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Xie Z, Sun Y, Ye Y, et al. Randomized controlled trial for time-restricted eating in healthy volunteers without obesity. *Nature Communications*. 2022;13(1):1003.

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

Somewhere in the past few years, periods of restricting energy intake became the new hot thing in diet and health. Such excitement may have been generated by the fact that you could stuff rodents with all the calories but if it was confined to a time-restricted period, our mammalian critter cousins did not gain bodyfat [1,2].

However, we know not to be overly excited about animal model data absent corroboration in human data, right? Good. And this is justified in the case of time-restricted feeding [TRF] because the body of human intervention evidence has been mixed. In a very well controlled human intervention in men with prediabetes, 5-weeks of early TRF [eTRF] led to significant reductions in insulin levels and blood pressure compared to eating over a 12hr period, without weight loss [3].

However, other studies using TRF in the middle part of the day [mTRF] did not always show significant benefits [4]. One open question in this research has been whether the timing of the TRF window matters. Hutchinson *et al*. [5] compared an eTRF [8am to 5pm] or mTRF [12pm to 9pm] protocol and found a beneficial effect of TRF on glucose and triglyceride levels, but no interactions between TRF and mealtime, suggesting that the timing of the window may not be as relevant.

However, the reality is that there has been no well-conducted intervention study eTRF to mTRF, with a control group. Until now…

The Study

90 otherwise healthy participants were recruited from the Beijing [China] area and randomised to one of the following groups for 5-weeks:

- eTRF [6am to 3pm]
- mTRF [11am to 8pm]
- Control [over 8hrs with no restriction on timing]

To be included, participants had to have a habitual daily eating window of >8hrs and not routinely engage in fasting. Participants were not given any instruction to change their diets, other than to eat within the specified windows for the interventions and with no restriction in the control group.

Participants were required to photograph the start and end of every meal with their smartphones, which were sent to the investigators. Energy content of each meal was estimated from the photographs according to Chinese national food and portion size databases.

The primary outcome was the change in insulin resistance assessed by HOMA-IR [a measure calculated from fasting insulin and fasting glucose values]. Secondary outcomes included energy intake, fasting glucose, bodyweight and composition, and blood pressure.

Results: Of the 30 participants in each group which began the study, 28, 26, and 28 participants completed the study in the eTRF, mTRF, and control groups, respectively. As the figures below from the paper are presented as boxplots, see the ***Geek Box** below for more on how to interpret boxplots.

- ***Insulin Resistance and Fasting Glucose*:** HOMA-IR decreased significantly in the eTRF group by 1.08 points compared to a 0.39 increase in the mTRF group and 0.05 decrease in the control group. Fasting glucose also decreased significantly in the eTRF group compared to the control group by 0.59mmol/L, but there were no significant differences between eTRF and mTRF groups.

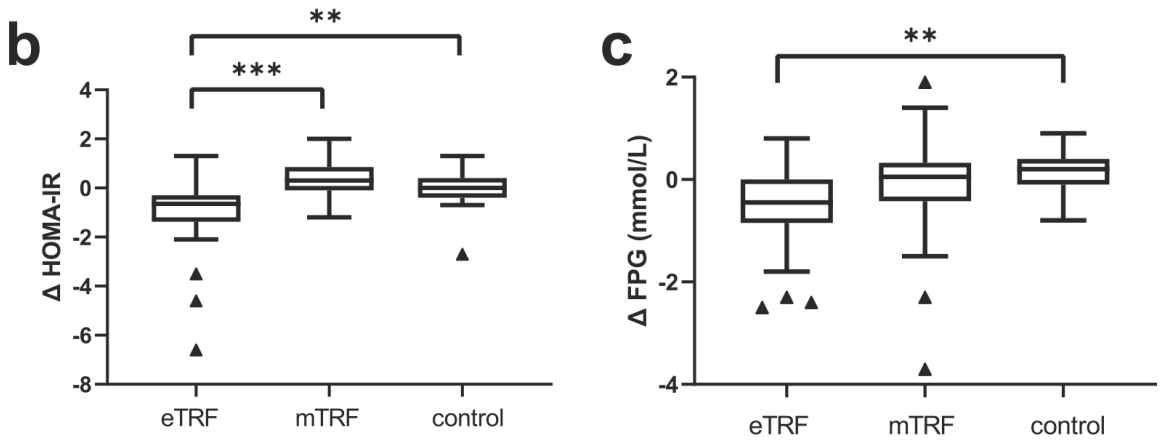


*Figure from the paper illustrating [**left**] the change in the primary outcome of HOMA-IR and [**right**] fasting plasma glucose levels. For more on interpreting box plots such as those depicted in these graphs, see the **Geek Box**, below. The bar with asterix above indicates which groups were significantly different from each other. In the case of insulin resistance [HOMA-IR], you can see that the eTRF group was significantly different from both the mTRF group and control group, and in fact showed a greater magnitude of effect compared to the mTRF group.*

- ***Energy Intake*:** Daily energy intake decreased by 240kcal per day and 159kcal/d in the eTRF and mTRF groups, respectively, while energy intake increased by 64kcal/d in the control group.

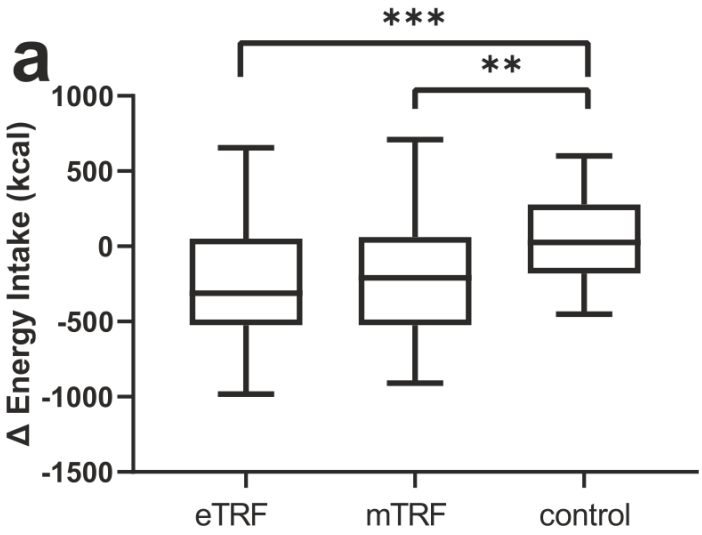


Figure from the paper illustrating the differences in average daily energy intake between groups.

- ***Bodyweight and Composition*:** The eTRF group lost a significant 1.6kg of bodyweight compared to 0.2kg in the mTRF group, while the control group gained 0.3kg. Of this weight loss in the eTRF group, 0.76kg was fat mass, corresponding to a 0.6% bodyfat decrease. There were no significant differences in either the mTRF or control groups.

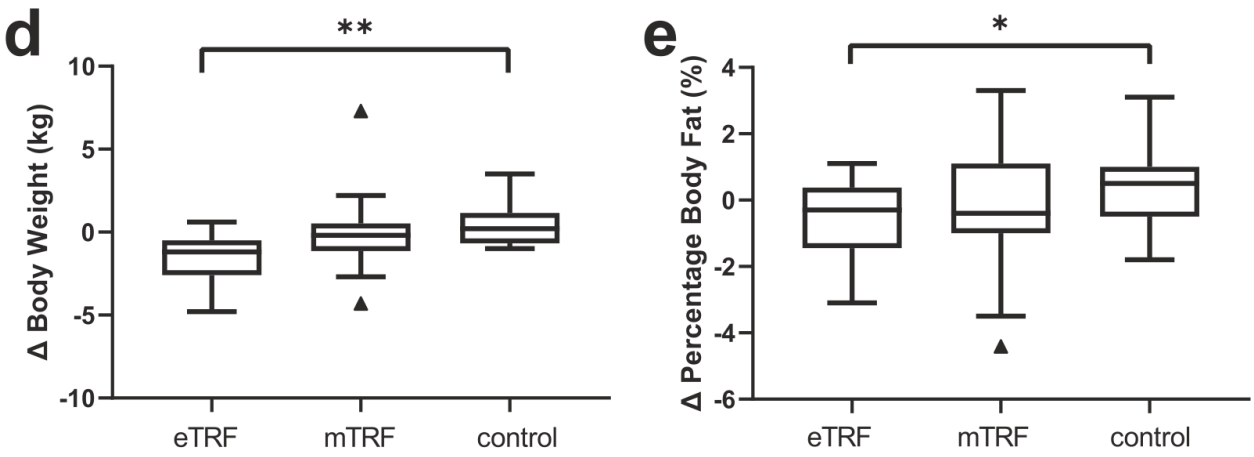


*Figure from the paper illustrating [**left**] the differences bodyweight between groups, with the eTRF group significantly different to the control group, and [**right**] percentage bodyfat loss, again with the eTRF group significantly different to the control group. The mTRF group showed little difference in these outcomes, a 0.2% bodyfat change and 0.3kg loss of body fat mass.*

- ***Other Outcomes*:** There were no significant differences between groups in blood pressure or blood cholesterol levels. Plasma ghrelin, the gut-derived hunger-signalling hormone, were measured at 7am, 12pm, 5pm, and 11pm in a small subset of each group, before and after the intervention. Following the intervention, in the eTRF group ghrelin levels were 0.49% higher at 11pm.

Geek Box: Interpreting Box Plots

Boxplots may appear confusing, but in fact are easy - and very informative - when you know what you are looking at. Boxplots are one of the best ways to display quantitative data, yet bar charts are often used in papers [generally bar charts are more appropriate for categorical data, such as frequencies, percentages, or scales], but boxplots provide substantially more information. So, let's start with the box itself: this represents the middle 50% of the data - known as the 'interquartile range', i.e., the top of the box is the 75th percentile, and the bottom is the 25th percentile. Across the box you can see a horizontal line: this is the median, i.e., the middle value(s) in the data. A large box, i.e., a large interquartile range indicates that there is large variability in the values in the data; a small box indicates that most values fall closely within the middle of the data, i.e., are gathered around the median. By looking at the median line, you can also gauge where it fell within the middle 50% of the data. You'll also notice 'whiskers' extending from the top and bottom of the box, and triangle-shaped 'dots' which lie beyond those whiskers. There are several options when plotting whiskers, but the often depict the minimum [bottom] and maximum [top] values. Any dot or symbol beyond these whiskers indicates any outlier(s), and in the graphs above you can see triangle symbols which represent the outliers whose values lay beyond the minimum and maximum values. As you can see, there is a lot of data presented in boxplots, which is very helpful to interpreting findings.

The Critical Breakdown

Pros: The study overall had a strong design. Both TRF interventions were compared to a control group, rather than just being compared against each other as pervious TRF/IF studies have. Randomisation was appropriate [computer-based random-number generator], and statisticians remained blinded for the data analysis. The study had a very high retention rate, with 91.1% completing the study. Compliance with the intervention, deemed as the number of reported days of photographed meals, was high at 96-98% between both groups.

Cons: This is yet another recent TRF study which somehow omitted to included data on meal timing and distribution of energy within the respective 8hr eating windows [more under ***Key Characteristic***, below]. There is no baseline data presented in raw data form; the only data presented is the figures of the changes during the study, but we have no way of putting that in context relative to what the raw baseline data was. Estimating energy intake from photographs alone is fraught with potential for error. The study was 5-weeks in duration, and based on recent longer studies [e.g., 12-weeks], it would be interesting to see if the benefits from eTRF hold out over longer periods or are primarily observed in the short-term. The sample size, while adequately powered for the primary outcome of HOMA-IR, is still modest.

Key Characteristic

I've raged a little about several recent TRF studies which have only quantified the eating window, despite apparently gathering data on diet [4,6]. Well, here we are again. The authors state in their own limitations that *"...the specific timing and duration of meals varied within each group, which may have influenced the results."* Toys, out of pram. Seriously, what is with investigators doing dietary interventions on meal timing and duration without analysing and presenting data on meal timing?

Even the timing of the first and last eating occasion would be useful to get a handle on when participants ate, and what their actual temporal timing of eating was. What if the mTRF group ate mostly between 2pm and 8pm? And if their distribution of energy was skewered to the evening? We know from the wider literature that distribution of energy is an important factor regarding metabolic responses to food intake [7–11]. I would argue that the distribution of energy is a more important factor than eating duration alone, based on this literature.

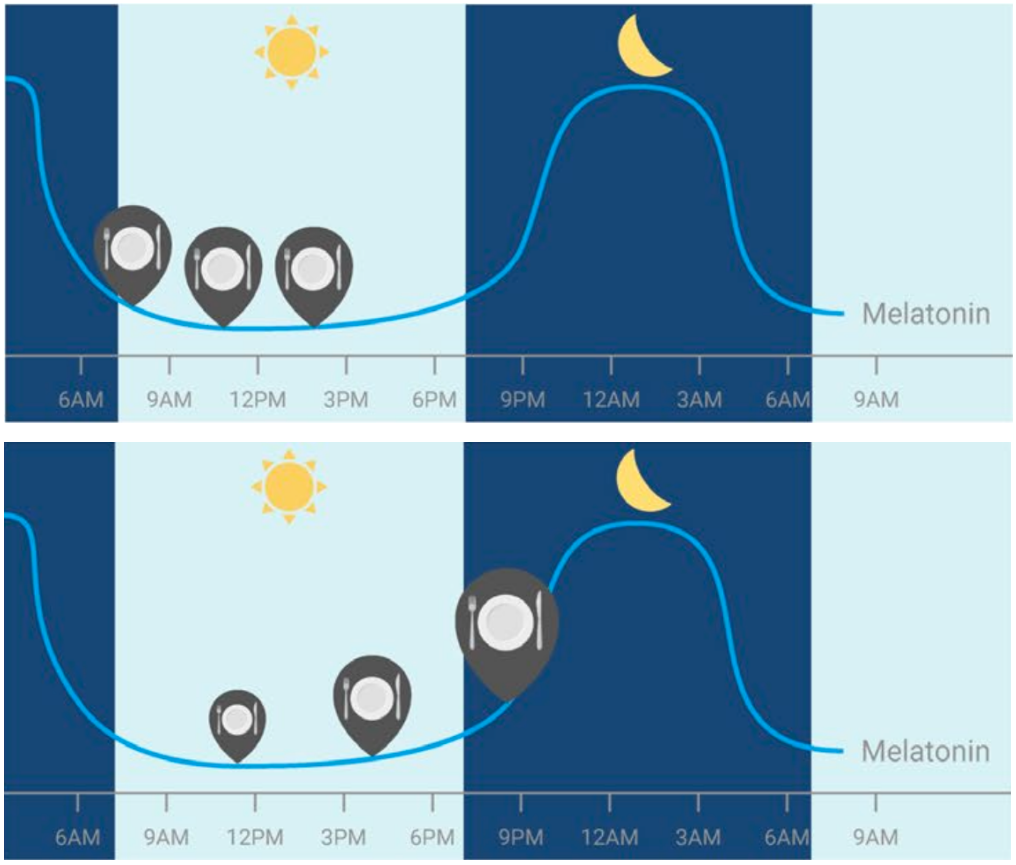
For example, in a metabolic ward study that compared breakfast omission to dinner omission during energy balance conditions, omitting breakfast resulted in significantly higher glucose and insulin levels in response to lunch, higher HOMA-IR, and higher overall 24hr blood glucose levels, compared to dinner skipping [12].

Thus, it appears that investigators of these recent TRF studies are assuming that the only exposure of interest is the duration of the eating window. This is short-sighted, for reasons we shall elaborate on under ***Interesting Finding***, below.

Interesting Finding

The reduction in insulin resistance as comparing the eTRF to mTRF offers some important evidence to the question over whether early distribution of energy is more favourable in a TRF context. So, let' s build on the Key Characteristic discourse regarding temporal distribution of energy perhaps being more important than the duration of the eating window *per se*.

In this study we nominally have a comparison between eTRF and mTRF, but we also have a comparison between early temporal distribution of energy and later temporal distribution of energy. Have a look at the following graphs to bring this point to life:



Assume that the size of the plate icon reflects the size of the meal in energy content; would you think these two are equivalent, even if they roughly were both within 8hr? One of the most well-established aspects of biological rhythms in metabolism is that glucose tolerance is amplified during the morning hours and diminished in the evening [13,14].

One reason for this is that incretin hormones, for example glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinoptropic polypeptide [GIP], are most responsive in the early part of the day, and these hormones facilitate more rapid insulin responses to food intake in the morning [7]. This enhancement of insulin function in the early phase of the day enhances glucose disposal, resulting in lower postprandial glucose responses and lower total daily blood glucose levels [8,9,11,15]. We could also expect that the elimination of evening energy intake, as would occur in eTRF, would also benefit glycaemic control and insulin resistance [according to HOMA-IR], as described above [12]. These factors may explain the significant improvement in HOMA-IR found in the present study, although the influence of weight loss would also be expected to contribute.

Relevance

It is highly plausible that the more favourable effects of eTRF observed in the present study relate more the temporal distribution of energy when compared to the mTRF regimen, but in the absence of any data on meal timing and distribution of daily energy intake, we are left to scratch our heads in some frustration.

In the chrono-nutrition review I led back in 2020, we made the point that there were several factors which could be influencing metabolic benefits associated with time-of-day: reductions in energy intake, the extended fasting duration, the temporal distribution of energy, or the elimination of evening energy intake [16]. These are generally expensive studies to conduct, so it is frustrating that recent research in this area has squandered the opportunity to probe these open questions with more refinement.

As a result, most of the commentary will focus solely on the eating duration, i.e., the extended fasting/restricted eating time, when that is merely one component of the overall exposure. My personal perspective, based on the wider literature on temporal distribution of energy and underlying metabolic effects, is that for eTRF it is more likely the alignment of daily energy intake with the optimal phase of the day for glucose-insulin responses that explains most of the metabolic benefit. The elimination of evening energy could have an additive effect in this respect which, yes, would mean that there is a role for the reduced window. But I' m not convinced the magnitude of the difference would be substantial in otherwise healthy individuals.

Nevertheless, the primary outcome of the present study warrants comment. Bear in mind that in the Chinese population, cut off points for HOMA-IR for impaired glucose tolerance and type-2 diabetes are, respectively, 1.4 and 2.0 [17]. Thus, the reduction in HOMA-IR of 1.8 in the eTRF group could be considered a large effect size for this population. And the difference in HOMA-IR of 1.47 between eTRF and mTRF groups would also be quite a large a difference, given these participants are otherwise metabolically healthy and lean.

There are a lot of open questions remaining to be resolved in this conflicting area of research.

Application to Practice

The evidence in humans to date certainly indicates that TRF is not a magic bullet, but then again, no dietary intervention is. Each stands on its own context. In another recent intervention from China conducted over 1-yr, there was no significant difference between an eTRF group [8am to 4pm] compared to a habitual control in either weight loss or other metabolic markers, including HOMA-IR, in participants with obesity [6].

The question begs, would a study over a longer duration washout the effects observed in the present study in otherwise healthy participants? This is arguable, however, the body of short-term eTRF interventions in consistent in demonstrating a metabolic benefit in both metabolically impaired and otherwise healthy participants [3,5,18–20]. Thus, it may be that the context of the applicability of eTRF is as a short-term intervention to achieve more immediate improvements in metabolic health. But it also may not be necessary, if factors like distribution of energy were considered, i.e., frontloading energy intake earlier in the day. This approach has shown quite a large magnitude of benefit in individuals with impaired glucose tolerance and T2D.

There is also the obvious question of the acceptability of eTRF in a normal, free-living context. The fact that this trial was conducted under those conditions is encouraging. Nevertheless, whether this type of eating regimen would be acceptable would seem to be an individual issue. At this point, it is difficult to recommend eTRF specifically, over and above modifying the distribution and overall timing of energy intake in individuals who may be skewered toward later evening energy intakes.

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