
# *Episode Transcript*

Danny Lennon: Hello, and welcome to another episode of Sigma Nutrition Radio. This is episode 469 of the podcast. My name is Danny Lennon and I'm here with Dr. Alan Flanagan. So for today's episode we are going to cover the topic of chrononutrition, which we have done so in quite some detail in previous episodes of the podcast, as well as in other forums.

And of course there's been some specific episodes on niche topics within that, as well as some big overview level episodes. And I'll link to some of those past episodes in the description box if anyone is new to the podcast or maybe hasn't heard those. But the goal today is to maybe give an update on our position on some of these things, talking about either some new research that has came out over the last year or two how that has influenced some of the conclusions we can come to and how that maybe has potentially changed what conclusions we can make going forward in practice based on the current evidence base.

So with that in mind, it might be useful to start with either an intro to chronobiology generally for people, maybe first hearing this, or for people who have listened to our past episodes, a refresher of some of the key terms and ideas that relate to this topic of chrononutrition, which of course is this branch underneath chronbiology.

Alan, given this is an area directly related to your research, what is the best way to introduce some of those terms to people around chronobiology, circadian rhythms and then how there's a connection to eating and essentially this field of chrononutrition, what we actually talking about?

Alan Flanagan: Yeah, so the concept 'chrono'; obviously, meaning time. So the overall field of chrononutrition is really the study of the interaction between our biological rhythms, circadian rhythms in metabolism and other rhythms; behavior, and the interaction with behavior as well. I'll explain what we mean by circadian and behavioral rhythms.

It's the interaction with those biological and behavioral rhythms and nutrition. And importantly for the conversation, which often becomes quite reductive in a lot of the conversations, particularly as we might see, claims made about, say, fasting or time-restricted feeding or otherwise.

Chrononutrition really covers a range of exposures potentially. So we could have: how energy is distributed across the day. We can have meal frequency, meal timing and they can be obviously distinct. We can have the regularity of meal intake, we can have the duration of the eating period. And these are obviously factors that could be considered as an exposure in isolation, but they obviously all do have interrelationships with each other.

So that's really how best to conceptualize this, is that chrononutrition is an umbrella term and that it's important that within that we're granular with defining what exactly the exposure is that we're talking about. And as I said, there may be an interrelationship between some of these factors.

So for example, the distribution of energy can often influence and relate to the timing of meals across the day. And the frequency with which those meals are consumed, like the spacing between meals and all of these then add up to potentially influence metabolic health and disease risk.

And so the question then is why would there be that potential relevance for metabolic health and disease risk over the long term? And that is this relationship with endogenous circadian rhythms. So the rhythms that we have in our body have different periods of their timing. Circadian rhythms are defined as being rhythms that have a period length of a little over 24 hours. That's in humans. And so because they're slightly longer than the 24 hour period of the earth's rotation, we need environmental time cues to synchronize those rhythms to the exact 24 hour day. The most important time cue in humans and most diurnal mammals is bright light that we have during the daytime.

And along with other time cues, we've come to appreciate, for example, the role of meal timing, potentially influencing timing in in what are known as peripheral clock. So light primarily influences the central clock, which is in the hypothalamus, the superchiasmatic nucleus or the SCN, is what's often known as the "central clock".

This kind of master regulator. And it's from there that circadian rhythms are generated. And then we have rhythms in peripheral tissues and organs. So for example, the liver or the pancreas. And they can actually respond to the timing of, for example, nutrient intake. And there are other behaviors that can input such as physical activity and otherwise, during the 24 hour day. So overall, I think from a nutrition perspective, to simplify this, we have light as the primary signal for the central clock in the brain. We have meal timing as an important additional signal to the overall circadian system, but particularly important for what we call peripheral clocks, which are the timing of these rhythms, metabolic rhythms in say the liver or the pancreas.

And that's why the interaction of these factors like distribution of energy or the timing of meals across the day is potentially a variable that is important for human metabolic health. And potentially long-term cardiometabolic disease risk.

Danny Lennon: Yeah, so I think one of the important things to note there is that when we're looking at this relationship between eating and these circadian cycles and these circadian rhythms, is that there's really a bidirectional effect we could look at, or we could look at it through two different ways.

One is this impact of when we eat that can act as a cue, as you just noted, to therefore influence these circadian rhythms or circadian cycles that happen in various different peripheral tissues around the body and impact different hormones and different processes. So we're having an impact there based on this cue of eating.

But then we also have a circadian cycle or circadian rhythmicity to certain things that might relate to digestion of those nutrients. So changes in insulin sensitivity or gastric emptying or beta cell function that may have infers of when or how. Would it be better to eat? And these are at least some of the hypothetical questions we can get to.

So there's these two different ways we can look at it. And I like that you note that this area of chrononutrition is much broader than maybe the narrow focus that sometimes gets reduced to of feeding and fasting windows or when to stop eating. And it's really anything to do with the, these temporal effects of frequency when we eat the composition of those meals at different times, the length of those windows.

And then as we'll probably come to most notably calorie distribution. And whilst these are all distinct, as you say, there's notable overlap between them, that it's one of the main challenges that we've highlighted before of when you're just looking at the length of a feeding and fasting window, for example just knowing that without knowing, how was energy distributed within that window? Or what was the composition of meals at different times in that window? Or the frequency of eating in that window doesn't give us the full picture. And so we really need to consider all of those

Alan Flanagan: There are interrelationships between these factors that, that are potentially quite important. For example, some kind of research in the early 2000s in this area noted that in individuals who had a tendency to have later meal timing, the satiety that they derived from a meal was less than it potentially could be earlier in the day.

And as a result of that, what you ended up with was less of a duration than between meals. So people would have earlier return to hunger, would eat another meal. The caloric content of that meal would be greater than before because they're less sated. And so you would actually have this pattern of energy where there was less time between meals and greater energy being consumed from meal to meal. So if we're thinking about that in some of these, we've got a number of factors there. We've got obviously the distribution of energy and where that is across the day. We've got the frequency, the meal frequency that is occurring within that. We've obviously got the timing component of that as it relates to say what we would call clock time. But an important factor that, that we'll elaborate on is this distinction between clock time and biological time. And this may be an important factor in mediating some of the outcomes and perhaps some of the inconsistencies that have been observed in this evidence.

We're probably at a point now, I would say where, were we to listen back over the last episode we did on this. I think that there's probably a couple of positions that we would be letting go of. And possibly some newer positions that we maybe didn't even mention or emphasize in that previous episode, which I think was 2019 or 18 even.

So it's been an area that I think we now have the ability to have a more evidence-based conclusion over what factors may be important in terms of underlying metabolic outcomes that may relate to why there may be time of day effects or interactions, timing of food intake and all of those, I use that term timing as a broad, all encompassing reference to these subdomains of say, distribution regularity, et cetera. And potentially metabolic health and circadian rhythms.

Danny Lennon: And as you note that I was thinking too, 2019 as well where I wrote a guest article on Stronger by Science on this topic, which I think most of the general ideas are probably still sound, but there are these specific areas where, if I were to go back now, would probably be able to change a number of those conclusions that were speculated on.

And one that will definitely come to is actually related to work you've done in the lab in relation to the potential impact or lack thereof of the thermic effect of feeding based on timing. And we'll certainly cover that off, but that would be certain something to change. And the other thing I think that is worth noting that came to mind as you were speaking is that when we think of something like a focus on time-restricted eating, which has been a lot of hype about, and a lot of the focus on the length of the window or where in the day that's placed.

And again, that just becomes, if that's the only focus we're missing out on all these other overlapping factors to the point where, it doesn't mean much because the actual calculus of putting all these things together is very complex. So as a hypothetical example for people, if we were trying to work out what is "better": an 8 hour window or a 12 hour window, that's one thing when we match, say, distribution between those two windows.

But what if for the eight hour window, we have the bulk of those calories at the end of that window and for the 12 hour window, we have the bulk of the calories at the start, how does that change the calculus here and which one of those factors is going to have more of an impact? And how do we even work that out again, quite complex before we even consider anything else.

So I think just wanted to put a pin in that kind of idea for people to hopefully appreciate, rather than us reductively looking at, okay, what is the best time-restricted eating or intermittent fasting regime based on the number of hours I should fast or not.

Alan Flanagan: Yeah. And that, that really is where I think the interpretation of this area really got drawn down certainly in the, I think even prior to more awareness of the evidence for chrononutrition. And in the scientific literature there was this kind of popular explosion of interest in fasting as a strategy. Martin Berkhan's LeanGains and these other kind of approaches that really blew up in terms of popularity way ahead of the research in this area.

So I think that meant that when the research did start coming out, there was almost like a bias towards jumping on time-restricted feeding studies. There was the Sutton and colleague's paper from Courtney Peterson's group in 2018, which was a really interesting, controlled study.

That really came on the back of some obviously quite suggestive and probably over exaggerated in terms of human context findings from rodent models where you could literally stop a rodent with energy excess, but if you restricted the period of its feeding, it was relatively protected against the adverse effects of that feeding in terms of, adiposity or increased obesity in, in, in the mice or rats.

And of course we never really want to rely overly on mechanistic speculation from animal models unless it's being reproduced in human data. And I think from the time restricted feeding research, this is something we can get into, I think largely the initial promise that showed and the initial, speculation of what that evidence meant.

And certainly I think this would be something going back to that previous episode where I would've been a lot more potentially optimistic about where that research seems to be going. Whereas now, it probably isn't the kind of exposure in terms of the magnitude of effect once we factor in, say, energy balance and other variables that, that it may have appeared to be from some in enthusiastic early findings.

But there are other dimensions within this overall picture. So one point that I think we could possibly say now based on current evidence is, I'm not sure, for example, that a restriction on the feeding period is particularly necessary. But I do think based on the evidence that some other factors here, like the overall distribution of energy and the proximity of energy intake to someone's biological night may be important factors.

And those factors are to me, probably more important now than just the feeding window or the duration of that feeding window itself.

Danny Lennon: Yeah. So maybe let's get into that because this is crucial and there's a couple of things I'll note for people. First as you've said, there's been, at least in maybe certain areas, and certainly as it pertains maybe to the fitness industry in particular, obviously interest in things like fasting, intermittent fasting, and then time restricted eating gets pulled into that. And of course then the focus is tending to be around body composition, which can lead to it only being viewed through that lens, for example. And that's something we discussed actually on a previous episode of the podcast that people can check out called 'Is Time Restrictive Feeding Dead?', where we talked about some of these issues in relation to one particular study, but this more broader point that you mentioned, I think is the really crucial thing here of how do we consolidate where the time-restricted eating literature has gone over the past couple of years with this broader evidence base we have in chrononutrition.

And what you've noted there is that it may be a function of potential benefit or the signal of a benefit. Was more a function of that distribution, of avoiding lots of calories distributed towards biological night. Because when we think about what restricting the feeding window does, going from say, 16 hours to 12 or to 10 or to eight is by nature it's probably, meaning it's less likely someone's going to have a lot of calories towards biological night, or at least it reduces the odds of that happening which again may be where that benefit is coming from as opposed to a specific number of hours fasted. Would that be where you tend to see this evidence as moving us more towards?

Alan Flanagan: I think so. I think it might be more related to, and not necessarily just the elimination entirely of evening energy intake, but certainly a more earlier, conclusion of eating, shall we say. Rather than just say eating within a certain window, and we do have a number of recent interventions that may suggest that there has been there was another publication this year in Nature Communications; Xie and colleagues, and this was an RCT comparing an early time-restricted feeding protocol to a mid time restricted feeding protocol.

So the early time-restricted eating period was between 6:00 AM and 3:00 PM The middle period was an eating window from 11:00 AM to 8:00 PM and then importantly, they had a control group, which was just, any eating duration over eight hours with no restriction on, when they were eating or not.

And overall, again, there was, fairly underwhelming differences between groups for certain outcomes like fasting blood glucose, and for insulin resistance. There was a difference in favor of the early time restricted feeding group. And that may again relate not necessarily to the duration of the eating window per se, which is what people typically start to focus on in interpreting these studies, but it might relate more to the alignment of the meals consumed in the early time-restricted feeding period to the phase of the day that we probably more robustly than most other findings aligns with the diurnal variation in glucose tolerance. So it may not be that it's because they ate within an eight hour window. It's likely more the alignment of those meal timings, in my opinion anyway. With the diurnal variation in glucose tolerance, such that more energy intake is coming at a time of day where we have very robust insulin and glycemic responses to food intake.

And, but overall, we have, studies that have, there was another, again, this was a study that I'm referencing now was conducted in China. There was another intervention that was published earlier this year as well, which was also conducted in China, and showed no difference between time restricted eating and a control group on weight loss, i.e., Both groups lost weight in the context of just energy restriction. So there, there are a couple of things now, I think from the time-restricted feeding standpoint that we could likely say and one limitation that I think has come out from these more recent studies, and this was the same with the low and colleague study that we discussed on that previous episode, is there's an assumption that the restriction on feeding time or the duration of the eating window is the exposure itself and that nothing else matters within that.

So quite a frustrating thing with some of these recent time-restricted feeding studies is that they've only quantified the eating window de despite gathering data on das. So we have no actual, so for example, if we've got these two eating windows in this study, three 6:00 AM to 3:00 PM and 11:00 AM to 8:00 PM and we take that 11:00 AM to 8:00 PM this mid time restricted feeding group, we'll based on, again, diurnal variation and for example in glucose tolerance, if someone within that mid group ate 50% of their energy at 11:00 AM with their first meal, they had a big breakfast and then they ate 25% at say 3:00 PM and then dinner at seven, that we would expect that to be different to someone who ate 20% of their energy at 11:00 AM another 40% at 5:00 PM and the other 40% at 8:00 PM. So we would expect those to be producing different outcomes as far as metabolic responses.

So it's frustrating that there hasn't been more granularity in defining and in considering that it's not just the duration of the feeding window that's potentially important. It is these other factors like the distribution of energy the timing between meals and other and otherwise.

So that's the kind of limitation on some of these recent studies. Nevertheless, what we do have, as far as a signal from the noise in the TRF research is there's definitively, I think at this point, nothing special about a restriction on the feeding window. In the context of say, a similar amount of energy between 8:00 AM and 12:00 PM or between, say, an eight hour duration and a 12 hour duration, considering those other factors there may be enhancement in some metabolic outcomes, particularly for glycemic control or insulin sensitivity.

But based on other research we have, that's likely not the restriction on feeding time that is leading to those outcomes. It's the alignment of those. With this period of, enhanced glucose tolerance early in the day rather than later in the day where we have slightly diminished glucose tolerance, we tend to end up with slightly more elevated blood glucose levels slightly more sluggish insulin responses and as a result a higher insulin area or glucose area under the curve in the evening.

And we have quite a lot of research demonstrating that diurnal variation in glucose tolerance between the early and later periods. So from a time restricted feeding perspective, I think right now, I think the overall conclusion would be there's really nothing. There's really nothing special about time-restricted feeding as far as weight loss goes there's likely when, calories and macronutrients are accounted for. There's likely no greater enhancement of weight loss or energy expenditure if someone just eats within an eight hour window versus say a 12 hour window. But that there is potentially important factors related to potentially metabolic health that relate to the distribution of energy.

And with the recent publication from the Aberdeen Group of their tightly controlled intervention and then another study published by Frank Scheer and Marta Garaulet's group which was a lab-based study looking at appetite. Between some of these recent tightly controlled studies of a variable that we can now add into the conversation around distribution and timing of energy is appetite regulation.

And that potentially provides a bit of a unifying explanation for some of the early studies that suggested greater weight loss or potentially enhanced energy expenditure, which was one of the theories offered for the reason that there was greater weight loss with some of the interventions by Oren Froy and the Jakubowicz group that showed greater weight loss with high morning energy intakes compared to high evening energy intakes.

Danny Lennon: So with this time-restricted eating literature a couple of those key points on the body composition front, we can say it's pretty clear that when you match for calories and macronutrients, there's going to be no superiority to shortening a feeding window versus a longer one once those are accounted for.

And much of that earlier associational data showing a potential difference in, say, weight loss can be attributed to that. People are eating different amounts. And that could be either behaviorally because they're eating have a shorter window or as you say, there's this appetite variable, which we'll come back to.

So that's on that body composition front. But as we've noted, then there are other benefits that we care about for example, on the metabolic health and particularly in relation to glucose and insulin there, that's been where there's been a lot of hypotheses around this potential benefit. And how that seems to line up now is considering what these TRF interventions are doing.

Based on those other facets we mentioned earlier, so how is it influencing timing of meals relative to those biological rhythms? How does that maybe change meal composition in that kind of meal closest to bedtime? And where is the percentage of people's energy coming? And we can almost consolidate a lot of the mechanisms and the findings in those different areas and explain why there's observations of benefit in some TRE studies and not in others.

That it, like you said, it's probably more down to considering what we know, these diurnal variations in beta cell function, in insulin sensitivity in the post pral response will get to consuming carbohydrates or fat. And therefore where we replace those energy. And then when we have those meals timed as opposed to specifically how many hours of the day did one fast four or not.

So I think that's really useful for tying in a lot of that associational evidence. We have those mechanisms and then those different layers of timing, composition, calorie distribution and so on. So one of the things that I did want to get to in particular, and that I made a note of in relation to the article on Stronger by Science was this area around thermic effect of feeding or diet induced thermogenesis, essentially the increase in energy expenditure after eating. And I think a number of years ago, this was one of the. Places where there was mechanistic speculation, where there could potentially be a benefit. In other words, if we eat a meal earlier in the day versus later in the day, we get this really enhanced diet induced thermogenesis or a thermic effective feeding after a meal.

And I think it was a study by Morris and colleagues that showed something like 44% increase. And so this, at least mechanistically would say, oh, if we're, if we were to do this over a long enough period of time, you're increasing your energy expenditure and therefore you could have some benefit from that.

But as I noted from work that was done from you and your colleagues has been very helpful in shining a light as to explain maybe why we were seeing those results and that. Potentially an artifact of something else as opposed to a direct benefit of aro nutrition protocol, so to speak.

Can you maybe just introduce people to that idea and what do you think is the most kind of current up-to-date position on the impact around meal timing tf and the potential implications for that?

Alan Flanagan: Yeah so this idea that there's diurnal variation in our thermic response to feeding goes back to the early nineties. There was a group that looked at circadian variation in a range of metabolic outcomes. Roman and colleagues, they were a French group. They looked at circadian variation and in lipid, metabolism and circulating lipids and also in thermic effective feeding. And what they showed was that in comparing a meal consumed at 9:00 AM clock time, morning, versus 5:00 PM that there was a higher, as a percentage of the energy in the meal consumed, there was a higher TEF response in the morning. Now again, it was modest, so they had a test meal of around 500 calories, of which around 15.9, nearly 16% of that energy consumed was calculated to be the thermic effect of feeding was 15 to 16% of that meal at 9:00 AM and then at 5:00 PM it was around 13 and a half percent of the energy consumed. And then at 1:00 AM it was near just about 11% of that meal consumed. So you could see these kind. Incremental lower thermic effect of feeding responses calculated as a percentage of the energy in that test meal, which as I said, was about 500 calories. Now, importantly, the method they used to calculate the thermic response is you need a baseline.

So typically that's going to be a fasted resting metabolic rate measure that's conducted in the morning, first thing after an overnight fast. So this is a true fasted baseline. There's been an extended overnight fast. There's no food intake. It is a genuine measure of someone's resting metabolic rate. And when they calculated the energy expenditure of the meal, it was over and above that fasting RMR baseline.

And so they were constantly referring back to a measure that was taken first thing in the early part of the day. And even at that, they showed relatively modest differences in terms of the percentage of the test meal that was ultimately burnt as the thermic response to that meal.

And later on, a number of groups. Looked similarly at this diurnal variation, and yet you referenced the Morris & colleagues study, which saw a 44% lower TEF response at 8:00 PM compared to 8:00 AM now again, the percentages are potentially over-emphasizing the actual magnitude of difference. So they calculated TEF as calories per minute.

And in the morning in the evening at the 8:00 PM meal that was 0.13 calories per minute. And in the morning that was 0.24. So we're talking about a difference in this 44% of point 11.11 calories per minute. And that was in response to a test meal that provided a third of daily energy, 33%, so a high energy meal.

But, and then perhaps the one that I think really exploded this, the suggestion that there was enhanced energy expenditure in the morning was a paper that was published in 2020 by Richter and colleagues, and this was a group in Germany that looked at variation and TEF response. And what they reported was that the TEF response to breakfast was two and a half times greater than the TEF response to dinner.

And what was interesting about this study was they had both a high energy and a low energy meal condition. So the high energy breakfast and dinner had over a thousand calories, around 69% of their daily energy intake. And the low energy only had 250 calories or about 11% of their daily energy. And this should have been something that more people I think, noticed in the bar charts that presented the TEF response to the low energy meal, for example, in when it was consumed in the evening, in dinner, it showed a negative test response. That's physiologically impossible. You can't consume energy and have a negative energy postprandial response.

So all of this is to lead into a bit of background as far as there was this obviously suggestion from this research that there was enhanced energy expenditure, specifically in the form of the thermic response to feeding in response to breakfast or in the early part of the day compared to the evening. And you also had, for example, the Daniela Jakubowicz and colleagues 2013 paper that showed around a six kilo greater weight loss in women with overweight and obesity, where their eating distribution pattern compared 700 calories of breakfast and a 200 calorie dinner lunch was always the same 500 calories versus the opposite of that 200 calories of breakfast, 700 at dinner.

And the group with the high morning energy intake lost around, give or take six kilos more. And one of the theories, or that they offered in their discussion as to what might explain that finding was this enhanced morning thermic effective feeding. Now, in the paper that I said, reported two and a half times greater thermic effective feeding in response to morning energy intake versus evening, the Richter colleagues' paper and indeed the Morris and colleagues' paper, they used another method of calculating the thermic effect of feeding, which basically used the pre-meal measurement.

As the measurement that you then calculated energy expenditure above that measurement. And so this is important because if you are, for example, consuming three meals a day, you've got a breakfast at 8:00 AM a lunch at 1:00 PM and a dinner at 6:00 PM and you've measured people fasted for the first measurement of the day after an overnight fast, which is their true fasted baseline.

And then you feed them a meal. And let's say that meal has 700 calories, but then you're measuring their thermic effective feeding response after lunch, but they've now had 700 calories. They're no longer in a true fasted baseline. Even if you leave five hours between those meals, there is some residual metabolism from that meal, right?

So now if you measure their resting metabolic rate before lunch, you've got a higher baseline. Because you've, because you've added energy into the mix. And then if you consume lunch, let's say that lunch has 500 calories and then you get to dinner, you, now you now have a higher baseline again, because if there's two meals under the belt, again, even if there's some degree of meal spacing between these and looking at this created a kind of difference in what your baseline values were.

And so our postdoc, now former postdoctoral researcher, on this project, she's now moved on, Dr. Leonie Ruddick-Collins, he had quite an energy expenditure background. And her PhD was very focused on energy expenditure. So this was like a topic, a question, a methodological issue that was really live for her.

And a question that she kept posing was: how do we actually think about the underlying potential circadian variation in energy expenditure? So we're measuring this TEF response, but there's potentially two factors at play here that's showing a big difference between morning and evening.

One is if you're using the baseline fasted measurement to calculate over and above your energy expenditure response to subsequent meals, but you're still just calculating that over that one baseline at that time of day. And then two, if you're calculating your energy expenditure over and above the preceding measure before a meal, then you've got different baselines essentially for those meals.

Based on research that came out, there was a paper published by the Harvard chrono group, Zitting & colleagues in 2018, where they pushed participants back over 36 days in a lab rest measuring fully rested metabolic rate after an overnight fast, an hour later each day. And they were able to map for the first time the circadian variation in resting metabolic rate.

And this circadian variation tracked energy or tracked body core temperature, such that your underlying resting metabolic rate was lowest when core body temperature was lowest on average, this was about 5:00 AM and then it increased over the course of the day, and it peaked around 5:00 PM in line with the peak in core body temperature.

Now, core body temperature is a central circadian rhythm. It's robustly tied to the central clock. And this implies that resting metabolic rate varies as a circadian rhythm across the day in line with core body temperature tied to the central clock, so to speak. And so using the values for what the energy expenditure the RMR would be at any given time of day, Leonie constructed a model that provided a means to adjust for that underlying circadian value in energy expenditure.

And so what was fascinating was when we did an analysis originally with our energy expenditure data that we had from the lab study in Surrey, we had 14 participants and we had the advantage that other studies didn't of having measured energy expenditure across essentially the entire waking day of the 16 hours, our participants were awake. We measured energy expenditure over 15 and a half hours. So basically using that data, we calculated the thermic effect of feeding using the pre-meal as a baseline. The pre-meal RMR measure is a baseline. And when we did that, we've replicated what the other groups had shown: we showed a twice as high TEF response to breakfast compared to dinner.

Then when we calculated it only using the fasted baseline RMR as our baseline calculation and then calculated the TEF response to breakfast, lunch, and dinner over the fasting RMR measure; that difference was largely abolished. But then when we further then did that analysis adjusting for the underlying circadian value in RMR, it was attenuated even further such that there was basically no difference across the day in the TEF response to meals and this is ultimately in line, I think more if we just put basic nutrition hats on, we know that nutrients have a fixed stoichiometry. So what do we mean by that? We have a fairly well quantified value for how much protein, for example, is expended as heat in the process of digestion metabolism. We have a fairly good handle on the value for carbohydrates and for fats.

So we know really that these nutrients have a relatively fixed contribution to thermogenesis. So in the context of mixed meals, obviously other factors are important, like the total energy size of that meal and postprandial responses can continue, over six hours if a meal has a thousand calories or more in it.

But ultimately what this was suggesting was that the studies that suggested a very enhanced, greater thermic effect of feeding in response to morning energy intake were likely a reflection of mathematical error; i.e., they were essentially the bias introduced by using that particular approach of calculating TEF above the pre-meal resting metabolic rate measure rather than above a fasting baseline. And two, while adjusting over the fasting baseline did abolish that apparent diurnal variation in thermic effect of feeding, what it didn't do was account for the underlying circadian energy expenditure. Because if you were to constantly calculate… if you did your fasting RMR measure at 8:00 AM you're constantly only calculating over and above whatever the energy expenditure from an underlying circadian RMR was at that time point. Whereas if you then factor in how that might change over the day, it's attenuated even further. So our suggestion from this paper, which was published in the Journal of Clinical Endocrinology and Metabolism, was that there is no diurnal variation really in the thermic effect of feeding. There is a diurnal variation in the underlying change in resting metabolic rate, in energy expenditure in that context such that the time of day that a TEF measure is conducted is going to have this feeding into whatever the apparent thermic effective feeding response is. So when this is accounted for the reality that we proposed was that the magnitude of the difference between the morning and the evening period is trivial.

And that there's the underlying energy expenditure. The circadian RMR removes this apparent artefact of a diurnal variation in thermic effective feeding. And that it's from this methodologically flawed approach to calculating TEF, importantly does not explain differences in weight loss observed in those studies because there is no hacking or enhancement of thermic effective feeding or energy expenditure according to time of day.

Danny Lennon: Yeah. And this is such an important and interesting finding, not only for explaining some of those previous studies you mentioned, but implications now for future research in this area when we're looking at timing and this potential benefit for energy expenditure, which has been hypothesized that this should really be something that's factored into all that future research.

And as a way just to recap for people. The previous study showing this really high thermic effective feeding response or this enhanced one, let's say earlier in the day versus later, most notably the Morris study and the Richter study. Both of those you said used a pre-meal measurement as the baseline to compare to, so a pre-meal measurement of their resting metabolic rate.

And then you, we can look at then that after the meal and then use that as a way to measure the TEF. But as you note there's two elements to this. The RMR is different across the day. There's this diurnal variation. And then second, we also know that because people had eaten earlier in the day, that is going to change their pre-meal RMR for later meal points because they're not completely fasted at this point.

And so what that's doing is if that's elevating that RMR slightly for your pre-meal measurement, then the difference you get afterwards is going to look smaller by comparison. And then you said you can take that finding Take that into account. And then the model also factors in this dal variation in resting metabolic rate across the day.

And when you factor in both of those things, that this enhanced t f response is actually not an enhanced TEF response. It's just explained by the fact that this diurnal variation in RMR as well as these differences on where you take that pre-meal measurement.

Alan Flanagan: Yes, exactly. And so bear in mind that we fed our participants isocaloric meals. So their energy, which was targeted at weight maintenance was also equally distributed between breakfast, lunch, and dinner. So once accounting for the circadian RMR, the actual percentage of the energy of that meal that was used as the in, in thermogenesis in the thermic response was around 7.4% for breakfast, 6.6% for lunch, 6.7% for dinner.

And again, that's what we would expect when, these meals are isocaloric and macronutrients are matched between these meals because nutrients just have a fixed value for their thermogenic effect. But of course where we to have distributed energy, another way we would expect that.

So let's say for example, that we. 60% of energy at breakfast and 20% respectively at lunch and dinner. We would expect the theft TEF response to breakfast to be higher as a function of the just greater energy intake. So the TEF response will just be proportional to the energy, content and macronutrients of the meal, but it won't be enhanced by the time of day that meal is consumed.

Danny Lennon: So if we then start getting into some of this distribution works specifically and how this factors in. Because as you noted and one of the studies I think we've referenced a number of times that was was put this distribution question on the map was the Jakubowicz paper from 2013. And as for some context for people that compares this large breakfast and small dinner to the reverse: a small breakfast and large dinner condition and showing this significant benefit for weight loss to the morning loaded condition, let's say. And that has led to a lot of the work that's gone on in Aberdeen and who are of course, quite tightly associated with your group in Surrey as well.

And this general "big breakfast study" project that encompasses probably going to be a number of publications and for premium subscribers. They would've listened to Alan do a detailed description of one of the publications recently from the big breakfast study that attempted to look at what was essentially found in papers like Jakubowicz and maybe tightly regulate things a bit more and look at some findings.

So in relation to that distribution, can you maybe, first of all, the lay of the land right now in relation to these comparisons between say, morning loaded versus evening loaded conditions.

Alan Flanagan: Yeah, so like you said we've had those studies that suggested that there was greater weight loss with this front loaded pattern of energy distribution, particularly where it was con compared to the inverse sequence i e people consuming low energy breakfasts and high energy dinners.

Although we have the diurnal variation in glucose tolerance that's very well established when these weight loss differentials were noted in some of these trials, there was a lot of emphasis then on the energy expenditure component that, a lot of which we've just discussed as it relates to the thermic effective feeding.

So there was a lot of emphasis that perhaps it's actually either energy expenditure or potentially other components of energy balance, like physical activity thermogenesis. So that the physical activity thermogenesis and the potential for other components of energy balance to be influenced was largely I think put to bed by the Bath Breakfast Project by James Betts' group at Bath.

And they did an intervention which generated a number of really interesting publications where the intervention group were going to consume 700 calories before 11:00 AM and at least 50% of that 700 calories was to come within about two hours of waking. And what they noticed was that when they compared it to an extended fasting condition, so there was this 700 calories before 11:00 AM group compared to a group that fasted until midday, and then eight, then you could see a increase in physical activity thermogenesis, but it was transient. It was only reflecting the extra energy intake in the breakfast group. So energy balance was ultimately the same between the. kind of breakfast group and the fast to midday group in this study. And the thermic effect of feeding response, for example, was again, was proportional to the additional morning energy compared to the extended fasting.

So when we extrapolated out to the 24 hour day, there was no energetic advantage to consuming the high energy breakfast versus fasting until midday. And the overall increase in physical activity thermogenesis wasn't actually different between groups. There was just this apparent difference, in that early kind of phase in the morning in response to breakfast.

So that suggested that high energy intake before 11:00 AM wasn't really leading to any kind of compensation or beneficial or adaptive effect on energy metabolism or other components of energy balance, specifically physical activity. And that I think, has really been bolstered then recently by the publication of the Aberdeen group's intervention.

So the Big Breakfast Study is the overall grant. We did the kind of circadian lab phase shift study at Sury, which we're hoping to submit imminently. And just working on the final drafts of that. and they pub conducted the intervention, which used a similar approach to these previous studies that had these kind of distribution sequences.

So for the Aberdeen study, they had a high energy breakfast, low energy dinner condition, and a low energy breakfast, high energy dinner condition. And what this was targeting was 45% of energy at breakfast, 35% at lunch, 20% at dinner in the morning distribution sequence. And again, the inverse of that 20% of energy at breakfast, 35% at lunch, 45% at dinner, and it was a crossover trial.

So participants were randomized to either front loaded energy or back loaded energy, and then they crossed over to whatever was the opposite that they started with participants on average were about 50 years old. BMI of 32; 16 men and 14 women. And what is most important about this study and what it's really added to this literature is it really has had the most robust and comprehensive assessment of all components of energy balance, of any study really published to date.

So it used doubly labeled water to which is the gold standard for free living measurements of energy expenditure in. To measure energy expenditure. All of the diets were individually tailored to energy, individual energy requirements targeting a hypocaloric weight loss diet. But the meals were all prepared in a metabolic kitchen and provided to participants during the study.

And this obviously extensive level assessment, has provided the ability to have a very global assessment of the role of the energetic side of this. And over the course of the intervention four weeks on each diet there no difference between groups in terms of weight loss between the morning loaded and the evening loaded, distribution of energy.

There was no difference necessarily in body composition or compositional weight changes or weight loss. So these were independent of the distribution of energy in the diet. All of these energetic related outcomes, either energy expenditure or weight loss, were all entirely equivalent between these two distribution strategies.

However, what they did show, and possibly the most important finding as it relates to these previous research findings was a significant effect of the distribution on appetite and hunger such that the morning loaded energy group showed significant benefits to appetite regulation. And that was looked at both across the day and acutely in response to test testing days that were conducted at the end of each diet phase.

And so that was when you were looking at composite hunger and appetite scores. But even when you looked at specific subdomains hunger or desire to eat or quantity or, for example, like preoccupation, these were all in favor findings in favor of morning loaded energy intake. And bearing in mind this is in the context of controlled energy for each participant, so it's not an ad libitum feeding study.

And the reason this is important is because if we think about that Jakubowicz and colleague study now, and we think about that differential in weight loss, what's more a likely explanation based on the absence of evidence at this point, that there's an enhancement of energetic components. Such that, energy expenditure or thermic effective feeding is enhanced. That would explain that weight loss.

It's likely more of a plausible explanation that studies manipulating temporal distribution of energy that found greater weight loss in response to greater morning energy intake we're likely, perhaps reflecting greater hunger and appetite and satiety in those dietary distribution patterns such that they simply consumed less energy and lost more weight over time.

And there's actually a lineage of evidence if we're thinking along those lines. We can go back to John de Castro's research at Texas where, he came up with this kind of concept of the Satiety ratio, which was a metric of Satiety that factored in both the energy content of a meal consumed and the time period between meals, and that decreased as the day went on. So people might have a tendency to eat a great a bigger meal in terms of its energy content, but also wait less time to eat again because they're not getting that level of sat at a later point in time. And this finding has ultimately been bolstered because another publication dovetailed the publication of the Aberdeen study.

And this was from Frank Scheer and Marta Garaulet's group. Nina Vujović was the lead author, I hope I'm pronouncing that correctly. And this was a laboratory inpatient study in participants that were around 37 years of age. BMI of 28; 11 men and five women, and they compared two isocaloric meal schedules.

One was where meals were consumed one hour, five hours, and nine hours after waking, and was individualized to that participant's circadian phase. So it was all relative to their own habitual timing. They then shifted those participants to delay their meal intake by five hours. So that meant that the other meal comparison condition was five hours, nine hours, and 13 hours.

And what they showed quite interestingly was that hunger was significantly higher in the late meal eating schedule. And that persisted not just through the kind of was higher in the evening, for example. But there was no carryover effect evidence. You would think if you had this later eating schedule in your eating, essentially one hour before bed, you're eating a big meal and all of your three meals that day have come later in the day that you would maybe wake up the next morning and have this carryover effect of being full.

But what was really interesting was that hunger levels in this group were particularly high in the waking period the next day. So there wasn't a carryover effect and the late eating condition was associated with significantly elevated subjective hunger. But they also measured ghrelin and leptin and there was a significantly elevated ghrelin leptin ratio in the early part of the day that persisted right across the day from this late meal schedule.

So we've had these two very tightly controlled interventions that have dovetailed each other in the timing of their publication that have really pointed the needle away from the whole energetic component. That was much of the focus of this literature for the past, certainly five years or so, and towards perhaps more of a behavioral effect of time of day energy intake that is more related to appetite and hunger overall satiety, and that may be an explanation for why in a free living context or an ad libitum context, there are certain people who might respond quite well to front loading energy intake.

Because it gives them greater satiety and appetite regulation over the course of the day. And obviously then in terms of real world implications, better control over energy intake and perhaps facilitating more spontaneous reductions in energy intake that explains the weight loss that was observed in some of those earlier studies.

Danny Lennon: Yeah. And so we touch on the big breakfast study just for another moment, and again, to note for anyone that's listening on the Premium feed, make sure to go back and listen to Alan's detailed discussion of that particular study because there's so much nuance. That was unfortunately, as is always the case lost in internet commentaries about that particular study and what it might mean.

And I think Alan's breakdown, which is over an hour going through some of those important aspects is worth listening back to. But one of those interesting places where context gets lost is you would often see people jumping to the results of that of kind of hand waving away of, "oh, this just shows that nothing here matters". But when we start thinking about some of what you've just said in relation to the findings of not only that study but the study out of Frank Scheer's lab as well, is that if we have situations here where we are controlling for calorie and macronutrient intake, and of course then we're going to expect that we're not going to see differences in body composition and weight loss per se, but when we're noting substantial differences in appetite and hunger, then if we were to think about what would an intervention like this mean, then out in the real world for a significant number of people?

That's where we could start maybe explaining cases where we don't control for that and then see maybe potential benefits of weight loss in certain populations, or these are connection there. And it also seems to connect to other areas of literature that had a bit of hype that maybe have fallen away a bit.

So again, if we look at time-restricted eating, one of the big comparisons was around early time-restricted eating to later time-restricted eating. And this is this where we get the superior benefit of an early time-restricted eating protocol. So what that might fit in here is, again, it might not be specifically arbitrary clock hours of when you start your fast per se, but what it's doing in an early time-restricted feeding protocol is by nature, it's forcing a morning loaded eating situation, right?

Your distribution of calories has to be in the morning if your final meal is at two or 3:00 PM as it was the case in some of these studies. And so it mirrors that in a matched sense. And then so when people are trying this out in the real world, they report lower appetite and then therefore their changes are overall caloric intake.

So I think there are a few things to note from that. And then one more piece of context for people listening. Alan referenced both the work of Alex Johnstone, who is the head of the group doing the work up at the Rowett Institute, University of Aberdeen, absolute superstar in the area, was on the podcast in episode 292, if you want to listen to that.

And then the Bath Breakfast Project headed up by James Betts. You can hear him on the podcast in episode 399. But with reference to some of these findings around appetite and hunger and then how. Potentially fits into these other places. Do you think that is one example of maybe many of the areas where this context of important and really well done studies gets lost?

Because again, when we look at that publication from the group of Aberdeen recently, some of the commentary online was, let's say reductionist or misguided in the best of terms.

Alan Flanagan: Yeah. It's just fairly predictable, right? It's like once someone, and certainly in the online popular nutrition conversations, once, there's no difference in weight loss, like it's as if there's just no further interest in whatever the study found, right? It's taking to Twitter for the hot take on how there's no difference between, or there's no advantage to it, in this case. We see this a lot with TRF, and again, like I said I'm fairly underwhelmed now by the TRF research.

But in this case, the distribution of energy is the factor. No benefit to higher morning energy intake because there's no difference in weight loss. With a study like this that has so many and is so robustly conducted it just really diminishes the value of what's been added in that research. And one other factor, for example, that I think is really important, is gastric emptying was measured using stable isotope analysis in, in, and we did the same in the lab study.

Now, obviously that's unpublished, but I can say that one of our main findings in that study was that we, when we did the phase shift and when people went from 8:00 AM 1:00 PM 6:00 PM kind of mealtime, and then instantly we delayed everything by five hours. That next day, the breakfast, which was now at 1:00 PM five hour delay to the breakfast as well as their sleep wake cycle, their gastric emptying halftime was about 90 minutes delayed.

And what they showed in the Aberdeen study was that obviously with the morning energy intake, the morning load, it's a larger meal size overall, but that gastric emptying halftime was significantly later in response to that morning meal. And this is again, using really, refined stable isotope analysis to determine the rate that food is leaving the stomach.

So this relates, of course, importantly to these effects on appetite because if you're having greater morning energy intake or energy in the early part of the day and you have slower rate of food leaving the stomach, and that obviously then translates into subjective hunger and appetite, that's something that feeds into the overall picture.

Whereas if you have the inverse of that, if you have a small meal in the morning it more rapidly empties the stomach and that corresponds to an earlier return to hunger. There were so many elegant measures in this study, and it was so tightly controlled that the idea that all that, that its primary contribution is the fact that there was no difference in weight loss, in my opinion, is really missing the forest for the trees.

Danny Lennon: Yeah. Like you say, it was such a well done study. It was very cool to see. The final thing that I'll maybe bring up before we round this out that I think is interesting and in fact for people listening, this will be covered in next week's episode, we're going to put out a discussion that Alan and I had specifically on meal timing and glucose metabolism, looking specifically at one paper from Marta Garaulet's lab.

But one of the ideas that will be discussed there in much more detail. But to connect to this particular conversation today, that is an important piece for people to realize is that when we're talking about timing of meals where that's distribution of meals or how close it is to biological night, it really is considering that in relation to these measures around what biological night actually means and getting away from this idea of clock time and that not being the thing that's as relevant as, say, measures of melatonin or melatonin onset or someone's chronotype.

So at an overview level, what is the best way to make that distinction for people? That when we're thinking about timing and the potential detriment in some of these cardiometabolic outcomes for eating at, say, biological night, that is in connection to things like melatonin and someone's chronotype rather than specifically an arbitrary clock time.

Alan Flanagan: Yeah. I think to best illustrate this verbally for listeners, to try and picture in your head. So we have our main anchor of our circadian rhythms is our rhythm in melatonin, and that's primarily responsive to obviously the light dark cycle. It's part of the central, it is the main central clock generator or generated by the central clock.

Imagine a peak and a trough in that rhythm. That's always over a 24 hour period. So all of our rhythms are tied to this 24 hour period. But imagine that the peak and the trough of that is is different. That the actual timing of how that rhythm looks, if we were to draw it over a 24 hour period, will actually differ between me and Danny and any of you listening. And that denotes our chronotype, so for someone who has an earlier rise in melatonin in the, what we would call the evening, if that's occurring at a clock time of 8:00 PM in me that's my biological nightmare. Melatonin is elevated. That's the rhythm that I have in melatonin. And if Danny's rises at say 11:00 PM that's his biological night. So there's now a difference of, three hours in our respective individual timing. And one interesting line of research, there's a number of cross-sectional studies that have suggested that food intake in close proximity to that nocturnal rise in melatonin is associated with increased body.

And we have intervention trials using either supplemental melatonin or that have considered endogenous melatonin that have suggested impaired insulin sensitivity when melatonin is elevated. Now, this might explain some of the discrepancies we have in research that only considers food intake related to clock time.

So when people say "oh, there was no difference in this metabolic outcome with evening energy intake", What does evening mean? Clock time? That's the first thing. And then how does that clock time relate to the internal biological time, the circadian time of those individuals?

And this is, I think, the kind of the real itch to be scratched in this area that could really provide some value in explaining where we actually stand in terms of, energy intake at, in the evening, at night, and how that might relate to metabolic risk. So for example, as that relates to the Aberdeen study, one of the findings in that was that there wasn't really much difference in even some of the glycemic control factors that we might expect from this diurnal variation in glucose tolerance we've talked about.

But if you look at the actual timing of the meals and participants were allowed to self-select their mealtime to habitually continue with their ordinary pattern of breakfast, lunch, and dinner. But the actual evening loaded energy intake group on average had their dinner at 6:30 PM and when the morning loaded energy group were having their dinner, it was, and these were crossover participants, right?

So this is just a slight difference. It was 6.45. So we're really talking about almost like a less than 15 minute difference in dinner that was occurring at what is a relatively early point in the evening. So it's possible, it's potentially likely, unless someone was at ridiculously early chronotype that this meal timing was occurring well in advance of the biological night, so to speak.

So this is important because, we have other research that has compared, for example, 7:00 PM dinner versus 10:00 PM and we see differences. I e the 10:00 PM metabolic responses are worse compared to, say, a dinner at 7:00 PM So I think that broad delineations or broad characterizations of say evening.

Or night even as a term is likely unhelpful for us to more appropriately characterize this relationship between the actual clock time at which a meal has occurred in this phase of the day and the relationship between that clock time and internal biological time. And I think that's really the next, the in really.

And it will need to be a well-funded, tightly controlled study just by the nature of the measures that will need to be undertaken is to really try and tease out what is this relationship between proximity of clock time to biological time in this evening period. And our hypothesis really based on these interventions that Marta Garaulet's group have produced regarding melatonin and indeed those cross-sectional studies would be, actually, it would be more the proximity of calorie intake to someone's individual biological night that would explain impaired metabolic responses to evening energy intake rather than just it's 8:00 PM or it's 7:00 PM and those clock times are likely not sufficient to actually explain the potential adverse effects of calorie intake in this part of the day.

Danny Lennon: And as we'll get into in next week's episode in more detail, we can look at things like dim light melatonin onset and where calories are coming close to that time or not. And importantly, I think that the main takeaway is that if one person's an earlier chronotype, one is a later and they have this different rise in melatonin, then the impact of a meal at let's say 8:00 PM or 9:00 PM is going to be different because we know that there's these poor postprandial responses to carbohydrate and fat at biological night. But of course, when biological night differs between people based on this rise in melatonin. And again, as we'll discuss next week, Garaulet's lab have a really nice kind of "timing model" to illustrate this to get to this idea of how do we reconcile this evidence around melatonin and glucose tolerance where we have conflicting research?

And they're essentially proposing that really it's the glucose intolerance that we see with this later eating is read the combination of eating at a time when melatonin is elevated. So that can happen at biological night or it could happen if someone during the day were to have an elevation in melatonin that you would still due to the effects of melatonin have this glucose intolerance. And so thinking about the combination of not just timing, but it's really the timing of food. In the context of what are someone's levels of melatonin, that's really the timing that we're concerned about as opposed to a specific clock time per se.

I think that does us for today. I think that is plenty for people to get through and hopefully it gives a nice update on some things that have emerged over the last couple of years. Some things where our positions of change or our conclusions that we can take from the literature have had to change and hopefully adds a bit more context to this interesting area of research. And like I said, there will be another episode related to this topic next week, but specifically focus in on glucose tolerance in the context of one study.

And that is it. Yeah. So from both Alan and myself, thank you for listening in today. Hopefully it was useful. And for those you listening on the premium feed, remember you can get detailed study notes this episode if you want to go and revise over this. And for everyone else, we hope you tune into the next episode and we'll back very soon.