Detailed Study Notes

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Introduction to this Episode

Research in the field of 'chrononutrition' has continued to grow in the past couple of years, with some important studies being published in recent times.

Chrononutrition is a research area that looks at the relationship between temporal (time-related) eating patterns, circadian rhythms, and metabolic health.

While past podcast episodes have covered various aspects of chrononutrition, the latest research has added important pieces to the puzzle and has led to both Alan and Danny updating their views on certain sub-topics.

In this episode, we look at recent research (including that from the Big Breakfast Project) and how understanding and conclusions from the field have shifted over time.

Dr. Flanagan also gives some insight into the important chrononutrition work published in the UK, which his doctoral work contributed to.

Connection to Previous Episodes

296: Circadian Entrainment, Chronotypes & Chrononutrition

- In this episode, Danny interviewed Alan about his area of research: chrononutrition.
- This is useful to listen back to as it explains some of the core concepts related to chronobiology and circadian rhythms.
- They discuss:
    - Chronotypes: genetic vs. trained
    - How feeding can entrain circadian clocks
    - Circadian alignment vs. misalignment
    - The inter-individual variation in response to light
    - The evidence linking nutrition & circadian biology
- You can find that episode here.

SNP12: The Big Breakfast Study

- As mentioned in the current episode, Ruddick-Collins *et al.* did an RCT looking at the impact of different calorie distributions across the day.
- In this study, 30 subjects underwent two 4-week calorie-restricted diets that were matched for calories.
    - One diet was **"morning-loaded"**, meaning that daily calories were distributed as 45% at breakfast, 35% at lunch, and 20% at dinner.
    - The other was **"evening-loaded"**, with an opposing calorie distribution; i.e. 20% at breakfast, 35% at lunch, and 45% at dinner.
- The trial received a lot of commentaries online after it was published. However, much of it lacked sufficient context, nuance, and understanding of the implications.
- In this Premium-only episode, Dr. Alan Flanagan gives an insight into the study.
- You can find that episode here.

355: Is Time-restricted Eating Dead?: A Closer Look

- An RCT on time-restricted eating, referred to as the TREAT trial, published by Lowe et al., received a lot of attention when published.
- Many people used the results to claim that time-restricted eating (or even meal timing more generally) was completely inconsequential.
- However, as discussed in episode 355 by Alan and Danny, many of these conclusions are short-sighted and narrow.
- You can find that episode here.

387: Shift Work and Health

- In this episode Danny and Alan discuss the relationship between shift work and health.
- They get into questions such as:
  - Why does shift work have negative health impacts?
  - How can one mitigate circadian misalignment?
  - How does shift work impact nutrient metabolism?
  - What nutrition, sleep and lifestyle strategies can help shift workers?
- You can find that episode here.

Connection to Previous Articles

Chrononutrition: Why Meal Timing, Calorie Distribution & Feeding Windows Really Do Matter

- Article by Danny Lennon.
- A sizable amount of research is mounting to suggest that there are very real and important implications for when we eat.
- In this article, we will explore the intersection of circadian biology and diet (termed “chrononutrition”) and offer some heuristics and guidance for practical application.
- You can read that article here.

How Does Meal Timing Impact My Blood Sugar?

- Article by Alan Flanagan.
- One specific area where meal timing may be an important factor is in relation to glycaemic control. This effect may be more pronounced as glucose tolerance progressively deteriorates, i.e., the magnitude of effect appears to be greater in individuals with pre-diabetes or diagnosed type-2 diabetes (T2D).
- In this Sigma Statement, the following sections are addressed:
  - The mechanistic underpinnings of potential differences in glycaemic control relative to time of day
  - Evidence from interventions comparing breakfast consumption vs. breakfast omission (i.e., fasting until lunch)
  - Evidence from interventions targeting distribution of energy across the day
  - Evidence from interventions targeting meal frequency
- You can read that article here.

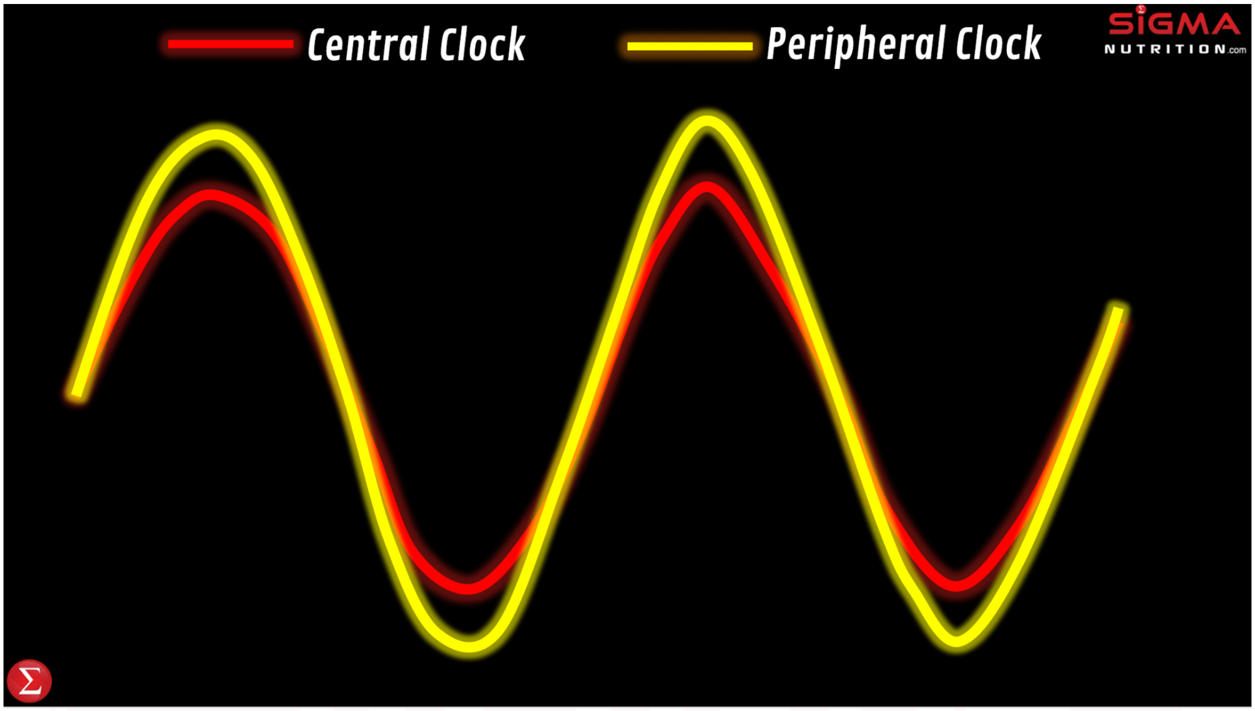
Chronobiology & Circadian Rhythms

- **Chronobiology** is a scientific field that looks at phenomena that occur in specific rhythms.
- The *"biology of time and internal biological clocks."*
- Under the umbrella of chronobiology, we have different branches based on classifying rhythms according to their duration. Namely:
    - **Ultradian rhythms:** A rhythm lasting less than 24 hours (e.g., a sleep cycle)
    - **Infradian rhythms:** A rhythm lasting more than 24 hours (e.g., the menstrual cycle)
    - **Circadian rhythms:** A rhythm lasting ~ 24 hours
- Biological processes that occur with a circadian rhythmicity include:
    - *Hormones* – e.g. melatonin, cortisol, leptin, etc.
    - *Sleep-wake cycle* – sleep anticipation in the brain default mode network (DMN)
    - *Core body temperature* – reaches peak during the day and minimum point at night

Circadian Clocks & Circadian Alignment

- Biological (circadian) clocks produce circadian rhythms and regulate their timing.
- Our "master clock" or central circadian clock, is found in the hypothalamus and is called the suprachiasmatic nucleus (SCN).
    - The SCN has ~ 20,000+ neuronal cells, which are responsible for circadian processes.
- In addition to our master/central clock, there are circadian clocks located in tissues all around the body. These are referred to as peripheral clocks.
- Circadian clocks (biological clocks) maintain an approximate (but not exact) 24 hour period for circadian processes, even without the influence of external stimuli.
- However, to synchronize these rhythms to the exact 24 hours of our solar day, we need to use external stimuli.
- Certain stimuli have the ability to entrain (or "set") circadian rhythms: zeitgebers.
    - Perhaps the most important zeitgeber is light.
- This process of a zeitgeber influencing the circadian rhythm is known as "entrainment."
- To maintain health, we want to have a synchronization between our: a) master clock, b) peripheral clocks, and c) external environment that influences the biological clocks.

Circadian alignment vs. misalignment:



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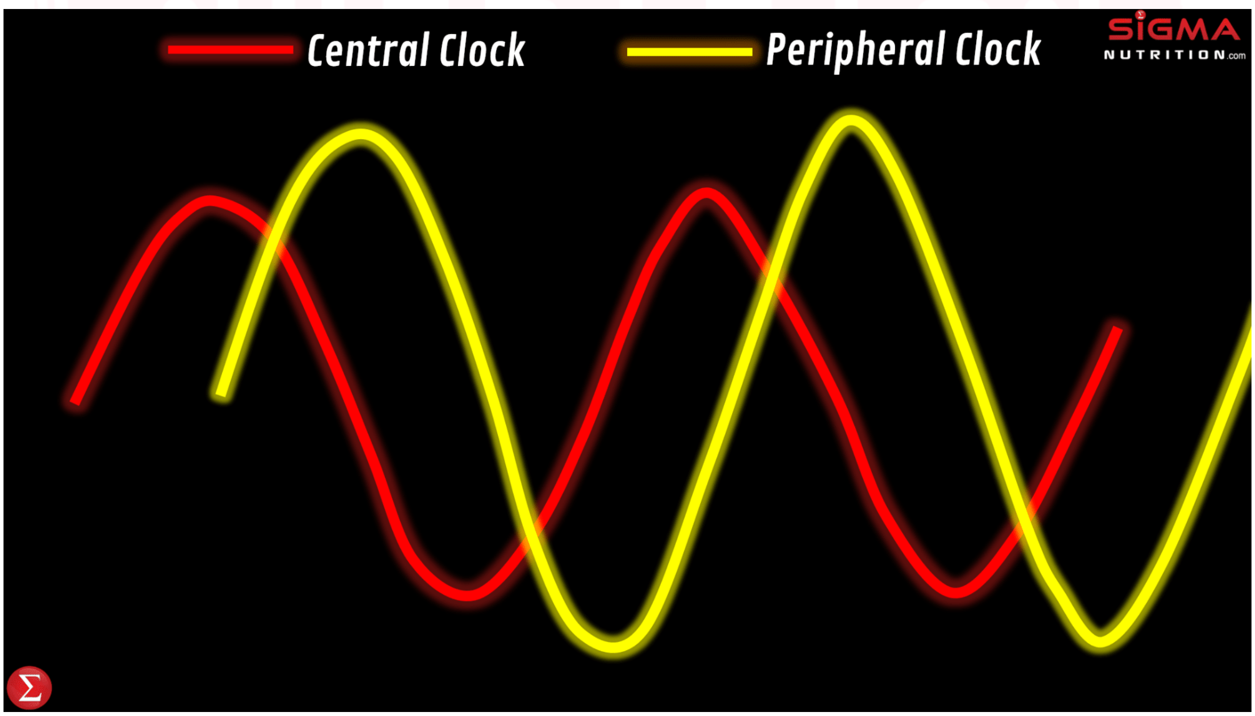

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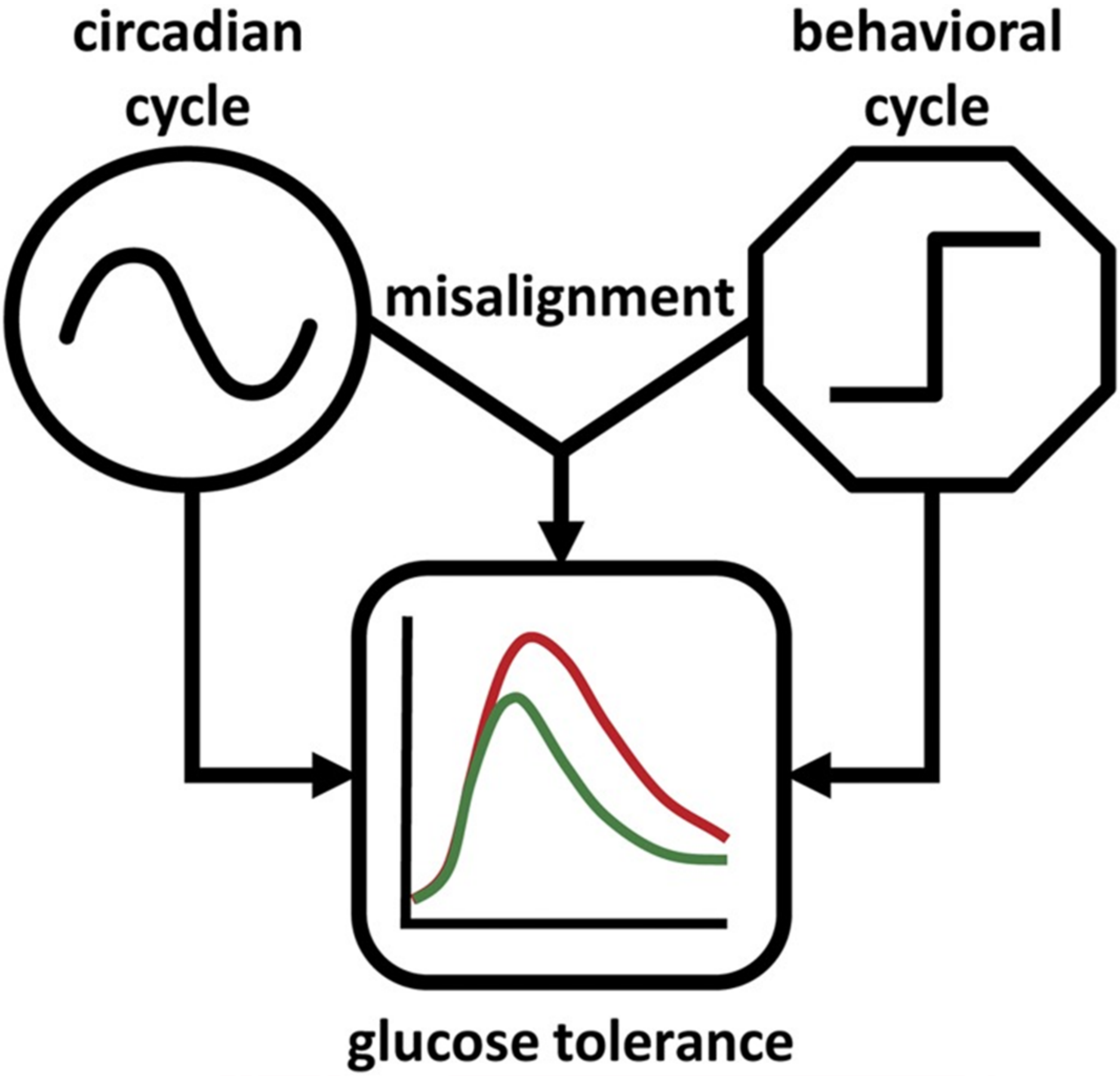

Image from: [Morris et al., Proc Natl Acad Sci U S A. 2015 Apr 28;112(17):E2225-34]

Jakubowicz et al., 2013 Study

Study: [Jakubowicz et al., 2013 - High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women]

- In this study, the researchers compared the impacts of two diets, matched for calories and macronutrients, but that differed in the distribution of that intake.
- Both groups dieted on 1,400 kcal per day, eating 3 meals per day, with each meal (breakfast, lunch and dinner) being eaten at about the same time (within a 3-hour window) for all individuals.
- As for the distribution, participants were either assigned to a "front-heavy" or "back-heavy" distribution. The front-heavy group had a large breakfast and small dinner, and the back-heavy group consumed a small breakfast and large dinner.
- Specifically:
    - **Front-heavy:** 700 kcal breakfast, 500 kcal lunch, 200 kcal dinner
    - **Back-heavy:** 200 kcal breakfast, 500 kcal lunch, 700 kcal dinner
- In these calorie/macro matched conditions, a front-heavy distribution of a large breakfast and a small dinner led to significantly (both statistically & pragmatically) more weight loss (8.7 vs 3.6 kg) than a back-heavy distribution (small breakfast and large dinner).

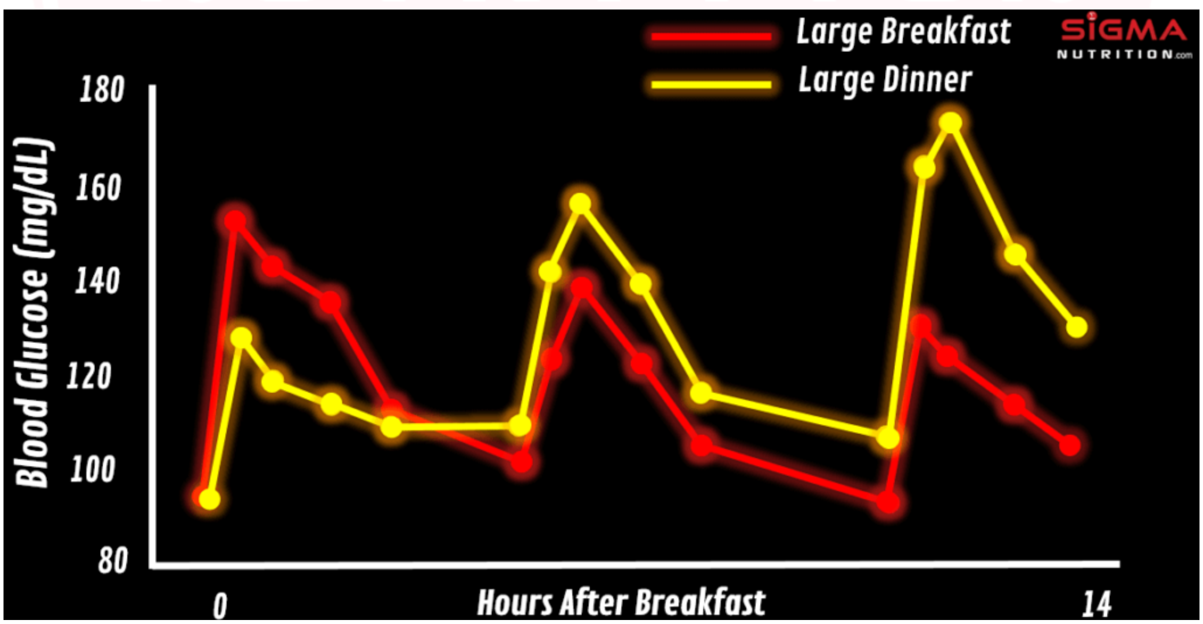

Image originally from: [Circadian Eating Lecture - Danny Lennon]

- Now, as discussed in the current episode, it's incredibly unlikely (essentially impossible) that such a large difference in body weight change between the groups could be explained solely through impacts of calorie distribution/timing on energy expenditure.
    - There are almost certainly differences that could be assigned to accuracy of tracking, adherence, and behavior that weren't captured in the study.
- However, it does tell us that something is going on when the distribution of intake is changed, regardless of how much is physiological and how much is behavioral.
- Other notable differences included lower blood sugar excursions (lower glucose AUC) for the day as well as lower ghrelin (an appetite hormone) levels throughout the day for those front-loading their calories.

Jakubowicz et al., 2015 Study

Study: Jakubowicz et al., 2015 - High-energy breakfast with low-energy dinner decreases overall daily hyperglycaemia in type 2 diabetic patients: a randomised clinical trial

- In this study in participants with type 2 diabetes, they compared two 1,500 kcal interventions:
  - **Large Breakfast:** 700 kcal at breakfast, 600 kcal at lunch, and 200 kcal at dinner
  - **Large Dinner:** 200 kcal breakfast, 600 kcal at lunch, and 700 kcal dinner
- The 700 kcal breakfast intervention resulted in a 20% lower whole-day glucose levels.
- Postprandial glucose was 24% lower after the 700 kcal meal at breakfast compared to the 700 kcal meal consumed at dinner.
- Further, the timing of the peak in insulin secretion, the magnitude of the peak in insulin, and the postprandial area under the curve (AUC) for insulin were all impaired in response to the 700 cal dinner, compared to the 700 cal breakfast.

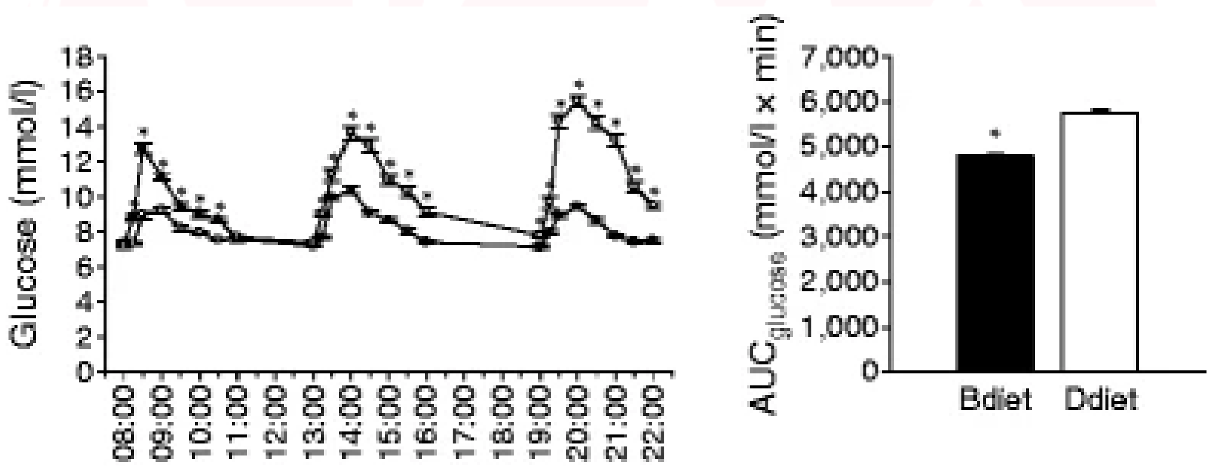

Image from: Jakubowicz et al., 2015, Diabetologia. 2015 May;58(5):912-9.
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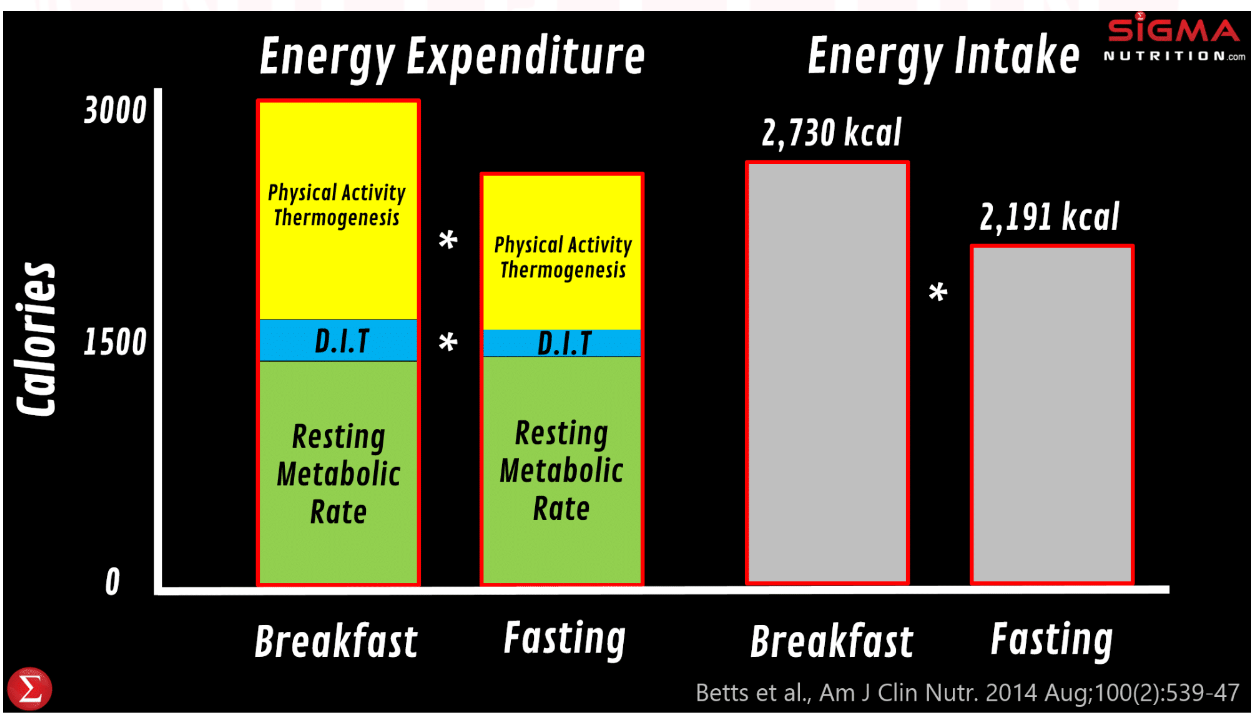
Bath Breakfast Project

Study 1: Betts et al., 2014 - The causal role of breakfast in energy balance and health: a randomized controlled trial in lean adults

- James Betts and colleagues at the University of Bath did a wonderfully insightful set of studies (the "Bath Breakfast Project") that examined the impact of eating a large breakfast on energy balance.
- In the first study, participants were randomized to either consume more than 700 kcal before 11 a.m. or to fast until lunch at 12 p.m.
- Metabolic control was improved in the high-energy morning group compared to morning fasting. There was improved insulin sensitivity in the breakfast group.
- They found that eating a relatively **large meal (> 700 kcal) early in the day** leads to much greater energy expenditure over the day compared to waiting until 12pm to have the first meal of the day.
- And most of this is explained by **greater physical activity thermogenesis**, specifically of light movement through the day (851 kcal vs. 442 kcal).
- And so whilst the breakfast group ingested more calories over the day than those fasting until 12pm, there was no difference in energy balance and body composition.



Results from Betts et al., 2014
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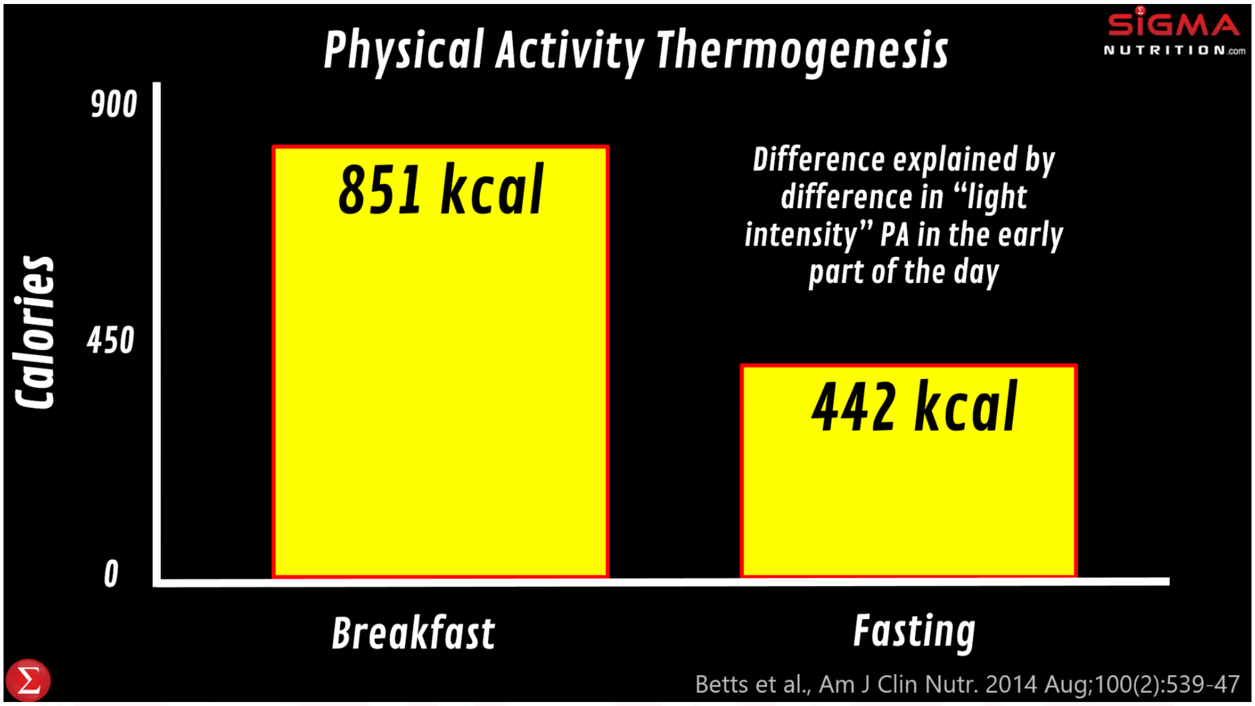

Results from Betts et al., 2014
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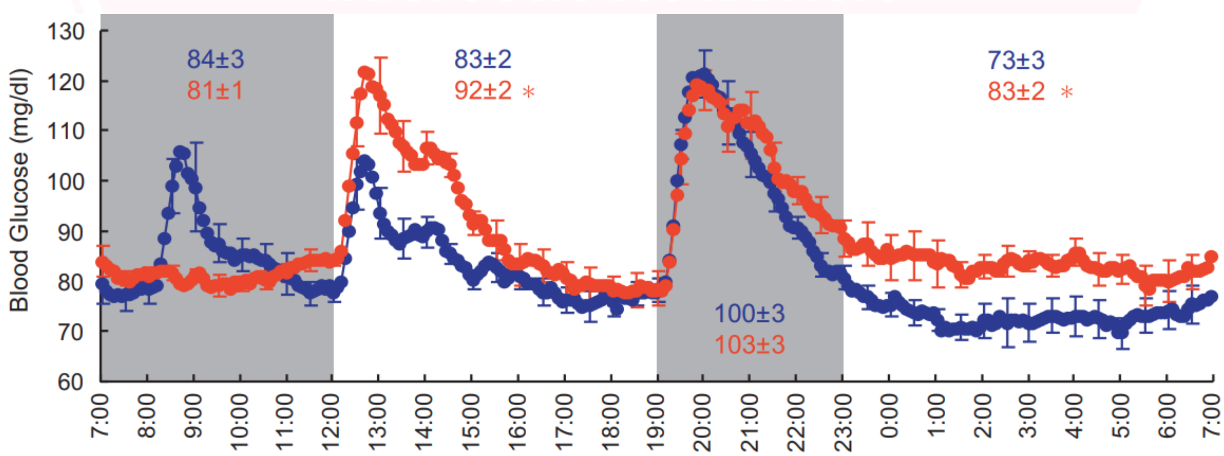
Study 2: [Chowdhury et al., 2016 - The causal role of breakfast in energy balance and health: a randomized controlled trial in obese adults]

- However, it should be noted that when the researchers repeated the study in participants with obesity (as opposed to lean participants), they found that physical activity thermogenesis was only different in the morning but not over 24 hours.

Breakfast vs. No Breakfast: Glucose Response

- In an intervention in healthy lean males, Kobayashi et al. compared two diets matched for calories:
    - one that included breakfast (3 meals/day)
    - one that skipped breakfast (2 meals/day)
- The study showed significantly greater postprandial glucose responses after lunch and dinner in the breakfast skipping condition.
- Overall 24-hour blood glucose levels were significantly higher in the breakfast skipping condition.
- However, it should be noted that while the total diets were isocaloric, this meant that the lunch and dinner meals of the breakfast-skipping condition contained significantly more calories than the lunch and dinner meals of the breakfast condition, where calories were spaced across three meals rather than two.
- Thus, the magnitude of glycaemic response in this study may reflect the difference in energy content of the specific meals.
- Of note, however, was the prolonged elevation of blood glucose levels in the breakfast skipping condition in response to the dinner meal administered at 8 p.m., which remained significantly elevated through the overnight period.
- Figure below shows the diurnal variations of blood glucose.
    - Mean values were plotted at every 5 minutes.
    - Mean values for morning, afternoon, evening and sleep periods are also shown.



Taken from: Kobayashi et al., Obes Res Clin Pract. May-Jun 2014;8(3):e201-98.

Thermic Effect of Food (TEF) and Meal Timing

Background to This Issue

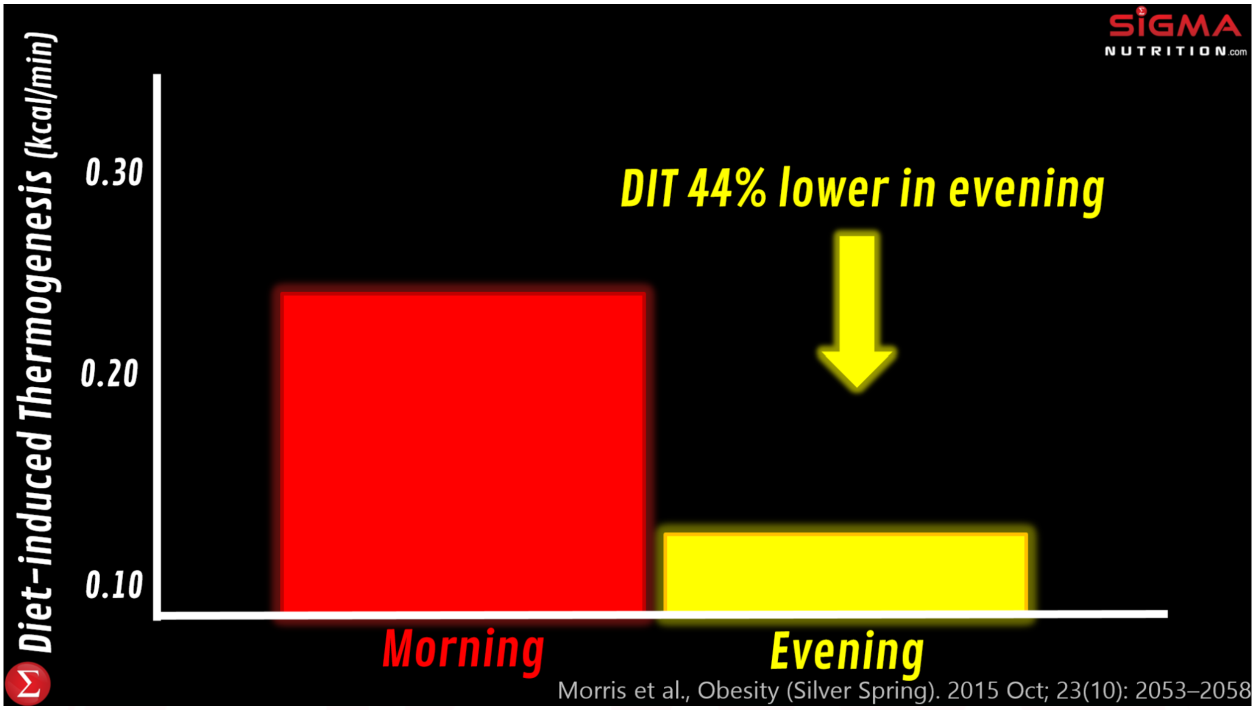
- Past work (most notably from Morris et al. and Richter et al.) suggested that eating early in the day leads to a greater TEF response to that meal.
- In other words, the same meal consumed in the morning versus in the evening, would lead to more calories being expended in the morning consumption situation.
- This hypothetically could lead to greater energy expenditure over the day, and thus benefits for body weight management or loss.
- However, recent work by Ruddick-Collins et al. has suggested that the previous findings have been interpreted incorrectly.

Zitting et al. - Harvard Chrono Group

- Study: Zitting et al., 2018 - Human Resting Energy Expenditure Varies with Circadian Phase
- Over 36 days in a lab, they did a 'forced desynchrony protocol' - i.e., pushed participants' circadian cycle back.
- Measuring fully rested metabolic rate after an overnight fast, an hour later each day.
- Researchers 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.

Morris et al., Study

- Study: Morris et al., 2015 - The human circadian system has a dominating role in causing the morning/evening difference in early diet-induced thermogenesis
- During baseline days, early DIT was 44% lower in the evening than morning.
- This was primarily explained by a circadian influence rather than any behavioral cycle effect; early DIT was 50% lower in the biological evening than biological morning, independent of behavioral cycle influences.



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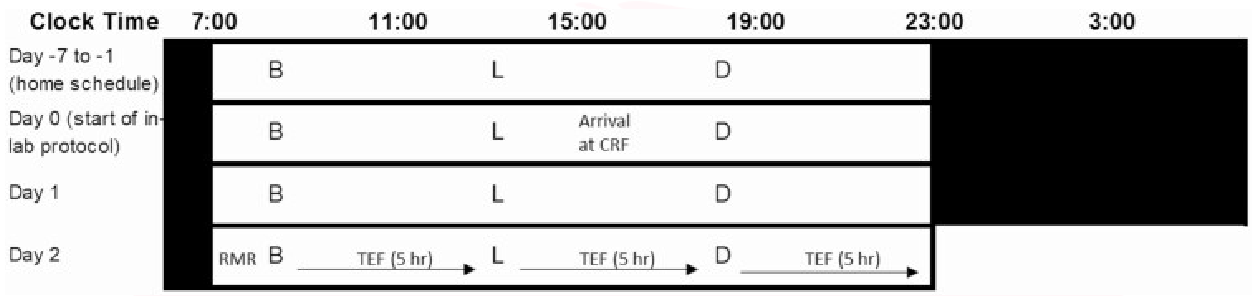
Richter et al., Study

- Study: [Richter et al., 2020 - Twice as High Diet-Induced Thermogenesis After Breakfast vs Dinner On High-Calorie as Well as Low-Calorie Meals]
- They had both a high energy and a low energy meal condition:
  - High energy meal = > 1,000 calories (around 69% of daily energy intake)
  - Low energy only = 250 calories (11% of their daily energy).
- Had the high-energy meal as either breakfast or dinner, with the low-energy meal as the opposite.
- They reported that the TEF response to breakfast was 2.5 times greater than the TEF response to dinner.
- This suggested 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.
- Weird data point: when the low-energy meal was consumed in the evening (dinner) it showed a negative test response. That's physiologically impossible. You can't consume energy and have a negative energy postprandial response.

TEF Findings Explained - Ruddick-Collins et al., 2022

Study: [Ruddick-Collins et al., 2022 - Circadian Rhythms in Resting Metabolic Rate Account for Apparent Daily Rhythms in the Thermic Effect of Food]



From: [Ruddick-Collins et al., J Clin Endocrinol Metab. 2022 Feb; 107(2): e708–e715.]

Overview:

- Fourteen individuals had their resting and postprandial energy expenditure (EE) measured over 15.5 hours at a clinical research unit.
- TEF was calculated for breakfast, lunch, and dinner using standard methods (above a baseline and premeal RMR measure) and compared to a method incorporating a circadian RMR.
- Main outcome measures were TEF at breakfast, lunch, and dinner calculated by different methods.

Results

- Standard methods of calculating TEF above a premeal measured RMR showed that:
    - Morning TEF (60.8 kcal ± 5.6) was 1.6 times greater than TEF at lunch (36.3 kcal ± 8.4)
    - **Morning TEF (60.8 kcal ± 5.6) was *2.4 times greater* than dinner TEF (25.2 kcal ± 9.6).**
- However, adjusting for modeled circadian RMR nullified any differences between:
    - breakfast (54.1 kcal ± 30.8)
    - lunch (49.5 kcal ± 29.4)
    - dinner (49.1 kcal ± 25.7)

The image below shows energy expenditure (EE) measured over a day with meals provided at:

- **Breakfast:** 1-hour after waking (0 minutes)
- **Lunch:** 5-hour after breakfast (300 minutes)
- **Dinner:** 5-hour after lunch (600 minutes)

Shown in the graph are:

- **Solid line =** measured EE over the entire day
- **Dotted line =** representation of baseline resting metabolic rate (RMR)
- **Short dashes =** representation of RMR directly before meals
- **Long dashes =** representation of circadian model of RMR.

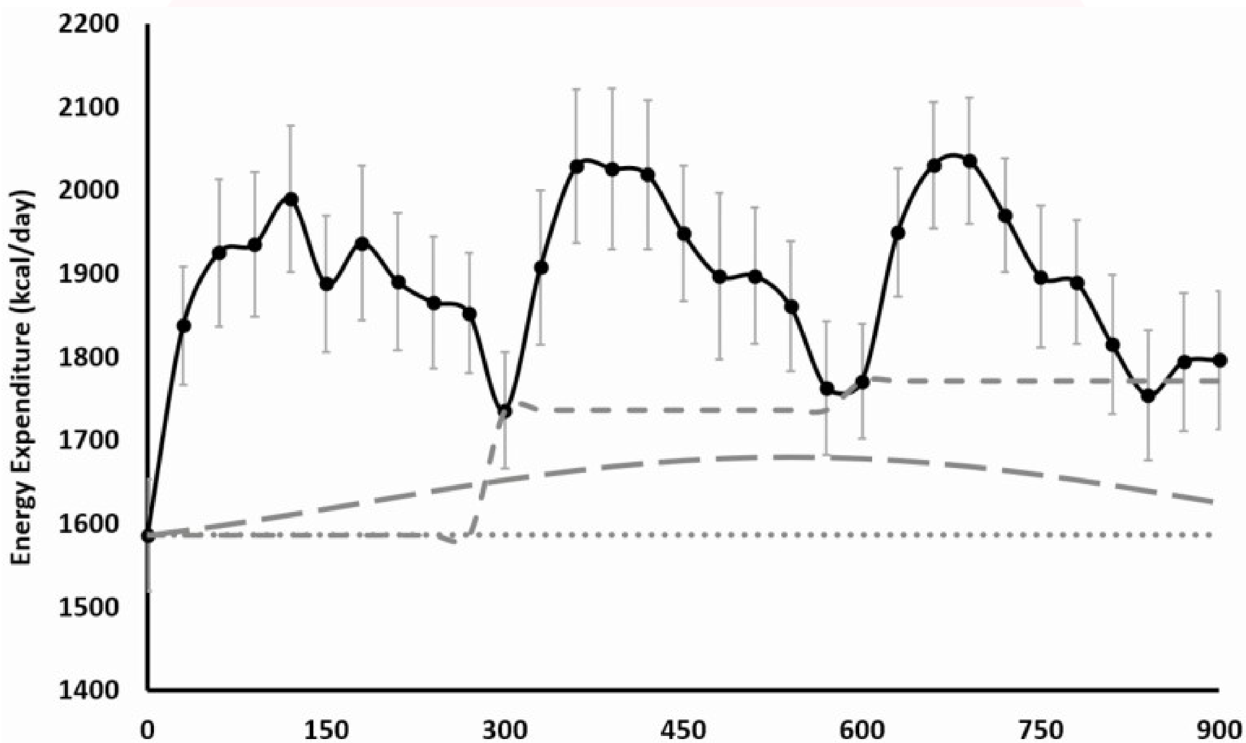


Image from: [Ruddick-Collins et al., J Clin Endocrinol Metab. 2022 Feb; 107(2): e708–e715]().

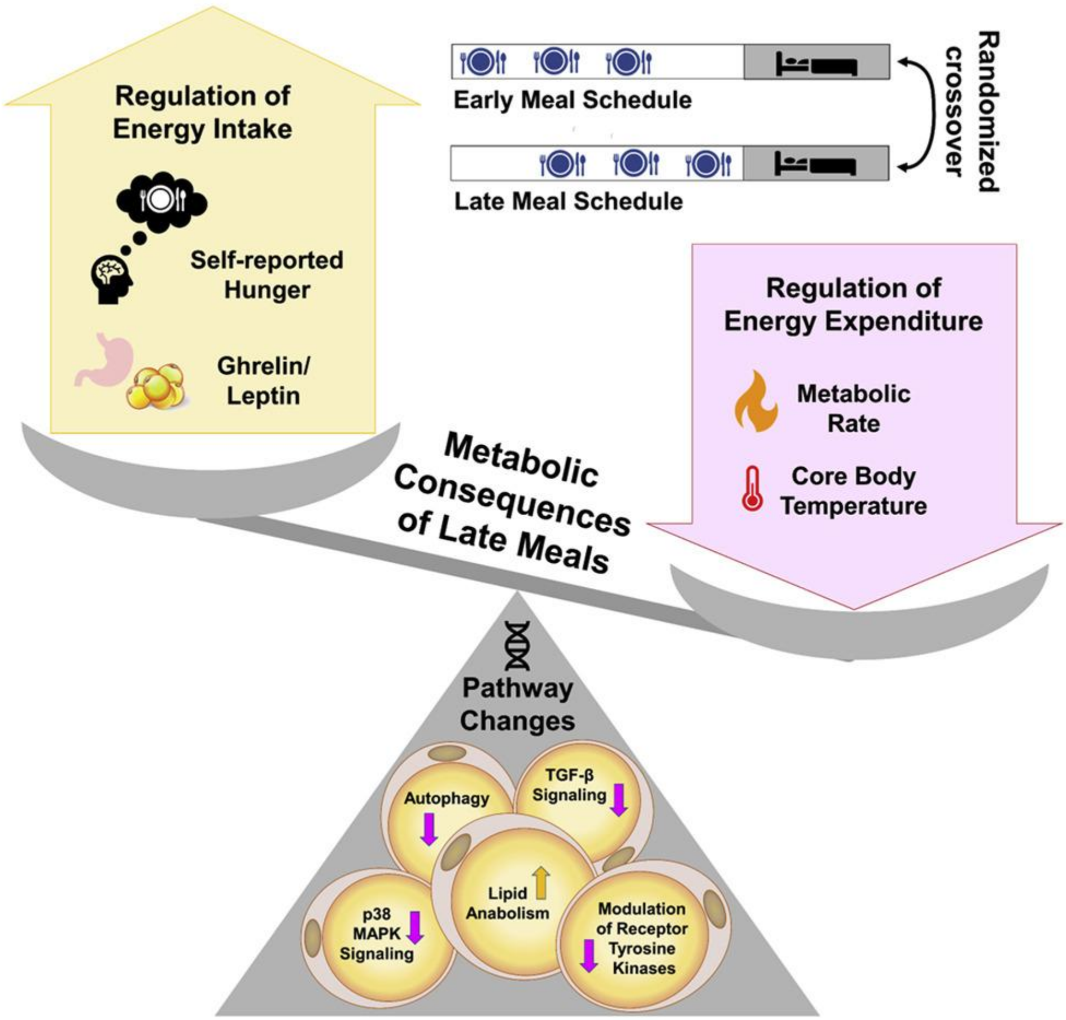
<u>Explanation:</u>

- 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.
- Using the values for what the RMR would be at any given time of day, Ruddick-Collins et al. constructed a model that provided a means to adjust for that underlying circadian value in energy expenditure.

- And they did an analysis of the energy expenditure data they had from their lab study (14 participants, measured energy expenditure across the waking day) and calculated the thermic effect of feeding using the **pre-meal RMR measure as a baseline**.
- And when they did that, they found the same results as Richter; i.e., a twice as high TEF response to breakfast compared to dinner.
- But when it was calculated only using the **fasted baseline RMR** as the baseline calculation, that difference was largely abolished.
- Then in addition, when they did a further 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.
- Ultimately what this was suggesting was that the studies that suggested a 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.
- So the suggestion by Ruddick-Collins *et al.* was that there is no diurnal variation in the thermic effect of feeding per se; rather, there is a diurnal variation in the underlying change in resting metabolic rate.
    - Therefore, 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.
- The circadian RMR removes this apparent artifact of a diurnal variation in thermic effective feeding.

Nina Vujovic et al. (Scheer & Garaulet) – Late Eating Study

Study: Vujović et al., 2022 - Late isocaloric eating increases hunger, decreases energy expenditure, and modifies metabolic pathways in adults with overweight and obesity



From: Vujović et al., Cell Metab. 2022 Oct 4;34(10):1486-1498.e7.

Author overview:

- Late eating increases waketime hunger and decreases 24-h serum leptin
- Late eating decreases waketime energy expenditure and 24-h core body temperature
- Late eating alters adipose tissue gene expression favoring increased lipid storage
- Combined, these changes upon late eating may increase obesity risk in humans

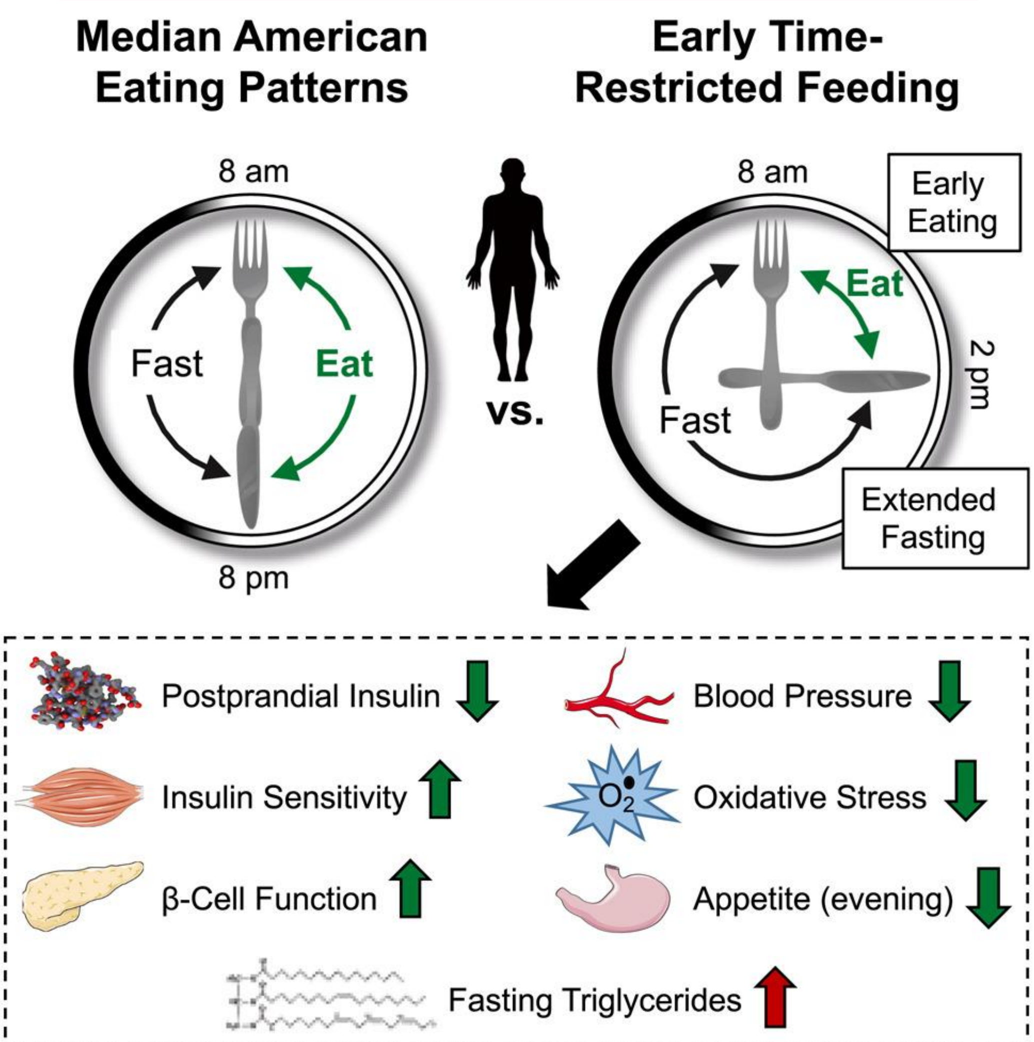
Study info:

- Laboratory inpatient study in participants that were around 37 years of age.
    - BMI of 28; 11 men and five women
- 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.
    - They then shifted those participants to delay their meal intake by five hours.
        - Meaning that the other meal comparison condition was five hours, nine hours, and 13 hours.
- They showed that hunger was significantly higher in the late meal eating schedule.
- 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.
- 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.

Mentioned Studies on Time-restricted Eating (TRE)

Sutton et al., 2018 - Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes

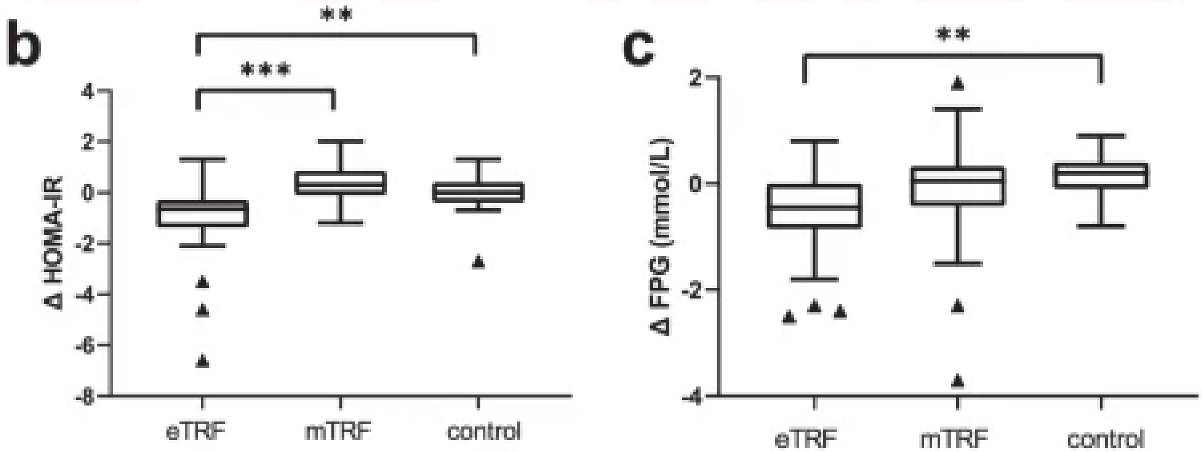
- Link to paper
- 5-week crossover trial
- Researchers used an *early* time-restricted eating protocol (eTRF) where the feeding window was from 7am to 1pm.
- Compared to a control diet, the eTRF led to a lower postprandial insulin response, better beta-cell function, and less insulin resistance.



From: Sutton et al., Cell Metab. 2018 Jun 5;27(6):1212-1221.e3.

Xie et al., 2022 - Randomized controlled trial for time-restricted eating in healthy volunteers without obesity

- [Link to paper]
- RCT comparing an 'early' time-restricted feeding protocol to a 'mid' time-restricted feeding protocol.
  - Early time-restricted eating period = 6:00 AM to 3:00 PM
  - Middle time-restricted eating period = 11:00 AM to 8:00 PM
  - Control group = any eating duration over eight hours with no restriction on when they were eating or not.
- Underwhelming differences between groups for certain outcomes like fasting blood glucose and insulin resistance.
  - There was a difference in favor of the early time restricted feeding group.
  - May again relate not necessarily to the duration of the eating window per se, but it might relate more to the alignment of the meals consumed in the early time-restricted feeding period
- Image below shows changes in insulin resistance index (measured with HOMA-IR) and in fasting plasma glucose (FPG).



Taken from: Xie et al., Nature Communications volume 13, Article number: 1003 (2022)