

### Intermittent fasting in overweight populations:

1. **The study:** Alternate day fasting – every other day, participants consumed an 85% energy (ie calorie) restricted low carbohydrate diet regiment in patients with asthma symptoms (2007) ( 1 )
  - *Principal goal of study:* does modified alternate day fasting help with moderate **asthma symptoms**
  - *Participants:* Ten subjects with BMI>30, 8 female, 2 male
  - *Length of study:* 8 weeks
  - *Method of data collection:* food diary cards
  - *Study details:* On the other day subjects ate ad libitum (AL). Diary cards and instructions were given to the subjects during the 14 day baseline period. On the last day of the baseline period subjects returned their diary cards and were given new cards and instructions in how to follow the diet, including the number of calories to be consumed on each CR day. They were told to eat on the AL day whatever they normally ate and to the point of satisfaction but not to intentionally overeat. ( 1 )
  - *Results:*
    - *Physical:* This study reported beneficial reductions in serum cholesterol and triglycerides, markers of oxidative stress and asthma inflammatory markers (reduction in serum TNF $\alpha$ , BDNF, and ceramides) ( 1 )
    - *Emotional:* all patients reported improved asthma symptoms and improved quality of life per the ACQ, ASUI and mini-AQLQ – *questionnaires all related to asthma* ( 1 )
  - *Study limitations:*
    - no comparison group, so hard to distinguish if the benefits were from intermittent fasting or caloric restriction in general( 1 )
    - small study, 10 participants (8 female, 2 male) ( 1 )
    - No mention of emotion / patterns of unhealthy restriction following intervention ( 1 )
  
2. **The study:** short term (10 week) modified alternate-day fasting (450 calories consumed on fasting days between 12-2pm) for weight loss and cardio-protection in obese adults (2009) ( 3 )
  - *Principal goal:* does consuming 25% of energy needs every other day result **in cardio-protection and weight loss** in obese adults
  - *Participants:* Sixteen obese subjects (12 women, 4 men) ( 3 )
    - age 35–65 y, BMI between 30 and 39.9, weight stable for 3 mo before the beginning of the study (ie, <5 kg weight loss or weight gain), nondiabetic, no history of cardiovascular disease, lightly active [ie, <3 h/wk of light-intensity exercise at 2.5–4.0 metabolic equivalent tasks for 3 mo before the study (10)], nonsmoker, and not taking weight loss or lipid- or glucose-lowering medications ( 3 )

- Perimenopausal women were excluded from the study, and postmenopausal women (absence of menses for >2 y) were required to maintain their current hormone replacement therapy regimen for the duration of the study. ( 3 )
      - Twenty subjects commenced the study, with 16 completing the entire 10-wk trial. Two subjects dropped out due to time constraints, whereas 2 others dropped out due to inability to comply with the ADF protocol ( 3 )
    - *Length of study:* 10-wk trial, which consisted of 3 phases: 1) a 2-wk control phase, 2) a 4-wk weight loss/ADF controlled food intake phase, and 3) a 4-wk weight loss/ADF self-selected food intake phase ( 3 )
    - *Method of data collection:* food log. During phase 3, subjects were provided with individualized meal plans that were consistent with their food preferences and prescribed calorie levels for the fast day. Subject was asked to report any extra food item consumed on the fast day that did not comply with their prescribed plan by using the extra food log.
    - *Social support:* Support: subjects met weekly with a registered dietitian.
    - *Results:*
      - *Physical:*
        - Weight loss: consume 25% of their energy needs on the fast day, resulted in a mean weight loss of 5.8% from baseline after only 8 wk of treatment ( 3 )
        - Decreases in several key biomarkers for CAD risk, such as total cholesterol, LDL cholesterol, triacylglycerols, systolic blood pressure, and heart rate, were also observed. ( 3 )
          - Total and LDL-cholesterol concentrations decreased by 21% and 25%, respectively, after 8 wks of diet. Triacylglycerol concentrations were also lowered by 32% when baseline values were compared with posttreatment values ( 3 )
      - Emotional: similar rate of weight loss was achieved during the ADF controlled food intake period when compared with the ADF self-selected food intake period. data suggest that subjects were able to maintain the ADF meal pattern when preparing their own meals at home (ie, when removed from a clinically controlled environment), indicating no promotion of bingeing tendencies ( 3 )
      - *After the study:* participants were able to maintain weight loss when they self-selected food intake during the last 4 weeks of the study ( 3 )
      - Limitations: small study, method of data collection was a food log (inherently susceptible to flaws), and perimenopausal women were excluded from the study
3. **The study:** zero calorie alternate day fasting to daily caloric restriction in adults with obesity for **WEIGHT LOSS (2016)** ( 4 )
  - *Principal goal:* tolerability of alternate-day fasting (ADF) and to compare changes in weight, body composition, lipids, and insulin sensitivity index to those

produced by a standard weight loss diet, moderate daily caloric restriction (CR) ( 4 )

- *Participants*: 26 adults with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>, age 18-55); 19 female, 6 male ( 4 )
- *Length of study*: 8 weeks ( 4 )
- *Method of data collection*: Daily energy and macronutrient intakes were calculated based on food return using software
- *Results*:
  - *Physical*:
    - *Weight loss*:
      - Average daily energy and macronutrient intakes were significantly higher in CR compared to ADF over the 8-week intervention, even after adjusting for differences in baseline weight. ( 4 )
      - relative (%) weight loss was greater in the ADF group at the end of the 8-week intervention, this difference was only marginally significant and may be driven by the differences in baseline body weight between groups ( 4 )
    - both groups had significant decreases in total cholesterol, HDL, and LDL and triglycerides decreased significantly in ADF ( 4 )
    - ADF induces long-term changes in BDNF secretion, which may contribute to improved weight loss maintenance through effects on energy balance ( 4 )
    - Fasting glucose decreased significantly at week 8 in ADF ( 4 )
    - Resting metabolic rate (RMR) decreased significantly in CR but not in ADF over the 8-week intervention ( 4 )
  - *Emotional*:
    - no significant changes in safety measures over the 8-week intervention ( 4 )
    - The study reports compliance issues, as some report hunger with IF and difficulty maintain daily living activities during restricted days ( 4 )
    - Questionnaire on Eating and Weight Patterns Revised (QEWP-R, assesses binge eating behaviors), and Center for Epidemiologic Studies Depression Scale (CES-D) were measured before and after the 36-hour test fast, at baseline prior to starting intervention, and at week 8 though the results are not reported in the study ( 4 )
- *Post-study results*:
  - individuals who did alternate day fasting kept the weight off after 6 months more than the CER group (400 cal/day below baseline intake) ( 4 )
  - During the 24-week follow-up, ADF lost fat mass and gained lean muscle while CR gained both fat mass and lean muscle ( 4 )

- After 24 weeks of follow-up, RMR decreased significantly from baseline in CR but not in ADF; however, differences between groups were not significant. When adjusted for FM and FFM, RMR decreased significantly from baseline to week 8 in CR ( 4 ). apparent impact of ADF on preserving RMR during weight loss could have clinical significance in preventing weight regain after weight loss and should be explored in larger studies ( 4 )
    - *Limitations:*
      - because of the small number of males (n=3 per group), we could not determine if there were any sex effects ( 4 )
      - No data on binge eating behaviors or mood changes provided in the study ( 4 )
4. **The study:** is intermittent fasting + calorie restriction effective for weight loss and cardio-protection in obese women (2012) ( 5 )
- *Principle goal:* effects of IF plus CR (with or without a liquid diet) on body weight, body composition, and CHD (coronary heart disease) risk ( 5 )
  - *Participants:* ALL female, age 35–65 y, BMI between 30 and 39.9 kg/m<sup>2</sup>, waist circumference >88 cm, weight stable for 3 months prior ( 5 )
    - Peri-menopausal women were excluded from the study, and post-menopausal women (defined as absence of menses for 2 y) were required to maintain their current hormone replacement therapy regimen for the duration of the study. ( 5 )
  - *Length of study:* 10 weeks ( 5 )
  - *Study details:* both groups restricted to 30% of daily needs
    - **IFCRL subjects** (n = 30) – intermittent fasting calorie restricted liquid diet → consumed a calorie-restricted liquid diet for the first 6 days of the week, and then underwent a fast on the last day of the week (water consumption + 120 kcal of juice powder only, for 24 h). The liquid diet (during the CR period) consisted of a liquid meal replacement for breakfast (240 kcal) and a liquid meal replacement for lunch (240 kcal). All liquid meal replacements were provided to the subjects in powder-form in premeasured packets (Isalean Shake, Isagenix LLC, Chandler, AZ). At dinnertime, IFCR-L subjects consumed a 400–600 kcal meal. ( 5 )
    - **IFCRF subjects** (n = 30)- intermittent fasting calorie restricted food diet → consumed a calorie-restricted food-based diet for the first 6 days of the week, and then underwent a fast on the last day of the week (water consumption + 120 kcal of juice powder only, for 24 h). IFCR-F subjects ate 3 meals per day in accordance with the TLC diet guidelines. Subjects were instructed to eat approximately 240 kcal for breakfast, 240 kcal for lunch, and 400–600 kcal for dinner. ( 5 )
    - trial had two phases: 1) 2-week weight maintenance period, and 2) 8-week weight loss period. ( 5 )

- *Social support*: subjects met with a Registered Dietician weekly to learn how to make healthy eating choices that are in compliance with the National Cholesterol Education Program Therapeutic Lifestyle Changes ( 5 )
  - *Results*:
    - Physical: decreased key indicators of CHD risk, such as LDL cholesterol, triglycerides, and the proportion of small LDL particles in both groups. When liquid meal replacements were incorporated into the IFCR regimen, greater reductions in body weight and indicators of heart disease risk were noted. ( 5 )
      - IF combined with CR is an effective means of improving lipid profile in a short-term (8 week) intervention. liquid diet component may enhance this lipid-lowering effect. ( 5 )
  - *Limitations*: study funded by the liquid meal replacement company; no baseline control
5. **the study**: effects of 5:2 intermittent or continuous energy restriction on weight loss and metabolic disease risk markers in young, overweight women (2011) ( 6 )
- *principle goal*: compare the feasibility and effectiveness of intermittent energy restriction (IER) with caloric energy restriction (CER) for weight loss, insulin sensitivity and other metabolic disease risk markers ( 6 )
  - *participants*: 107 premenopausal women aged 30 to 45 years with adult weight gain since the age of 20 exceeding 10kg, and a body mass index (BMI) between 24 and 40 kg/m<sup>2</sup> ( 6 )
  - *length of study*: 6 months ( 6 )
  - *study details*:
    - CER group were prescribed a daily 25% restriction based on a Mediterranean type diet (30% fat, 15% monounsaturated, 7% saturated fat, 7% polyunsaturated fatty acids, 45% low glycemic load carbohydrate, and 25% protein) ( 6 )
    - IER group were asked to undertake a very low calorie diet (75% restriction) on 2 consecutive days and to consume estimated requirements for weight maintenance for the remaining 5 days according to the nutrient composition above ( 6 )
      - (2 pints) of semi skimmed milk, 4 portions of vegetables (~80 g/portion), 1 portion of fruit, a salty low calorie drink and a multivitamin and mineral supplement. ( 6 )
    - Both diets involved a 25% energy restriction from estimated baseline energy requirements using reported METs x estimated basal metabolic rate ( 6 )
  - *Method of data collection*: 7 day food diaries
  - *social support*:
    - to maximize compliance patients received fortnightly motivational phone calls and monthly clinic appointments where weight and anthropometrics were measured and reported back to patients. ( 6 ) All subjects were

encouraged to use cognitive behavioral techniques such as self monitoring, obtaining peer/family support and stimulus control to maintain diets ( 6 )

○ *results:*

▪ *physical:*

- Both groups experienced comparable reductions in body fat, FFM, hip, bust and thigh circumference and composition of weight loss. Percentage of weight lost which was fat in the IER and CER groups was 79% in both groups ( 6 )
- Both groups experienced modest declines in fasting serum insulin and improvements in insulin sensitivity which were greater amongst the IER group
- Both diets led to comparable reductions in total and LDL cholesterol, triglycerides, systolic and diastolic BP. Neither group experienced changes in HDL levels ( 6 )

▪ *Emotional:*

- small number of the IER group but none of the CER group experienced minor adverse physical symptoms including lack of energy, headaches, feeling cold and constipation. 15% of the IER and none of the CER complained of hunger, 6% of the IER and 13% of the CER group reported increased energy and improved health. 15% of the IER and 7% of the CER group reported minor adverse psychological effects including lack of concentration, bad temper and preoccupation with food, whilst 32% of the IER and 46% of the CER group reported increased self confidence and positive mood. More of the IER group reported problems fitting the diet into daily routine; 51% IER vs. 30% CER ( 6 )
- in comparison there was a slightly greater increase in the mental component summary score in the CER compared to the IER group ( 6 )

○ *limitations:* food diary used as data collection; no control group

6. *The study:* 5:2 Modified intermittent fasting – aka intermittent energy and calorie restriction (IECR) vs daily energy restriction (DER) vs IECR + PF (IECR + unrestricted protein and fat) (2013) ( 2 )

○ *Primary aim:* the effects of intermittent energy and calorie restriction (IECR) vs daily energy restriction (DER) on weight loss and metabolic disease risk markers in overweight women ( 2 )

○ *Participants:* 115 overweight women

- Women were eligible for the study if their BMI was 24–45 kg/m<sup>2</sup> and/or body fat was >30% of total weight, and their reported adult weight gain since the age of 20 years exceeded 7 kg. There was no age restriction but subjects entered were between 20 and 69 years of age. Women were excluded if they were currently dieting or losing weight, or suffering from

diabetes, major CVD, respiratory, psychiatric or musculoskeletal morbidity.

- *Study details:*
  - Intermittent energy and carbohydrate restriction (IECR): restriction of energy and carbohydrate on two consecutive days each week (70% energy restriction and 40 g carbohydrate) and to consume a euenergetic Mediterranean-type diet that met their estimated energy requirements for the remaining 5 d of the week. ( 2 )
  - Daily energy restriction (DER): daily energy-restricted Mediterranean-type diet that was relatively high in protein, with moderate carbohydrate, and moderate fat. included five fruit and vegetable portions, nuts and seeds, whole-grain cereals, olive oil, fish and seafood, a moderate consumption of dairy products, poultry, eggs, and lean red meat and processed meat ( 2 )
  - Intermittent energy and carbohydrate restriction with ad libitum protein and fat (IECR + PF): diet virtually identical to the IECR group but were allowed unlimited lean meat, fish, eggs, tofu, MUFA and PUFA on restricted days ( 2 )
- *Length of study:* 3-month weight-loss period and a further 1-month period of weight stabilization ( 2 )
- *Method of data collection:* 7 day food diaries
- *Social support:* This study had a LOT of emotional support and not just food based interventions. “Women received fortnightly motivational phone calls and monthly clinic appointments where they received feedback on their progress with weight and anthropometric measurements, and the revision of diet and exercise behavioral goals. All participants were encouraged to use a range of established cognitive behavioral techniques to adhere to their diet and exercise” ( 2 )
- *Results:*
  - Physical:
    - IECR diet is superior to the DER diet with respect to the improvements in insulin sensitivity and the loss of body fat ( 2 )
    - The IECR + PF diet achieved greater reductions in body fat and a trend to improved insulin sensitivity both before and after the 2 d restriction compared with the DER diet, but was not more acceptable than the IECR diet ( 2 )
    - There was spontaneous restriction of energy and carbohydrate of IECR group on non-restricted days ( 2 )
    - greater reduction in insulin resistance with the IECR *v.* DER diet (5 d after restriction) in the present trial is consistent with greater reductions in adiposity in the IECR group ( 2 )
    - Labs: Reductions in insulin resistance, weight, adiposity, circumferences, leptin, IL-6 and lipids were maintained during the final weight maintenance month in all groups ( 2 )

- Emotional: IF does not appear to lead to compensatory overconsumption on the non-dieting days in any of the trials. ( 2 )
    - Adverse effects: symptoms such as feeling cold, decreased energy levels, constipation, headaches, bad breath on energy-restricted, feeling light-headed, lack of concentration, mood swings or bad temper, and being preoccupied with food ( 2 )
    - Average weekly hunger scores did not differ between the three groups throughout the study. At 1 month, hunger and desire-to-eat scores were marginally greater after the first restricted day of IECR compared with the first restricted day of IECR + PF and an average DER day. This difference was no longer evident after 3 and 4 months, indicating that women had become used to the restriction ( 2 )
    - the success of both IECR diets is not only linked to the adherence to the 2 d restriction, but is also attributable to the spontaneous restriction of energy and carbohydrate on non-restricted days. Intakes on these days in the IECR groups were comparable with those of the DER group. This is an important observation and confirms the present data and the data of others which show that intermittent dieting does not lead to disordered eating and overconsumption on non-restricted day ( 2 )
  - *Post-study results:* 1 d of restriction per week maintained weight loss and the reductions in disease risk markers in the short term, similarly to the DER group who were asked to have the recalculated euenergetic DER. ( 2 )
  - Limitations: 7 day food diaries used for data collection
7. **The study:** systematic review of human findings of IF vs DCR for T2DM in overweight or obese populations (2014) ( 18 )
- On average, ADF appears to produce a 0.75 kg weekly reduction in body weight, whereas IF produces a 0.25 kg weekly weight loss. As such, clinicians may want to recommend ADF to their patients who are eager to lose weight more rapidly, and IF to patients who would prefer to lose weight at a slower pace. ( 18 )
  - CR produces slightly superior weight loss when compared with IF/ADF after similar durations of treatment. For instance, after 3–24 weeks of IF or ADF, 3%–8% reductions in body weight were observed. As for CR, 6–24 weeks of diet produced reductions ranging from 4% to 14%. Not surprisingly, greater degrees of energy restriction and longer treatment durations produced larger reductions in body weight. IF, ADF, and CR appear to be effective for reducing body weight in men and women, older and younger adults, and prediabetic individuals. ( 18 )
  - The impact of IF, ADF, and CR on fasting glucose concentrations in prediabetic subjects was variable. Although IF and ADF studies demonstrated minor decreases in glucose. CR studies general report no effect after 6–12 weeks of diet. Fasting insulin, on the other hand, was highly responsive to all 3 interventions. In general, insulin concentrations were reduced by 20%–31% after 8–12 weeks of IF and ADF, and by 11%–41% after 6–12 weeks of CR. Reductions

in insulin concentrations by IF, ADF, and CR appeared to be most strongly related to the degree the of imposed restriction and amount of weight loss. ( 18 )

- Consistent improvements in insulin sensitivity were noted by all 3 interventions after 3–24 weeks of treatment. These improvements occurred in prediabetic subjects and subjects with normal fasting glucose values. ( 18 )
- In sum, IF, ADF, and CR regimens appear to be effective for reducing body weight, although CR may result in slightly greater weight loss. As for visceral fat mass, and fasting insulin and insulin sensitivity, the effect of IF, ADF, and CR on these diabetic risk parameters appears comparable. ( 18 )

### **Non-overweight Intermittent Fasting**

1. The study: effects of alternate-day fasting on body weight, body composition, and energy metabolism in nonobese subjects (2005) ( 7 )
  - *Primary goal:* whether alternate day fasting is a feasible method of dietary restriction in nonobese humans and whether it improved known biomarkers of longevity ( 7 )
  - *Participants:* Healthy, nonobese [BMI range 20.0–30.0], men ( $n = 8$ ) and women ( $n = 8$ ) aged between 23 and 53 y ( 7 )
  - *Duration of study:* 3 weeks ( 7 )
  - *Study details:* 2 consecutive days at baseline (days –2 and –1) and on 2 consecutive days after 3 wk of alternate-day fasting following a “feast” day (day 21) and following a “fast” day ( 7 )
    - On each fasting day, the subjects were allowed to consume energy-free beverages, tea, coffee, and sugar-free gum and were instructed to keep their water intake high. On each feasting day, the subjects were instructed to eat whatever they wished and were informed that double their usual food intake would be required to maintain their usual body weight. ( 7 )
  - *Social support:* none disclosed
  - *Results:*
    - *Physical:*
      - Percentage weight loss did not differ significantly between the men and the women, but weight loss correlated negatively with considering oneself a big eater after adjustment for sex ( 7 )
      - women had significantly lower glucose, insulin, free fatty acid, triacylglycerol, and LDL-cholesterol concentrations and significantly higher HDL-cholesterol and ghrelin concentrations than did the men ( 7 )
      - Fasting glucose was not significantly changed from baseline in the men or the women. Fasting insulin was lower on day 22 in both the men and the women ( 7 )
      - Fasting ghrelin was not significantly altered from baseline on day 21 (results not shown) or day 22 ( 7 )

- systolic and diastolic blood pressure were not significantly altered by the intervention (data not shown). HDL was elevated from baseline in the women only ( 7 )
  - RMR was not significantly changed after 3 wk of alternate-day fasting. The effects of 36-h fasts on RMR have not been previously reported
  - the subjects lost  $2.5 \pm 0.5\%$  of their initial body weight ( 7 )
  - alternate-day fasting is feasible in nonobese subjects for short time periods, although unlike rodents, the subjects were unable to maintain their body weight. Furthermore, fat oxidation was increased and translated into fat mass loss
  - *Emotional*
    - significant increase was found in feelings of hunger and a significant decrease was noted in feelings of fullness. However, repeated-measures analysis over time showed no significant changes in the subjects' perception of hunger, thirst, desire to eat, or feelings of satisfaction, although feelings of fullness increased slightly over time ( 7 )
    - One participant reported feeling lightheaded once, and 4 subjects reported constipation. No subjects withdrew during the study, but many reported feeling irritable on their fasting days, perhaps indicating the unlikelihood of continuing this diet for extended periods of time. ( 7 )
    - Hunger on fasting days did not habituate over the course of the study, which perhaps indicates the unlikelihood of subjects continuing on this diet for extended periods of time. Whether alternate-day fasting would promote weight loss in an obese population is uncertain ( 7 )
    - these results suggest that a prolonged schedule of fasting and feasting would be marred by aversive subjective states (eg, hunger and irritability), which would likely limit the ability of most individuals to sustain this eating pattern. Hunger on fasting days did not habituate over the course of the study, which perhaps indicates the unlikelihood of subjects continuing on this diet for extended periods of time. ( 7 )
  - *Limitations:* short study with few participants
2. **The study:** if 5:2 intermittent fasting in lean female students causes lower perceived work performance due to distraction vs hunger ( 8 )
- *Primary goal:* investigate the impact of fasting on perceptions of hunger, distraction, mood, and perceived work performance, and the degree to which the effects on mood and performance were accounted for by perceptions of hunger and distraction. ( 8 )
  - *Participants:* 16 lean female students (aged 18-22 years, BMI 20.2-23.9 kg/m<sup>2</sup>)
    - participants were non-smokers, in good physical and mental health, and not on any energy restricting diet. The researchers chose this group due to the

high likelihood of food restriction in this group and therefore predicted higher level of compliance with the intervention. Eye roll. ( 8 )

- *Study duration:* 2 consecutive fast days
- *Study details:*
  - Participants were asked to undertake two consecutive days of fasting, where consumption of no more than 500 kcal. was permitted. (recorded via FFQ)
  - Hunger, distraction, mood and perceived work performance were measured at 6pm on each study day, using 100mm visual analogue scales, anchored from 'not at all' to 'extremely'. ( 8 )
  - Distraction was measured using five questions assessing: current distraction - 'How attentive are you feeling?', and whole day distraction - 'How distracted do you feel you have been today?', 'How focused on particular tasks have you felt today?' (reversed scored), 'How often do you feel you've been daydreaming today?', and 'How difficult have you found it to concentrate today?'. ( 8 )
  -
- *Results:*
  - Physical: not mentioned
  - Emotional:
    - Higher positive mood was initially associated with non-fasting as opposed to fasting ( 8 )
    - effects of fasting on mood and perceived work performance were found to result largely from the consequent distraction, as opposed to the act of fasting or the resulting hunger. ( 8 )
    - Researchers thought there would be decreased cognitive load given participants wouldn't have to think about eating, as they're consuming nothing or only one small meal, but in fact the preoccupation / distraction led to reduced cognitive resources available for other tasks, such as decision making and work performance ( 8 )
    - **reduced blood sugar impacts on mood and perceived work performance, not through hunger or physiological deprivation, but through an increased cognitive load as a result of an increased attention toward food and** - increased cognitive load and a redirection of attention as a result of dieting/fasting **eating.** ( 8 )
    - poorer positive mood and poorer perceived work performance on fast days compared to non-fast days were associated with higher distraction, as opposed to the act of fasting or higher hunger ( 8 )
    - suggests that intermittent fasting offers no benefits for mood or perceived work performance over traditional dieting as a result of reduced distraction during fast days ( 8 )
- *Limitations:* ( 8 ) : extremely small study, FFQ used, small duration of time
  - The use only of lean young females may also be considered a limitation. This population group was used to test a theoretical hypothesis, due to their likely

high compliance, as well as the high relevance of this group for real world implications. ( 8 )

3. **The study:** feasibility and impact of low-protein and low-calorie fasting medical diet (FMD) in humans (2015)(17 )

○ *Primary aim:* to determine if a FMD vs a control diet is feasible (17 )

● *Subjects:*

○ Control group: 19 (9 females, 10 males) with average age 35-38 yo (17 )

○ FMD group: 7 females, 12 males, average age 41-42 yo (17 )

○ generally healthy adult volunteers, 18–70 years of age, BMI: 18.5 and up (17 )

● *study duration:* 3 months

● *Study details:*

○ subjects were randomized either to the FMD for 5 days every month for 3 months (3 cycles) or to a control group in which they continued to consume their normal diet (17 )

○ The human fasting mimicking diet (FMD) program is a plant-based diet program designed to attain fasting-like effects while providing micronutrient nourishment (vitamins, minerals, etc.) and minimize the burden of fasting. It comprises proprietary vegetable-based soups, energy bars, energy drinks, chip snacks, chamomile flower tea, and a vegetable supplement formula tablet. The human FMD diet consists of a 5 day regimen: day 1 of the diet supplies ~1,090 kcal (10% protein, 56% fat, 34% carbohydrate), days 2–5 are identical in formulation and provide 725 kcal (9% protein, 44% fat, 47% carbohydrate) (17 )

● *results:*

○ *physical:*

▪ In the FMD subjects, fasting blood glucose levels were reduced by and remained lower than baseline levels after resuming the normal diet following the third FMD cycle (17 )

▪ CRP levels were reduced by the FMD cycles. 8 of the 19 FMD subjects had CRP levels in the moderate or high cardiovascular disease risk range at baseline. For 7 of them, the levels returned to the normal range after 3 FMD cycles (17 )

▪ The FMD resulted in a 3% reduction in body weight that remained lower at the completion of the study. fat loss accounts for most of the weight loss. Pelvis bone mineral density was not affected by the FMD (17 )

○ *Emotional:*

▪ Adverse effects were higher after completion of the first FMD cycle compared to those during the second and third FMD cycles. However, the average reported severity of the side effects was very low and below “mild” (<1 on a scale of 1–5). (17 )

## COMBINATION WEIGHTS

1. **The study:** 5:2 FMD and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease (2017) ( [33](#) )
  - *Primary aim:* the effects of the FMD on risk factors and markers for aging, cancer, metabolic syndrome, and CVDs in generally healthy participants ranging from 20 to 70 years of age. ( [33](#) )
    - Intervention: 3 cycles FMD
    - Control: no FMD
  - *Participants:*. 37 male, 63 female total
    - Mean BMI 26-27 (ranged from <25->30)
    - No significant differences in metabolic markers / risk factors for age-related diseases and conditions between subjects in both groups
  - *Duration* From April 2013 to July 2015
  - *Study details:* 100 study participants were randomized and assigned to either subjects who followed 3 months of an unrestricted diet to subjects who consumed the fasting mimicking diet for 5 consecutive days per month for 3 months
    - The FMD is a plant-based diet designed to attain fasting-like effects on the serum levels of IGF-1, IGFBP-1, glucose, and ketone bodies while providing both macro- and micronutrients to minimize the burden of fasting and adverse effects. Day 1 of the FMD supplies ~4600 kJ (11% protein, 46% fat, and 43% carbohydrate), whereas days 2 to 5 provide ~3000 kJ (9% protein, 44% fat, and 47% carbohydrate) per day. The FMD comprises proprietary formulations belonging to USC and L-Nutra of vegetable-based soups, energy bars, energy drinks, chip snacks, tea, and a supplement providing high levels of minerals, vitamins, and essential fatty acids ( [33](#) )
  - *Results:*
    - Physical:
      - Weight: Participants in the FMD arm lost on average  $2.6 \pm 2.5$  kg of weight, which was due in part to a reduction in total body fat and trunk fat. Subjects on the control diet did not lose body weight. No change in the percentage of lean body mass was observed ( [33](#) )
      - The FMD cycles also resulted in a decrease in IGF-1 concentrations. Systolic blood pressure was reduced, and diastolic blood pressure was reduced. Fasting glucose, triglycerides, cholesterol, and the acute-phase inflammatory marker CRP did not differ significantly between groups ( [33](#) )
      - At the end of the first FMD cycle and before resuming the normal diet, body weight, BMI, absolute lean body mass, waist circumference, fasting glucose, IGF-1, diastolic blood pressure,

triglycerides, and LDL were significantly reduced compared to baseline. In contrast, relative lean body mass Both absolute and relative total body fat, systolic blood pressure, as well as CRP were not significantly changed after completion of the first FMD cycle compared to baseline. These results indicate that subjects did follow the dietary changes imposed by the FMD and responded to them as anticipated. ( 33 )

- In subjects who completed three FMD cycles and who returned to the normal diet for 5 to 7 days, body weight, BMI, total body fat, trunk fat, absolute lean body mass, waist circumference, IGF-1, systolic and diastolic blood pressure, total cholesterol, LDL, and HDL were significantly reduced, and relative lean body was increased. Fasting glucose,  $\beta$ -hydroxybutyrate, triglycerides, and CRP were not significantly changed. ( 33 )
- In summary, the combined FMD groups from arms 1 and 2 confirmed that the FMD cycles promoted potent effects on many metabolic markers and disease risk factors, which are maintained after subjects return to their normal diet ( 33 )
- FMD was particularly beneficial among subjects who were obese (BMI >30) at baseline. The FMD-dependent reduction in IGF-1 was also larger in participants with baseline IGF-1  $\geq 225$  ng/ml ( 33 )
- FMD had more pronounced effects in at-risk participants than in those subjects with risk factor values within the normal range, with the exception of HDL. ( 33 )
- Emotional: participants reported no adverse effects during the FMD cycles. The most common self-reported grade 1 (mild) or grade 2 (moderate) symptoms experienced by the participants were fatigue, weakness, and headaches. No adverse effects of grade 3 or higher were reported. Note that 25% of the subjects who tested the FMD dropped out of the trial, whereas 10% of the participants opted out of the control arm. This indicates that, despite our efforts to reduce the burden of low-calorie/protein diets, adherence to this dietary regimen requires committed study participants. ( 33 )

### **Time restricted feeding in non-overweight individuals**

#### **1. The study:** restricting night-time eating to reduce overall daily energy intake (2013) ( 9 )

- *Primary goal:* short-term effect of night eating restriction (NER) on daily energy intake (EI) in healthy young men (mean BMI 24.4). It secondarily examined body weight and moods associated with NER. ( 9 )
- *Participants:* 29 unmarried men, 18–26 years of age, healthy, and non-smokers or drinkers and had their weight stable for the previous month. ( 9 )

- *Duration of study:* 2-week NER intervention (elimination of energy intake from 19.00 to 06.00 hours) and a 2-week control condition, counterbalanced and separated by a 1-week washout period. ( 9 )
  - *Study details:* in the night eating restriction group, the participants were instructed to avoid consumption of all food or beverages that included any energy (kJ) from 19.00 to 06.00 hours for two consecutive weeks. The consumption of water after 19.00 hours was considered acceptable and preferable. ( 9 )
  - *Method of data reporting:* food diary
  - *Social support:* each participant was called 3 d/week to report on whether or not he had adhered to the NER protocol and to encourage further compliance. ( 9 )
  - *Results:*
    - *Physical:* 2 weeks of NER resulted in a significant difference in energy intake and body weight in healthy young men. ( 9 )
    - *Emotional:* Mood was assessed using the Profile of Mood States (POMS) scale at the beginning and end of each condition. There was no pre/post-change for total mood score or its sub- scales within the NER and control conditions ( 9 )
  - *Limitations:* under-reporting of energy intake or that some other study factor influenced energy intake, particularly during the control condition. ( 9 )
    - obvious limitation – done in young healthy men
2. **The study:** impact of meal frequency without caloric restriction in glucose regulation in healthy, normal weight middle-aged men and women (2007) ( 10 )
- *Primary aim:* evaluated the influence of reduced meal frequency without a reduction in energy intake on glucose metabolism in normal weight healthy male and female subjects. ( 10 )
  - *The participants:* healthy 40–50 year-old men and women with body mass indexes between 18 and 25 kg/m<sup>2</sup> with a usual eating pattern of three-meals-per-day (15 women, 8 men) ( 10 )
  - *Length of study:* 2 eight-week treatment periods (with an intervening 11 week off-diet period) ( 10 )
  - *Study details:*
    - Each subject underwent two 8-week controlled diet periods during which they consumed all of their calories for weight maintenance in either 3 meals/day (breakfast, lunch and dinner) or 1 meal/day (during a 4 hour time period in the early evening; 16:00 – 20:00 hours) in a randomized cross-over design with an 11 week off-diet period between the two controlled diet ( 10 )
    - each subject consumed the same amount of calories each day regardless of whether they ate one or three meals, and all subjects maintained their body weight within 2 kg of their initial weight throughout the 6 month period ( 10 )
    - Measured levels of glucose, insulin, glucagon, leptin, ghrelin, adiponectin, resistin and brain-derived neurotrophic factor (BDNF). ( 10 )

- **Results:**
    - **Physical:**
      - Subjects consuming 1 meal/d exhibited higher morning fasting plasma glucose levels, greater and more sustained elevations of plasma glucose concentrations, poorer glucose tolerance, and a delayed insulin response in the OGTT compared to subjects consuming 3 meal/d. ( 10 )
      - consumption of one unusually large meal per day worsens morning glucose tolerance compared to an isocaloric diet spread across three meals. However, when on 1 meal/d the subjects would have eaten less than those on 3 meals/day if we had not asked them to consume the same amount of food that they normally eat on a 3 meal/d schedule. ( 10 )
      - fasting plasma insulin concentrations were not significantly affected by meal frequency and there were no significant effects of diet on insulin responses to glucose during the OGTT ( 10 )
      - when on 1 meal/d, subjects exhibited: a significant reduction of fat mass, and significant increases in levels of total and LDL and HDL cholesterol ( 10 )
      - there were no significant effects of meal frequency on plasma levels of ghrelin, adiponectin, resistin or BDNF. ( 10 )
    - **long term effects:** Whether the effect of the 1 meal/d diet on glucose tolerance would persist, exacerbate or resolve over time beyond the 2 month experimental diet period of our study is an important question relevant to long-term effects of the diet. However, we did find that the effect of the 1 meal/d diet on glucose tolerance was rapidly reversed upon return to the 3 meal/d diet, indicating that the diet had no long-lasting effect on glucose metabolism. ( 10 )
3. **the study:** harmful effects of skipping breakfast on insulin sensitivity and fasting lipid profiles in healthy, lean women (2005) ( 13 )
- **primary aim:** if eating breakfast (EB) or omitting (OB) affects energy intake, energy expenditure, and circulating insulin, glucose, and lipid concentrations in healthy women ( 13 )
  - **participants:** 10 women (BMI ~23) ( 13 )
    - i. who were menstruating regularly or were taking the oral contraceptive pill, who were neither pregnant nor lactating, and who had no self-reported history of hypercholesterolemia, hyperglycemia, or any serious medical conditions ( 13 )
  - **length of study:** 6 weeks ( 13 )
  - **study details:** In the EB period, subjects consumed breakfast cereal with 2%-fat milk before 0800 and a chocolate-covered cookie between 1030 and 1100. In the OB period, subjects consumed the cookie between 1030 and 1100 and the cereal and milk between 1200 and 1330. Subjects then consumed 4 additional meals with content similar to usual at predetermined times later in the day and recorded food intake on 3 d during each period. ( 13 )

- The timetable for the 4 additional eating occasions during both the EB and the OB periods was 1330–1400, 1530–1600, 1800–1830, and 2030–2100. Subjects were asked to consume their main evening meal (dinner) between 1800 and 1830. ( 13 )
  - *results:*
    - *physical:*
      - Body weight did not differ significantly between the preintervention and postintervention periods ( 13 )
      - Fasting blood glucose did not differ significantly between the pre-EB and pre-OB period visits, and there was no effect of either intervention on fasting blood glucose ( 13 )
      - OB impairs fasting lipids and postprandial insulin sensitivity and could lead to weight gain if the observed higher energy intake was sustained. ( 13 )
      - in healthy lean women, OB led to a higher plasma total and LDL-cholesterol concentrations and lower postprandial insulin sensitivity than did EB. Mean reported total EI was significantly lower during the EB period than during the OB period. ( 13 )
      - plasma total and LDL-cholesterol concentrations increased after the OB period more than they did after the EB period. Fasting plasma HDL-cholesterol and triacylglycerol concentrations, however, showed no significant differences between the EB and OB periods. ( 13 )
    - i. *emotional:* none reported
  - *limitations:* small study with young women, recorded food with food intake record; Underreporting of EIs, especially for snacks, might lead to errors in data interpretation and also to inconsistent results. We also had underreporting in this study, but the similar degree of underreporting between the habitual diet and the EB period, as well as the crossover design, suggests that the higher total intake in the OB period is a reliable observation even if the absolute intake is not. ( 13 )
4. **The study:** 8 weeks 16/8 time restricted feeding on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males ( 29 )
- Primary aim: investigate the effects of an isoenergetic TRF protocol on body composition, athletic performance, and metabolic factors during resistance training in healthy resistance trained males. We hypothesized that the TRF protocol would lead to greater fat loss and improvements in health-related biomarkers as compared to a typical eating schedule. ( 29 )
  - Participants: 34 healthy males with history of resistance training ( 29 )
  - Length of study: 8 weeks ( 29 )
  - Study details:

- Thirty-four resistance-trained males were randomly assigned to time-restricted feeding (TRF) or normal diet group (ND). TRF subjects consumed 100 % of their energy needs in an 8-h period of time each day, with their caloric intake divided into three meals consumed at 1 p.m., 4 p.m., and 8 p.m. The remaining 16 h per 24-h period made up the fasting period. Subjects in the ND group consumed 100 % of their energy needs divided into three meals consumed at 8 a.m., 1 p.m., and 8 p.m. Groups were matched for kilocalories consumed and macronutrient distribution ( 29 )
- TRF approach utilized in the present study is that total daily calorie intake remained the same while the frequency of meals (i.e. time between meals) was altered ( 29 )
- Fat mass and fat-free mass were assessed by dual-energy x-ray absorptiometry and muscle area of the thigh and arm were measured using an anthropometric system. Total and free testosterone, insulin-like growth factor 1, blood glucose, insulin, adiponectin, leptin, triiodothyronine, thyroid stimulating hormone, interleukin-6, interleukin-1 $\beta$ , tumor necrosis factor  $\alpha$ , total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured. Bench press and leg press maximal strength, resting energy expenditure, and respiratory ratio were also tested. ( 29 )
- Data collection: 7-day food diary ( 29 )
- Social support: Every week, subjects were contacted by a dietician in order to check the adherence to the diet protocol. The dietician performed a structured interview about meal timing and composition to obtain this information. ( 29 )
- Results:
  - After 8 weeks, the 2 Way ANOVA showed a decrease in fat mass in TRF compared to ND, while fat-free mass, muscle area of the arm and thigh, and maximal strength were maintained in both groups. Testosterone and insulin-like growth factor 1 decreased significantly in TRF, with no changes in ND. Adiponectin increased in TRF while total leptin decreased, although not when adjusted for fat mass. Triiodothyronine decreased in TRF, but no significant changes were detected in thyroid-stimulating hormone, total cholesterol, high-density lipoprotein, low-density lipoprotein, or triglycerides. Resting energy expenditure was unchanged, but a significant decrease in respiratory ratio was observed in the TRF group. ( 29 )
  - Our results suggest that an intermittent fasting program in which all calories are consumed in an 8-h window each day, in conjunction with resistance training, could improve some health-related biomarkers, decrease fat mass, and maintain muscle mass in resistance-trained males. ( 29 )

- However, we did not find any significant differences between groups in fat-free mass, indicating that the influence of nutrient timing may be negligible when the overall content of the diet is similar. ( 29 )
- reduction of inflammatory markers is related to the improvement of insulin sensitivity ( 29 )
- Based on the present study, a modified IF protocol (i.e. TRF) could be feasible for strength athletes without negatively affecting strength and muscle mass. Interestingly, even though androgen concentrations were lowered by TRF, there was no difference in muscle mass changes between groups
- Leg press maximal strength increased significantly, but no difference was present between treatments ( 29 )

### **Reduced Time Feeding – Overweight Adults**

#### **1. The study:** role of breakfast in energy balance and health (2016) ( 11 )

- *primary aim:* to examine causal links between breakfast habits and energy balance in free-living obese humans; compares the effects of daily breakfast consumption relative to extended morning fasting on energy balance and human health ( 11 )
- *participants:* 23 total participants (15 women, 7 men) ( 11 )
  - participants were randomly assigned (1:1 allocation ratio) into either a group prescribed an energy intake of  $\geq 700$  kcal before 1100 daily, with at least half consumed within 2 h of waking (breakfast group), or a group to extend their overnight fast by abstaining from ingesting energy-providing nutrients (i.e., plain water only) until 1200 each day (fasting group). ( 11 )
- *length of study:* 6 weeks ( 11 )
- *results:*
  - *physical:*
    - in obese adults, daily breakfast leads to greater physical activity during the morning, whereas morning fasting results in partial dietary compensation (i.e., greater energy intake) later in the day. There were no differences between groups in weight change and most health outcomes, but insulin sensitivity increased with breakfast relative to fasting. ( 11 )
    - significantly higher rate of physical activity thermogenesis in the breakfast group than the fasting group before 1200 daily but no difference after 1200 such that there was no consistent difference between groups over the entire day ( 11 )
    - resting metabolic rate was stable from baseline to follow-up, with no difference between groups in response to the intervention ( 11 )
    - Thyroid hormones that regulate resting metabolic rate were unresponsive to either treatment, with systemic concentrations of

triiodothyronine (free-T3) and thyroxine (free-T4) closely matched between treatments at baseline and follow-up ( 11 )

- range of hormones implicated in the regulation of appetite and energy balance also did not differ in response between treatments (of leptin, total ghrelin, acylated ghrelin, peptide YY, active glucagon-like peptide-1, and adiponectin) ( 11 )
- Body mass increased from pre- to postintervention when all participants from both groups were considered. The absolute change was greater in the breakfast group compared with the fasting group by 1.0kg. ( 11 )
- glycemic response to the OGTT was unaffected by either intervention ( 11 )
- 1) no difference in reported total energy intake between interventions, indicative that those fasting during the morning at least partially compensated for the  $\geq 700$  kcal deficit imposed; 2) lower physical activity thermogenesis in those fasting before 1200 than in those who consumed breakfast; 3) similar blood lipid, appetite regulatory hormone, and C-reactive protein responses to the intervention between groups but with a decreased insulinemic response to an OGTT in those consuming breakfast relative to an increase in those extending their fast; and 4) no evidence that the omission of breakfast had any effect on body weight. ( 11 )
- emotional: none mentioned

## 2. **The study:** role of breakfast in obesity treatment in women (1992) ( 14 )

- *Primary aim:* does eating breakfast assist with weight loss ( 14 )
- *Participants:* 52 women ( 14 )
- *Length of study:* 12 weeks ( 14 )
- *Social support:* both groups received behavior-modification program consisting of a 90-minute group meeting each week for 12 weeks. Subjects earned \$50 for attending sessions
- *Study details:* Stratified by baseline breakfast eaters vs non-eaters. The no-breakfast group ate two meals per day and the breakfast group ate three meals per day. The energy content of the two weight-loss programs was identical. ( 14 )
- *Results:* , baseline breakfast eaters lost 8.9 kg in the no-breakfast treatment and 6.2 kg in the breakfast treatment. Baseline breakfast skippers lost 7.7 kg in the breakfast treatment and 6.0 kg in the no-breakfast treatment. ( 14 )
  - that eating breakfast helped reduce dietary fat and minimize impulsive snacking and therefore may be an important part of a weight-reduction program. ( 14 )
  - those who had to make the most substantial changes in eating habits to comply with the program achieved better results. ( 14 )

## 3. **the study:** food patterns and behaviors after skipping breakfast in normal weight and overweight adults (2014) ( 15 )

- *participants*: 37 participants (16 male, 21 female) adults ( 15 )
- *Length of study*: 2 weeks ( 15 )
- *Study details*:
  - participants were assigned to one of four groups according to their BMI and normal habitual breakfast habit. Two groups were made up of participants with BMIs under 25, described as normal weight, and two other groups were composed of participants with BMI over 25 kg/ comprising overweight and obese participants; hereafter referred to as overweight.
  - One of the normal weight groups and one of the overweight groups comprised habitual breakfast eaters whereas the other normal weight group and overweight group comprised habitual breakfast omitters. Verbal information on usual breakfast habit was collected upon recruitment. A breakfast eater was classified as someone who normally ate breakfast (at least 100 kcal from food) more than 5 days a a breakfast omitter only ate breakfast on two or fewer occasions per week. adults ( 15 )
- *Results*
  - overweight participants consumed greater amounts of energy than normal weight participants in the early evening, and breakfast omitters consumed more late at night compared to breakfast eaters, independent experimental condition. ( 15 )
  - removing breakfast also affected the timing of subsequent energy intakes with more energy being consumed during the afternoon. Regardless of BMI and usual breakfast habit, significantly less energy, carbohydrate and fibre were consumed in no breakfast conditions. ( 15 )
  - Breakfast omitters consumed more than breakfast eaters later in the evening. All groups consumed significantly less energy, carbohydrate and fibre in the no breakfast condition however overweight participants increased their sugar intakes. ( 15 )
  - To summarise the above findings, during the afternoon (12:00 – 18:00 hrs.) more calories were consumed in the no breakfast condition compared to the breakfast condition. After 18:00 h the overweight and obese individuals consumed more irrespective of experimental manipulation and breakfast habit, and after 21:00 h breakfast habit influenced energy intake with breakfast omitters consuming more than breakfast eaters. ( 15 )
- *Limitations*: food frequency questionnaire for data collection- underreporting, small study, short study ( 15 )

**4.the study:** collecting daily eating pattern data on adults to discern weight patterns in healthy and overweight adults ( 21 )

- *study goals*: whether reducing the eating interval to 10–11 hr without an overt attempt to change nutrition could lead to weight loss in healthy overweight individuals ( 21 )
- *participants*: healthy, non-shift-worker adult males and females for 3 weeks (65 male, 90 female; ages 24-30), BMI 24-30 ( 21 )
- *duration of study*: 3 weeks ( 21 )

- *data collection*: record an ingestive event, the participants used the camera function of the smartphone to take a picture of the food or beverage. food picture and text entries along with timestamp and geolocation were immediately transferred to a server ( 21 )
  - *study details*: wanted to test whether longer eating duration and erratic eating pattern are contributing factors in subjects with co-occurrence of >25 BMI and >14 hr eating duration. We tested if reducing the eating duration and metabolic jetlag associated with weekday/weekend differences in a subset of individuals would lead to reduction in body weight ( 21 )
    - the participants were requested to reduce their caloric-containing eating duration to a self-selected window of 10–12 hr and to consistently follow this duration during both weekdays and weekends so that the metabolic jetlag could be minimized. ( 21 )
    - No overt suggestion concerning nutrition quality, quantity, or caloric content was provided. The individuals continued logging their food pictures using the same app as used in the baseline period for the next 16 weeks and also received a weekly summary of their feedograms and daily eating duration. ( 21 )
  - *results*:
    - *physical*:
      - intervention group reduced the estimated daily caloric intake (average reduction 20%) ( 21 )
      - reducing the temporal eating period in a feasibility study imparted measurable benefits of clinically relevant magnitude in terms of body weight reduction and sleep improvement without increasing the subjective sense of hunger. ( 21 )
      - relatively large effect on body weight reduction, even in the small intervention cohort, implies that the benefits might result from multiple changes: restoration of the diurnal rhythm of feeding/fasting, reduction of the weekday/weekend metabolic jetlag, and a reduction in the daily caloric intake. ( 21 )
    - *emotional*:
      - in a subjective self-assessment of sleep satisfaction, hunger at bedtime, reand energy level (in the mornings, and overall over the past few days), statistically significant improvement was observed. All participants voluntarily expressed an interest in continuing unsupervised with the 10–11 hr time-restricted eating regimen after the conclusion of the 16-week supervised intervention. After 36 weeks (1 year since the intervention began), the participants maintained weight loss and sleep improvement and felt more energetic ( 21 )
5. the study: early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes ( 34 )
- primary aim: test whether IF has benefits independent of weight loss by feeding participants enough food to maintain their weight and to determine whether eTRF can improve cardiometabolic health ( 34 )

- participants: 8 men with prediabetes (elevated HbA1c levels and impaired glucose tolerance) ( [34](#) )
- study duration: 5 weeks
- study details: eating in a 6 hour feeding period (7am – 3pm) per day for 5 weeks
- results:
  - i. physical:
    1. Although 5 weeks of eTRF did not improve glucose levels, it dramatically lowered insulin levels and improved insulin sensitivity and  $\beta$  cell responsiveness. ( [34](#) )
    2. the reductions in insulin levels were largest in participants with worse hyperinsulinemia at baseline ( [34](#) )
    3. the one participant whose insulin levels worsened on eTRF had reported a long history of overnight shift work prior to enrolling in the trial. Given that circadian rhythms are altered in adults who perform overnight shift work, it will be important to determine whether some subpopulations have altered circadian rhythms and would benefit more from alternative meal timing interventions. ( [34](#) )
    4. eTRF did not affect HDL cholesterol or LDL cholesterol . eTRF did increase morning fasting levels of triglycerides ( [34](#) )
    5. dramatically lowered systolic and diastolic blood pressure by 11 and 10 mmHg on average, which is on par with anti-hypertensive medications ( [34](#) )
    6. eTRF can be used to treat insulin resistance and to improve pancreatic  $\beta$  cell function; however, its effects on 24-hr glucose levels remain to be determined.
    7. did not affect morning fasting levels of the hunger hormone ghrelin ( [34](#) )
    8. Also improvements in blood pressure and oxidative stress levels (f 8-isoprostane, a marker of oxidative stress to lipids ( [34](#) )
    9. eTRF substantially reduced the desire to eat and the capacity to eat in the evening and non-significantly decreased hunger levels ( [34](#) )
    10. Participants also reported that eTRF dramatically increased sensations of fullness in the evening and nearly significantly increased sensations of a full stomach ( [34](#) )
  - ii. emotional: there were no serious adverse events. There were about one dozen adverse events identified as possibly related to the study intervention. These included vomiting (one participant in the eTRF arm), frequent urination and drowsiness (one participant in the control arm), and headaches, increased thirst, and diarrhea (each of which afflicted two participants in the eTRF arm and one participant in the control arm). ( [34](#) )
- Limitations: small sample size done only in men

## *Other reasons for fasting*

### **Rheumatoid Arthritis:**

**The study:** Systematic review looking at reports on fasting and rheumatoid arthritis (1996-1997) (19)

- Four different controlled studies have indicated that fasting periods lasting from 1 to 3 weeks reduce the symptoms of RA, although these effects are reversed by a return to the normal diet unless the PF is followed by a vegetarian diet (19)
- fasting followed by vegetarian diets might be useful in the treatment of rheumatoid arthritis. More randomised long-term studies of better methodological quality are needed to confirm this view (19)

### **Hormone levels:**

The study: growth hormone in men (23)

- 5-d fast resulted in a significant increase in discrete GH pulse frequency
- 6 men in the study ages 21-36 with normal weight (BMI 21.8-28)
- Men lost ~5kg weight
- Done in an inpatient environment, closely monitored, with water, KCl and vitamin supplements provided
- Glucose, free fatty acids, B-hydroxybutyrate, acetoacetate and blood chemistries were obtained during the fast, weighed daily
- Limitations: extremely small, done inpatient, doesn't translate clinically, ?longterm effects
- Similar results in a 2 day fast – also done in men (n=9) (5 fold increase in growth hormone) (24)

### **Inflammatory markers:**

(25) **The study:** interleukin-6, CRP and biochemical parameters during prolonged intermittent fasting (Ramadan)

- Primary aim: effects of long-lasting modifications of food intake on inflammatory markers and biochemical parameters 40
- Study details: Venous blood samples were taken 1 week before Ramadan, during the last week of Ramadan and 3 weeks after Ramadan. Serum interleukin-6 (IL-6), C-reactive protein (CRP), homocysteine, vitamin B(12), folate, total cholesterol (TC), triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were measured.
- Participants: 40 volunteers (20 female ages 20-38, and 20 males aged 23-39) with BMI <25
- Study duration:

- Results: No significant changes were observed in serum total cholesterol, triglycerides and LDL levels. TC/HDL ratio (HDL risk factor) was decreased during and after Ramadan in both genders in the fasting group while there were no changes in the nonfasting group. IL-6 ( $p < 0.001$ ), CRP ( $p < 0.001$ ) and homocysteine ( $p < 0.01$ ) levels were significantly low during Ramadan in the fasting subjects of both genders when compared to basal values (1 week before Ramadan).
  - prolonged intermittent fasting in a model like Ramadan has some positive effects on the inflammatory status of the body and on the risk factors for cardiovascular diseases such as homocysteine, CRP and TC/HDL ratio.

#### **Fasting for the gut:**

- Fasting regimens appear to have positive impacts on the gut microbiota by enhancing gut epithelial integrity, though the type of fasting wasn't mentioned in the study ( [12](#) )
- Chronic circadian misalignment in mice and time-shift-induced jet lag in humans result in dysbiosis and transmissible metabolic consequences, including obesity and glucose intolerance. These observations provide the first example of how a symbiotic community may synchronize its interdependent physiologic activities to the geophysical clock and how this promotes homeostasis of the metaorganism. ( [20](#) )

### **Background info**

**The study:** systematic review on fasting, circadian rhythms, and time-restricted feeding healthy lifespan (2016) ( [16](#) )

- Several major obstacles may be responsible for the very limited contribution of periodic fasting to standard medical practice:
  - the lack of pre-clinical and clinical data supporting specific and consistent effects of fasting on the prevention and treatment of diseases, and the mechanisms involved ( [16](#) )
  - the safety concerns related to the adoption of water-only consumption or the frequently adopted very low calorie diets (~200 kcal) outside of a clinic ( [16](#) )
  - the difficulties associated with compliance to these extreme diets. ( [16](#) )
- Overall, evidence suggests that intermittent fasting regimens are not harmful physically or mentally (i.e., in terms of mood) in healthy, normal weight, overweight, or obese adults. ( [16](#) )
- It appears that almost any intermittent fasting regimen can result in some weight loss. Among the 16 intervention trials included in this review, 11 reported statistically significant weight loss. ( [16](#) )
- Alternate-day fasting appeared to result in weight loss, as well as reductions in glucose and insulin concentrations, in the three studies evaluating this regimen. However, this fasting regimen may not be practical because it leads to intense hunger on fasting days. Modified alternate-day fasting regimens result in reduced weight, with reductions ranging from 3.2%, in comparison with a control group ( [16](#) )

- circadian clock intimately interacts with nutrient-sensing pathways. Frequent eating and the absence of a defined fasting period likely sustain modestly elevated levels of fed-state physiology and disturb the normal counter-regulatory metabolic state that occurs during fasting. ( 16 )
- Circadian rhythms are daily ~24 hr rhythms in metabolism, physiology, and behavior that are sustained under constant light or dark conditions. ( 16 )
- Daily feeding/fasting rhythms drive signaling pathways that interact with the circadian oscillator to increase the robustness or peak-to-trough differences of these transcriptional oscillations. These transcripts then mediate anabolic and catabolic processes that are appropriate for specific phases of the feeding/fasting cycle. In the absence of a functional circadian clock, feeding- and fasting-driven pathways can drive some oscillations in transcription, downstream metabolites and even the gut microbiota, but these signals cannot fully compensate for the loss of the circadian clock. Therefore, synergistic interactions between the circadian oscillator and feeding/fasting signals ensure that anabolic and catabolic types of metabolism are coordinately regulated in harmony with the animal's activity/rest cycle. ( 16 )

#### **Background info re: metabolic shift ( 26 )**

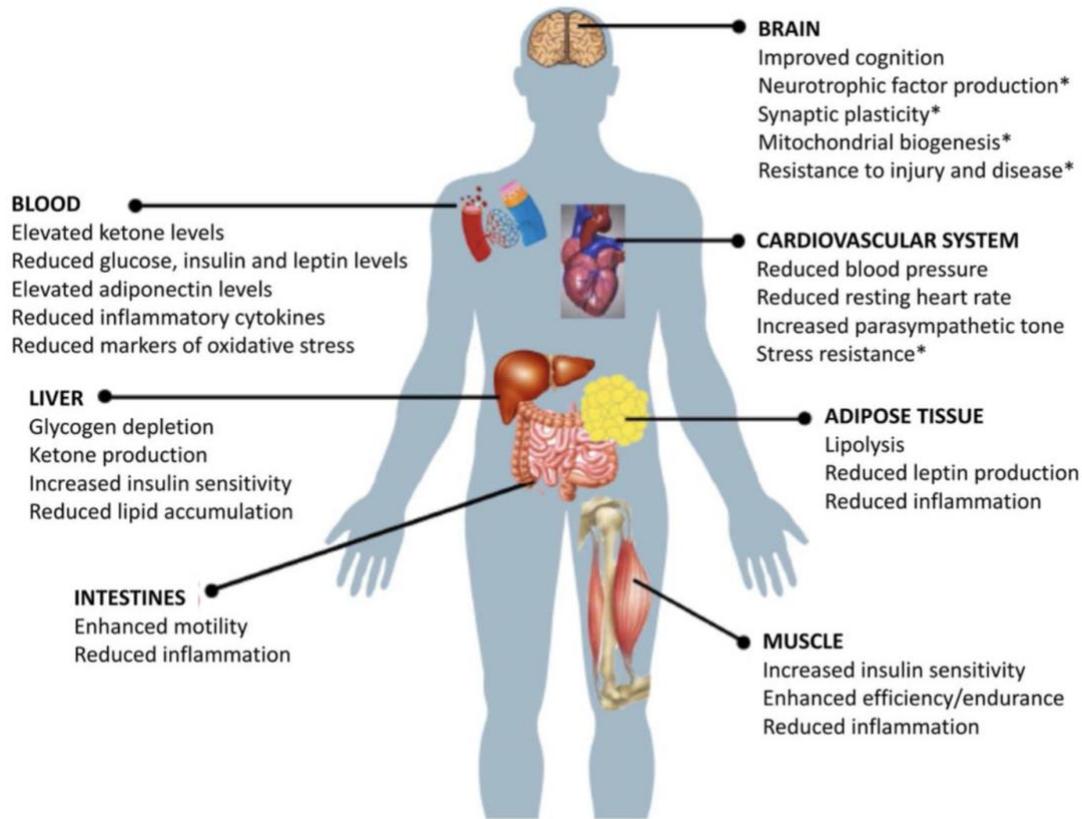
- Diets that markedly reduce caloric intake on 1 day or more each week (e.g., a reduction to 500 to 700 calories per day) result in elevated levels of ketone bodies on those days (all 3 studies performed in overweight / obese adults)
- influencing these major cellular pathways, ketone bodies produced during fasting have profound effects on systemic metabolism. Moreover, ketone bodies stimulate expression of the gene for brain-derived neurotrophic factor, with implications for brain health and psychiatric and neurodegenerative disorders
- Cells respond to intermittent fasting by engaging in a coordinated adaptive stress response that leads to increased expression of antioxidant defenses, DNA repair, protein quality control, mitochondrial biogenesis and autophagy, and down-regulation of inflammation
- Animal models show that intermittent fasting improves health throughout the life span, whereas clinical studies have mainly involved relatively short-term interventions, over a period of months.
- clinical studies have focused mainly on overweight young and middle-age adults, and we cannot generalize to other age groups the benefits and safety of intermittent fasting that have been observed in these studies.

#### **Background info re: metabolic shift ( 27 )**

- the metabolic switch as the body's preferential shift from utilization of glucose from glycogenolysis to fatty acids and fatty acid-derived ketones. The reason we use the word "preferential" is because there is now a growing body of research to indicate that ketones are the preferred fuel for both the brain and body during periods of fasting and extended exercise

- a shift from lipid synthesis and fat storage to mobilization of fat in the form of free fatty acids (FFAs) and fatty acid-derived ketones. For this reason, many experts have suggested that IF regimens may have potential in the treatment of obesity and related metabolic conditions, including metabolic syndrome and type 2 diabetes
- metabolic switch usually occurs between 12 and 36 hours after cessation of food consumption, depending on the liver glycogen content at the beginning of the fast, and on the amount of the individual's energy expenditure/exercise during the fast.
- when the metabolic switch is flipped, the primary energy source for the body shifts from glucose to FFA derived from adipose tissue lipolysis and ketones, which serve to preserve muscle. In support of this, retention of lean mass is increased following IF regimens for weight loss, as compared with continuous CR regimens in humans
- IF eating patterns may result in a wide range of beneficial effects on health, including improved glucose metabolism, reduced inflammation reduced blood pressure, improved cardiovascular health and increased resistance of cells to stress and disease in humans
- in humans and rodents, IF results in decreased levels of circulating insulin and leptin, elevated ketone levels, and reduced levels of pro-inflammatory cytokines and markers of oxidative stress. Liver cells respond to fasting by generating ketones and by increasing insulin sensitivity and decreasing lipid accumulation. Markers of inflammation in the intestines are reduced by IF. The insulin sensitivity of muscle cells is enhanced and inflammation reduced in muscle cells in response to the metabolic switch triggered by fasting and exercise. Emerging findings further suggest that exercise training in the fasted state may enhance muscle growth and endurance. Robust beneficial effects of IF on the cardiovascular system have been documented and include reduced blood pressure, reduced resting heart rate, increased heart rate variability (improved cardiovascular stress adaptation), and resistance of cardiac muscle to damage in animal models of myocardial infarction. Studies of laboratory animals and human subjects have shown that IF can improve cognition (learning and memory); the underlying mechanisms may involve neurotrophic factors, stimulation of mitochondrial biogenesis and autophagy, and the formation of new synapses. IF also increases the resistance of neurons to stress and suppresses neuroinflammation. \*Demonstrated in animal models but not yet evaluated in humans.
- ADMF regimens appear to produce consistent reductions in body weight and body fat mass but have less consistent effects on changes in lean mass
- IF regimens have been shown to reduce overall fat mass and visceral fat, both of which have been linked to increased diabetes risk (139). IF regimens ranging in duration from 8 to 24 weeks have consistently been found to decrease insulin resistance
- Human trials of IF that include cognitive and physical performance outcomes are unfortunately limited. Studies of cognition and mood during extended fasts, however, suggest few or no adverse effects, and improvements in performance in some cognitive domains, including executive function, have been reported (142-144). In regards to physical performance, a recent randomized controlled trial (RCT) of IF (20h of fasting 4 d/wk) during 1 month of resistance training in men demonstrated superior

improvements in upper- and lower-body endurance in the IF group compared with the control group



( 28 )

- while fasting and vigorous exercise are different challenges to the body and brain, emerging findings are revealing that they each elicit similar adaptive cellular responses that can enhance neuroplasticity and stress resistance. As reviewed elsewhere these include upregulation of neurotrophic factor signaling, autophagy, and DNA repair; suppression of oxidative stress and inflammation; stabilization of neuronal calcium homeostasis and neuronal network activity; and stimulation of mitochondrial biogenesis and neurogenesis
- While humans in modern societies have the opportunity to consume food throughout the day and night (ad libitum), our ancestors typically had to compete amongst themselves and with other species for a limited supply of food. Energy intake was relatively low and intermittent, and energy expenditure relatively high.

### OVERALL!

Even if a review summary of evidence based studies makes certain claims, it's important not to take them at face value. A [healthline article](#), for example, states that there's increase in human growth hormone which may facilitate fat burning and muscle gain. This study, however, was done exclusively in very small subsets of men. It also reports an improvement in cellular repair

and gene expression, though this study was done exclusively in mice / animals. Not to at all imply that this research isn't valid, but it also doesn't translate to the general population. It takes diving a little deeper and knowing what to look for. Aka be wary of what you read on the internet, and what is deduced from research studies. They are often done on very specific populations of people and imply CORRELATION, not causation.

### **Clinical recommendations: ( 26 )**

- most physicians are not trained to prescribe specific intermittent-fasting interventions. Physicians can advise patients to gradually, over a period of several months, reduce the time window during which they consume food each day, with the goal of fasting for 16 to 18 hours a day. Alternatively, physicians can recommend the 5:2 intermittent-fasting diet, with 900 to 1000 calories consumed 1 day per week for the first month and then 2 days per week for the second month, followed by further reductions to 750 calories 2 days per week for the third month and, ultimately, 500 calories 2 days per week for the fourth month. A dietitian or nutritionist should be consulted to ensure that the nutritional needs of the patient are being met and to provide continued counseling and education. As with all lifestyle interventions, it is important that physicians provide adequate information, ongoing communication and support, and regular positive reinforcement.

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