets for total calories, energy density, macronutrients, fiber, sugar, and sodium, but widely differing in the percentage of calories derived from ultra-processed versus unprocessed foods (Table 1) as defined according to the NOVA classification scheme (Monteiro et al., 2018). Snacks appropriate to the prevailing diet and bottled water were available throughout each day. The meals plus snacks were provided at an amount equivalent to twice each subject's estimated energy requirements for weight maintenance as calculated by 1.6 × resting energy expenditure measured at screening. Details of the diet menus are provided as Supplemental Information.

Food Intake

Figures 2A and 2B show that daily energy intake was 508±106 kcal/d greater during the ultra-processed diet (p=0.0001). Neither the order of the diet assignment (p=0.64) nor sex (p=0.28) had significant effects on the energy intake differences between the diets. Baseline BMI was not significantly correlated with the energy intake differences between the diets (r=0.11; p=0.66).

The increased energy intake with the ultra-processed diet resulted from consuming greater quantities of carbohydrate (280±54 kcal/d; p<0.0001) and fat (230±53 kcal/d; p=0.0004), but not protein (-2±12 kcal/d; p=0.85) (Figure 2B). The remarkable stability of absolute protein intake between the diets, along with the slight ~1.6% decrease in presented energy from protein with the ultra-processed versus the unprocessed diet

(Table 1), suggests that the protein leverage hypothesis could partially explain the increase in energy intake with the ultra-processed diet in an attempt to maintain a constant protein intake (Martinez Steele et al., 2018; Simpson and Raubenheimer, 2005). Using the mathematical relationship between energy intake changes expected from the observed differences in the protein fraction of the provided diets (Hall, 2019), we calculated that protein leverage could potentially explain ~50% of the observed energy intake differences between the diets assuming perfect leverage.

Figure 2C illustrates that the ultra-processed diet resulted in increased energy intake at breakfast (124±42 kcal/d; p=0.008) and lunch (213±48 kcal/d; p=0.0003), but there were no significant increases at dinner (66±46 kcal/d; p=0.17) or with snacks (8±46 kcal/d; p=0.86). Carbohydrate intake was significantly increased during the ultra-processed diet at breakfast (67±23 kcal/d; p=0.01) and lunch (114±25 kcal/d; p=0.0002), but not with dinner (35±26 kcal/d; p=0.2) or snacks (-3±25 kcal/d; p=0.91). Fat intake was significantly increased during the ultra-processed diet at breakfast (76±17 kcal/d; p=0.0002), lunch (157±28 kcal/d; p<0.0001), and dinner (53±18 kcal/d; p=0.008), but not with snacks (8±27 kcal/d; p=0.76). Protein intake was significantly lower during the ultra-processed diet at lunch (-21±6 kcal/d; p=0.0015) but was not significantly different with other meals or snacks (p>0.42).

Despite the presented meals having similar energy densities (Table 1), the foods and beverages that were consumed had greater energy density during the ultra-processed versus unprocessed diet (1.38±0.07 kcal/g vs. 1.08±0.02 kcal/g; p=0.0002). Whereas sodium intake was significantly increased during the ultra-processed versus the unprocessed diet (5.8±0.4 g/d vs. 4.6±0.3 g/d; p<0.0001), there were no significant differences in consumption of fiber (48.5±4.5 g/d vs. 45.8±3.4 g/d; p=0.41) or total sugars (93.3±7.6 g/d vs. 96.6±9.8 g/d; p=0.57).

Appetitive measurements and eating rate

Participants did not report significant differences in the pleasantness (4.8±3.1; p=0.13) or familiarity (2.7±4.6; p=0.57) of the meals between the ultra-processed and unprocessed diets as measured using 100-point visual analogue scales (Figure 2D). This suggests that the observed energy intake differences were not due to greater palatability or familiarity of the ultra-processed diet. Furthermore, differences in the energy intake-adjusted scores for hunger (-1.7±2.5; p=0.5), fullness (1.1±2.5; p=0.67), satisfaction (1.9±2.4; p=0.42), and capacity to eat (-2.9±2.5; p=0.25) (Figures 2E) were not significant between the diets suggesting that they did not differ in their subjective appetitive properties.

Interestingly, Figure 2F illustrates that meal eating rate was significantly greater during the ultra-processed diet whether expressed as kcal/min (17±1 kcal/min; p<0.0001) or g/min (7.4±0.9 g/min; p<0.0001). Individual differences in average eating rate in kcal/min between the ultra-processed and unprocessed diets were moderately correlated with overall energy intake differences (r= 0.45; p=0.047). Previous studies have demonstrated that higher eating rates can result in increased overall energy intake (de Graaf and Kok, 2010; Forde et al., 2013; McCrickerd et al., 2017; Robinson et al., 2014).

Body weight and composition

Figure 3A illustrates that participants gained 0.8±0.3 kg (p=0.01) during the ultra-processed diet and lost 1.1±0.3 kg (p=0.001) during the unprocessed diet. The differences in weight change between the diets was not significantly correlated with baseline BMI (r=0.18; p=0.46).

Body fat mass increased by 0.5±0.1 kg (p=0.0016) during the ultra-processed diet and decreased by 0.3±0.1 kg during the unprocessed diet (p=0.04) (Figure 3A). Whereas fat-free mass was not significantly increased during the ultra-processed diet (0.3±0.3 kg; p=0.27), it decreased by 0.8±0.3 kg during the unprocessed diet (p=0.01), possibly due to fluid shifts related to decreased sodium intake (Figure 3A).

Figure 3B shows that differences in the individual body weight changes between the diets were highly correlated with energy intake differences (r=0.8, p<0.0001). Thirteen subjects completed measurements of liver fat content by magnetic resonance spectroscopy at baseline and the end of each diet period (Ouwerkerk et al., 2012). Baseline liver fat was 1.2±0.1% and Figure 3C shows that liver fat was not significantly changed by either the unprocessed diet or the ultra-processed diet (p>0.23).

Energy expenditure and physical activity

Subjects spent one day each week residing in respiratory chambers to measure the components of 24hr energy expenditure. Table 2 shows that there was no significant difference in energy intake between the diets on the chamber days, but the food quotient differences indicated that subjects consumed relatively more carbohydrate versus fat during the chamber days on the ultra-processed diet. While subjects tended to have greater 24hr energy expenditure during the ultra-processed diet (51±27 kcal/d; p=0.06), there were no significant differences in sleeping energy expenditure, sedentary energy expenditure, or physical activity. These results contrast with a previous study suggesting that energy expenditure was ~60 kcal lower for 6 hours following consumption of processed versus unprocessed sandwiches (Barr and Wright, 2010).

The significantly lower 24hr respiratory quotient observed during the unprocessed diet indicated that fat oxidation was increased compared to the ultra-processed diet. This was likely due to differences in food quotient between ultra-processed and unprocessed diet periods during the chamber days along with differences in energy intake and energy balance on the days prior to the chamber stays.

Table 2 also shows the average daily energy expenditure as measured by the doubly labeled water method during each 2-week diet period. The ultra-processed diet led to slightly higher energy expenditure compared to the unprocessed diet (141±61 kcal/d; p=0.033). Since overall physical activity quantified by accelerometry did not detect significant differences between the diet periods (Table 2), the energy expenditure differences were likely due to the differing states of energy balance between the diets.

Despite the subjects losing weight and body fat during the unprocessed diet, Table 2 shows that the average daily energy expenditure appeared to be slightly lower than the corresponding energy intake over the same period (106±111 kcal/d; p=0.35). It is possible that the assumed digestibility factors used in the calculation of metabolizable energy intake overestimated the energy absorbed in the unprocessed diet. Future studies should include fecal collections to directly assess diet digestibility.

Fasting blood measurements

Table 3 presents the fasting blood measurements obtained at baseline and on the final days of the ultra-processed and unprocessed diet periods. Overall, compared to the unprocessed diet, the measurements obtained after the ultra-processed diet were largely unchanged from baseline suggesting that these subjects likely consumed a habitual diet high in ultra-processed foods which might be expected given the high prevalence of ultra-processed food consumption in America (Martinez Steele et al., 2016).

Interestingly, the appetite-suppressing hormone PYY increased during the unprocessed diet as compared with both the ultra-processed diet and baseline. In contrast, the hunger hormone ghrelin was decreased during the unprocessed diet compared to baseline. The unprocessed diet led to reduced adiponectin, total cholesterol, hsCRP, and total T3, whereas free T4 and free fatty acids were increased compared to baseline. Uric acid decreased after the ultra-processed diet compared with baseline. Triglycerides and HDL cholesterol were significantly decreased compared to baseline after both diets. After the unprocessed diet, fasting glucose and insulin levels tended to decrease compared to baseline and the homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews et al., 1985) was significantly decreased. There were no significant differences in HOMA-IR after the ultra-processed diet as compared to either baseline or the unprocessed diet.

Glucose Tolerance

Despite substantial differences in energy intake and body weight changes between the ultra-processed and unprocessed diets, oral glucose tolerance tests performed at the end of each diet period indicated no significant differences in glucose tolerance (Figure 4A and B). Therefore, insulin sensitivity as measured by the Matsuda index (Matsuda and DeFronzo, 1999) was not significantly different between the ultra-processed and unprocessed diets (3.9±0.4 versus 4.5±0.4, respectively; p=0.34). Furthermore, continuous glucose monitoring detected no significant differences in either average daily glucose concentrations or glycemic variability between the diets (Figure 4C).

It is possible that differences in glucose tolerance and insulin sensitivity would have emerged after longer periods on each diet. However, shorter durations of overfeeding have previously been demonstrated to result in rapid impairments in glucose tolerance and insulin sensitivity (Lagerpusch et al., 2012; Walhin et al., 2013), albeit with greater increases in energy intake than the present study.

Another possible explanation for the similar glucose tolerance and insulin sensitivity following ultra-processed and unprocessed diets is that exercise can prevent changes in insulin sensitivity and glucose tolerance during overfeeding (Walhin et al., 2013). Our subjects performed daily cycle ergometry exercise in three 20-minute bouts at a constant intensity corresponding to 30-40% of each subjects' estimated heart rate reserve. This relatively low intensity exercise was mandated to avoid the sedentary behavior that often occurs during inpatient metabolic ward studies. It is intriguing to speculate that perhaps even this modest dose of exercise prevented any differences in glucose tolerance or insulin sensitivity between the ultra-processed and unprocessed diets.

Study Limitations

Many of the potential negative effects of ultra-processed foods have been hypothesized to relate to their typically high energy density and elevated sugar, fat, and sodium content while being low in protein, and fiber (Poti et al., 2017). Because we attempted to match these variables in the presented meals, the observed differences in energy intake may have underestimated the effects of ultra-processed versus unprocessed diets that typically differ more than the experimental diets used in our study.

In our attempt to match energy density and fiber between the ultra-processed and unprocessed meals, we included a low-calorie lemonade as a vehicle for the dissolved fiber supplements with the ultra-processed meals. However, because beverages have limited ability to affect satiety (DellaValle et al., 2005) the higher energy density of the non-beverage foods in the ultra-processed diet likely also contributed to the observed excess intake (Rolls, 2009). The ultra-processed diet presented to the subjects was also slightly lower in protein which could have partially contributed to increased overall energy intake according to the protein leverage hypothesis (Simpson and Raubenheimer, 2005).

Our study was not designed to identify the cause of the observed differences in energy intake. In addition to the protein and energy density factors described above, the diets were not matched for texture or sensory properties. Perhaps the oro-sensory properties of the ultra-processed foods (e.g., softer food that was easier to chew and swallow) led to the observed increased eating rate and delayed satiety signaling thereby resulting in greater overall intake (de Graaf and Kok, 2010). The current findings are aligned with previous research which has shown that a 20% change in eating rate can impact energy intake by between 10-13% (Forde, 2018). Future studies should examine whether the observed energy intake differences persist when ultra-processed and unprocessed diets are more closely matched for dietary protein and non-beverage energy density while at the same time including ultra-processed foods that are typically eaten slowly.

Finally, the inpatient environment of the metabolic ward makes it difficult to generalize our results to free-living conditions. However, current dietary assessment methods are insufficient to accurately or precisely measure energy intake outside the laboratory (Schoeller, 1990; Schoeller et al., 2013) and adherence to study diets cannot be guaranteed in free-living subjects. While the 28-day duration of our study was relatively modest, most laboratory-based studies of food intake are typically much shorter in duration, often occurring within a single day of testing with one or two meals (Gibbons et al., 2014).

Conclusion

Our data suggest that eliminating ultra-processed foods from the diet decreases energy intake and results in weight loss whereas large quantities of ultra-processed food in the diet increases energy intake and leads to weight gain. Whether reformulation of ultra-processed foods could eliminate these deleterious effects while retaining their palatability and convenience is unclear. Until such reformulated products are widespread, limiting consumption of ultra-processed foods may be an effective strategy for obesity prevention and treatment. However, advocates of policies that discourage consumption of ultra-processed foods should be mindful that the time, skill, expense, and effort to prepare meals from minimally processed foods requires resources that are often in short supply for those who are not members of the upper socioeconomic classes.

Experimental Procedures

Study protocol

The study protocol was approved by the Institutional Review Board of the National Institute of Diabetes & Digestive & Kidney Diseases (NCT03407053). Eligible subjects were between 18-50 years old with a body mass index (BMI) > 18.5 kg/m^2 and were weight-stable (< ± 5% over the past 6 months). Volunteers were excluded if they had anemia, diabetes, cancer, thyroid disease, eating disorders or other psychiatric conditions such as clinical depression or bipolar disorder. Volunteers with strict dietary concerns, including food allergies or adherence to particular diets (e.g., vegetarian, vegan, kosher, etc.) were also excluded.

Subjects were told that the purpose of the study was to learn about how a processed versus unprocessed diet affects the amount of food they eat, glucose tolerance, hormone levels, markers of inflammation, body weight and composition, energy expenditure, and liver fat. The subjects were told that this was not a weight loss study. They wore loose fitting clothing throughout the study and were blinded to daily weight and continuous glucose measurements.

Diets

The diets were designed and analyzed using ProNutra software (version 3.4, Viocare, Inc., Princeton, NJ) with nutrient values derived from the USDA National Nutrient Database for Standard Reference, Release 26 and the USDA Food and Nutrient Database for Dietary Studies, 4.0. The ultra-processed and unprocessed meals were provided on 7-day rotating menus (see the Supplemental Information for detailed menu information). Foods and beverages were categorized according to the NOVA system (Monteiro et al., 2018).

When subjects had finished each meal, a nurse removed the meal and documented the time of completion. Remaining food and beverages were identified and weighed by nutrition staff to calculate the amount of each food consumed. The measured meal duration and amount thereby allowed for calculation of the meal eating rate.

Subjective assessment of appetite, sensory, and palatability:

During each diet period, subjects were asked to complete appetitive surveys over the course of three separate days implemented using REDCap (Research Electronic Data Capture) electronic data capture tools (Harris et al., 2009). The surveys comprised visual analog scales (VAS) in response to four questions: 1) "How hungry do you feel right now?" 2) "How full do you feel right now?" 3) "How much do you want to eat right now?" and 4) "How much do you think you can eat right now?". Subjects answered the questions using 100-point VAS line scale anchored at 0 and 100 by descriptors such as “not at all” and “extremely”. The questions were answered immediately prior to each meal and at least every 30 to 60 minutes over the 2-3 hours following the consumption of each meal. We calculated the mean values of the responses adjusted for the energy consumed using multiple linear regression.

On the last two days of the first diet period and the first two days of the second diet period, subjects were asked to complete another survey to assess the palatability and familiarity of the meals provided. The questions were embedded amongst distracter “mood” ratings (e.g., alert, happy, and clear-headed). Survey items were completed after the first bite of the meal.

Body weight and composition

Daily body weight measurements were performed at 6am each morning after the first void (Welch Allyn Scale-Tronix 5702; Skaneateles Falls, NY, USA). Subjects wore hospital-issued top and bottom pajamas which were pre-weighed and deducted from scale weight. To minimize the influence of fluctuations in body fluids, weight changes during each 14-day diet period were calculated by linear regression. Body composition measurements were performed at baseline and weekly using dual-energy X-ray absorptiometry (General Electric Lunar iDXA; Milwaukee, WI, USA). Liver fat measurements were performed using T1 and T2 corrected proton magnetic resonance spectroscopy with a breath-holding technique in a 3T scanner (MAGNETOM Verio; Siemens, Tarrytown, NY) (Ouwerkerk et al., 2012).

Physical Activity Monitoring

Overall physical activity was quantified by calculating average daily metabolic equivalents (MET) using small, portable, pager-type accelerometers (Actigraph, Pensacola, FL) sampled at 80 Hz and worn on the hip (Freedson et al., 1998).

Energy expenditure via respiratory chamber

All chamber measurement periods were >23 hours and we extrapolated the data to represent 24hr periods by assuming that the mean of the measured periods was representative of the 24hr period. Energy expenditure was calculated as follows:

$$EE_{chamber}(\text{kcal}) = 3.85 \times VO_2(\text{L}) + 1.075 \times VCO_2(\text{L})$$

where VO_2 and VCO_2 were the volumes of oxygen consumed and carbon dioxide produced, respectively.

Sleeping energy expenditure was determined by the lowest energy expenditure over a continuous 180 minute period between the hours of 00:00-06:00 (Schoffelen and Westerterp, 2008). Sedentary energy expenditure and physical activity expenditure were defined as previously described (Hall et al., 2016).

Energy expenditure via doubly labeled water

Subjects drank from a stock solution of ^2H_2O and $H_2{}^{18}O$ water where 1 g of ^2H_2O (99.99% enrichment) was mixed with 19 g of $H_2{}^{18}O$ (10% enrichment). An aliquot of the stock solution was saved for dilution to be analyzed along with each set of urine samples. The water was weighed to the nearest 0.1 g into the dosing container. The prescribed dose was 1.0 g per kg body weight and the actual dose amounts were entered in a dose log. Spot urine samples were collected daily. Isotopic enrichments of urine samples were measured by isotope ratio mass spectrometry. The average CO_2 production rate (rCO_2) were estimated from the rate constants describing the exponential disappearance of the labeled ^{18}O and D water isotopes (k_O and k_D) in repeated spot urine samples collected over several days and were corrected for previous isotope doses (Bhutani et al., 2015). We used the parameters of Racette et al. (Racette et al., 1994) with the weighted dilution space calculation, R_{dil}, proposed by Speakman (Speakman, 1997):

$$rCO_2 = \left(N/2.078\right)\left(1.007k_O - 1.007R_{dil}k_D\right) - 0.0246r_{GF}$$
$$r_{GF} = 1.05\left(1.007k_O - 1.007R_{dil}k_D\right)$$
$$R_{dil} = \left[\left(N_D/N_O\right)_{ave} \times n + 1.034 \times 255\right] / \left(n + 255\right)$$

where $(N_D / N_O)_{ave}$ is the mean of the ratio of the body water pool sizes N_D / N_O from the n subjects. In cases where the individual values for the total body water, N, differed from that calculated as 73% of the fat-free mass determined by DXA within a few days of the dose, N was adjusted to agree with the DXA data.

The average total energy expenditure (EE_{DLW}) from the doubly labeled water measurement of rCO_2 was calculated as:

$$EE_{DLW}\,(\text{kcal}) = \left[\frac{3.85}{RQ} + 1.075\right] \times rCO_2\,(\text{L})$$

where RQ was calculated by adjusting the respiratory chamber RQ measurements for the overall degree of energy imbalance of each subject as determined by body composition changes during the DLW period as previously described (Hall et al., 2019).

Continuous glucose monitoring

Subjects wore the Dexcom G4 Platinum (Dexcom Inc, San Diego, CA, USA) continuous glucose monitor (CGM) daily during the inpatient stay. The device consisted of a small sensor, a transmitter, and a hand-held receiver. The sensor was inserted subcutaneously in the lower abdomen to measure interstitial glucose concentrations every 5 minutes which were transmitted to the receiver. Finger stick calibrations were required at insertion as well as each morning and night. The sensor was changed every 7 days. Subjects were blinded to their glucose readings. The CGM was removed during MRI/MRS procedures and DXA scans. All the data was downloaded at the end of the inpatient stay.

Statistical analyses

This study was powered to detect a difference in mean ad libitum energy intake over each 14-day test diet period (the primary endpoint) of 125-150 kcal/d in 20 subjects with probability (power) of 0.8 with a Type I error probability of 0.05. This sample size calculation was informed by previous studies measuring day to day variability of *ad libitum* energy intake having a standard deviation of about 500-600 kcal/d (Bray et al., 2008; Edholm et al., 1970; Tarasuk and Beaton, 1992). Using the conservative assumption that within-subject energy intake correlations were zero, over the 14-day diet period each subject was expected to have a mean energy intake with a standard error of about 130-160 kcal/d and the mean energy intake difference between the study diets was therefore estimated to have a standard error of about 190-230 kcal/d.

Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC, USA). The baseline data are presented as mean ± SE. Data were analyzed by analysis of variance (PROC GLM, SAS). The data tables and figures present least squares mean ± SE and two-sided t-tests were used to compare the diet groups. Significance was declared at $p < 0.05$.

Author Contributions

Conceptualization, KDH; Formal Analysis, KDH, JG; Methodology, RB, KYC, CGF, AMG, RO; Investigation, AA, SB, RB, HC, TC, EC, AC, VD, LF, RH, PVJ, SM, KR, IR, MS, MW, PW, MZ; Writing – Original Draft, KDH; Writing – Reviewing & Editing, KDH, RB, SB, AC, VD, LAF, CGF, RH, PVJ, KYC, STC; Supervision, KDH, STC.

Declaration of Interests

CG Forde has received reimbursement for speaking at conferences sponsored by companies selling nutritional products, serves on the scientific advisory council for Kerry Taste and Nutrition, and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, and Danone. The other authors have no conflicts of interest.

Acknowledgements

This work was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Diabetes & Digestive & Kidney Diseases. We thank the nursing and nutrition staff at the NIH MCRU for their invaluable assistance with this study. We are most thankful to the study subjects who volunteered to participate in this demanding protocol.

References

Barr, S.B., and Wright, J.C. (2010). Postprandial energy expenditure in whole-food and processed-food meals: implications for daily energy expenditure. Food & nutrition research *54*.

Bhutani, S., Racine, N., Shriver, T., and Schoeller, D.A. (2015). Special Considerations for Measuring Energy Expenditure with Doubly Labeled Water under Atypical Conditions. Journal of obesity & weight loss therapy *5*.

Blatt, H. (2008). America's food: What you don't know about what you eat. (Cambridge: The MIT press).

Bray, G.A., Flatt, J.P., Volaufova, J., Delany, J.P., and Champagne, C.M. (2008). Corrective responses in human food intake identified from an analysis of 7-d food-intake records. Am J Clin Nutr *88*, 1504-1510.

de Graaf, C., and Kok, F.J. (2010). Slow food, fast food and the control of food intake. Nature reviews. Endocrinology *6*, 290-293.

DellaValle, D.M., Roe, L.S., and Rolls, B.J. (2005). Does the consumption of caloric and non-caloric beverages with a meal affect energy intake? Appetite *44*, 187-193.

Edholm, O.G., Adam, J.M., Healy, M.J., Wolff, H.S., Goldsmith, R., and Best, T.W. (1970). Food intake and energy expenditure of army recruits. Br J Nutr *24*, 1091-1107.

Forde, C.G. (2018). From perception to ingestion; The role of sensory properties in energy selection, eating behaviour and food intake. Food Quality and Preference *66*, 171-177.

Forde, C.G., van Kuijk, N., Thaler, T., de Graaf, C., and Martin, N. (2013). Texture and savoury taste influences on food intake in a realistic hot lunch time meal. Appetite *60*, 180-186.

Freedson, P.S., Melanson, E., and Sirard, J. (1998). Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc *30*, 777-781.

Gibbons, C., Finlayson, G., Dalton, M., Caudwell, P., and Blundell, J.E. (2014). Metabolic Phenotyping Guidelines: studying eating behaviour in humans. The Journal of endocrinology *222*, G1-12.
Gibney, M.J., Forde, C.G., Mullally, D., and Gibney, E.R. (2017). Ultra-processed foods in human health: a critical appraisal. Am J Clin Nutr *106*, 717-724.
Hall, K.D. (2019). The potential role of protein leverage in the US obesity epidemic. NutriXiv *https://doi.org/10.31232/osf.io/59x87*.
Hall, K.D., Chen, K.Y., Guo, J., Lam, Y.Y., Leibel, R.L., Mayer, L.E., Reitman, M.L., Rosenbaum, M., Smith, S.R., Walsh, B.T., et al. (2016). Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. Am J Clin Nutr *104*, 324-333.
Hall, K.D., Guo, J., Chen, K.Y., Leibel, R.L., Reitman, M.L., Rosenbaum, M., Smith, S.R., and Ravussin, E. (2019). Methodologic considerations for measuring energy expenditure differences between diets varying in carbohydrate using the doubly labeled water method. Am J Clin Nutr, In press.
Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., and Conde, J.G. (2009). Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics *42*, 377-381.
Jones, J.M. (2018). Food processing: criteria for dietary guidance and public health? Proc Nutr Soc, 1-15.
Katz, D.L., and Meller, S. (2014). Can we say what diet is best for health? Annual review of public health *35*, 83-103.
Kessler, D.A. (2009). The end of overeating: controling the insatiable American appetite. (New York: Rodale Inc.).
Lagerpusch, M., Bosy-Westphal, A., Kehden, B., Peters, A., and Muller, M.J. (2012). Effects of brief perturbations in energy balance on indices of glucose homeostasis in healthy lean men. Int J Obes (Lond) *36*, 1094-1101.
Martinez Steele, E., Baraldi, L.G., Louzada, M.L., Moubarac, J.C., Mozaffarian, D., and Monteiro, C.A. (2016). Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. BMJ open *6*, e009892.
Martinez Steele, E., Raubenheimer, D., Simpson, S.J., Baraldi, L.G., and Monteiro, C.A. (2018). Ultra-processed foods, protein leverage and energy intake in the USA. Public Health Nutr *21*, 114-124.
Matsuda, M., and DeFronzo, R.A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care *22*, 1462-1470.
Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., and Turner, R.C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia *28*, 412-419.
McCrickerd, K., Lim, C.M., Leong, C., Chia, E.M., and Forde, C.G. (2017). Texture-Based Differences in Eating Rate Reduce the Impact of Increased Energy Density and Large Portions on Meal Size in Adults. J Nutr *147*, 1208-1217.
Melo, E.A., Jaime, P.C., Monteiro, C.A., and Nutrition, G.C.o.F.a. (2015). Dietary Guidelines for the Brazilian population. (Brasília: Ministry of Health of Brazil), p. 152.

Monteiro, C.A., Cannon, G., Moubarac, J.C., Levy, R.B., Louzada, M.L.C., and Jaime, P.C. (2018). The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr *21*, 5-17.
Monteiro, C.A., Moubarac, J.C., Cannon, G., Ng, S.W., and Popkin, B. (2013). Ultra-processed products are becoming dominant in the global food system. Obes Rev *14 Suppl 2*, 21-28.
Moss, M. (2013). Salt, sugar, fat: how the food giants hooked us. (New York: Random House).
Moubarac, J.C. (2015). Ultra-processed food and drink products in Latin America: Trends, impact on obesity, policy implications. (Washington D.C.: Pan American Health Organization), p. 60.
Ouwerkerk, R., Pettigrew, R.I., and Gharib, A.M. (2012). Liver metabolite concentrations measured with 1H MR spectroscopy. Radiology *265*, 565-575.
Poti, J.M., Braga, B., and Qin, B. (2017). Ultra-processed Food Intake and Obesity: What Really Matters for Health-Processing or Nutrient Content? Current obesity reports *6*, 420-431.
Poti, J.M., Mendez, M.A., Ng, S.W., and Popkin, B.M. (2015). Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households? Am J Clin Nutr *101*, 1251-1262.
Racette, S.B., Schoeller, D.A., Luke, A.H., Shay, K., Hnilicka, J., and Kushner, R.F. (1994). Relative dilution spaces of 2H- and 18O-labeled water in humans. Am J Physiol *267*, E585-590.
Roberts, P. (2008). The end of food. (New York: Houghton Mifflin Harcourt Publishing Company).
Robinson, E., Almiron-Roig, E., Rutters, F., de Graaf, C., Forde, C.G., Tudur Smith, C., Nolan, S.J., and Jebb, S.A. (2014). A systematic review and meta-analysis examining the effect of eating rate on energy intake and hunger. Am J Clin Nutr *100*, 123-151.
Rolls, B.J. (2009). The relationship between dietary energy density and energy intake. Physiol Behav *97*, 609-615.
Schatzker, M. (2015). The dorito effect: The surprising new truth about food and flavor. (New York, NY: Simon & Schuster).
Schoeller, D.A. (1990). How accurate is self-reported dietary energy intake? Nutr Rev *48*, 373-379.
Schoeller, D.A., Thomas, D., Archer, E., Heymsfield, S.B., Blair, S.N., Goran, M.I., Hill, J.O., Atkinson, R.L., Corkey, B.E., Foreyt, J., et al. (2013). Self-report-based estimates of energy intake offer an inadequate basis for scientific conclusions. Am J Clin Nutr *97*, 1413-1415.
Schoffelen, P.F., and Westerterp, K.R. (2008). Intra-individual variability and adaptation of overnight- and sleeping metabolic rate. Physiol Behav *94*, 158-163.
Shewfelt, R.L. (2017). In defense of processed food: It's not nearly as bad as you think. (Springer International Publishing).
Simpson, S.J., and Raubenheimer, D. (2005). Obesity: the protein leverage hypothesis. Obes Rev *6*, 133-142.
Small, D.M., and DiFeliceantonio, A.G. (2019). Processed foods and food reward. Science *363*, 346-347.
Speakman, J.R. (1997). Doubly labelled water: Theory and practice. (London: Chapman & Hall).
Stuckler, D., McKee, M., Ebrahim, S., and Basu, S. (2012). Manufacturing epidemics: the role of global producers in increased consumption of unhealthy commodities including processed foods, alcohol, and tobacco. PLoS medicine *9*, e1001235.
Tarasuk, V., and Beaton, G.H. (1992). Day-to-day variation in energy and nutrient intake: evidence of individuality in eating behaviour? Appetite *18*, 43-54.

Walhin, J.P., Richardson, J.D., Betts, J.A., and Thompson, D. (2013). Exercise counteracts the effects of short-term overfeeding and reduced physical activity independent of energy imbalance in healthy young men. J Physiol *591*, 6231-6243.
Weaver, C.M., Dwyer, J., Fulgoni, V.L., 3rd, King, J.C., Leveille, G.A., MacDonald, R.S., Ordovas, J., and Schnakenberg, D. (2014). Processed foods: contributions to nutrition. Am J Clin Nutr *99*, 1525-1542.

Figure Legends

Figure 1. Overview of the study design. Twenty adults were confined to metabolic wards where they were randomized to consumed either an ultra-processed or unprocessed diet for 2 consecutive weeks followed immediately by the alternate diet. Every week, subjects spent one day residing in a respiratory chamber to measure energy expenditure, respiratory quotient, and sleeping energy expenditure. Average energy expenditure during each diet period was measured by the doubly labeled water (DLW) method. Body composition was measured by dual-energy X-ray absorptiometry (DXA) and liver fat was measured by magnetic resonance imaging/spectroscopy (MRI/MRS).

Figure 2. Ad libitum food intake, appetite scores, and eating rate. A) Energy intake was consistently higher during the ultra-processed diet. B) Average energy intake was increased during the ultra-processed diet because of increased intake of carbohydrate and fat, but not protein. C) Energy consumed at breakfast and lunch was significantly greater during the ultra-processed diet, but energy consumed at dinner and snacks was not significantly different between the diets. D) Both diets were rated similarly on visual analogue scales (VAS) with respect to pleasantness and familiarity. E) Appetitive measures were not significantly different between the diets. F) Meal eating rate was significantly greater during the ultra-processed diet.

Figure 3. Body weight and composition changes. A) The ultra-processed diet led to significantly increases in body weight and fat mass whereas the unprocessed diet led to significant losses of weight, fat-free mass, and fat mass. B) Differences in body weight change between the ultra-processed and unprocessed diets were highly correlated with the corresponding energy intake differences. C) Liver fat was not significantly changed by the diets.

Figure 4. Glucose tolerance and continuous glucose monitoring. A) Glucose concentrations following a 75g oral glucose tolerance test (OGTT) was not significantly different between the diets. B) Insulin concentrations following the OGTT were not significantly different between the diets. C) Continuous glucose monitoring throughout the study did not detect significant differences in average glucose concentrations or glycemic variability as measured by the coefficient of variation (CV) of glucose.

	Ultra-processed Diet	Unprocessed Diet
Three Daily Meals		
Energy (kcal/d)	3905	3871
Carbohydrate (%)	49.2	46.3
Fat (%)	34.7	35.0
Protein (%)	16.1	18.7
Energy Density (kcal/g)	1.024	1.028
Sodium (mg/1000 kcal)	1997	1981
Fiber (g/1000 kcal)	21.3	20.7
Sugars (g/1000 kcal)	34.6	32.7
Saturated Fat (g/1000 kcal)	13.1	7.6
Omega-3 Fatty Acids (g/1000 kcal)	0.7	1.4
Omega-6 Fatty Acids (g/1000 kcal)	7.6	7.2
Energy from Unprocessed (%)[1]	6.4	83.3
Energy from Ultra-processed (%)[1]	83.5	0
Snacks (available all day)		
Energy (kcal/d)	1530	1565
Carbohydrate (%)	47.0	50.3
Fat (%)	44.1	41.9
Protein (%)	8.9	7.8
Energy Density (kcal/g)	2.80	1.49
Sodium (mg/1000 kcal)	1454	78
Fiber (g/1000 kcal)	12.1	23.3
Sugars (g/1000 kcal)	24.8	95.9
Saturated Fat (g/1000 kcal)	7.7	4.4
Omega-3 Fatty Acids (g/1000 kcal)	0.3	4.0
Omega-6 Fatty Acids (g/1000 kcal)	9.6	21.9
Energy from Unprocessed (%)[1]	0	100
Energy from Ultra-processed (%)[1]	75.9	0
Daily Meals + Snacks		
Energy (kcal/d)	5435	5436
Carbohydrate (%)	48.6	47.4
Fat (%)	37.4	37.0
Protein (%)	14.0	15.6
Energy Density (kcal/g)	1.247	1.126
Sodium (mg/1000 kcal)	1843	1428
Fiber (g/1000 kcal)	18.7	21.4
Sugars (g/1000 kcal)	31.9	51.0
Saturated Fat (g/1000 kcal)	11.5	6.7
Omega-3 Fatty Acids (g/1000 kcal)	0.6	2.2

Omega-6 Fatty Acids (g/1000 kcal)	8.1	11.5
Energy from Unprocessed (%)[1]	4.6	88.1
Energy from Ultra-processed (%)[1]	81.3	0

Table 1. Diet composition of the average 7-day rotating menu presented to the subjects during the Ultra-processed and Unprocessed diet periods.

[1] The calculated energy percentages refer to the fraction of diet calories contributed from groups 1 and 4 of the NOVA classification system: 1) unprocessed or minimally processed; 2) processed culinary ingredients; 3) processed foods; 4) ultra-processed foods.

	Ultra-processed Diet	Unprocessed Diet	P-value
Respiratory Chamber Period			
Energy Intake (kcal/d)	2651±53	2627±53	0.75
Food Quotient	0.853±0.002	0.845±0.002	0.002
Energy Expenditure (kcal/d)	2341±19	2290±19	0.062
24hr Respiratory Quotient	0.903±0.003	0.872±0.003	<0.0001
Sleeping Energy Expenditure (kcal/d)	1502±71	1537±46	0.85
Sedentary Energy Expenditure (kcal/d)	1592±51	1551±44	0.096
Physical Activity Expenditure (kcal/d)	749±56	738±56	0.67
Doubly Labeled Water Period[1]			
Energy Intake (kcal/d)	2963±74	2491±74	0.0003
Food Quotient	0.854±0.002	0.855±0.002	0.93
Energy Balance Adjusted Respiratory Quotient	0.901±0.007	0.842±0.007	<0.0001
Daily CO_2 production (L/d)	473±7.5	422±7.5	0.0001
Daily Energy Expenditure (kcal/d)	2526±43	2385±43	0.033
Daily physical activity METs (via accelerometry)	1.506±0.002	1.506±0.002	0.71

Table 2. Energy expenditure and intake during the respiratory chamber and doubly labeled water periods. [1] N=19 because one subject's doubly-labeled water data failed quality control for the calculated deuterium dilution space. Mean ± SE.

	Baseline	Ultra-processed Diet	P-value Ultra-processed vs. Baseline Diet	Unprocessed Diet	P-value Unprocessed vs. Baseline Diet	P-value Ultra-processed vs. Unprocessed Diet
Leptin (ng/ml)	44.3±1.7	45.1±1.7	0.75	40.4±1.7	0.11	0.058
Active Ghrelin (pg/ml)	61.4±3.5	54.1±3.5	0.15	48.3±3.5	0.01	0.24
PYY (pg/ml)	28.9±1.9	25.1±1.9	0.15	34.3±1.9	0.047	0.001
FGF-21 (pg/ml)	397±59	289±59	0.21	362±59	0.67	0.39
Adiponectin (mg/L)	7.3±0.7	8.0±0.7	0.43	4.6±0.7	0.007	0.0007
Resistin (ng/ml)	13.5±0.4	12.4±0.4	0.05	12.1±0.4	0.01	0.49
Active GLP-1 (pg/ml)	1.88±0.19	1.25±0.19	0.027	1.57±0.19	0.26	0.25
Total GIP (pg/ml)	79.7±5.4	67.9±5.4	0.13	64.3±5.4	0.052	0.64
Active GIP (pg/ml)	27.4±2.8	20.0±2.8	0.07	18.2±2.8	0.025	0.65
Glucagon (pmol/L)	12.0±0.8	11.0±0.8	0.42	9.8±0.8	0.07	0.29
Hgb A1C (%)	4.98±0.03	5.02±0.03	0.28	5.00±0.03	0.55	0.64
Glucose (mg/dl)	90.5±0.9	88.6±0.9	0.16	88.0±0.9	0.06	0.62
Insulin (µU/ml)	11.9±0.9	11.3±0.9	0.64	8.9±0.9	0.03	0.09
C-Peptide (ng/ml)	2.19±0.06	2.14±0.06	0.62	1.94±0.06	0.01	0.032
HOMA-IR	2.8±0.3	2.5±0.3	0.50	1.9±0.3	0.03	0.56
HOMA-Beta	152±10	159±11	0.63	129±10	0.13	0.63
Total Cholesterol (mg/dl)	155±3	152±3	0.54	137±3	0.0002	0.001
HDL Cholesterol (mg/dl)	58.2±0.8	55.0±0.9	0.01	48.3±0.8	<0.0001	<0.0001
LDL Cholesterol (mg/dl)	82±3	84±3	0.61	77±3	0.21	0.085
Triglycerides (mg/dl)	72±3	62±3	0.02	59±3	0.003	0.45
Free Fatty Acids (µmol/L)	409±40	384±40	0.67	556±40	0.013	0.004
Uric Acid (mg/dl)	4.9±0.3	4.5±0.3	0.0007	4.9±0.3	0.55	0.004
TSH (µIU/ml)	2.2±0.1	2.6±0.1	0.054	2.5±0.1	0.24	0.42
Free T3 (pg/ml)	3.17±0.06	3.20±0.06	0.72	3.03±0.06	0.11	0.051
Free T4 (ng/dl)	1.19±0.02	1.22±0.02	0.36	1.27±0.02	0.019	0.13
T4 (µg/dl)	6.8±0.1	6.9±0.1	0.70	6.8±0.1	0.91	0.79
T3 (ng/dl)	113±2	112±2	0.80	104±2	0.011	0.019

PAI-1 (ng/ml)	4.0±0.5	4.6±0.5	0.42	4.7±0.5	0.34	0.89
hsCRP (mg/L)	2.7±0.3	2.5±0.3	0.48	1.5±0.3	0.014	0.072

Table 3. Fasting blood measurements at baseline and at the end of the ultra-processed and unprocessed diet periods. Mean ± SE.

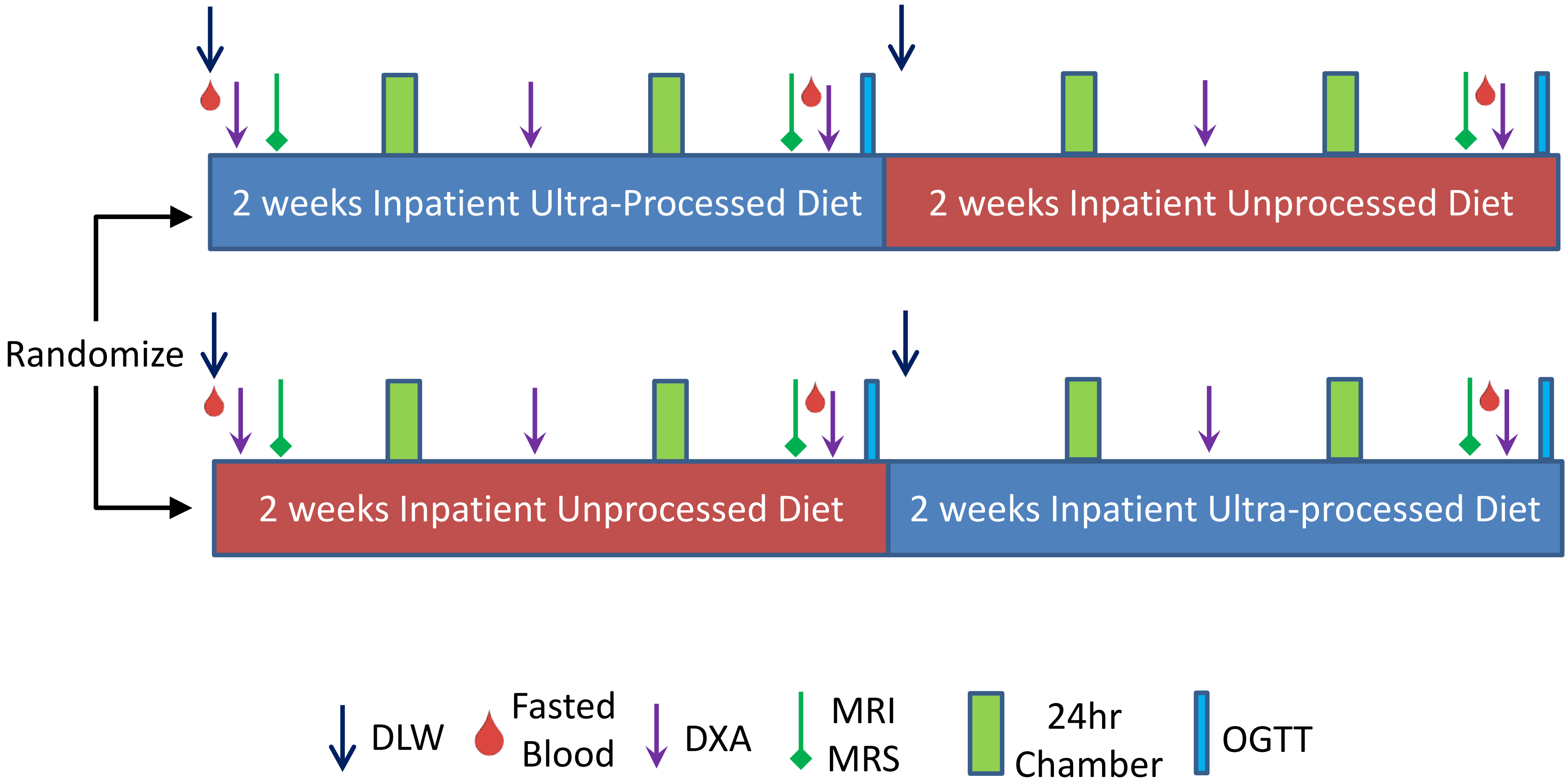

2 weeks Inpatient Ultra-Processed Diet
2 weeks Inpatient Unprocessed Diet
Randomize
2 weeks Inpatient Unprocessed Diet
2 weeks Inpatient Ultra-processed Diet
DLW
Fasted Blood
DXA
MRI MRS
24hr Chamber
OGTT

Figure 1

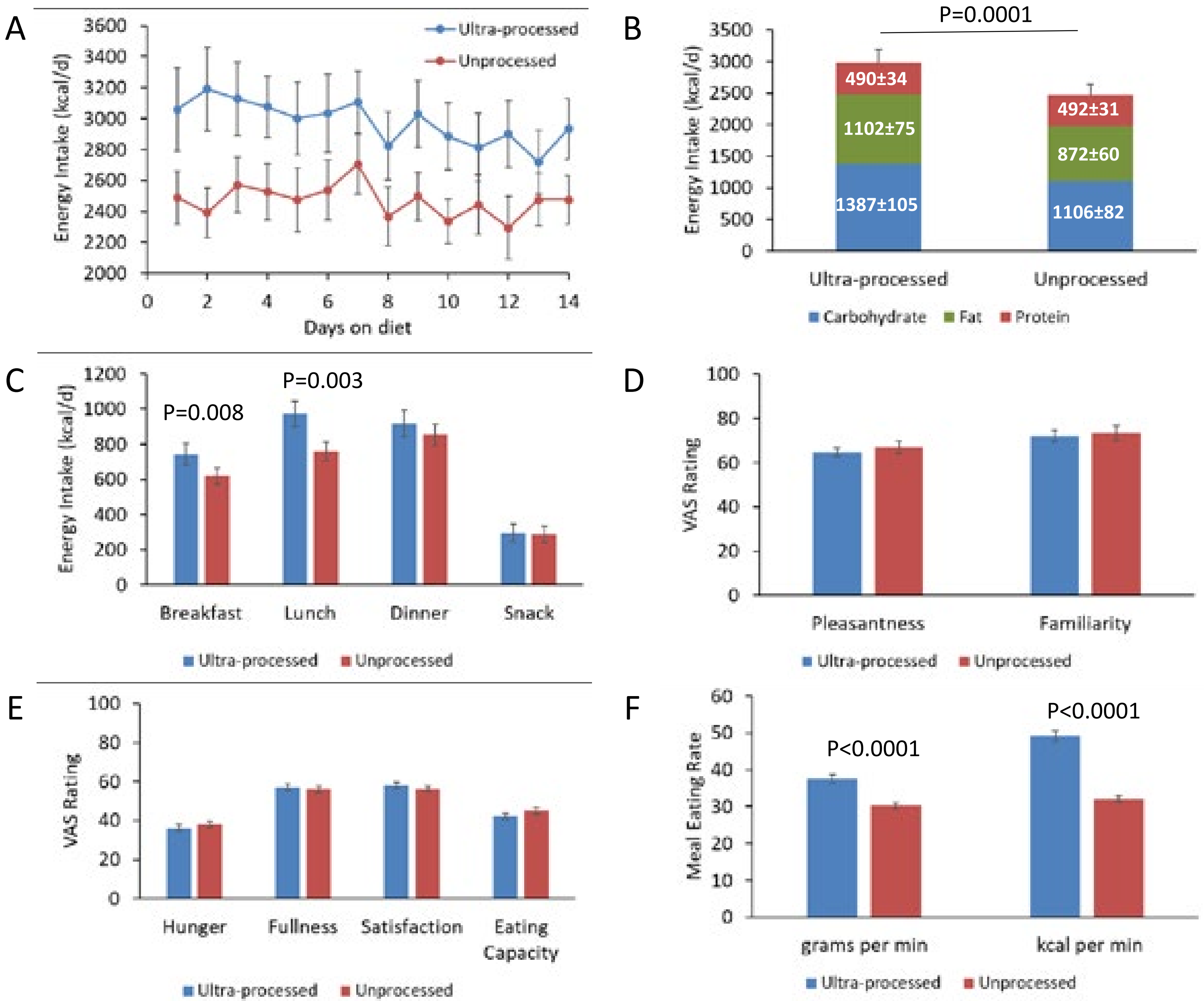

A
Energy Intake (kcal/d)
Days on diet
Ultra-processed
Unprocessed
B
P=0.0001
Energy Intake (kcal/d)
490±34
1102±75
1387±105
492±31
872±60
1106±82
Ultra-processed
Unprocessed
Carbohydrate
Fat
Protein
C
P=0.008
P=0.003
Energy Intake (kcal/d)
Breakfast
Lunch
Dinner
Snack
Ultra-processed
Unprocessed
D
VAS Rating
Pleasantness
Familiarity
Ultra-processed
Unprocessed
E
VAS Rating
Hunger
Fullness
Satisfaction
Eating Capacity
Ultra-processed
Unprocessed
F
P<0.0001
P<0.0001
Meal Eating Rate
grams per min
kcal per min
Ultra-processed
Unprocessed

Figure 2

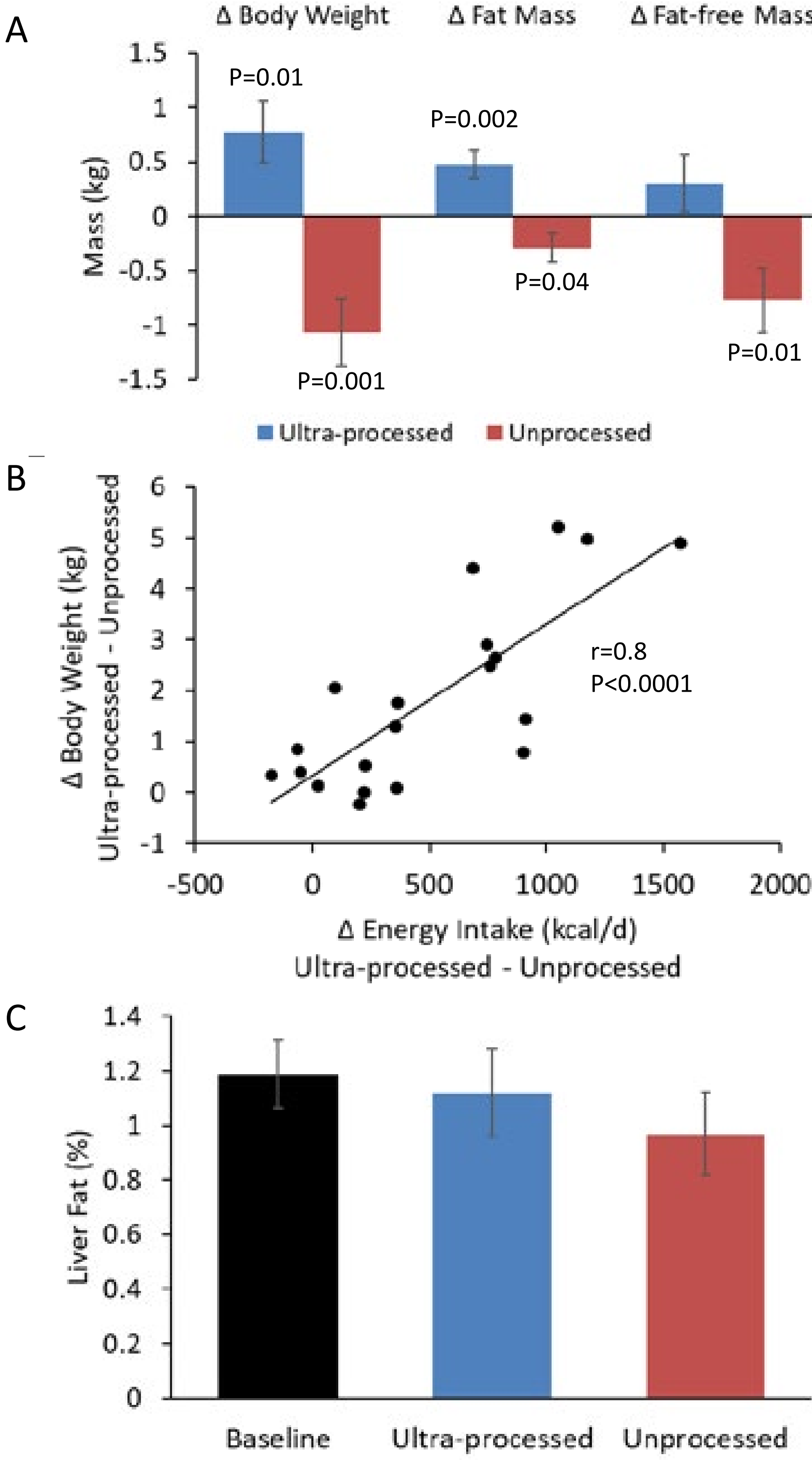
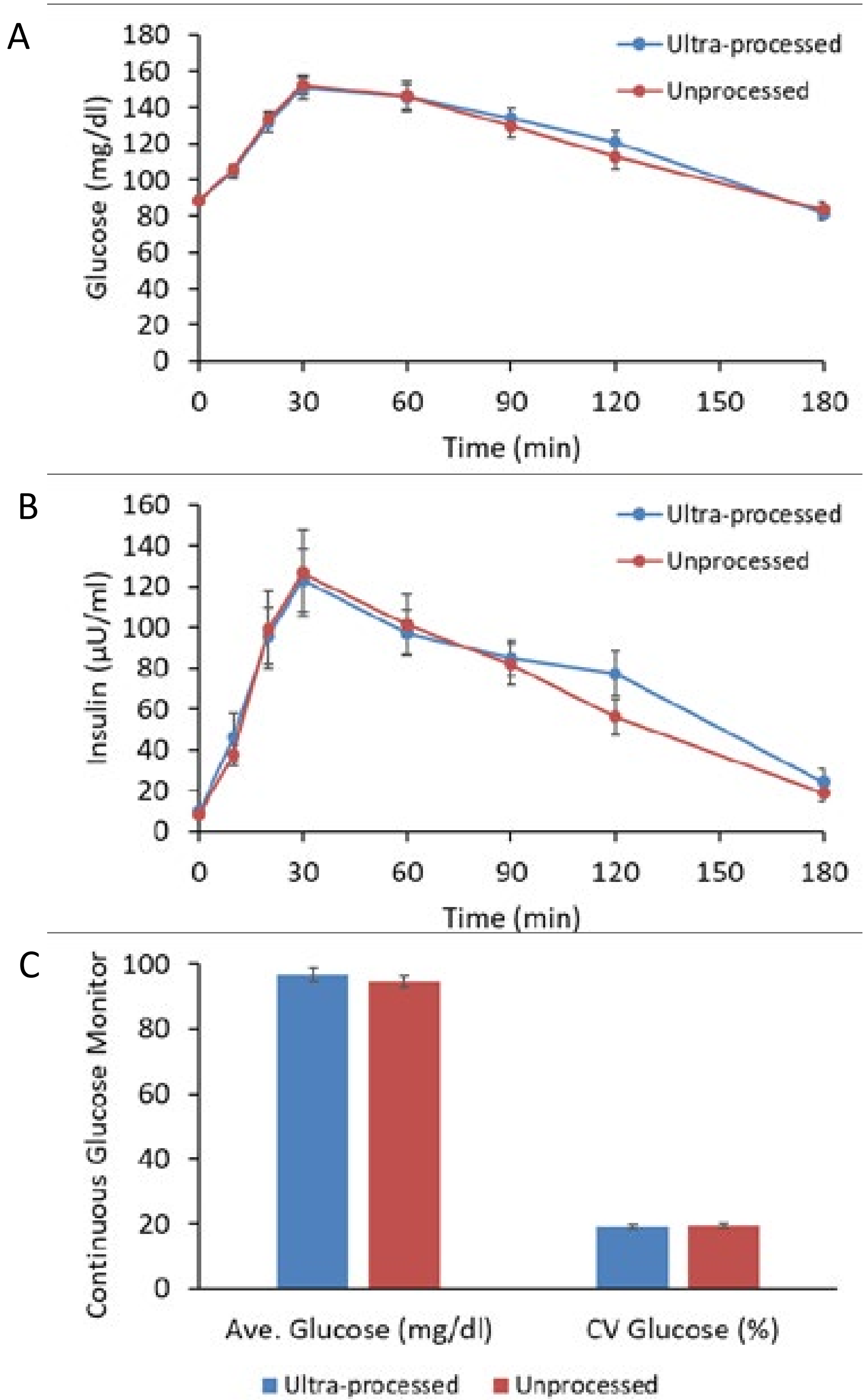

A
Δ Body Weight
Δ Fat Mass
Δ Fat-free Mass
Mass (kg)
1.5
1
0.5
0
-0.5
-1
-1.5
P=0.01
P=0.001
P=0.002
P=0.04
P=0.01
Ultra-processed
Unprocessed
B
Δ Body Weight (kg)
Ultra-processed - Unprocessed
6
5
4
3
2
1
0
-1
-500
0
500
1000
1500
2000
r=0.8
P<0.0001
Δ Energy Intake (kcal/d)
Ultra-processed - Unprocessed
C
Liver Fat (%)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Baseline
Ultra-processed
Unprocessed

Figure 3



A
Ultra-processed
Unprocessed
Glucose (mg/dl)
Time (min)
B
Ultra-processed
Unprocessed
Insulin (μU/ml)
Time (min)
C
Continuous Glucose Monitor
Ave. Glucose (mg/dl)
CV Glucose (%)
Ultra-processed
Unprocessed

Figure 4

Supplemental Information

Ultra-processed diets cause excess calorie intake and weight gain: A one-month inpatient randomized controlled trial of ad libitum food intake

KD Hall, A Ayuketah, S Bernstein, R Brychta, H Cai, T Cassimatis, KY Chen, ST Chung, E Costa, A Courville, V Darcey, LA Fletcher, CG Forde, AM Gharib, J Guo, R Howard, P Joseph, S McGehee, R Ouwerkerk, K Raisinger, I Rozga, M Stagliano, M Walter, PJ Walter, M Zhou.

The daily menus described below include photographs depicting meals representing the average values corresponding to the values listed in Table 1 of the main text.

Ultra-processed Menu

<u>Day 1</u>

<u>Breakfast</u>

Honey Nut Cheerios (General Mills)

Whole milk (Cloverland) with NutriSource fiber

Blueberry muffin (Otis Spunkmeyer) Margarine (Glenview Farms)

Ultra-processed Menu

Day 1

Lunch

Beef ravioli (Chef Boyardee)

Parmesan cheese (Roseli)

White bread (Ottenberg)

Margarine (Glenview Farms)

Diet lemonade (Crystal Light) with NutriSource fiber

Oatmeal raisin cookies (Otis Spunkmeyer)

Ultra-processed Menu

<u>Day 1</u>

<u>Dinner</u>

Steak (Tyson)

Gravy (McCormick)

Mashed potatoes (Basic American Foods)

Margarine (Glenview Farms)

Corn (canned, Giant)

Diet lemonade (Crystal Light) with NutriSource fiber

Low fat chocolate milk (Nesquik) with NutriSource fiber

Ultra-processed Menu

Day 2

Breakfast

Croissant (Chef Pierre)

Margarine (Glenview Farms)

Turkey sausage (Ember Farms)

Blueberry yogurt (Yoplait) with NutriSource fiber

Ultra-processed Menu

Day 2

Lunch

Deli turkey (Jenni-O) and cheddar and Monterey Jack cheese (Glenview Farms) quesadilla (Pasado tortilla)

Refried beans (Old El Paso)

Sour cream (Glenview Farms)

Salsa (del Pasado)

Diet lemonade (Crystal Light) with NutriSource fiber

Ultra-processed Menu

Day 2

Dinner

Chicken salad (Giant canned chicken, Heinz pickle relish, Hellmann's mayonnaise) sandwich on white bread (Ottenberg)

Peaches canned in heavy syrup (Giant)

Shortbread cookies (Keebler)

Fig Newtons (Nabisco)

Diet lemonade (Crystal Light) with NutriSource fiber

Ultra-processed Menu

<u>Day 3</u>

<u>Breakfast</u>

Egg (Papetti's), turkey bacon (Jenni-O) and American cheese (Glenview Farms) on an English muffin (Sara Lee)

Tater tots (Monarch) with ketchup (Heinz)

Orange juice (Sun Cup) with NutriSource Fiber

Ultra-processed Menu

Day 3

Lunch

Tempura fried chicken nuggets (Pierce) with ketchup (Heinz)

Baked potato chips (Lay's)

Diet lemonade (Crystal Light) with NutriSource fiber

Ultra-processed Menu

Day 3

Dinner

Turkey meatballs (Devault Foods) with marinara sauce (Angelina Mia) on a hoagie roll (Ottenberg) with provolone cheese (Roseli)

Diet lemonade (Crystal Light) with NutriSource fiber

Cheese and Peanut Butter Sandwich Crackers (Keebler)

Ultra-processed Menu

Day 4

Breakfast

Scrambled egg, prepared from liquid (Fresh Start)

Pork sausage (Hormel)

Honey bun (Little Debbie)

Orange juice (Sun Cup) with NutriSource fiber

Ultra-processed Menu

<u>Day 4</u>

<u>Lunch</u>

Hot dog (Patunxent Farms) on bun (Hilltop Hearth) with ketchup (Heinz) and yellow mustard (Monarch)

Baked potato chips (Lay's)

Cranberry juice (Sun Cup) with NutriSource fiber

Blueberry yogurt (Yoplait) with NutriSource fiber

Ultra-processed Menu

<u>Day 4</u>

<u>Dinner</u>

Steak (Tyson) and Cheddar and Monterey Jack Cheese (Glenview Farms) burrito (Pasado Tortilla) with canned black beans (Pasado)

Sour cream (Glenview Farms)

Salsa (del Pasado)

Tortilla chips (Tostitos)

Diet Lemonade (Crystal Light) with NutriSource fiber

Ultra-processed Menu

Day 5 (Respiratory Chamber)

Breakfast

Plain bagel (Lender's) and cream cheese (Philadelphia) with NutriSource fiber

Turkey bacon (Jenni-O)

Ultra-processed Menu

<u>Day 5 (Respiratory Chamber)</u>

<u>Lunch</u>

Spam sandwich with American cheese (Glenview Farms) on white bread (Ottenberg)

Potato chips (Lay's)

Ultra-processed Menu

Day 5 (Respiratory Chamber)

Dinner

Beef and bean chili (Hormel)

Shredded cheddar and Monterey Jack cheese (Glenview Farms)

Sour cream (Glenview Farms)

Tortilla chips (Tostitos)

Salsa (del Posado)

Diet Ginger Ale (Shasta)

Peaches, canned in heavy syrup (Giant)

Ultra-processed Menu

Day 6

Breakfast

Pancakes (Eggo)

Margarine (Glenview Farms)

Syrup (Smucker’s)

Turkey sausage (Ember Farms)

Tater tots (Monarch)

Apple juice (Sun Cup) with NutriSource Fiber

Ultra-processed Menu

Day 6

Lunch

Cheeseburger with American cheese (Glenview Farms) on a Kaiser roll (Anzio & Sons)

French fries (Monarch)

Ketchup (Heinz)

Diet lemonade (Crystal Light) with NutriSource fiber

Ultra-processed Menu

<u>Day 6</u>

<u>Dinner</u>

Deli turkey (Jenni-O) with American cheese (Glenview Farms) and mayonnaise (Hellmann's) on white bread (Ottenberg)

Baked potato chips (Lay's)

Peaches canned in heavy syrup (Giant)

Vanilla nonfat greek yogurt (Dannon) with NutriSource fiber

Ultra-processed Menu

<u>Day 7</u>

<u>Breakfast</u>

Cinnamon french toast sticks (Eggo)

Butter (Giant)

Pancake syrup (Smucker's)

Turkey sausage (Ember Farms)

Diet lemonade (Crystal Light) with NutriSource fiber

Ultra-processed Menu

Day 7

Lunch

Macaroni and cheese (Stouffer's)

Chicken tenders (Perdue)

Canned green beans (Giant)

Diet lemonade (Crystal Light) with NutriSource fiber

Ultra-processed Menu

Day 7

Dinner

Peanut butter (Monarch) and jelly (Monarch) sandwich on white bread (Ottenberg)

2% milk (Cloverland) with NutriSource fiber

Baked Cheetos (Frito-Lay)

Graham crackers (Nabisco)

Chocolate pudding (Snack Pack) with NutriSource fiber

Ultra-processed Menu

Daily Snacks

Baked Potato Chips (Lay's), Dry Roasted Peanuts (Planters), Cheese & Peanut Butter Sandwich Crackers (Keebler), Goldfish Crackers (Pepperidge Farm), Applesauce (Lucky Leaf).

Unprocessed Menu

Day 1

Breakfast

Greek yogurt (Fage) parfait with strawberries, bananas, with Walnuts (Diamond), Salt and Olive Oil

Apple Slices with Fresh Squeezed Lemon

Unprocessed Menu

<u>Day 1</u>

<u>Lunch</u>

Spinach salad with chicken breast, apple slices, bulgur (Bob's Red Mill), sunflower seeds (Nature's Promise) and grapes

Vinaigrette made with olive oil, fresh squeezed lemon juice, apple cider vinegar (Giant), ground mustard seed (McCormick), black pepper (Monarch) and salt (Monarch)

Unprocessed Menu

Day 1

Dinner

Beef tender roast (Tyson)

Rice pilaf (basmati rice (Roland) with garlic, onions, sweet peppers and olive oil)

Steamed broccoli

Side salad (Green leaf lettuce, tomatoes, cucumbers) with balsamic vinaigrette (balsamic vinegar (Nature's Promise)

Orange slices

Pecans (Monarch)

Salt and Pepper (Monarch)

Unprocessed Menu

Day 2

Breakfast

Scrambled egg (made from fresh eggs)

Hash brown potatoes (potato, garlic, paprika (Simply Organic), ground turmeric (McCormick), cream (Stoneyfield) and onions)

Salt and Pepper (Monarch)

Unprocessed Menu

Day 2

Lunch

Entrée salad with grilled chicken breast, baked sweet potato, corn (Monarch, from frozen), avocado, onions, tomatoes, carrots on green leaf lettuce

Vinaigrette (red wine vinegar (Giant) and olive oil)

Skim milk (Cloverland)

Apple slices with fresh squeezed lemon juice

Unprocessed Menu

Day 2

Dinner

Stir fried beef tender roast (Tyson) with broccoli, onions, sweet peppers, ginger, garlic and olive oil

Basmati rice (Roland)

Orange slices

Pecan halves (Monarch)

Salt and Pepper (Monarch)

Unprocessed Menu

Day 3

Breakfast

Oatmeal (Quaker) with blueberries and raw almonds

Salt (Monarch)

2% milk (Cloverfield)

Unprocessed Menu

Day 3

Lunch

Entrée salad with grilled chicken breast, farro (Bob's Red Mill), apples, grapes

Vinaigrette (fresh squeezed lemon juice, apple cider vinegar (Giant), olive oil)

Salt and Pepper (Monarch)

Unprocessed Menu

Day 3

Dinner

Beef tender roast (Tyson)

Couscous (Near East) with fresh squeezed lemon juice, garlic and olive oil

Green beans, from frozen (Monarch)

Side salad with green leaf lettuce, cucumber and tomatoes

Vinaigrette (red wine vinegar, honey (Monarch), olive oil

Salt and Pepper (Monarch)

Black bean hummus (black beans cooked from dried, garlic, sweet pepper, olive oil, fresh squeezed lemon juice, ground cumin (Monarch), chili powder (Giant)) and baby carrots

Unprocessed Menu

Day 4

Breakfast

Spinach, onion and tomato omelet (fresh eggs) cooked in olive oil

Sweet potato hash (sweet potato, olive oil and cinnamon)

Salt and Pepper (Monarch)

Skim milk (Cloverland)

Unprocessed Menu

Day 4

Lunch

Baked cod filet (Harbor Banks) with fresh squeezed lemon juice

Baked russet potato with olive oil

Steamed broccoli with olive oil and garlic

Side salad (green leaf lettuce, tomatoes, cucumber and carrots)

Vinaigrette (balsamic vinegar (Nature's Promise) and olive oil)

Salt and Pepper (Monarch)

Unprocessed Menu

Day 4

Dinner

Southwest entrée salad with green leaf lettuce, tomatoes, cucumbers, carrots, black beans (cooked from dried), corn (cooked from frozen), and avocado

Vinaigrette (red wine vinegar, fresh squeezed lemon juice and flaxseed oil (International Collection))

Salt and Pepper (Monarch)

Raw almonds (Giant)

Grapes

Unprocessed Menu

Day 5 (Respiratory Chamber)

Breakfast

Oatmeal (Quaker) with skim milk (Cloverland), cinnamon (Monarch), salt (Monarch), walnuts (Diamond), bananas, coconut (Nature's Promise) and fresh squeezed lemon juice

Unprocessed Menu

<u>Day 5 (Respiratory Chamber)</u>

<u>Lunch</u>

Grilled beef tender roast (Tyson)

Barley (Bob's Red Mill) with olive oil and garlic

Steamed broccoli

Side salad (green leaf lettuce, tomatoes, cucumber and baby carrots)

Vinaigrette (apple cider vinegar (Giant) and olive oil)

Salt and Pepper (Monarch)

Apple slices with fresh squeezed lemon juice

Unprocessed Menu

Day 5 (Respiratory Chamber)

Dinner

Shrimp (Xcellent) scampi with spaghetti (Barilla), olive oil, garlic, cream (Stoneyfield), tomatoes, parsley, basil and fresh squeezed lemon juice

Side salad (green leaf lettuce, tomatoes, cucumber)

Vinaigrette (balsamic vinegar (Nature's Promise) and olive oil)

Salt and Pepper (Monarch)

Plain Greek yogurt (FAGE) with blueberries (from frozen, no sugar added (Giant)

Unprocessed Menu

Day 6

Breakfast

Berry and walnut Quinoa breakfast cereal (quinoa (Nature's Earthly Choice), skim milk (Cloverland), ground cinnamon (Monarch), salt (Monarch), frozen strawberries and blueberries (no sugar added, Giant) and chopped walnuts (Diamond)

Unprocessed Menu

<u>Day 6</u>

<u>Lunch</u>

Salmon (Harbor Banks) with garlic and fresh squeezed lemon juice

Baked sweet potato with olive oil, ground cumin (Monarch) and chili powder (Giant)

Green beans (from frozen, Monarch) with olive oil and garlic

Plain Greek yogurt (Fage) with strawberries (from frozen, no sugar added (Giant)

Salt and Pepper (Monarch)

Unprocessed Menu

Day 6

Dinner

Entrée salad with beef tender roast (Tyson), barley (Bob's Red Mill), spinach, cucumber and tomatoes

Vinaigrette (balsamic vinegar (Nature's Promise), garlic, olive oil, basil, parsley, rosemary)

Salt and Pepper (Monarch)

Orange slices

Unprocessed Menu

Day 7

Breakfast

Spinach, onion and tomato omelet (fresh eggs) cooked with olive oil and salt (Monarch)

Hash browned potatoes (russet potatoes with garlic, olive oil, rosemary (Nature's Promise) and salt (Monarch))

Skim milk (Cloverfield)

Unprocessed Menu

<u>Day 7</u>

<u>Lunch</u>

Grilled chicken breast

Quinoa (Nature's Earthly Choice) salad with raisins (Monarch), onions, chopped walnuts (Diamond), parsley, fresh squeezed lemon juice and olive oil

Side salad (spinach, tomato and cucumber) with vinaigrette (balsamic vinegar (Nature's Promise) and olive oil)

Salt and Pepper (Monarch)

Unprocessed Menu

Day 7

Dinner

Penne pasta (Barilla) primavera (olive oil, garlic, pinto beans (cooked from dried), spinach, basil, tomatoes)

Side salad (green leaf lettuce, baby carrots, broccoli)

Vinaigrette (red wine vinegar (Giant) and olive oil)

Salt and Pepper (Monarch)

Grapes

Unprocessed Menu

Daily Snacks

Fresh oranges and apples, raisins (Monarch), raw almonds (Giant), chopped walnuts (Diamond)