Episode Transcript

Today we're going to take a look at a specific study in the context of a wider topic of whether there is any advantage to high energy intakes in the morning at breakfast compared to high energy intakes in the evening. Now, some of you may have seen a study published in Cell Metabolism in October of this year, and it's predictably given the type of intervention and the design of the trial generated a lot of commentary, but some of these perspectives and "hot takes" were really missing the point in many respects and we thought that this would be a good opportunity to actually discuss the specific study, the background context to why this study was undertaken, and to discuss the findings of the study and place those findings in the context of the prior research that existed.

And also some wider knowledge that we now have in relation to the time of day influence of energy intake on various measures, whether they relate to energy expenditure, metabolic outcomes, for example, like glucose tolerance and other behavioral aspects, which will be, particularly in relation to appetite, quite a big focus of our discussion today.

The paper in question was Ruddick-Collins and colleagues: "Timing of daily calorie loading affects appetite and hunger responses without changes in energy metabolism, in healthy subjects with obesity". And it was published in

Cell Metabolism from Professor Alex Johnstone's research group at the University of Aberdeen.

The overall grant that this study was conducted from is also the grant from which the main study that I undertook for my PhD came from. So I have some familiarity with the background context of the application and why this study was undertaken. And so this is how we will approach today. First, we'll discuss what research questions were generated by prior evidence, which ultimately led to the decision to want to do a more rigorously controlled interventions, looking at timing of calorie loading, what this specific study actually undertook in terms of its design. What the findings of the study were. And then we'll have some discussion around the potential ways that we might think about interpreting the findings of the paper. And certainly in relation to some of the predictable hot takes that came out which typically either focused entirely on the calorie balance and said, aha, because there's no difference in weight loss, we can basically throw out every other outcome.

So that's the hashtag calorie deficit crowd. And their response to this was fairly typically shortsighted by overlooking some of the really important findings of the study and how they might apply else. . And so we'll contextualize that once we've actually discussed the findings themselves.

So where do the suggestions of the distribution of energy potentially being an important factor for weight loss arise from the first study to really be popularly cited in relation to this was produced by Oren Froy's research group in Israel, and Daniela Jakubowicz was lead author on a number of publications in the early 2010 decade. So in 2012, 2013, 2014, 2015, there were a number of publications from this research group, which were particularly interested in the effects of energy distribution. And that was either comparing high energy intake in the morning to high energy intake in the evening. They also did interventions where they would compare consumption of breakfast versus breakfast, skipping and fasting until lunch.

They conducted these studies in participants with overweight and obesity, but otherwise healthy in terms of metabolic status. And they also conducted some interventions in participants with a diagnosis of type two diabetes, but perhaps their quote, big black and splash study was published in 2013 and this study in particular, compared a 700 calorie breakfast to a 200 calorie

dinner and the inverse order of that, a 200 calorie breakfast to a 700 calorie dinner.

The lunch in this trial was always the same at 500 calories. And as you can probably guess from the calorie content of each of these individual meals, this was not a particularly high energy intake. The study was conducted in women with overweight and obesity. It was a weight loss intervention, and they were not targeting the consumption of anymore than 1400 calories.

Now over the course of 12 weeks in this intervention, there was an enormous differential in weight loss observed, such that the group consuming the 700 calorie breakfast lost in and around six kilos more than the group consuming the low energy breakfast and a high energy dinner pattern of energy distribution.

Now, if we had really dug into all of the findings in that study that may have provided some sort of explanation for the differential in weight loss observed, we may have noticed that their data very clearly indicated significantly greater hunger and lower Satta on the high energy evening group, but that finding was missed.

And the emphasis on the differential in weight loss became the focus of the study and its findings. In particular, the authors offered a suggestion in their discussion that the differential in weight loss, maybe due to enhanced thermic effective feeding, such that there was a enhancement of overall energy expenditure, which favored an enhanced rate of weight loss.

Now, this suggestion was not necessarily without supporting evidence. At the time, a number of studies had measured the thermic effect of feeding, which is the energy expenditure generated in response to the consumption of a meal. It's typically measured above a fasting, resting metabolic rate measure. So the resting metabolic rate being the energy expenditure when someone is at rest after an extended overnight fast without any food consumption.

So it is your resting metabolic rate with no other inputs yet into the energy expenditure equation. And we know that total daily energy expenditure in humans is comprised of a number of compartments. We have resting metabolic rate, which provides the most substantial contribution to someone's total daily energy expend.

We also have the thermic effective feeding, which as previously stated, is the energy generated in response to the processes of digestion and absorption of a meal. And we know that the thermic effective feeding or TEF is influenced by the macronutrient content of meals. And this is because each individual macronutrient has a slightly different thermic effect in terms of the energy required to digest that macronutrient.

We know, for example, that dietary protein contributes the most substantial thermic effect of feeding, and in and around a quarter of dietary protein ingested maybe. Utilized as heat and ultimately not necessarily absorbed. So it's generating heat generating thermogenesis in the process of digestion.

A distant second would be dietary carbohydrate intake and dietary fat contributes relatively minimally then to the overall thermic effect of food. Now, these are fixed values, and this is quite important when we start to think about some of the time of day effects, and particularly then when we start to dig a little deeper into the methodology and findings of the particular study that we're going to discuss today, the thermic effect of feeding typical.

Will be measured by taking the fasted resting metabolic rate measure. Now as stated, a measure of RMR undertaken in the morning after an overnight fast will be a measure of RMR that is not confounded by other variables such as the intake of a meal. So it is a true fasted baseline. Now, if we then served participants a breakfast and we measured over a number of hours after that breakfast, their energy expenditure, we could calculate the difference between the energy expenditure after the meal over and above the fasted resting metabolic rate or RMR value, and that would give us an indication of the thermic effect of that meal.

Now a challenge in terms of research methodology arises when the thermic effect of feeding is then measured in response to multiple meals over the course of the day because there's the potential for carryover effects to be observed and that carryover effect may relate to the macronutrient composition and total energy content of a meal.

So for large meals that may be 700 calories or over, it could be up to five to six hours that there is a post prandial energy expenditure response to that meal. So studies that potentially only measure TEF over one to two hours,

maybe three hours, are likely if they're using higher calorie meals, not capturing the entire thermic effective feeding response to that.

Now when the Jakubowicz and Colleagues 2013 paper demonstrating this quite significant differential in weight loss was published as stated, they offered as a potential explanation for the discrepancy in weight loss in their study observed, particularly in the high morning energy intake group, a potential explanation related to TEF.

And this was based on research that showed a diurnal variation, diurnal simply meaning time of day related. So a variation related to time of day in TE responses, depending on the time that they were measured at. There was a publication in the early nineties in 1993 by Roman and colleagues in the American Journal of Clinical Nutrition, which had measured the thermic effect of feeding response to an ISO caloric meal.

So the same energy content and macronutrient composition of a meal served at 8:00 AM compared to meals also served at 8:00 PM and midnight. And what this study found, and it calculated the thermic responses to the later meals, also above the fasted resting metabolic rate baseline, was that there was a lower thermal effect of feeding response to the later meals.

And this was even less in response to the meal at midnight than it was to the meal at 8:00 PM But the difference in this context was relatively modest. And one of the interesting aspects to that paper is the authors also discussed that there was likely an underlying circadian rhythm in resting metabolic rate itself, but that at that point in time, they were speculating as to how that would be captured.

How would that actually be measured? This is going to also be relevant when we come to discuss the findings of this study.

A number of more recent interventions then also measured thermic effective feeding in response to high morning energy versus evening energy meals. However, they used a method of calculating TEF where they assumed that the baseline was the RMR measure taken before. Each meal. Now, recall that we stated that an issue with trying to measure TEF over the course of the day is that the only meal that follows a true fasted baseline would be breakfast.

And then we have a carryover effect of that meal. And then what these studies were doing is they would take the energy expenditure measurement before lunchtime as then the baseline for the lunch meal, and they would measure energy expenditure after lunch. And that they would then calculate the difference.

How much did energy expenditure increase over and above? Not the baseline resting metabolic rate measure, but the energy expenditure measure before the lunch meal. And they would repeat that for dinner. And what these studies consistently showed with quite impressive consistency in terms of the magnitude of effect, was that there was an apparent enormous discrepancy in how much energy expenditure was generated in response to breakfast relative to how much energy expenditure was generated in response to Jenn.

And so this gave more support, at least conceptually to the theory that energy expenditure itself might be enhanced in the morning. And that energy expenditure in response to breakfast, particularly if there was more energy consumed at breakfast, might actually generate an increase in. Daily energy expenditure.

That would explain why certain studies in particular, the Jakubowicz and colleagues 2013 paper appear to show a significant enhancement of weight loss with high morning energy intake. And it's against that background that what is known as the big breakfast study grant application was made. The project full title is "the Big Breakfast Study: ChonoNutrition, influence on energy, expenditure, and body weight".

The outline of the proposed research the background to the proposed research was published previously in Nutrition Bulletin, and we'll link to that below so you can read it. It's open access and this overall research grant from the Medical Research Council. Had a number of objectives. The first was to investigate the impact of timing of eating on mechanisms related to energy expenditure and substrate utilization.

And the second was to see whether there is a contribution of biological circadian rhythms on energy expenditure and related hormonal pathways during a controlled laboratory study. So that second objective was to say, okay, if there is an effective energy expenditure that is time of day

dependent, do we know whether the effect is mediated by circadian rhythms or behavioral patterns. And in order to do that, then it would be necessary to do a more controlled laboratory study to separate the behavioral cycle from the circadian cycle in a way that allowed for deducing whether any related effects of circadian or metabolic outcomes may be driven by circadian rhythms rather than the behavioral cycle.

So this was going to be achieved with two intervention trials. The assessment and investigation of the impact of calorie distribution was undertaken as an intervention trial by the University of Aberdeen. And that's the study that is the subject of today's discussion. The study that was an inpatient laboratory study to tease apart the respective contributions of the behavioral cycle versus the circadian cycle was the primary study of my PhD. That paper is as yet unpublished, although there is some data that has come from that study that we have already previously published in relation to a model proposed by Leonie Ruddick-Collins, the lead author on the paper that we're discussing today, and the post-doctoral researcher that was on the big breakfast grant project.

And that model proposed that based on a prior study by Zitting in colleagues at the Harvard Chrono Research Group, chronobiology and chrononutrition research group that actually there is a circadian rhythm in underlying resting metabolic rate, going back to the speculation of the group who first suggested a diurnal variation in energy expenditure in the early 1990s, it took until 2018 for the kind of experimental design that would allow this to be elucidated, to be undertaken, and that required a nearly 40 day inpatient stay where resting metabolic rate was measured every day, but incrementally put back by one hour every day.

So every day, the resting metabolic rate measure was one hour later than the day before, and this allowed for a delay in time that exerts minimal change on the circadian system, particularly the timing of the central clock in the hypothalamus. While measuring energy expenditure in terms of resting metabolic rate across the day.

And in mapping this resting metabolic rate, it was evident that there is a circadian rhythm in resting metabolic rate in underlying resting metabolic rate. And that rhythm is tied to rhythms in core body temperature, such that the peak of the underlying circadian value in r mr is at around 5:00 PM clock

time and the trough where the lowest point of that circadian RMR is in the morning, 12 hours from that.

So 5:00 AM clock time now based on data from the laboratory study where we had measured. Energy expenditure, not just resting metabolic rate, but we had measured post prandial energy expenditure across almost the entire waking day, 15 and a half hours out of 16 hours. And this is very important in the context of capturing almost the entirety of the TE response, particularly given the calorie content of the meals that were served in the laboratory study.

And using that data from our laboratory study in terms of underlying themic effective feeding and using the data from the zitting in colleagues paper, which mapped circadian variation in resting metabolic rate across the day. Dr. Ruddick-Collins' model, when applied to the time of day that the measures were taken at in our laboratory study by correcting for the value of the underlying circadian rhythm in RMR, so what was that value in energy expenditure terms at any given time of day? And then matching that to the time of day that our thermic effective feeding measurements were conducted at and essentially adjusting for that circadian RMR value ultimately negated and abolished any apparent difference in thermic effective feeding between meals.

And I mentioned this study. Before we go into the recent publication, not only because chronologically it was published first, but because it's going to provide further context to some of the outcomes of this trial. So in some, the proposal from this modeling paper, which we published in the Journal of Clinical Endocrinology and Metabolism, is also open access and we are linked to below.

Was that this apparent difference that papers had, as I previously said, quite consistently shown a higher thermic effect of feeding response in the morning compared to the evening. That was almost twice the magnitude. I e twice as high themic effective feeding responses after breakfast compared to. And this was being pushed as an explanation for differential weight loss in studies using these types of energy loading interventions and investigating weight loss.

So this is going to be important when we discuss the findings of the present study. So that was the background context. We have these differential weight loss outcomes observed in some trials where they feed high morning energy intake and compare it to high energy intake in the evening. We have a potential explanation offered that the difference observed is in relation to the thermic effective feeding, and that thermic effective feeding is greater in the morning compared to the evening.

And against that background, the big breakfast study grant was submitted and approved. And the intervention that we're going to discuss today was undertaken. So what is the design and methodology of this paper? As I said, the paper was published in cell metabolism in September of this year. Timing of daily calorie loading affect, appetite and hunger responses without changes in energy metabolism, in healthy subjects with obesity.

And this paper is also open access, so we will link to this below. The paper recruited 37 odd participants. A number were excluded in baseline screenings, and ultimately 31 participants were randomized. Now, this was a crossover intervention design, so participants were randomized to the order of intervention, but because it was a crossover design, all participants underwent both interventions.

So the interventions were energy distribution. There was a morning loaded energy diet aiming for a distribution of energy of 45% of total daily energy intake at breakfast, 35% at lunch and 20% at dinner. And the evening loaded diet was the inverse of this. 20% of total daily energy intake was consumed at breakfast, 35% was consumed at lunch and 45% was consumed at dinner. So participants were randomized to the order of diet. Some participants began with the morning loaded dietary intervention before crossing over to the evening loaded dietary intervention, and other participants began with the evening loaded dietary intervention before crossing over to the morning loaded dietary intervention.

There was a baseline period of dietary intake where our participants were consuming a diet, matching the typical macronutrient and energy content of the habitual UK diet. And there were a number of test days at baseline including body weight, blood samples for example, glucose, insulin, and otherwise grelin and some other appetite related hormones.

There were body composition scans and there were assessments of energy expenditure. The dietary intervention itself distributed energy across these three meals, but with no specific timing per se. I e participants were not told that they had to eat the breakfast at 8:00 AM or they had to eat the lunch at 1:00 PM and so on.

So participants ultimately were free to continue with their. Habitual meal times, but they were asked to maintain the same meal time across the duration of the study, and they were also asked to record those meal times at the end of each study phase for three consecutive days. Now, overall, there was no significant difference in, in total between the actual meal timings, which were consumed, give or take for breakfast around 7 45 to 8:00 AM lunch similar around one 1:00 PM and dinner similarly around 6 45 to 7:00 PM so ultimately that aspect of the diet was left to part.

But we can see that there was actually no real difference in, in that timing factor which is a positive when we're thinking about the actual outcomes in relation to weight loss and otherwise. So the diets were designed to be hypo caloric. This was a weight loss intervention where participants were fed to equal to their resting metabolic rate.

All of the diets were tailored to the individual in terms of their height, weight, sex, and otherwise. So the diet was specific to individual RMR requirements. Participants were provided... all of the meals which were prepared in the Rowett Institute at the University of Aberdeen metabolic kitchen. And the participants attended the institute in order to collect their meals.

And they did that a number of times during the week brought their meals out of the center and consumed the meals in their day to day free living context. So it is potentially possible of course with any sort of intervention as tightly controlled as diets wear in the preparation of diets that some energy intake could have been consumed, that was not part of the actual dietary intervention or foods provided.

Nevertheless, when we look at the actual weight loss outcomes, measurements of energy, expenditure, resting metabolic rate, and otherwise, It does not really appear that there could have been any significant differences in those. And we would from the overall data in the study, think

that compliance with the dietary intervention and adherence to the intervention was very high.

So for the dietary intervention itself, the distribution of energy intake we have also, we have already mentioned was 35% energy at breakfast. Sorry, 45% energy at breakfast, 35% at lunch, 20% at dinner. And the inverse of that order. But we also importantly should highlight that the macronutrient content of the diet was 30% protein, 35% carbohydrate, and 35% fat.

So this was targeting, deliberately in the context of a hypo caloric intervention, applying prior knowledge of the efficacy of higher protein diets in relation to weight loss sat and otherwise. Now the major strength from an energy perspective, energy expenditure, or overall energetics perspective of this study isn't simply that the dietary intake was controlled as tightly as it was in terms of full meal preparations, full quantification of energy, content of meals, of micronutrient content of meals and the full provision of all meals for the duration of the dietary intervention to participants, tailored to that individual resting metabolic rate requirement of each individual participant. That's the energy intake side of the equation of the study, which is as robust as it would be possible to achieve for a free living dietary intervention. It's also that the energy expenditure method of measurement was the gold standard, which is doubly labeled water.

Now, doubly labeled water is a method of stable isotopes. Now, one of our previous nutrition understanding nutrition science segments, we discussed specifically stable isotopes and their use in nutrition research. So we'll link to that previous episode before. And I won't go over too much in detail the methods of stabilize isotope use in nutrition research because we'll refer you to that prior episode to listen to in more detail.

But essentially this is a way of quote, labeling a food, or in this case a water and being able to recover based on a certain output, whether that's, for example, a blood draw, or whether that's breath samples or in this context, it's based on urine samples. So doubly labeled rotor requires the consumption of water that is labeled with a specific isotope that then appears in the urine, and there are methods that have been developed to then use the appearance of that isotope in urine to calculate energy expenditure. That's based on carbon dioxide production. So this is the gold standard method of assessing energy expenditure in a free living human

population. And this was used in this trial. And then crucially, there were also measurements of resting metabolic rate and the thermic effective food.

And those measurements were taken when participants attended for testing days at the end of each dietary intervention, before and after each dietary intervention, the thermic effect of feeding measurements. However, in this particular study, Were conducted over six hours following a standardized breakfast test meal.

Now this is why prior to discussing this study, we mentioned the prior laboratory based study where we had conducted measurements over 16, essentially 15 and a half of 16 waking hours. And eventually when that paper is published, it will dovetail on the findings in this paper particularly as it relates to the theory that energy expenditure has a time of day advantage.

So RMR was measured for 30 minutes after an overnight fast, and then the thermic effective feeding was measured over a six hour period following the test breakfast that was consumed at the end of each. There were also other outcomes assessed gastric emptying was assessed also using stable isotopes, but these were isotopes that were derived from breath samples.

There were also subjective measurements of appetite using visual analog scales. And a visual analog scale is a 100 millimeter horizontal line or 10 centimeter horizontal line. And on the left side is, for example, if we were measuring hunger using a visual analog scale on the left side of that, us of that 10 centimeter or 100 millimeter horizontal line would be a verbal anchor, such as not at all i.e. Not hungry at all.

And on the far right side of that, horizontal line would be an opposite verbal anchor, something along the lines of, as Hungary as I've ever been, and participants complete a visual analog scale by then marking a vertical line across the horizontal line that's on the scale. So for example, a participant has marked out their horizon, their line, and we take a ruler and we look at where on that line, that 10 centimeter line that the participant has marked.

And this sounds imprecise, but these tools are very well validated. So for example, if that participant had, when we measure it, it was 8.1, we would know that indicated that they were quite full. And you can use visual analog

skills for hunger. For appetite desire to eat and different subjective assessments of appetite, hunger, and satiety.

There was also continuous glucose monitoring used for the periods at the end of each study phase. So when they had these testing periods after the four week periods of each diet glucose monitoring was continuous over a 72 hour period. And they also used the blood samples to look at, for example, plasma glucose, plasma insulin, plasma cholesterol levels and also there is assessments of gut derived hormones that may influence appetite such as ghrelin, GLP-1, GIP.

So both dietary interventions were followed for four weeks, ie. Because this was a crossover trial participants consumed the first diet they were randomized in the order to for four weeks. Then there was a period of the three days of testing, then there was a washout, and then they crossed over onto whichever other diet they did not start with, and they followed that for another four weeks before there was another period of testing.

So the ultimate number of participants completing the trial from the 31 randomized was 30. So there was one dropout of the overall study. And that placed the study right on its estimated power calculation for statistical power, which was estimated two B 30 of the, those participants there was 16 men and 14 women and their average age was around 51 years. Their weight at baseline on average was 94 kilos, and their BMI was 32.5 kilograms per meters squared. In terms of the order of randomization, 14 started with the morning loaded diet and then crossed over to the evening loaded diet and 16 started with the evening loaded diet and crossed over to the morning loaded diet. Baseline characteristics were similar between groups other than the characteristics we've previously described. But for example, body weight was also similar between groups. And percentage body fat was similar between groups.

Waists circumference was similar between groups of baseline and was to hip ratio. So these were well matched participants with overweight and or obesity. The mean BMI would indicate class one obesity. But these were participants who were also otherwise metabolically healthy.

Okay, so what of the results?

The result that has really had everyone taking the hot takes on this paper has been weight loss. And over the course of the total period of the intervention, there was no significant difference in weight loss between the morning loaded temporal distribution of energy diet and the evening loaded temporal distribution of energy diet.

Both participants lost essentially equal amounts of weight, 3.3 kilos in the morning, loaded group, 3.38 kilos in the evening loaded group. They lost almost the identical amount of weight. And of course that has led to the kind of predictable, it's all about calories. And in a certain context that's not necessarily incorrect. It's just relatively devoid as always of context.

The fact that there was no difference in weight loss between these groups. Is also in the context of the fact that there was no significant relationship between either temporal distribution of energy pattern and total daily energy expenditure. Total daily energy expenditure was essentially similar between groups, and importantly, there was no significant difference in any component of energy expenditure.

Physical activity was also assessed using actigraphy, which is a device worn on the wrist that essentially tracks motion and movement, but can be used with various algorithms to determine physical activity and in relation to the components of total daily energy expenditure; resting metabolic rate, thermic effective feeding physical activity.

We can discussing each of these in turn, because ultimately what was observed was that, for example, with total daily energy expenditure, which remember was measured using the gold standard measurement of energy expenditure and free living humans, there was no significant difference in total daily energy expenditure between either group, but there was no significant difference in their resting metabolic rate.

It decreased as a function of weight loss, which would be expected, but the magnitude of the decrease was practically identical between the groups such that resting metabolic rate in both morning loaded and evening loaded groups was I. After the intervention. Now, the thermic effective feeding appeared to be slightly higher in response to the breakfast group.

But recall when we discussed the methods that TEF was only measured in response to a morning test meal. And thus, this difference simply reflects the difference in calorie content of the respective morning loaded and evening loaded meals. I e the morning loaded breakfast had higher calorie content than the evening loaded diet breakfast, which was lower in energy.

And so the difference observed here is not a difference of diurnal effect or time of day effects, but simply lightly more related to the caloric content of the meal. So in terms of the components of total daily energy expenditure, no difference in resting metabolic rate. No apparent difference in terms of daily steps, significant difference or in a calculated activity, energy expenditure, and a apparent very modest difference in the thermic Effective feeding only measured in response to breakfast.

But that difference slightly reflecting the difference in the calorie content of the morning loaded breakfast versus the breakfast in the evening loaded diet. Now, this is why we ultimately discussed the laboratory study and the previous publication in the Journal of Clinical Endocrinology and Metabolism before going into this paper, because taking this in its context, the lack of evidence, diurnal variation in the thermic effect of feeding once accounting for underlying circadian RMR values.

Ultimately suggests that any apparent difference in TEF is really an artifact of the method of calculation i e. It's not a real effect of time of day differences in energy expenditure. Indeed, based on wider studies, we would assume that if the meals in this study were ISO caloric in terms of that TEF comparison, then we would not see any difference in our laboratory study.

That's precisely the design of the meals. So this study, the present study in under discussion was looking specifically at temporal loading of energy. Whereas in the laboratory study, the meals were isocaloric from meal to meal, 33% of energy at breakfast, 33% at lunch, and 33% at dinner. And in that context, once calculating only above a circadian or above a fasted rmr, there was no difference in the TEF response to each meal.

And then further adjusting for that underlying calculation estimate of circadian rmr, further attenuated and abolished any apparent time of day differences in the themic effect of feeding. So ultimately, while the weight loss outcome is apparently a major focus here, really what's been overlooked

in much of the discussion is that for a free living intervention, this is the most rigorously controlled assessment of all components of human energy expenditure in any dietary intervention trial to date.

And this really drives. A nail in the coffin of the theory that energy expenditure can be manipulated by time of day energy intake effects. And so that theory that was offered as an explanation for greater weight loss in the Jakubowicz and colleague study, for example, with higher morning energy intake, is likely not related to energy expenditure.

However, this is where the findings of this study that appear to be very important have somewhat been overlooked. Recall that this was a controlled dietary intervention. Participants were provided with all of the food. That food was tailored to have a specific macronutrient composition, and it was tailored to their resting metabolic rate requirements in creating an energy deficit relative to that individual's energy expenditure requirements.

So although it was free living in the context of the meals were taken away and consumed in the individual's day to day life, their total energy intake was still controlled. Could there be potential effects of time of day energy distribution where that not to be the case where participants given a prescription for a way to eat as in the Jakubowicz and colleagues papers, but not actually controlled for the provision of foods to participants.

And this is where we need to discuss the main positive finding of this study, which is in relation to appetite. This study measured a number of appetite related outcomes. Recalled that at the end of the intervention periods, participants underwent a three day testing period. And then they also went underwent an in laboratory test day where they were given a standardized their test breakfast.

And they also completed a range of for example, the TEF measurement in response to that breakfast during the three days at the end of these dietary interventions, they also completed visual analog scales, as we previously described, across three consecutive days across each hour that they were awake until bedtime.

So for each day of these three days, each hour, they completed a visual analog scale on hunger, appetite, and otherwise. And then they also

completed that same visual analog scale over 720 minutes in response to the breakfast served in the in laboratory testing.

And what this study showed was that across every specific domain of visual analog scale appetite assessment, the morning loaded temporal distribution of energy produced more favorable appetite and hunger regulation outcomes compared to the evening loaded intervention pattern. For example, hunger was significantly higher in the evening loaded group compared to the morning loaded group Fullness was higher in the morning loaded.

Although that was not statistically significant, desire to eat was statistically significantly higher in the evening loaded group, as was prospective consumption. I e how much did someone think they could eat before a meal? Thirst was higher in the evening. Loaded group preoccupation with food was also higher, although that was not statistically significant.

An overall appetite score was higher in the evening loaded group, although that was not statistically significant. When we look at the average visual analog scale rating over the course of the three consecutive days for which it was recorded on hourly basis, we can see that the morning loaded group had significantly lower appetite across the entire day, beginning, obviously early in the morning, but with sustained reduction in appetite across the period between breakfast and lunch.

And again, across the period between lunch and dinner, the only time in which these rated average appetite scores averaged over three days were similar between the morning and evening energy loaded groups was in the evening after the evening. Energy loaded group had its dinner, ie. Between around the hours of six o'clock, which is give or take roughly when on average dinner was consumed to 10 o'clock going to bed, and this was only bringing the evening loaded energy group appetite ratings equal to the morning loaded energy appetite groups for that period in the evening. In response to the breakfast served in the in laboratory test day, this was also the same. There was greater suppression of appetite across the period from consumption of the breakfast to 360 minutes after that breakfast, and then again, then following the consumption of a lunch, which the participants were free to consume themselves.

And although we would expect that finding because of the energy content differences between the morning loaded and evening loaded groups, it gives a snapshot of plausibility to the fact that in the average of the three consecutive days, there was appetite suppression extended across the day in the morning loaded group.

The metabolic correlates of this appetite suppression in terms of grelin, the quote, hunger hormone, or in terms of the in cretin hormones. GLP-1 and GIP were also measured in this study. And although at baseline on the in laboratory test day, these appetite hormones were all equal between the morning and evening loaded energy groups.

Two hours after these respective meals for the breakfast in the morning, loaded and evening loaded groups, grelin was significantly higher in the evening. Loaded group, G i P and GLP one were lower, ie. They were significantly higher in the morning loaded group, and PYY was also lower in the evening group.

The study also, if you recall from the methods used, stabilize the top analysis to look at the rate of gastric emptying. And what was found in this study was that in response to the high energy breakfast, the morning loaded dietary pattern, there was a significant delay in the time of gastric emptying.

Conversely, in the evening loaded group with the lower energy breakfast, gastric emptying was significantly more rapid in the morning and piecing all of this data together, it appears that in effect, in response to a small meal in the morning, there is a faster, more rapid rate of gastric emptying of food, leaving the stomach an earlier return to hunger, less regulation of appetite in terms of appetite, hormones like ghrelin and GLP-1 and GIP.

And also a higher than level of subjective appetite, desire to eat and otherwise that extends across the entire day. And this is the context that's slightly being missed in some of the discussion in relation to this study because if we look at those other papers that appeared to suggest greater weight loss in morning loaded energy groups, what we see is that, as stated, those diets were not controlled.

Those diets were consumed in a free living context and participants self-reported energy intake. So when those papers said our participants

consumed equal amounts of energy, that's probably misreporting. And if we take away the fact that this particular study controlled for all the components of energy intake and total daily energy, output or expenditure in the way that it did.

The findings in relation to gastric emptying objectively measured appetite hormones and subjectively measured appetite, desire to eat hunger and otherwise would actually provide a plausible explanation for the differential in weight loss Observed in these previous trials, i e that there is a time of day effect, not of energy expenditure, but of appetite regulation and.

There are some other findings in this paper that do warrant discussion very briefly. One is that overall there was no difference in much of the metabolic outcomes. For example, there was no difference in any of the outcomes related to blood cholesterol levels. There was no difference in any of the outcomes related to, for example, in measured insulin resistance or in relation to HbA1C or in relation to fasting glucose or in relation to blood pressure.

However, one interesting finding that does warrant common is in relation to the continuous glucose monitoring data because while most people in the area of chrononutrition, even prior to the publication of this study, probably were starting to infer that there was likely unlikely to be any energetic advantage to time of day energy intake, one thing that has been demonstrated is diurnal variation in, for example, insulin sensitivity and glucose tolerance.

Now, in this context, the distribution of energy observed between these two diets in the present study does not appear to have influenced any of these outcomes. However, this is a hypo caloric intervention and ultimately the significant improvements in some of these outcomes that were observed, and not all of them were statistically significant in their difference, for example.

But the differences that were observed are primarily explained by weight loss. And this could also potentially be viewed as well. There's no time of day effect necessarily of temporal distribution of energy as it relates to metabolic outcomes. But a tab to be left open in this particular study is in relation to their continuous glucose monitoring data, which again, was monitored for

the three consecutive days at the end of each dietary phase and overall weight loss significantly reduced their mean daily glucose level and their glucose areas under the curves and their maximum glucose levels and their glycemic variability, which is a measure of how much blood sugar, correction, interstitial glucose, which is what a continuous glucose monitor measures at vary over the course of the day.

But they conducted an analysis where they looked at. The diets and the time of day in four distinct time blocks. So from midnight to 4:00 AM, 4:00 AM to 8:00 AM, 8:00 to midday, midday to 4:00 PM 4:00 to 8:00 PM and 8:00 PM to midnight. And what they showed was that there was significantly higher increases in postprandial interstitial glucose in the evening loaded diet between 8:00 PM and midnight.

And while, yes, we could say that this simply reflects the fact that they were consuming their highest energy content of the diet in the evening, a concomitant rise in interstitial glucose was not actually observed in the morning loaded energy diet. And so this. Suggests that when that large breakfast was consumed in the morning, there was not necessarily the statistically significant increase in postprandial interstitial glucose or the rise in those interstitial glucose levels that were observed.

Now there's no point in making too much of this finding, but it is a signal in the data, which as stated in terms of these metabolic outcomes, is primarily driven by weight loss, which we would expect based on prior knowledge that there is that diurnal at rhythm in glucose metabolism still somewhat indicated despite the fact that this was out that these overall metabolic outcomes were primarily driven by weight loss ultimately.

So where does this leave us in the context of. The wider literature well published very recently after this again, in cell metabolism, was a paper by vvi and colleagues from the Harvard Krono Nutrition Group that I referred to earlier. And this compared an early meal schedule to a late meal schedule in a very tightly controlled inpatient laboratory study.

The early meal schedule had meals consumed an hour, five hours and nine hours after waking for breakfast, lunch, and dinner respectively. And then the late meal schedule had participants delaying their meal schedule by five hours and then consuming their first meal five hours after waking, and then

lunch and dinner 9 and 13 hours after waking respectively. And what they showed was that late eating significantly increased hunger led to a significant daily increase in the leptin to growlin ratio, and the elevation in hunger persisted across the day. So this is dovetailed nicely in relation to the University of Aberdeen Big Breakfast study by confirming that there is a time of day effect of appetite.

And while the Aberdeen Big Breakfast intervention was important as a dietary intervention providing the most robust assessment of all components of energy expenditure and controlling energy intake in the context of a weight loss dietary intervention, such that it concretely showed that there is no energetic advantage to time of day energy intake.

But even in that context of controlled energy intake and hypo caloric conditions and weight loss improving metabolic outcomes, it clearly demonstrated that there is a significant time of day effect in relation to appetite regulation, hunger, and related objective measures of appetite hormones, and this, not enhanced energy expenditure, is more likely to be the explanation for differentials in weight loss observed with higher morning energy intake when their energy intake is not controlled. And participants are free to pursue the intervention themselves and stick to it as best they can on. So relevant links will be below and accompanying this.

And for any questions that arise from the discussion of this paper, please submit them to Danny and myself. And this is likely to be a topic that we will revisit. So please do submit any questions that you have arising from this discussion. I hope that was helpful, and we will see you again for another segment of understanding nutrition science in the future.