January 22, 2021

I have reproduced the text of this blog post below that I received in pdf format from Ivan Oransky at Retraction Watch on January 19. I prepared a partial response and submitted that version to Ivan Oransky on January 21 which was uploaded on the Retraction Watch website. My updated comments to date are provided below in red font.

(Preamble: This post is timed to appear with a related post by Ethan and Sarah

Ludwin-Peery, who have some pertinent questions about patterns in the data

associated with the article that is discussed. *I strongly recommend that you read*

*their analysis first*, not least because it provides a much more comprehensive

introduction to the study. Here I discuss a variety of other apparent problems with

the same article.)

This post looks at an article that first appeared in May 2019 describing a

randomised controlled nutrition study. The authors claimed that people who were

allowed to eat as much as they wished of a diet based on either "ultra-processed" or

"unprocessed" food(\*) consumed around 500 kcal/day more on the ultra-processed

diet, and gained an average of 0.9 kg (2 lbs) in two weeks, compared to people on

the unprocessed diet, who lost an average of 0.9 kg in the same period. The same

20 participants ate both diets, in a randomised order. Importantly, the amount of

macronutrients (protein, fat, and carbohydrates) provided in the meals was closely

matched across diets, as was the number of calories offered (logically, since

calories are a function of the macronutrients). That is, the claim is that the mere

fact that the food was ultra-processed, versus unprocessed, caused people to

consume 500 kcal/day more and gain, rather than lose, weight in a controlled inpatient

setting.

Perhaps not surprisingly, the study attracted a lot of attention. It has already been

cited more than 360 times according to Google Scholar. The National Institutes of

Health (NIH), which funded and conducted the study, put out an extensive news

release about it, and the story was covered by both Science and Nature, as well as

the BBC, the Guardian, the Washington Post, and many other major media outlets.

Here is the full reference of the article. For the first time since the appearance of

the 7th edition of the APA Publication Manual (which says that we now have to

list up to 20 authors’ names in a reference) I'm actually going to need an ellipsis to

omit some of the 25 authors:

Hall, K. D., Ayuketah, A., Brychta, R., Cai, H., Cassimatis, T., Chen, K. Y., Chung, S. T.,

Costa, E., Courville, A., Darcey, V., Fletcher, L. A., Forde, C. G., Gharib, A. M.,

Guo, J., Howard, R., Joseph, P. V., McGehee, S., Ouwerkerk, R., Raisinger, K., ...

Zhou1, M. (2019). Ultra-processed diets cause excess calorie intake and weight

gain: An inpatient randomized controlled trial of ad libitum food intake. *Cell*

*Metabolism*, *30*(1), 67–77. https://doi.org/10.1016/j.cmet.2019.05.008

The article is published on an Open Access basis; you can find the full

text here (PDF, 2 MB) or a fuller version, including the Supplemental

Information, here (PDF, 23 MB). A small erratum, correcting a number of minor

issues, was published on August 6, 2019; all of the issues mentioned in the erratum

are already corrected in the PDF files, so you don't need to keep that to hand while

reading the article.

Importantly, another erratum was published in October 2020 and is available here: <https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30427-7>

The correction relates one of the questions raised below and we realize that the updated data and code were not yet deposited on the OSF website. We will do so.

This study has already been the subject of a comment on PubPeer by Edward

Archer, who, I think it is fair to say, is a prolific critic of the way that much

nutritional research is carried out. I am not a nutrition scientist, so this blog post

will mostly concentrate on the data and statistics of the study. I do have one or two

small methodological questions too, but these are based only on my 60 years of

experience of consuming food and 40 or so of preparing it, rather than any

understanding of how nutrition studies are run.

**The study**

The authors recruited 20 volunteers, 10 male and 10 female, and kept them in an

in-patient environment for 28 days at the NIH Clinical Center in Bethesda,

Maryland. The data show that between one and four people were in the facility at

any point between the first admission on April 17, 2018 and the last recorded data

collection on November 19, 2018.

Participants spent 14 days on each of two diets, one described as "processed" and

the other as "unprocessed". The diets were presented on a 7-day rotation, so each

participant ate the same meal twice, 7 days apart. Although the purpose of the

study was to examine the effect of an "ultra-processed" diet, and that term tends to

be used in nutrition science with a specific meaning that is different from

"processed" (it's complicated), I will mostly follow the authors' use of the terms

"processed" and "unprocessed" to distinguish between the two. I hope that this will

avoid any confusion that might be caused by the fact that "ultra-processed" and

"unprocessed" both start with the same letter. The participants were randomised to

receive the processed diet first (N=10, 6 male, 4 female) or the unprocessed diet

first (N=10, 4 male, 6 female); after 14 days on one diet they immediately switched

to the other, as shown here.

Timeline of participants in the study. Reproduced from Figure 1 of Hall et al.'s

article.

**The code and data**

The authors have made their data and analysis code available here. There are two

datasets, named ADLDataSAScode and ADLDataSAScode1, each in its own ZIP

file. The only difference between these seems to be that ADLDataSAScode1,

which was uploaded on August 20, 2019 (three months after the article was first

published online, which was on May 16, 2019), contains one extra data file, and

the code has been extended with a few lines to produce a table from that file (more

on this later). All of the analyses in this post refer to the ADLDataSAScode1

dataset.

Screenshot of the timestamps of the OSF repository for the study. A full-size

version of this image is available as part of the supporting files for this post (see

"Code and data", below).

The SAS code is not, as one might have hoped, a run-once script that generates all

of the tables and figures from the article. Indeed, as supplied, the main script file

(ADLDocumentation1.sas) produces two runtime errors at line 61 because the

variables created within the SAS data file DLW at lines 42 and 43 are lost when

this file is overwritten twice at lines 45 and 46. It seems that the code is best

regarded as a collection of "building blocks" of code that can be run individually,

possibly with minor modifications to use different subsets of the data. However,

for completeness, I patched up the code so that it would run without error

messages, and also to include both the original and adjusted analyses of the figures

from Table 3D (see "The adjusted weight data", below), and ran it in SAS

University edition. I have made the resulting code ("Nick-

ADLDocumentation1.sas") and output ("(Annotated) Results\_Nick-

ADLDocumentation1.pdf") files available online (see "Code and data", below).

**The exact length of the study**

An issue that stands out immediately when one looks at any of the data files

containing daily records is that there seems to be a fencepost error. Participants

spent 14 days on each of two diets, with no break in between; their weight at the

start of day 1 was the baseline for the first phase (processed or unprocessed diet,

assigned at random), and their weight at the start of day 15 was the baseline for the

second phase, when they received the other diet. It would seem, therefore, that they

should have been weighed 29 times—once at the very start of the study, and then

28 more times after eating a day's worth of meals each time—but there are only 28

daily weight records for each participant. That is, we apparently do not know the

effect on their weight of the last (14th) day of the second diet, because the last

measurement of their weight on that second diet was the one conducted on the

morning of the 14th day (their 28th in the study), *before* they proceeded to eat their

food and undergo whatever other measurements were performed on that day. This

seems to make little sense, from the standpoint of either study design or ethics.

Why feed your participants the controlled diet on the last day if you are not going

to collect weight data from them relating to that day?

Participants were admitted the afternoon before the study began. An overnight fasted body weight measurement was collected the next morning (day 1) which served as the fiducial point for the weight change calculations during the next 14 days on the first diet. On the morning of day 15, subjects were weighed which served as the fiducial point for weight change calculations on the alternate diet that was provided after an oral glucose tolerance test (OGTT). Fasted body weight measurements were then collected each morning including day 29 when the final OGTT was performed after which the subject was discharged. Thus, there were 29 fasted body weight measurements for each subject corresponding to the fiducial markers on days 1 and 15 prior to delivery of each diet and 14 days thereafter. However, the reported body weight changes in the manuscript correspond to days 1-14 of the first diet period and days 15-28 of the second diet period as shown in Figure 3A of the manuscript as described as the weight changes on each respective day on the diet. It would have been possible to report body weight changes corresponding to days 1-15 of the first diet period and days 15-29 of the second diet period, but we thought this would have been confusing to readers.

**Which days did participants spend in the respiratory chamber?**

Participants spent one day per week in a respiratory chamber to enable their energy

expenditure to be studied in detail. The article states that "On the chamber days,

subjects were presented with identical meals within each diet period, and those

meals were not offered on non-chamber days" (p. 72), which makes sense from an

experimental control point of view, in that all participants would have consumed

the same food on that day. The article's Supplemental Information [PDF, 21MB]

further states (on pp. 15, 16, 17, 37, 38, and 39) that the chamber day was day 5 of

each weekly diet rotation, corresponding to days 5 and 12 of each participant's time

on each diet.

However, the records in the data file chamber appear to contradict this. I looked

for precise matches between the recorded energy intake on the chamber days and

the records for each participant in the dailyintake file, and found exactly one

match for each participant and chamber day. Support for the idea that these

matches are not coincidental is provided by the fact that the calendar dates of each

record of the matched pairs (one in chamber and one in dailyintake) are

identical. The matched records imply that of the 80 chamber days (20 participants

x 2 diets x 2 chamber days per diet), only 7 took place on day 5 of the weekly diet

rotation (whereas 2 were on day 1, 24 on day 3, 3 on day 4, 31 on day 6, and 13 on

day 7). Furthermore, of the 40 pairs of chamber days within the same diet, 15 were

on different diet rotation days within the pair (e.g., for participant ADL002 on the

unprocessed diet, the chamber days were 3 and 8, corresponding to the third and

first days of the diet rotation, respectively), meaning that the participant would

have eaten different meals on their two chamber days for a given diet in 37.5% of

cases. Of course, it is possible that the participants did indeed all spend days 5 and

12 of each diet in the chamber, as reported in the article and supplement, but that

would mean that 73 out of 80 records in the data file chamber of both the date

and how much they ate on those days are inconsistent with the equivalent records

for diet days 5 and 12 in dailyintake.

The article and supplement do not claim that “participants did indeed all spend days 5 and 12 of each diet in the chamber”. Rather, the main manuscript describes that participants spent one day each week in the respiratory chambers but does not specify the days of the week. The Supplementary Materials provide information about the rotating 7-day menu of meals provided on each diet and the chamber days were listed as occurring on day 5 of each week. This was not intended to indicate that the chamber days only occurred on day 5 but rather that the meals provided during the chamber days were prespecified and did not vary between subjects on the same diet no matter what day the chamber days occurred. The clinical protocol (available on the OSF website) indicates in Appendix A that the proposed schedule (page 34) had chamber days planned for days 3 and 10 on each diet. However, the protocol also notes on pages 13-14 that “Every effort will be made to adhere to the proposed timelines, but some flexibility is required for scheduling of other studies, unanticipated equipment maintenance, etc. Scheduling variations will not be reported.” Thus, while chamber days varied to accommodate such scheduling challenges, the meals provided on the chamber days were constant within each diet.

**Counting the calories**

The data file dailyintake contains information about the amount of calories

and individual nutrients consumed by the participants on each day. The total

number of calories consumed is reported to two decimal places, but the individual

readings of calories for protein, fat, and carbohydrates that sum to that total are

reported to six decimal places, which on visual inspection do not appear to contain

any regular patterns (recurring decimals, etc).

Extract from dailyintake file, showing six digits of precision for

macronutrient calorie counts. Some columns have been reduced to zero width to

enable the image to fit on this web page.

It is not clear how such numbers could have been generated, however, as the

process for calculating the amount of calories consumed presumably ought to have

been a fairly simple multiplicative one, based on estimates of the numbers of

grams of protein, fat, carbohydrates, and water in the uneaten portions of each food

that was offered. (Edward Archer's comment on PubPeer mentions this issue, and

suggests that a bomb calorimeter might have been a better measure.) The authors

report that the diets were designed and analyzed using ProNutra software, made by

Viocare of Princeton, NJ. I wrote to Viocare to ask how this software calculate

calories from macronutrients—for example, whether it uses the Atwater values of

4.0 kcal/g for protein and carbohydrates and 9.0 kcal/g for fat, and whether it

typically generates long mantissas in its output. Its founder and president, Rick

Weiss, sent me this reply:

ProNutra’s standard nutritional database is from USDA which we load into

ProNutra with the resolution as USDA provides. Typically a research group using

ProNutra would round off to the decimal place that they need. So I agree, seeing a

value to the 6th decimal doesn’t make sense. The analysis of calories from

macronutrients does use Atwater values.

More specifically, ProNutra uses specific Atwater factors which can deviate from the general values of 4.0 kcal/g for protein and carbohydrates and 9.0 kcal/g for fat. Therefore, the assumption immediately below is invalid.

But if the calories per gram are always integers, the presence of six decimal places

of precision in the macronutrient information of every meal would seem to imply

that the authors calculated the amount of food that was (a) served and (b) remained

uneaten to the nearest microgram, which seems like it would require a lot of effort.

The six decimal points for the macronutrient kcals in the data files are easily explained. The data for the total energy consumed and the percentage from each macronutrient were provided to 2 decimal places. For example, 15.68% of energy consumed as protein and a total energy intake of 2003.47 kcal. Therefore, the kcal provided from protein was calculated to six decimal places in the data file as follows: 2003.47\*0.1568 = 314.144096 kcal from protein.

I also wonder what was done in the case of processed snacks, where one would

expect the authors to have simply used the nutrition information provided by the

manufacturers.

The assumption that we used manufacturer provided nutrition information is not correct. As indicated in the manuscript, nutrient information was obtained from the USDA standard reference databases or if an item was not found in that database, we pulled from the Food and Nutrition Database for Dietary Studies, (also through the USDA).

For example, on four days of the processed diet, three participants

(ADL006 on days 3 and 4, ADL007 on day 8, and ADL015 on day 9) are in the

data file intakebymeal as having consumed 403.14 kcal in snacks,

with 42.007956, 202.218222, and 158.933010 kcal coming from protein, fat, and

carbohydrates respectively (these amounts are precisely identical on all four days).

The chances that three people left exactly the same amount of snack food

unfinished on a total of four occasions would seem to be negligible, so this

duplication presumably corresponds to these participants having completely

finished the contents of the same combination of snack packages on each day.

But the nutrition information for each of these packaged snacks reports the amount of

macronutrients with a precision of 1 g, so the calories from each of these

macronutrients ought also to be an integer (a multiple of 4 or 8), unless the authors

perhaps contacted the manufacturers and obtained analyses down to the microgram

level. Three different participants, four different days, identical snack consumption

Indeed, ADL006 consumed the same snack items on days 3 and 4 as did ADL007 on day 8 and ADL015 day 9. From the mass consumed (grams), the subjects did finish the entire package of the snacks (28g, 39 g and 113 g for peanuts, cheese & peanut butter crackers, and applesauce, respectively). As explained above, we did not use manufacturer provided nutrition information, but rather nutrition information from the USDA database. Specific Atwater factors were used for the applesauce and the peanuts, whereas general Atwater factors were used for the cheese & peanut butter crackers. As also explained above, the six decimal points in the reported macronutrient kcals resulted from multiplying the macronutrient percentages by the total energy consumed.

A further problem here is that these records show that the three participants in

question consumed more calories in the form of fat than carbohydrates from their

snacking on these four days, but substantially fewer calories from protein than

from carbohydrates. The only processed snack in the image on p. 24 of the

Supplemental Information that has more calories from fat than from carbohydrates

is the 28 g package of Planters salted peanuts (see my file snacks.xls), but this

also has more calories from protein than from carbohydrates. I have not been able

to identify any combination of packaged snacks that would get even close to the

proportions of calories from protein, fat, and carbohydrates that is reported for

these four participants, especially given the presumed constraint of counting only

entire packages.

The combination of foods that result in these proportions of calories from protein, fat, and carbohydrates was indicated above: 28g, 39 g and 113 g for peanuts, cheese & peanut butter crackers, and applesauce, respectively.



As an approximate calculation using general Atwater factors, we have:

Peanuts 28 g providing 163.8 kcal, 6.63 g protein, 13.9 g fat, 6.02 g carbohydrates

Cheese & Peanut butter crackers 39 g providing 191.88 kcal, 4.21 g protein, 9.55 g fat, 23.01 g carbohydrates

Applesauce 113 g providing 47.46 kcal, 0.19 g protein, 0.11 g fat, 12.74 g carbohydrates

When summed, these snacks provide 403.1 kcal, 11.03 g protein (44.12 kcal using general Atwater factor), 23.56 g fat (212.04 kcal using general Atwater factor), 41.77 gm carbohydrates (167.08 kcal using general Atwater factor). Thus, most of the total calories come from fat, followed by carbs, and then protein.

Nutrition information for Planters salted peanuts snack package (source), showing

total grams of protein, fat, and carbohydrate. The corresponding calorie amounts

would be protein, 7 x 4 = 28 kcal; fat, 14 x 9 = 126 kcal; carbohydrates, 5 x 4 = 20

kcal.

**The participants**

Participants are identified in the data by sequentially numbered labels from

ADL001 through ADL021. That represents a span of 21 unique values, but there

are no records with the label ADL011. Whether this is due to an error in assigning

a label or a participant dropping out is not clear; however, there is no mention in

the article of anyone dropping out of the study.

ADL011 declined to participate in the study after their successful screening visit when they were assigned their subject number. No participants dropped out or were withdrawn from the study after admission.

Participation in this study seems to have been what many people would probably

regard as a major undertaking. The subjects spent 28 days in a highly controlled

environment. The study was invasive, with subcutaneous sensors to monitor

glucose levels as well as multiple finger stick operations daily. Yet no mention is

made of how participants were recruited, how they were compensated, and what

resources were available to look after their mental and physical wellbeing.

We encourage the blogger to read the clinical protocol (available on the OSF website) that was approved by the NIDDK Institutional Review Board which describes recruitment, risks, care, and compensation of our research volunteers.

This last point seems important, since some of the participants would appear to have been potentially rather vulnerable:

 Participant ADL006 (male) had a baseline BMI of 18.050 kg/m², which is

below the minimum specified in the inclusion criteria on pp. e1–e2 of the

article (18.5 kg/m²). That is, on the authors' own terms it seems that he

ought to have been excluded from the study.

This participant met inclusion criteria at their screening visit, but their starting BMI was lower once admitted for the study.

 Participant ADL005 (female) had a baseline BMI of 42.459 kg/m². One

might perhaps question the ethics of including a morbidly obese 40-year-old

in a study where participants are encouraged to eat as much as they want.

Participants were instructed to eat as much *or as little* as they desired. We did not encourage overeating by instructing participants “to eat as much as they want”. One might perhaps question the ethics of excluding volunteers with obesity in a study designed to investigate determinants of ad libitum calorie intake.

Participants ADL019 (female, BMI 38.762 kg/m²) and ADL008 (male, BMI

36.404 kg/m², who consumed an average of 5,228 kcal/day and gained 2.64

kg on the processed diet) were also severely obese.

While the blogger describes the weight gain of these participants during the ultra-processed diet, these participants gained an average of only ~1 kg during the entire study which amounted to < 1% of their body weight.

 Participant ADL020 (a 32 year old female) had a baseline BMI of 26.853.

During her 14 days on the unprocessed diet she consumed an average of just

836 kcal/day and lost a total of 4.3 kg (9.4 lbs) in weight, accounting on her

own for nearly a quarter (23.7%) of the total weight loss of the sample on

the unprocessed diet. On day 12 of the same diet she obtained 22% of her

calories (128 kcal out of 578 kcal total) from carbohydrates, which was the

lowest daily percentage of anybody on any day on either diet in the entire

study, whereas on the next day, day 13, she obtained 62% of her energy

intake (602 kcal out of 962 kcal total) calories from carbohydrates, which

was the *highest* daily percentage of anybody on any day on either diet in the

entire study. This combination of extraordinary weight loss, very low levels

of energy intake, and highly variable eating patterns make me wonder how

much we can generalise from this participant to a broader understanding of

the effects of different types of diet on the wider population.

The limitations of our study regarding generalizability were discussed in the manuscript. It is well-known in human nutrition research that individual subjects have large day-to-day diet variability and that there is large individual variability in weight loss.

**Errors in the data for individual participants**

ADL002

The data file intakebymeal contains one record for every meal consumed by

participants during the study (breakfast, lunch, dinner, and one record for all of the

snacks that they took) containing an assortment of nutritional information about

that meal, including the type of diet that the participant was following on that day

(and, hence, at each meal). For participant ADL002, however, something strange

seems to have happened. The three meals (but not the snacks) that he consumed on

days when he was on the processed diet are marked with the "unprocessed" diet

flag, and vice versa, for all 14 days of each diet.

Extract from data file intakebymeal showing that participant ADL002

apparently consumed unprocessed meals and processed snacks on the same

day. Some columns have been reduced to zero width to enable the image to fit on

this web page.

It is not at all clear how this could have happened, because one would expect the

data to have been recorded directly at the end of the day in question (in a

spreadsheet or directly into the ProNutra software) such that the type of diet would

either have been completed automatically by the system, or obvious based on the

records from the preceding day. Certainly one would expect the snacks for any

given day to have the same diet code as the three meals. (I believe that the three

meals have the wrong diet code and the snacks have the right one, rather than the

reverse, based on the fact that the dailybw and dailyintake files both show

ADL002 being on the processed diet for the first 14 days of the study and the

unprocessed diet for the last 14 days, whereas intakebymeal shows

"unprocessed" as the diet for the breakfast, lunch, and dinner records for the first

14 days, and "processed" for the last 14 days.)

This error was previously discovered and an erratum was published in October of 2020 that corrected this error and is available here: <https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30427-7>

We realize that we have yet to update the files in the OSF website to correct this previously identified error and apologize for the delay.

ADL010

Participant ADL010 has a baseline weight of 91.97 kg in the data

file deltabw but 93.17 kg in the data file baseline. This affects the results

shown in Table S1. If 91.97 kg is the correct weight then the Total mean for weight

is correct but the Male mean (79.2 reported, 79.0 actual) and Male SE (6.6

reported, 6.5 actual) are not. If 93.17 kg is correct then the Male mean and SE are

correct, but the Total mean (78.2 reported, 78.3 actual) isn't.

This problem might appear to be trivial, but it is not at all clear how it could have

arisen. ADL010's weight on day 2 is recorded as 93.17 kg in deltabw, so one

possibility is that for this participant only, the copying process (which one might

hope would have been automated) that generated the baseline table somehow

picked up the day 2 value rather than the day 1 value. Interestingly, according to

that same file, this participant's weight fell back again to exactly 91.97 kg on day 3,

which seems like quite a strong yo-yo effect.

Weight of participant ADL010 in the data files baseline (top; I renamed the

variable from "Bw" to "Day1BW" for my own clarity while performing the

analyses in Excel) and deltabw (bottom).

The baseline information in Table S1 contains body composition measurements obtained by DXA. All of the subjects except ADL001 and ADL010 had their first DXA measurement on day 1, but ADL001 and ADL010 were measured on day 2. For ADL001, their body weight measurements were the same on days 1 and 2, but ADL010 had different weights on these days. Therefore, the body weight measurement on day 2 for ADL010 was included in the baseline information to correctly correspond to the day of the DXA measurement.

**Other oddities in the data**

As mentioned above, data file intakebymeal contains a record for each meal

(plus snacks), with information such as macronutrient and total calories, free water

consumption, the total mass of the food consumed, etc. Meanwhile, data

file dailyintake has a record for each day's consumption for each participant,

broken down similarly. One would therefore expect the values in the four records

in intakebymeal to sum to the values in the corresponding record

in dailyintake. Curiously, however, this is not the case. Indeed, while the

energy intake (EI) field in dailyintake matches the sum of the per-meal EI

values in intakebymeal to within 0.05 kcal in every case (once the diet code

error for participant ADL002, discussed above, has been corrected), the calories

for protein, fat, and carbohydrates from the four meal records each day almost

never sum to anything even close to the equivalent values in the daily record.

Per-meal (top, with sum for all four meals under "Total") and per-day intake for

participant ADL001 on the first day of the processed diet. Note that while the total

energy intake ("EI") from the meals is identical to within 0.01 kcal, the total for

each of the macronutrients (protein, fat, and carbohydrates) is different by between

9 and 26 kcal. Some columns have been reduced to zero width to enable the image

to fit on this web page.

We have been able to reproduce this problem using the data from several subjects and it appears to be an issue with the ProNutra software. We have contacted the manufacturer to identify the reason for the problem but have yet to receive a reply. However, we agree with the blogger that the magnitude of the discrepancy is very small (tens of calories) and we note that it does not affect the primary study outcome of total energy intake. This issue may be related to the next problem below.

A related problem is that, within intakebymeal, the three macronutrient calorie

observations for a meal frequently do not sum to the overall energy intake from

that same meal. A spectacular example of this is the dinner of participant ADL005

on day 3 of her unprocessed diet, which provided 393.523334 kcal from protein,

311.910799 kcal from fat, and 530.105951 kcal from carbohydrates, for a total of

1235.540084 kcal, but whose total energy content is shown as 1720.21 kcal—a net

discrepancy of about 484.67 kcal. A total of 639 of the 2,240 participant x day x

meal records in intakebymeal suffer from this problem, whereas none of the

records in dailyintake do. Put simply, a large number of the per-meal

macronutrient values in the intakebymeal data file seem to bear little relation

to the necessities of arithmetic. (Interestingly, all of these discrepancies are on the

positive side—that is, when the overall energy intake differs substantially from the

total of the energy intake from the macronutrients, the overall energy intake is

always larger— suggesting that whatever process is responsible for these

discrepancies might not be entirely random.)

We noticed this problem with the meal data (and not the daily data) when preparing our correction published in *Cell Metabolism* in October of 2020. We identified that this was an error in the ProNutra software that listed the fraction of calories coming from all three macronutrients as 0% while correctly providing a value for the total calories for the following food items:

Garlic, raw

Lemon juice, fresh squeezed

NutriSource Fiber

OLD FOODS- Oil, olive (Nina)

Oil, olive

Oil, olive (Nina)

Oranges, raw

Pepper, black (Monarch)

Salsa (del Pasado)

Tomatoes, raw

We contacted the manufacturer of ProNutra at the time, but we have yet to receive a satisfactory explanation for this error. Nevertheless, we corrected these data in the erratum published in *Cell Metabolism* in October of 2020. We realize that we have yet to update the files in the OSF website to correct this previously identified error and apologize for the delay.

**The adjusted weight data**

I noted earlier that the OSF repository for the project contains two ZIP files. The

second of these included an extra data file named deltabcadj14, and the SAS

code has been extended with a few lines that analyse it. This code seems to be

quite important as it claims to generate the results for figure 3D of the article,

which presents what are arguably the headline findings of the study: a mean weight

gain of 0.9 kg per participant on the processed diet and a mean weight loss of 0.9

kg on the unprocessed diet. The code file contains this comment:

Update1: Body composition changes presented in Figure 3D are adjusted for 14

days because the body compositions were not measured exactly 14 days apart. In

the previous version of SAS code and data, such adjustment was not provided.

Here we have updated the SAS code at the section "data for figure 3D" and added a

dataset "DeltaBCadj14";

It is not clear what adjustments were performed to make this new data file. The

provided code merely re-runs the comparisons of before/after weight, fat mass, and

fat-free mass for the two types of diet, using the adjusted data. When the new code

is run, it produces results for the mean weight loss/gain that are around 20%

different from the originals, and would presumably have been reported as a mean

gain of 0.8 kg on the processed diet and a mean loss of 1.1 kg on the unprocessed

diet.

Comparison of pre- and post-study weights (first two lines of each panel, for the

processed and unprocessed diets, respectively) and fat/non-fat mass, using the

original (top) and adjusted (bottom) data. The output from the original data file

contains a descriptive label for each line, which I have removed here to allow the

figures in the tables to appear in the same size font for both images.

Interestingly, the sample size for fat mass and fat-free mass on the unprocessed

diet is higher with the adjusted data than the original data. The data

file deltabc is missing these values for participant ADL002,

whereas deltabcadj14 is not. Thus, whatever the adjustment process was, it

seems to have extrapolated or interpolated in some way whatever data relating to

fat mass might have been missing for this participant, such that he could now be

included. (I assume that fat-free mass is calculated as weight minus fat mass, so

that only one missing value needs to have been inferred in this way.)

I wonder if this adjustment might be an attempt to compensate for the issue that I

raised earlier under the heading "The exact length of the study". But if that is the

case, it is not clear why it would be necessary to adjust the values for both diets for

each participant. After all, the start of day 15 of the study—the day on which the

participants changed to the other diet—ought to correspond to exactly 14 days after

they were weighed on day 1.

The article states that participants were weighed at 6am every day. If it turns out

that they were weighed substantially later on day 1 (or earlier on the last day), the

question then arises of whether they skipped one or more meals on that day,

although there are records for every scheduled meal in intakebymeal. On the

other hand, if they were weighed only an hour or so late, the adjustment hardly

seems necessary, especially since the Welch Allyn Scale-Tronix 5702 weighing

scale that was used for the study has a precision of only 0.1 kg (a fact that I

confirmed by e-mail correspondence with the manufacturer; see also Ethan and

Sarah's post, which explores the consequences of this constraint in more detail).

The adjusted values are reported to 10 or more decimal places, which—assuming

that the adjustment was indeed a function of the difference between the actual

elapsed time from the first to last measurement, and exactly 14 days—suggests that

the time at which participants' weight and fat mass was measured must have been

recorded to a very high degree of precision indeed.

The question about the precision of the body weight measurements is addressed in our response to the blog post by Ethan and Sarah Ludwin-Peery. These apparent high-precision body weight measurements and the statistical anomalies noted by Ethan and Sarah Ludwin-Peery are explained by subtracting pre-weighed pajamas worn during the body weight measurements as described in the manuscript Method Details section.

Two questions arise from this operation:

 First, it would be interesting to know what the adjustment process was. It

seems to have been quite powerful, because some of the differences between

the original and adjusted values are substantial. For example, for participant

ADL014, the loss in weight on the unprocessed diet has been adjusted from

0.10 kg to 0.95 kg, and for ADL005 the equivalent loss has gone from 0.26

kg to 1.79 kg; participant ADL019's gain of 0.30 kg on the unprocessed diet

has been adjusted to a loss of 0.24 kg, while participant ADL021's loss of

0.30 kg on the processed diet has been adjusted to a gain of 0.16 kg. These

changes appear to affect principally the fat-free mass rather than the fat

mass, which in numerous cases (8 out of 20 on the processed diet, 2 out of

19 on the unprocessed diet) is identical to two decimal places after

adjustment. For example, participant ADL010's original weight gain of 3.60

kg on the processed diet becomes 2.69 kg in the adjusted file, but his fat

mass did not change at all.

 Second, if the authors believe that these adjusted figures provide a better

estimate of the effects of the diets, one might wonder why they have not

submitted a correction, updating the claims about weight loss that featured

in the abstract of their article, rather than allowing this important new

information to languish in an OSF repository. Otherwise it is not clear what

the point of performing these "adjusted" analyses was.

The results in the published manuscript correspond to the unadjusted data and code that was originally deposited on the OSF website. The adjustments in the second file on the OSF website were performed to address the fact that the DXA body composition measurements were not performed on exactly at the same time points for all subjects. Furthermore, subject ADL002 was missing one DXA measurement during the unprocessed diet period. The adjusted data attempt to estimate the mean changes in body composition that would have occurred had the DXA measurements been aligned on day 14. To do this, we calculated the slope of the best fit regression line to the fat mass measurements over each diet period to estimate the fat mass change on day 14. The DXA measurement at the end of the first diet period was also used as the fiducial measurement for the start of the second diet period and subject ADL002 contributed only 2 fat mass measurements during the unprocessed diet period. The corresponding body weight measurements on those days were used to calculate the fat-free mass estimates by subtracting the estimated fat masses on those aligned days. This explains the minor differences between mean results reported in the original file deposited in OSF (which correspond to the results published in the manuscript) and the first updated file. The mean results are not materially different between these analyses, and the adjusted data merely address the potential criticism that the DXA measurements were not all conducted on the same days in all subjects. The reported data in the manuscript are not in error.

**Conclusion**

Hall et al.'s article seems to have had a substantial impact on the field of nutrition

research. However, both Ethan & Sarah's post and this one raise a number of

concerning questions about the reliability of this study. There seem to be problems

with the design, the data collection process, and the analyses. I only looked at

about half of the 23 data files, so there may be other problems lurking. I hope that

the authors and the editors of *Cell Metabolism* will take another look at this study

and perhaps consider issuing a correction of some kind.

A correction was published in *Cell Metabolism* in October of 2020 and is available here: <https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30427-7>

This correction regards an error described by the blogger that we previously independently discovered. Many of the other questions raised above are the result of misinterpretations of the data and the study. We hope that we have now clarified these issues. One remaining question appears to involve the ProNutra software used to calculate the individual macronutrient amounts, but the discrepancies are very small and do not affect the primary study outcome.

**Code and data**

I have made my R analysis code, which reproduces most of the results reported

above, here. Some of my results can probably best be checked by examining the

data files in a spreadsheet, so my code also includes a loop (which you need to

enable, following what I hope are clear instructions) that will export the original

SAS data files to CSV format. Also included at the same location is a spreadsheet

file named snacks.xls which summarises the nutrition information for the

snacks that were served on the processed diet, plus the OSF screenshot and the

SAS code and results files mentioned earlier.

**Acknowledgements**

Thanks to Andrew Althouse and James Heathers for help with the analyses, and to

Ethan and Sarah Ludwin-Peery for sharing their discoveries about the Hall et al.

article and some very interesting discussions about what it all might mean.

**Note on copyright**

I believe that the reproduction of two images in this post (Figure 1 of Hall et al.'s

article and the Planters nutrition information label) constitute fair use.

**Footnotes**

(\*) I have put these terms in quote marks to emphasise that they have a specific

technical meaning. I don't know if that it a good idea, though; perhaps it looks like

I am putting Dr Evil-style air quotes around them. That isn't my intention.

(\*\*) I asked James Heathers, my go-to person for all things physiology, to explain

these numbers. He replied: "No-one did too much of anything... even slow walking

to the shops is 2.5 METs. An hour's proper exercise including walking to and from

the gym, even if you do nothing else all day, will push your daily MET up to a hair

under 2".

While it is unclear what this second (\*\*) footnote refers to, free-living people have an average physical activity level (defined as the total energy expenditure divided by resting energy expenditure) of ~1.6-1.8. Despite being admitted as inpatients when subjects often become very sedentary, our subjects had physical activity levels in the free-living range as was intended by mandating 60 minutes of daily cycle ergometry exercise at fixed wattage.