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Lowe DA, Wu N, Rohdin-bibby L, Moore AH, Kelly N, Liu YE, et al. Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity The TREAT Randomized Clinical Trial. JAMA Intern Med. 2020;94143:1–9.

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

There remains much to be teased out in research on timing of food intake and metabolic health in humans. Historically, the research focus on the word "timing" related to meal frequency, and the question that meal frequency may have a relationship to energy expenditure, and therefore energy balance. The hypothesis that greater meal frequency may increase metabolic rate, and therefore greater weight loss, has been tried, tested, and come up short [(1)].

Ah, the pendulum swings in nutrition are extreme. As the meal frequency research found no effect of various numbers of meal on energy expenditure or body weight, the rhetoric shifted to consider timing irrelevant. In the past decade, however, a number of research groups demonstrated that, in mice, restricted food availability to certain phases of their biological waking period conferred protection against increasing adiposity, even with deliberate high-fat rodent diets designed to induce obesity in mice [(2,3)].

This paralleled a growing body of controlled mechanistic studies in humans demonstrating circadian rhythms in metabolic processes, including glucose tolerance, lipid metabolism, and energy expenditure [(4-7)]. Logically, the question begged: what would the effects of restricting food intake to a specific period be in humans?

One early study in this area published in 2015 used a mobile app to track timing of food intake, and demonstrated that on average the duration of the daily eating period was ~15hrs [(8)]. Based on this data, the app-based study then conducted an intervention where participants self-selected a 10-12hr daily window to eat within, which resulted in an average eating duration reduction of ~4hrs, and 3.27kg weight loss. However, this was a pilot study* in 8 participants, with no control group [(8)]. Other interventions in small sample sizes directly examining the effects of time-restricted eating [TRE] on weight loss have also lacked a control group [(9)]. The present study sought to test the effects of a TRE intervention compared to a 3-meal-per-day control group.

The Study

The study was a randomised controlled trial conducted over 12-weeks in men and women aged 18-64 [mean age in the trial 46.5yr], with overweight or obesity [mean weight 99.2kg]. The intervention was delivered through a mobile app, and participants were provided with a bluetooth weight scale to weigh weekly, which the app would record.

Participants were randomised to either a time-restricted eating [TRE] group, instructed to confine food intake to between 12.00pm-8pm daily, outside of which it could consume non-caloric drinks. The control group was a conventional meal timing [CMT] group, with instructions to eat 3 main meals per day: between 6-10am; 11am-3pm; 5pm-10pm.

Each group received specific prompts to assist adherence with the respective interventions. For example, the TRE group received the following messages:

- "DO NOT eat between 8 pm tonight and 12 noon tomorrow" for the restricted time period (message appeared at 8 pm)
- "DO NOT eat until 12 noon today" (message appeared at 8 am)

Conversely, the CMT group received the following messages:

- "Fruits and vegetables are healthy snacks" (message appeared at 8 pm)
- "Start your day with a healthy breakfast" (message appeared at 8 am)

No limitations were placed on calorie intake or dietary prescription provided.

A subset of 46 participants completed 4 separate in-person visits to the university research centre for metabolic testing.

The primary outcome was weight loss. Secondary outcomes, based on data from the in-person metabolic testing subgroup, included changes in weight, fat mass, lean mass, fasting insulin, fasting glucose, hemoglobin A1c levels, estimated energy intake, total energy expenditure, and resting energy expenditure.

Results: 105 participants [from 141 originally randomised] completed the 12-week intervention, and self-reported adherence was high: 92.1% in CMT group [i.e., did not miss meals] vs. 83.5% in TRE group [i.e.,ate only within 8hr window]. The adherence in the TRE group appears to have decreased over time relative to the CMT group.

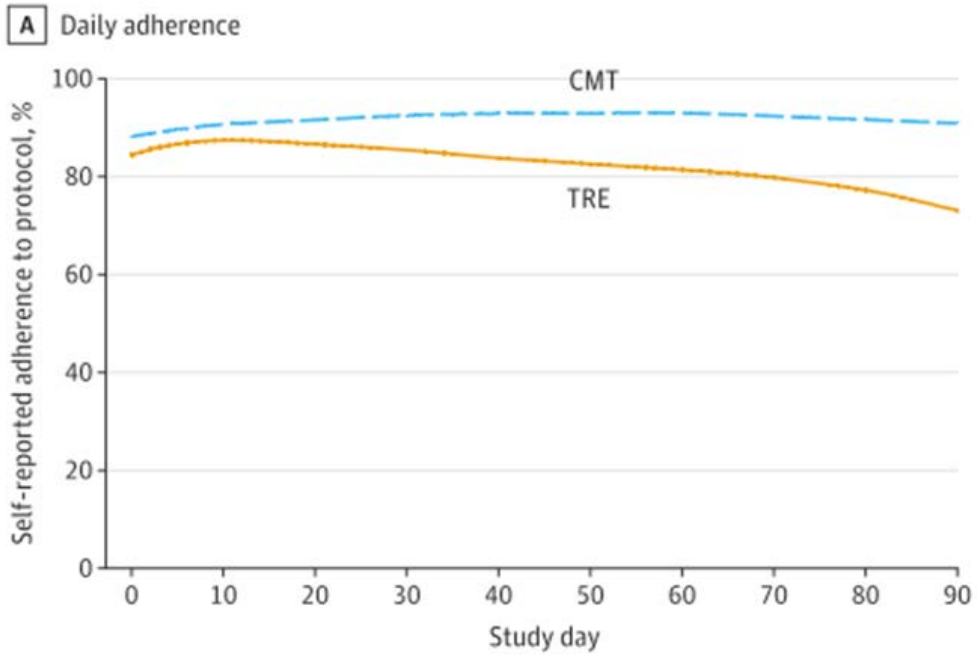

Figure *from paper illustrating adherence to both the TRE [**orange**] and CMT [**blue**] diets. Adherence was high in both groups, however, it appears adherence to the CMT control diet was constant over the course of the intervention period, and greater than the TRE group. The TRE group appears to have had decreasing adherence as the intervention progressed. Differences in adherence may thus have influenced the magnitude of effect of the diets.*

> ***Primary Outcome - Weight:*** The TRE group lost 0.94kg [95%CI, −1.68kg to −0.20kg] vs. while the CMT group lost 0.68kg [95% CI, −1.41kg to 0.05kg, and the difference between groups was not statistically significant*. As a percentage of baseline weight, the TRE group lost 1.17% of initial bodyweight vs. 0.75% in the CMT group, and the difference between groups was not significant. Based on the in-person metabolic testing, however, there was a significant decrease in weight in the TRE group of 1.70kg, while the CMT group lost 0.57kg. The between-group difference was borderline significant [p=0.07].

> ***Secondary Outcomes:*** In the TRE group, there was a significant decrease in lean mass of 1.10kg, but no significant difference in the CMT group [−0.35kg], and the difference between groups was not significant. Appendicular lean mass, a measurement of skeletal strength of lower limbs, decreased significantly in the TRE group [−0.64 kg], but there was no significant difference in the CMT group [−0.17kg]. This difference between groups was statistically significant. Trunk lean mass also decreased significantly in the TRE group by −0.47kg vs. −0.15 kg in the CMT group, but there difference between groups was not statistically significant. There was no significant difference between groups in markers of blood glucose, insulin, or lipids.

*Geek Box: P-values vs. Confidence Intervals

Most of us are not statisticians, and yet statistics are at the core of science. This means that often, ideas and misconceptions about statistics frustrate statisticians, when those misconceptions are actually coming from within researchers! For most of you who constantly read scientific literature, the p-value - as a significance test - and confidence intervals as parameters of reliability in an estimated mean - are the most common you' ll come across. Yet, both have their own misconceptions, and it is important to understand that while p-values and confidence intervals are related, they are providing different information. A p-value is the result of a hypothesis test. In this way, it relates directly to the null hypothesis, i.e., "there is no difference between Diet A and Diet B". The threshold of p=0.05 for significance is arbitrary, and more an industry standard than any hard and fast rule. When the hypothesis is tested, if the p-value is <0.05, then this is deemed to be statistically significant and the null hypothesis is rejected, i.e., there is a difference between Diet and Diet B. A p-value, therefore, is only saying that there is either a statistically significant difference or a statistically insignificant difference. A confidence interval indicates the precision of the estimate, and generates an interval with a lower and upper limit for the mean value [or whatever the measure is]. Generally, the narrower the estimate, the more precise the estimate, and the wider the interval, the less precise an estimate. 95% simply means that if the same study was repeated multiple times from the same population, 95% of the confidence intervals generated from the study would contain the actual true population mean Confidence can relate to the p-value, for example intervals can be used in this way for calculating risk ratios [e.g., relative risk, hazard ratio, etc.], and if the confidence interval contains 1, the finding will be a p-value of >0.05 and is not significant; conversely, if the internal does not contain 1, then the finding will have a p-value of <0.05 and be statistically significant. It is commonly misinterpreted that if confidence intervals overlap, there is no statistically significant difference between two means; this is not the case. It is also a common misinterpretation that if the mean of one group is outside the interval of the other, there is a statistically significant difference. It' s important to note that just because the result of a p-value is not statistically significant, that this means there is no difference or no effect. It' s also helpful to know that a confidence interval may not necessarily contain the true population mean [it' s 95% probability coverage, not 100%!]. Both are still valuable. Confidence intervals in particular, beyond the statistical significance in the hypothesis test, contain key information to help in the interpretation of the data.

Critical Breakdown

Pros: The study had a decent sample size, particularly relative to previous TRE research. Conducting metabolic testing allowed for greater quantitative precision in both primary and secondary outcomes, and nearly 50% of the final sample size underwent full testing, with 25% each from the TRE and CMT groups. Importantly, there was a designated control group, unlike certain previous interventions.

Cons: There is no data on dietary intake, other than a mathematical modelling of energy expenditure. There are no details on meal times, composition, or any other variables which may be relevant to outcomes [more under ***Key Characteristic***, below]. The differences in the daily prompts to groups may also not be inconsequential, as "gain-framed" messages [i.e., positively described, per the CMT group] vs. "loss-framed" messages [i.e., negatively described, per the TRE group] can have differential effects, with gain-framed messages associated with greater motivation (10). The difference in adherence may have influenced the results.

Key Characteristic

Conducting the metabolic testing in the subgroup of 46 participants from both TRE and CMT groups. Four study visits were conducted, with measurements performed in the morning following an overnight fast from 8pm the previous night. These visits allowed for precise measures, for example doubly-labelled water, which is the gold standard for measuring energy expenditure in free-living humans, in addition to blood samples, DXA scans, and muscle function testing. This additional metabolic testing provided important insights, both in relation to the primary outcome of weight loss where the metabolic testing measures show a difference in effect size to the overall data, and in relation to certain key secondary outcomes, like the decrease in muscle mass and skeletal strength in the TRE group.

Interesting Finding

The difference in the primary outcome of weight loss when confining the analysis to the subgroup of participants who completed metabolic testing, suggests a greater overall benefit to TRE. This is an example of why it is important to look beyond the mean, beyond the average treatment effect and statistical significance finding.

Per above, the average treatment effect in the TRE group was a weight loss of 1.70kg, while the CMT group lost 0.57kg, and this finding was borderline statistically significant [p=0.07]. The 95% confidence intervals in the TRE group were −2.56kg to −0.83kg, and −1.40kg to 0.26kg in the CMT group, which implies a minimum benefit to the TRE group that is greater than the mean of the CMT group.

What is clear, like many dietary interventions, is that there were responders and non-responders. The mean invites us to say *"there is no difference between TRE and CMT"*, while clearly there is a difference in effect, and that difference between responders and non-responders is evident in both diets. However, per the above, closer scrutiny of the data implies that a more participants lost more weight in the TRE group compared to the CMT group.

It could simply be that people undergoing the additional metabolic testing were more motivated, due to more regular contact with study personnel, or that of the spectrum of individual responses, more 'responders' were in the testing subgroup. Nonetheless,

the data implies that the overall effect of the TRE intervention was greater than the CMT group, but these effects are confined to the subgroup of 46 participants who completed this aspect of the intervention.

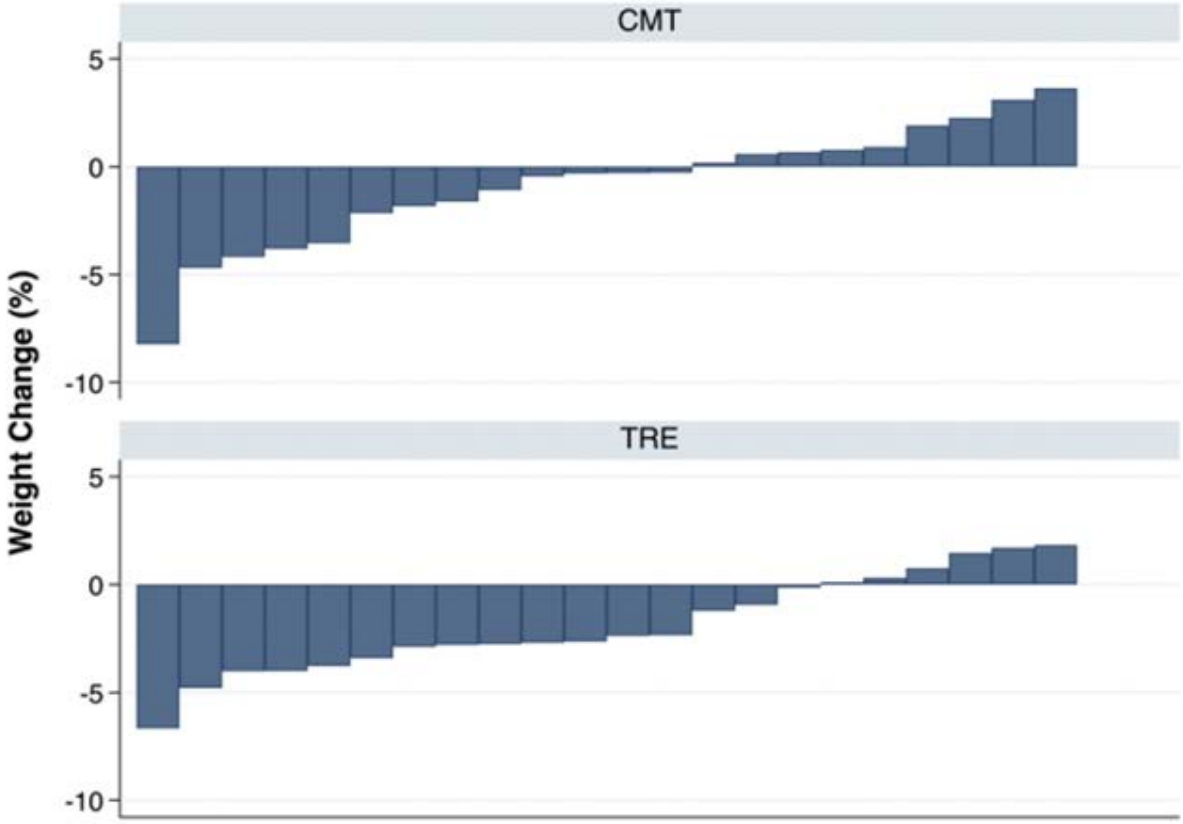

Figure *from supplemental data illustrating the percentage of weight loss for each individual in the in-person metabolic testing subgroup [each bar represents a participant].*

Relevance

There are still only a handful of controlled intervention studies which have directly tested the effects of TRE in humans [4,8,9,11,12,13]. Most of these studies don't actually have weight loss as an outcome, with several having been designed specifically to examine metabolic effects in the absence of weight loss [4,11]. Of the few studies to directly investigate the effects of TRE on weight loss, two have lacked control groups [8,9].

Thus, this remains a nascent, emerging area of research, and higher quality trials remain few, and this study added a well-executed intervention study with a full control group to this evidential picture. And this study found no overall major differences in weight loss or metabolic health between TRE and the regular meal pattern.

However, a number of more tightly controlled studies have demonstrated significant improvements to cardiometabolic risk factors, in particular blood pressure, and glycaemic control [4,11,12,13], including in the absence of weight loss [11]. These studies were, largely, early time-restricted feeding protocols, and thus the timing of the TRE window in the present study, relative to the timing of the CMT diet, may not necessarily be a true test of TRE vs. conventional meal patterns. For example, with the eating window

in the CMT group, it is possible that some participants had breakfast at 10am, lunch at 2pm, and dinner at 8pm: this is still a 10hr, time-restricted eating window. Cienfuegos et al. [14] recently showed that, between a 4hr and 6hr feeding window, there was no difference between groups: both TRE groups reduced energy intake, body weight, insulin resistance, and markers of oxidative stress.

The present study is important because it was a 12-week, free-living intervention with an adequate control group. The overall negative findings need to be contextualised against the wider research in this area, and there remain many variables which could explain differences between study outcomes that need to be reconciled: timing of the daily eating window, duration, effects of energy balance and/or independent of energy balance, and whether specific population subgroups benefit more [i.e., hypertensive, prediabetes] than others. There are vital data missing from this study - actual timing of meals and dietary intake in particular - which leave a few a holes in our ability to plug the gaps from this study alone.

This isn' t about picking sides, it' s simply about acknowledging that at this point, we don' t have sufficient data to reconcile the evidence either way. But when a study like this comes out, you can almost anticipate the rush of people ready to declare irrelevance to the intervention. Hold the space for now.

The pendulum swings.
Extreme, they are.

Application to Practice

To date, the weight of evidence suggests that in free-living conditions, time-restricted eating may benefit, particularly if individuals have extended daily eating durations and/or a propensity to eat late into the night. But it is not a magic bullet nor panacea; nothing in nutrition is. What is clear is that individual preference, as it relates to adherence, remains a critical factor.

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