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Hall KD, Ayuketah A, Brychta R, et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. Cell Metab. 2019;30(1):67–77.e3.

What We Know, Think We Know, or Are Starting to Know

The focus of relationships between diet and disease outcomes has historically emphasised nutrients, rather than the actual properties of foods themselves. However, while the nutrients of interest have largely remained the same - fat, sugar, salt, fibre, and particular micronutrients, like vitamin D or calcium - the past decade saw a shift towards examining the characteristics of foods.

Factors like energy density [the amount of calories in a given weight of food], palatability [the pleasurable response to food], satiety [the effect of food on fullness, after eating has ended], and the influence of differing compositions of fats, sugars, salt, and other properties in a food matrix, on these variables, may influence total energy intake and body weight, beyond what a nutrient alone could explain. Physical properties of food, such as texture, viscosity [thickness or stickiness], solid or liquid form, may influence satiety [(1)]. Humans may be biologically predisposed to overconsume when energy is easily available [(2)]. The scare availability of energy-dense, highly digestible foods in natural environments may have precipitated adaptations toward increasing consumption beyond daily energy requirements for future energy storage [(3)].

To account for the characteristics of a food, rather than a nutrient-based classification, the NOVA categorisation was developed, separates foods and beverages according to degree of processing:

- Unprocessed or minimally processed foods, defined as fresh, dry or frozen fruits and vegetables; packaged grains and pulses; grits, flakes or flours made from corn, wheat, rye; pasta, fresh or dry, made from flours and water; eggs; fresh or frozen meat and fish; fresh or pasteurized milk;
- Processed culinary ingredients, including sugar, oils, fats, salt and other substances extracted from foods or nature, that are used in kitchens to season and cook unprocessed or minimally processed foods and to make dishes and meals.
- Processed foods, including vegetables preserved in brine, fruits in syrup, salted meat and fish, cheese, freshly made unpackaged breads and other similar ready-to-consume products manufactured with the addition to unprocessed or minimally processed foods of salt, sugar, oil or other substances of culinary use.
- Ultra-processed foods, defined as *industrial food and drink formulations mostly or entirely made from processed culinary ingredients, such as sugar, oils and salt, and other substances derived from foods but not normally used in kitchens, such as protein isolates, modified starches and hydrogenated fats*." It also includes additives to enhance sensory qualities of foods, such as colorants, artificial sweeteners, flavourings, and emulsifiers [(4)].

Recent observational research has suggested that ultra-processed foods contribute a significant proportion of daily energy in numerous Western countries, with 45% of total daily energy derived from ultra-processed foods in Ireland, and 50% in the UK [5]. However, up to the publication of the present study, no tightly controlled intervention had examined the influence of UFP compared to unprocessed foods on energy intake and body weight.

The Study

10 females and 10 males resided for 28-days in a metabolic clinical research centre, and were randomised to consume an ultra-processed foods [UPF] diet or minimally processed foods [MPF] diet for two weeks, followed by the alternate diet [i.e., the order in which the participants consumed the diets differed based on which they were randomised to first].

Three meals per day were provided to participants, and they were allowed to eat ad libitum [as much as desired] in a 60-minute period. Food intake was measured, and eating rate was calculated by dividing measured food intake by duration of the meal. The energy and macronutrients that were presented to participants in both diets was relatively well matched, however, certain factors, like the ratio of added sugar to total sugar, insoluble fibre to total fibre, saturated fat to total fat, could not be matched due to the characteristics of the foods in both diets. Menus for both diets were rotated every 7-days.

*Geek Box: Respiratory Quotient

To determine how much energy we use at rest, known as 'resting metabolic rate' [RMR], how much energy we are using after a meal, and what fuel sources we are using for this energy - carbohydrate or fat - researchers can use a technique called 'indirect calorimetry'. It's an indirect measure, because it measures the exchange of oxygen [O2] and carbon dioxide [CO2], to determine energy expenditure. This is possible, because all macronutrients - protein, carbohydrate, and fat - contain carbon. By measuring the ratio of CO2 being produced to O2 being consumed, either fasting or following food, it is possible to calculate the 'respiratory quotient', known as the 'RQ'. Normal RQ ranges from 0.7-1.0; an RQ of 0.68-0.7 roughly indicates either a fasted state, or purely fat metabolism [such as during a ketogenic diet], while an RQ of 1.0 would reflect purely carbohydrate oxidation, which could be observed during high-intensity anaerobic exercise. For meals with mixed carbohydrate and fats, an RQ of around 0.8 is typical. Measuring RQ can be done using any apparatus that allows for collecting the breath of the person being measured, either breathing under a hood, or in modern facilities, in a whole room which allows for constant flow of O2 and CO2 to be inspired and expired, and measured.

Results: Energy intake during the UPF diet was 508kcal per day greater on average, compared to the MPF diet. The order of which diet was consumed first did not affect the outcome. In contrast, energy intake during the MPF diet remained relatively constant. The increased energy on the UPF diet was derived from increasing carbohydrate [280kcal/d] and fat [230kcal/d], which were increased at breakfast and lunch, but not dinner. Protein remained unchanged throughout the study.

Meal eating rate was significantly higher, both in grams per minute and calories per minute, however, there was no difference in subjective appetite or perceived palatability of the diets. The increased eating rate correlated to energy intake. During the UPF diet, participants gained 0.9kg, while participants lost 0.9kg during the MPF diet.

RQ measurements during the metabolic chamber days indicated that fat oxidation was reduced on the UPF diet compared to the MPF diet. There was a trend toward higher glucose and insulin levels on the UPF diet, measured during the metabolic chamber days. However, there was no difference between diets in response to an oral glucose tolerance test conducted at the end of each diet period.

The Critical Breakdown

Pros: This was a tightly controlled metabolic ward study, and in terms of design is the strongest achievable for showing cause-effect relationships in nutrition science [more under *Key Characteristic*]. The researchers attempted to balance factors like total energy, energy density, and macronutrients, in the meals presented to participants in both diets, and factors like dietary fibre, which may influence satiety, were similar. Randomising participants to start with either the UPF or MPF diet meant that an effect of diet order was minimised. This was a food-based intervention, and the foods making up both diets were commonly available and consumed food items. For example, breakfast on Day 1 of the UPF vs. MPF diet, as well as the available snacks, was as follows:

- UFP Breakfast: Croissant (Chef Pierre); Margarine (Glenview Farms); Turkey sausage (Ember Farms); Blueberry yogurt (Yoplait).
- UFP Snacks: Baked Potato Chips (Lay' s), Dry Roasted Peanuts (Planters), Cheese & Peanut Butter Sandwich Crackers (Keebler), Goldfish Crackers (Pepperidge Farm), Applesauce (Lucky Leaf).
- MFP Breakfast: Greek yogurt (Fage) parfait with strawberries, bananas, with Walnuts (Diamond), Salt and Olive Oil; Apple Slices with Fresh Squeezed Lemon
- MFP Snacks: Fresh oranges and apples, raisins (Monarch), raw almonds (Giant), chopped walnuts (Diamond).

Conducting the study in a metabolic ward allowed for precise control of food, precise measurements of energy intake, and precise measurements of all metabolic outcomes (energy expenditure, etc.).

Cons: The energy derived from UFP was significantly greater than anything observed in populations to date; 81% of total energy was derived from UFP, which is not be reflective of even populations with high intake, like the UK, Ireland, and the US. While 28-days is a long-time for an in-patient study, the short-term nature of the study - 14 days on both diets - means that it is difficult to extrapolate the findings to long-term eating behaviour in a free-living context. During the UPF diet, the greater intake of carbohydrate and fat may have been nutrient factors that influenced results, rather than degree of food processing. This limitation is acknowledged by the authors. While RQ fat oxidation was reduced on days spent in the metabolic chamber, this likely reflected diet composition on those days, rather than a specific difference in metabolic effects of the foods.

Key Characteristic

Any study of eating behaviour in humans, and indeed any nutrition study in general, faces a methodological dilemma between conducted a study in a free-living or laboratory setting. This dilemma is one between internal vs. external validity*, i.e., the difference between precision [internal validity] and naturalness [external validity]. Food intake studies can be difficult, given the extensive range of factors that influence food intake in the real world, including sensory factors, cognitive factors, environmental factors, and the influence of food itself on the post-ingestive and post-absorptive state.

This study was designed for internal validity, and to minimise and control for the potential influence of factors, other than the influence of the foods themselves on the outcomes. In this sense, the study may disentangle other factors that might influence food intake, but we can never entirely separate the role of cognitive factors on energy intake. This is important, as factors like dietary restraint, disinhibition, weight status, may all influence response to eating opportunities [1], which the study did not assess.

The reason these factors are important, is because during the UPF diet, energy intake actually decreased over time, which could be an adaptive response itself. It is possible that this hedonic response is dampened over time, an effect known as ' sensory specific satiety' , which depends more on the actual amount of food consumed, than the energy content [6]. The key point is that even with a high degree of internal validity, the complex web of inter-relating factors influencing energy intake in response to foods means we can' t be certain that the cause for increased energy intake was degree of food processing, rather than other properties of the foods, or psychological factors.

*Geek Box: Internal and External Validity

To determine how much energy we use at rest, known as 'resting metabolic rate' [RMR], how much energy we are using after a meal, and what fuel sources we are using for this energy - carbohydrate or fat - researchers can use a technique called 'indirect calorimetry'. It's an indirect measure, because it measures the exchange of oxygen [O2] and carbon dioxide [CO2], to determine energy expenditure. This is possible, because all macronutrients - protein, carbohydrate, and fat - contain carbon. By measuring the ratio of CO2 being produced to O2 being consumed, either fasting or following food, it is possible to calculate the 'respiratory quotient', known as the 'RQ'. Normal RQ ranges from 0.7-1.0; an RQ of 0.68-0.7 roughly indicates either a fasted state, or purely fat metabolism [such as during a ketogenic diet], while an RQ of 1.0 would reflect purely carbohydrate oxidation, which could be observed during high-intensity anaerobic exercise. For meals with mixed carbohydrate and fats, an RQ of around 0.8 is typical. Measuring RQ can be done using any apparatus that allows for collecting the breath of the person being measured, either breathing under a hood, or in modern facilities, in a whole room which allows for constant flow of O2 and CO2 to be inspired and expired, and measured.

Interesting Finding

Eating rate was increased significantly, in both calories per minute and grams per minute. The greatest increase was calories per minute, with the UPF diet resulting in an increase of 17kcal per minute compared to the MPF diet. The additional energy consumed during the UPF diet was entirely derived from additional carbohydrate and fat, and this increase in eating rate could be the main effect of UPF.

In an ad libitum study investigating the effects of macronutrients in energy dense foods on energy intake and weight gain, consumption of foods high in fat and simple sugars was shown to predict overeating and weight gain, independent of other characteristics of the foods [(7)]. Previous lab studies had suggested that dietary energy density predicted energy intake, independent of macronutrient variations [(1)]. Energy density from foods [not drinks] was 85% higher on the UFP diet in this study, compared to the MPF diet, and thus it is also possible that dietary energy density was the factor driving increased consumption of carbohydrate and fat.

This may all be a case of chicken-and-egg; energy density is generally inseparable, in the food supply, from high fat/sugar content. It suggests, however, that the interrelationship between energy density and increased energy intake may be driven eating rate, which may be a result of the properties of UPF. Although the correlation between energy intake and eating rate was modest, this leaves us wondering whether it is processing influencing eating rate, or the relationship between energy density and nutrient profile, which drove overeating.

Relevance

The definition of “ultra-processed foods” [UFP] characterises many typical foods in the food supply. When we can look at actual food and drinks contributing the most to increased calories from the 1970’ s to the 2000’ s: potato chips, pizza, sugar-sweetened beverages, French fries, processed animal meats, refined grain products, sweets and desserts. That is an energy dense food diet, that is characterised by both a nutrient profile and a processing profile. The arguing over the use of the NOVA categorisations, which insists processing>nutrients, and the traditional public health nutrition model, which insists nutrients>processing, may be missing the forest for the trees.

In addition, environmental factors influence the availability of UPF; we know that the greatest density of fast food outlets is in areas of greatest social deprivation, and that intake of processed foods correlates strongly to socio-economic status. Consider that the cost of the MPF diet in the present study, based on supermarket chain prices, was $45 dollars more expensive. This is not a trivial cost difference. When we factor in the clear socio-economic drivers of food intake in the population, the real relevance of this study is arguably in providing better quality evidence for policy change.

While the NOVA may be imperfect, it is a useful classification for foods in the food supply with poor nutritional quality. However, it still can’ t be taken as a proxy for high intakes of nutrients which may have adverse impacts on health status. One study investigating nutrient intake relative to NOVA processing categories, found that saturated fat and sodium were in fact similar across categories, indicating that the processing data may not always provide subtle detail about the influence of changing nutrients of interest (8).

However, one of the major criticisms of the NOVA classification was that there were no controlled studies comparing the effects of MPF vs. UPF on a calorie-for-calorie basis (9). There is now, and this study adds important findings with real significance for the food environment, and policy.

Application to Practice

It’ s important we don’ t over-moralise foods that are ubiquitous in our food supply and environment. Equally relevant is the need to be mindful of the food environment, and the reality of the situation facing many people in society that influences their daily nutritional choices. It is arguable a nutritional “no-brainer” for any practitioner helping a client improve their diet quality, that reducing UPF is a positive step. But it is important to put this study in context; a tightly controlled intervention with with UPF diet consisting of 81% energy from UPF, and 0% of MPF, is not reflective of typical diets. It is informative, but we need to continuing developing our understanding of how food processing influences energy balance. For the short-term, the real level at which this study should be impacting is policy.

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