SICOM & AOCO 2024
SOMS International Conference on Obesity & Metabolism
in conjunction with Asia-Oceania Conference on Obesity
Hosted by SOMS Society for Korean Obesity and Metabolism Studies
Co-Hosted by aoaso Asia Oceania Association for the Study of Obesity
Empowering Health, Inspiring Change: Practical Solutions for Obesity
Date October 24 (Thu)~26 (Sat), 2024
Venue aT Center, Seoul, Republic of Korea (3F Segyero Room & 4F Changjo Room)

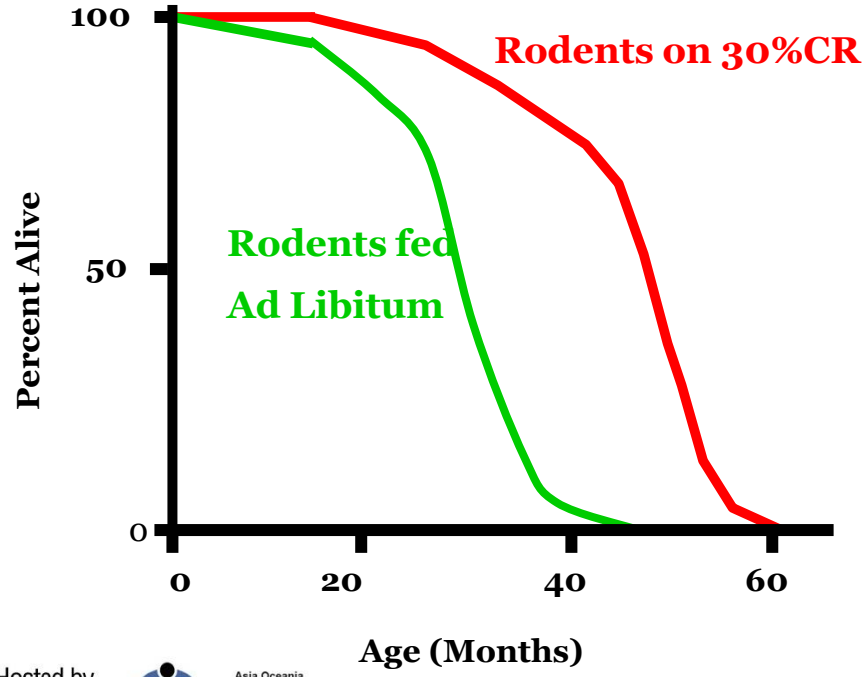
Dietary interventions for weight and health management: Caloric Restriction Versus Intermittent Fasting

Prof Leonie Heilbronn, University of Adelaide

THE UNIVERSITY of ADELAIDE

Calorie restriction reduces aging-related pathologies and increases lifespan in preclinical models

- Extends lifespan
- Cardio-protective
- Neuro-protective
- Improves insulin sensitivity
- Stimulates autophagy
- Delays cancer progression



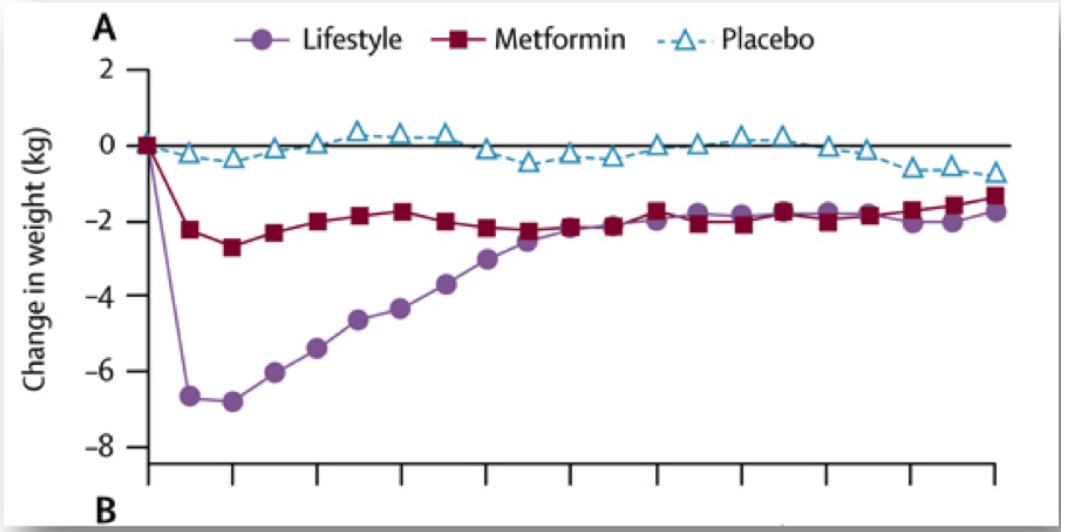
Weight management is chronic disease management

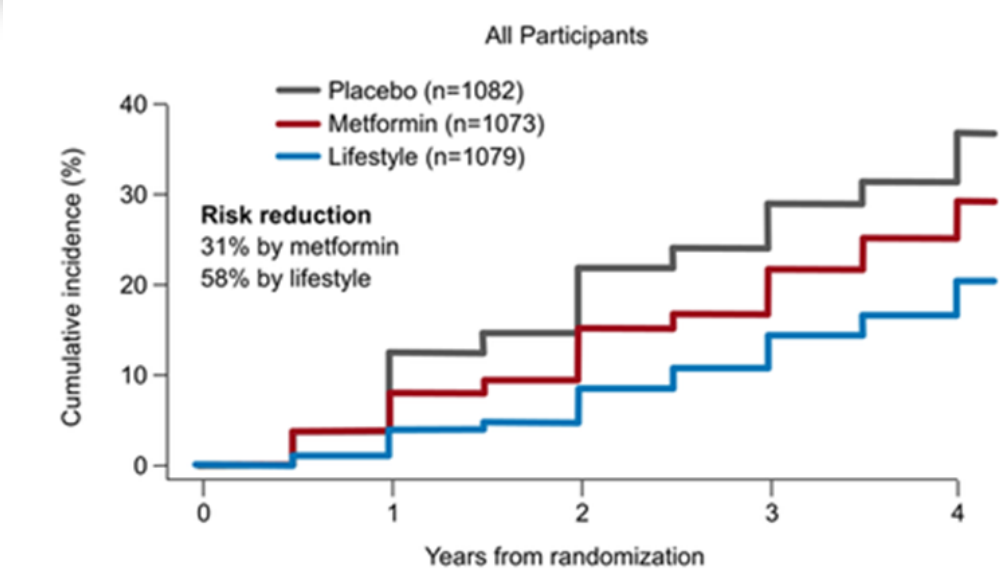
Modest weight loss of 5 -10 %

- Reduced insulin and insulin resistance
- Improve glycemic control
- Reduced blood pressure
- Reduced liver fat
- Reduced blood triglycerides
- Reduced blood cholesterol
- Reduce CKD risk factors

Moderate caloric restriction prevents type 2 diabetes and all cause mortality

DPP, Knowler et al 2002





Da Qing, Gong et al, 2019 = 30 y follow up

Lancet Diabetes Endocrinol.

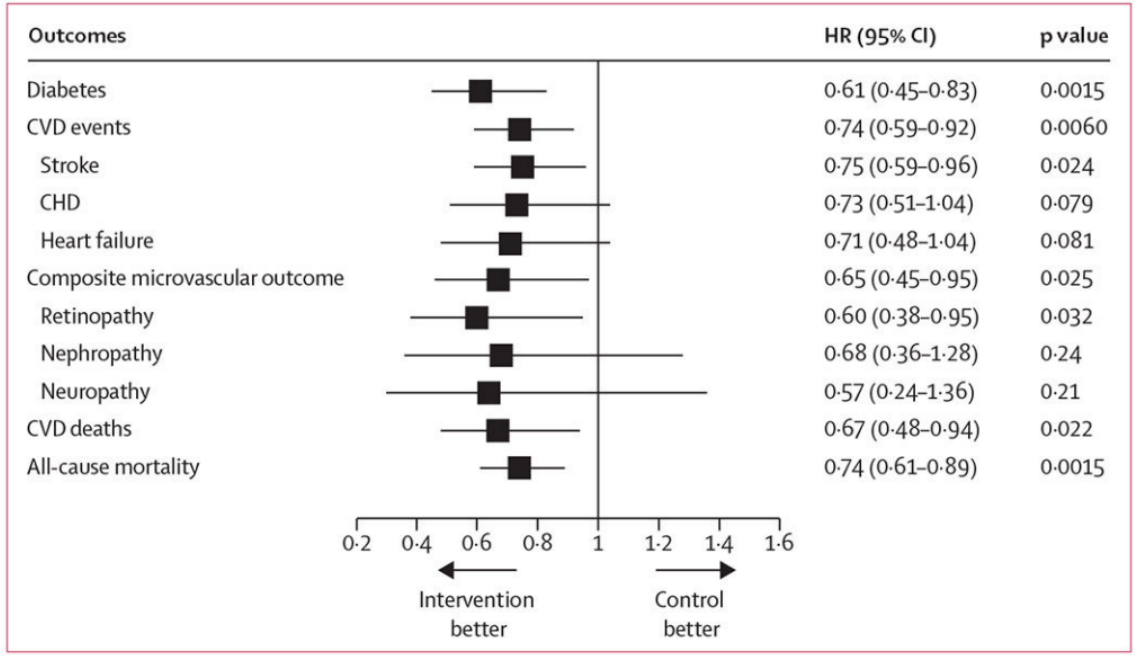
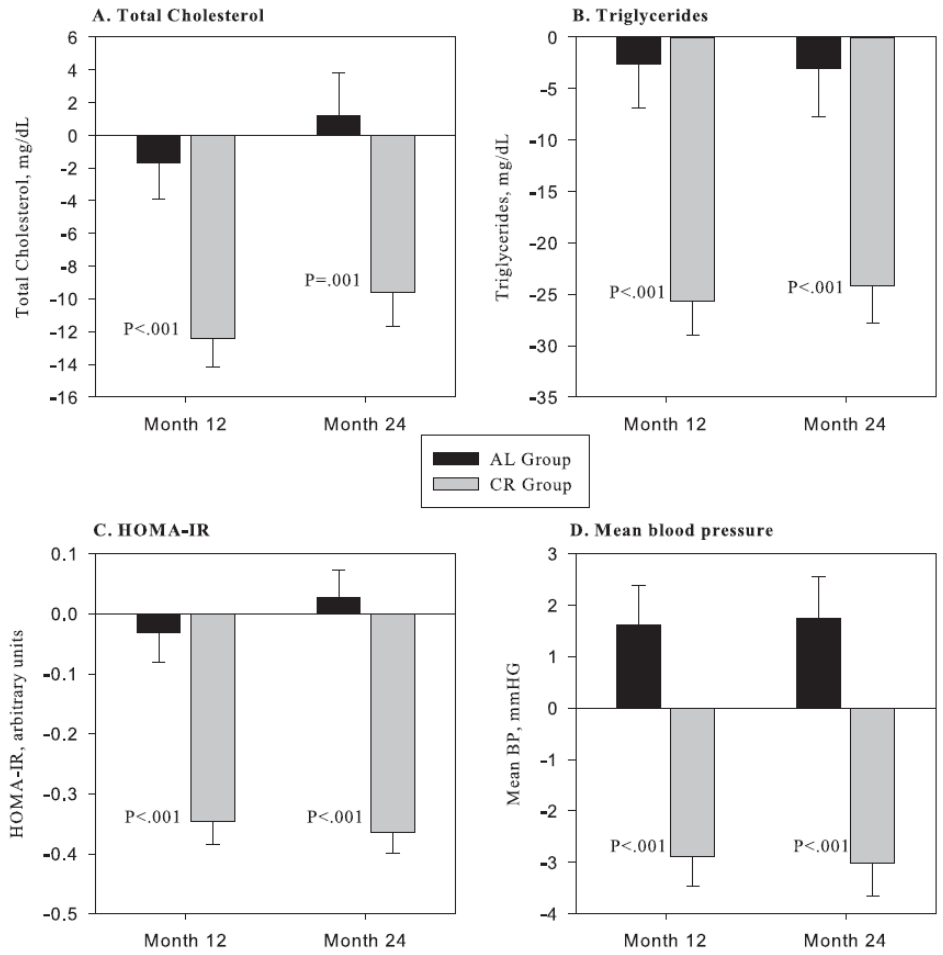


Figure 3: Forest plot of primary and secondary outcome events at 30-year follow-up
The reference category is the control group. Hazard ratios (HRs) are derived from proportional-hazards models, controlled for clinic randomisation. CVD=cardiovascular disease. CHD=coronary heart disease.

540 (94%) of 576 assessed for outcomes at 30 y
(135 in the control group, 405 in the intervention group).

Caloric restriction improves biomarkers of health in individuals without obesity (N=228).

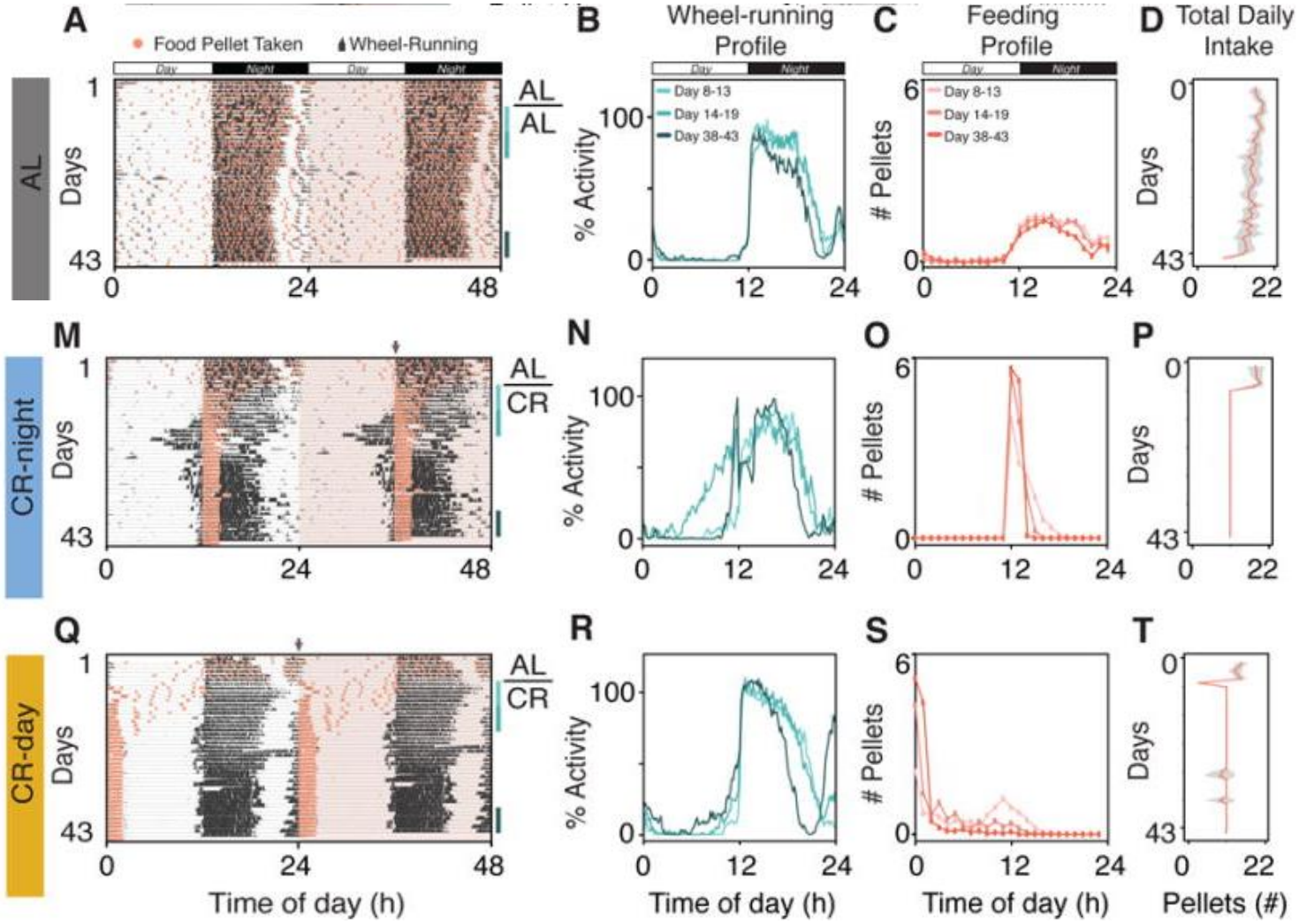
	AL (*n*=75)	CR (*n*=143)	*p-value*
Fasting Insulin (μIU/mL)			
Baseline	5.79	5.38	0.27
Δ Month 12	−0.14 (0.24)	−1.59 (0.18)***	<0.0001
Δ Month 24	0.14 (0.21)	−1.71 (0.16)***	<0.0001
AUC Insulin (μIU-h/mL)			
Baseline	98.8	96.2	0.68
Δ Month 12	7.33 (6.25)	−23.61 (4.86)***	<0.0001
Δ Month 24	6.25 (4.98)	−19.34 (4.08)***	<0.0001
AUC Glucose (mg-h/mL)			
Baseline	260.8	260.1	0.97
Δ Month 12	4.52 (4.70)	−4.70 (3.72)	0.23
Δ Month 24	2.89 (4.82)	0.10 (3.88)	1.0
hsCRP (nmol/L)			
Baseline	0.114	0.155	0.91
Δ Month 12	0.030 (0.037)	−0.045 (0.028)	0.105
Δ Month 24	0.002 (		



Raviussin E et al. J Gerontol A Biol Sci Med Sci. (2015)

Achieved 10% caloric restriction over two years

Mouse models of CR are actually models of intermittent fasting



Acosta-Rodríguez 2017

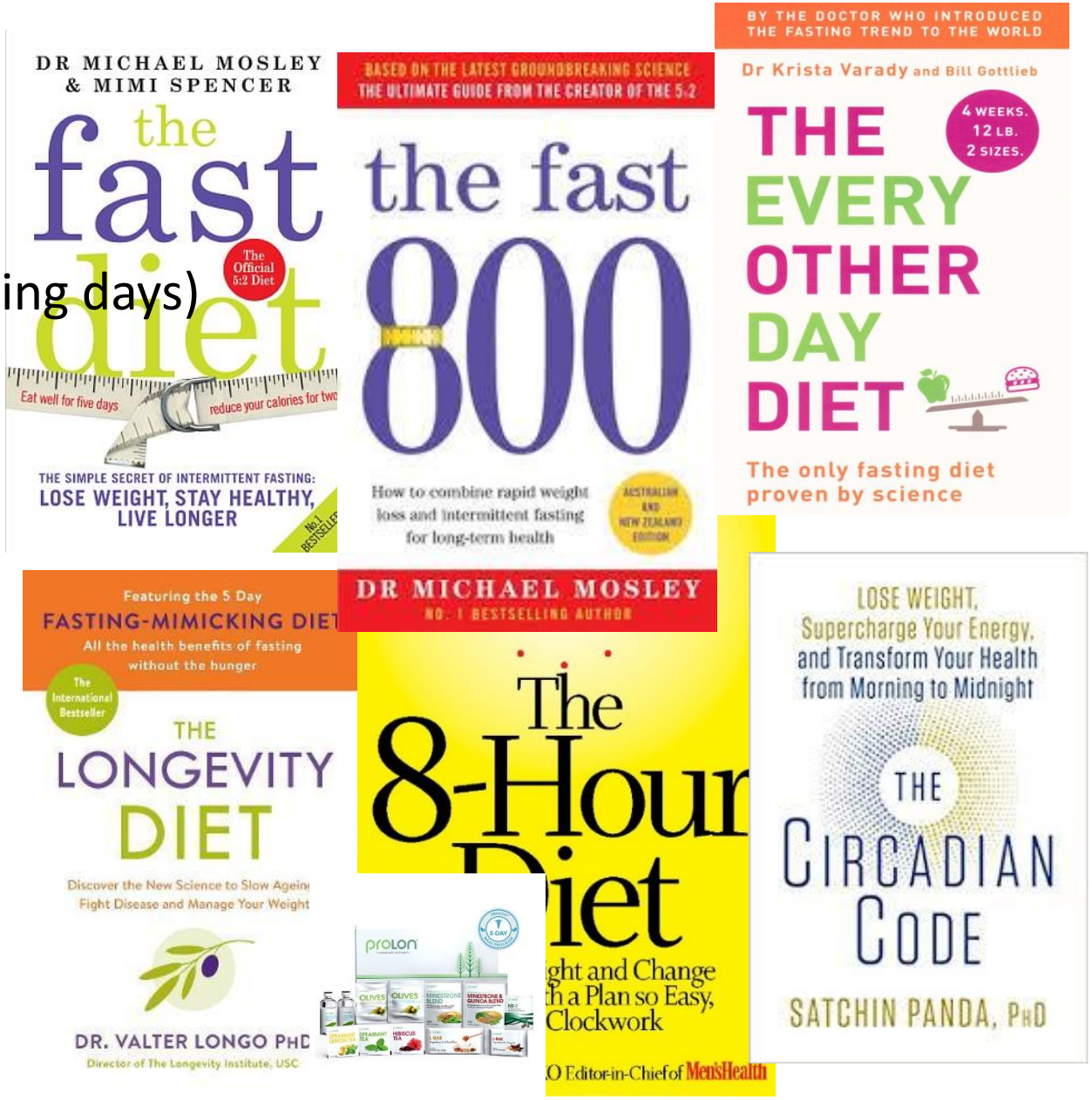
Alternate day fasting promotes longevity and health benefits, without weight loss in rodent models

- Extends lifespan
- Cardio-protective
- Neuro-protective
- Improves insulin sensitivity
- Stimulates autophagy
- Delays cancer progression

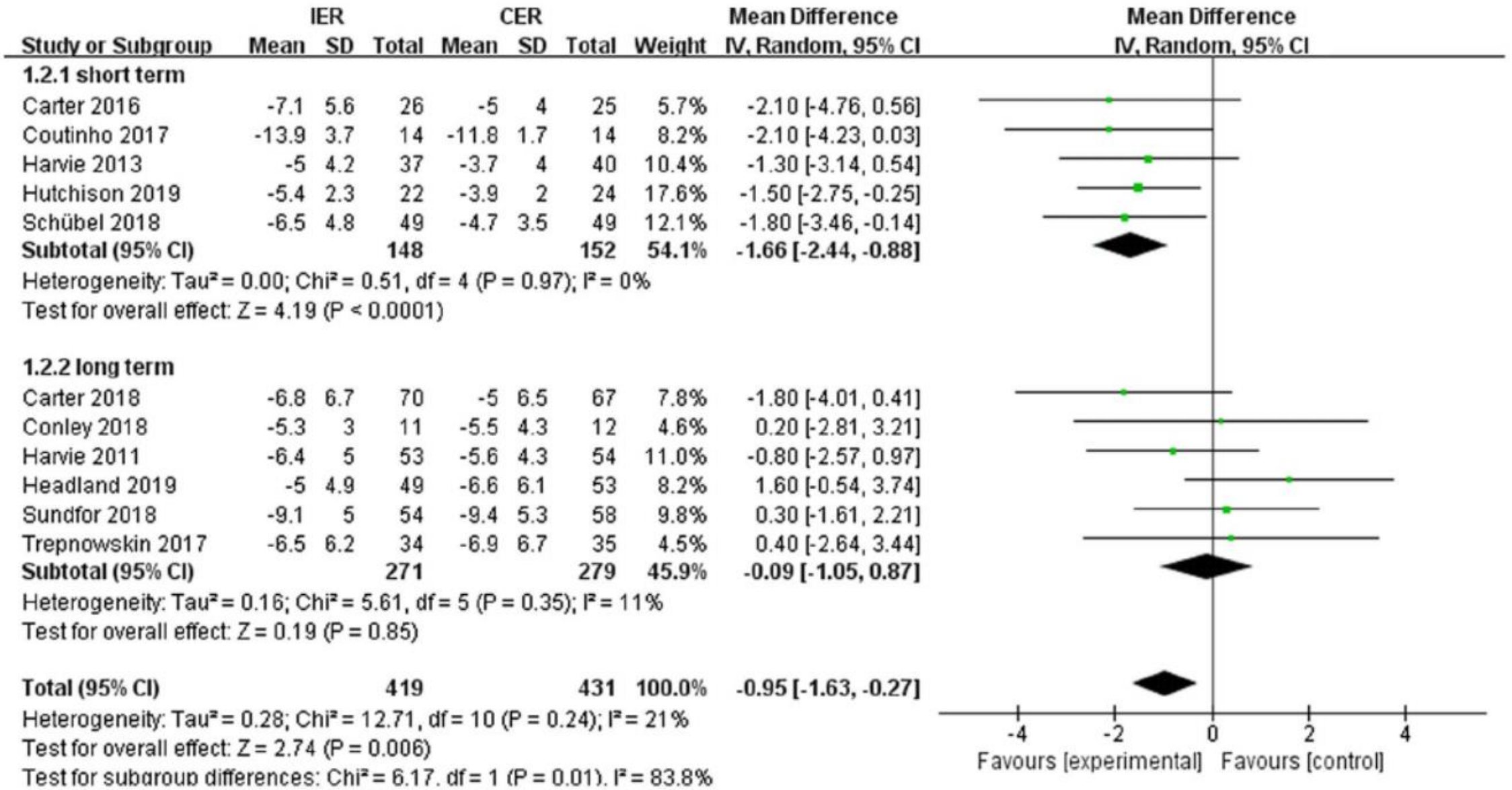
Unlike mice, humans don’t undertake prolonged periods of fasting, we don’t recommend it as a nutritional strategy when they undertake CR – Have we been limiting the health benefits that can be achieved with CR in humans??

Types of intermittent fasting diets under investigation

- Intermittent fasting
  - 24h complete fast every other day
  - Modified ADF (500-800 kcal eaten on fasting days)
  - 2 fasting days per week aka 5:2 diet
- Time restricted eating (TRE)
  - Limiting food intake (4 -10h daily)
- Fasting mimicking diet
  - 5 days/mo with low calories and protein



Meta-analysis of IF vs CR on weight loss in humans



He et al. 2021

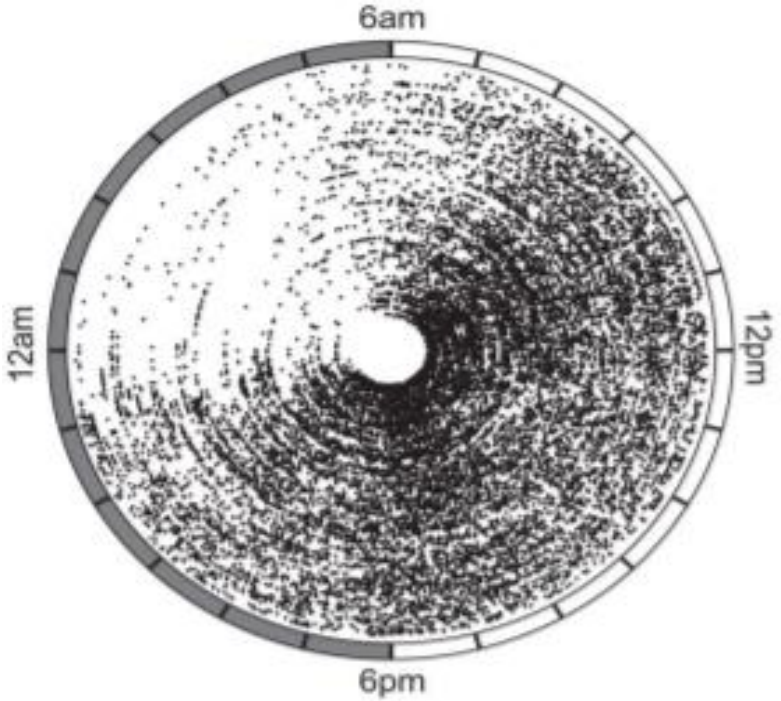
Is there a health advantage in IF vs CR?

First author, year	Months	Sample size (M/F)	Fasting Day Calories allowed (Length of fast)	Non-fasting day Diet type	Glycaemia	CVD
2 fasting days/week						
Harvie, 2011 [14]	6 m	IF: 0/53 CR: 0/54	~650kcal and 50g protein (not specified)	Eucaloric Mediterranean	↓ insulin, HOMA-IR	↔
Harvie, 2013 [25]	3 m	IF: 0/37 CR: 0/40	~600kcal and 40g CHO (not specified)	Eucaloric Mediterranean	↓ insulin, HOMA-IR	↔
Sundfor 2018 [29]	6 m	IF: 28/26 CR: 28/30	400/600 (F/M) kcal (not specified)	*Ad libitum* Mediterranean	↔	↔
Schubel 2018 [41]	3 m	IF: 25/24 CR: 25/24	25% energy needs (not specified)	Eucaloric balanced diet	↔	↔
Coutinho 2018 [44]	3 m	IF: 4/10 CR: 2/12	550/660 (F/M) kcal (not specified)	Eucaloric diet	↔	N/A
Carter 2018 [27]	12 m	IF: 31/39 CR: 29/38	500-600 kcal (not specified)	*Ad libitum*	↔	N/A
Gray, 2021 [30]	12 m	IF: 0/61 CR: 0/60	600 kcal (not specified)	*Ad libitum*	↔	N/A
Headland 2019 [42]	12 m	IF: 21/97 CR: 19/85	500/600 (F/M) kcal (not specified)	*Ad libitum*	↔	↔
≥ 3 NON-consecutive fasting days/week						
Varady 2011 [46]	3 m	IF: 3/10 CR: 2/10	25% energy needs at lunch (not specified)	*Ad libitum*	N/A	↓ triglycerides
Trepanowski, 2017 [31]	6 m	IF: 4/30 CR: 6/29	25% energy needs at lunch, (not specified)	125% energy needs	↔	↑HDL
Hutchison 2019 [28]	2 m	IF: 0/25 CR: 0/26	30% energy needs at breakfast 24 hours fast	Eucaloric diet	↔	↓total cholesterol, LDL, NEFA

- Most IF studies were powered to detect **weight** change (CR=IF)
- Majority report equivalence for **health** as exploratory analysis (CR=IF).
- Most studies have not advised participants on **when** to eat in the ‘fast’ day.

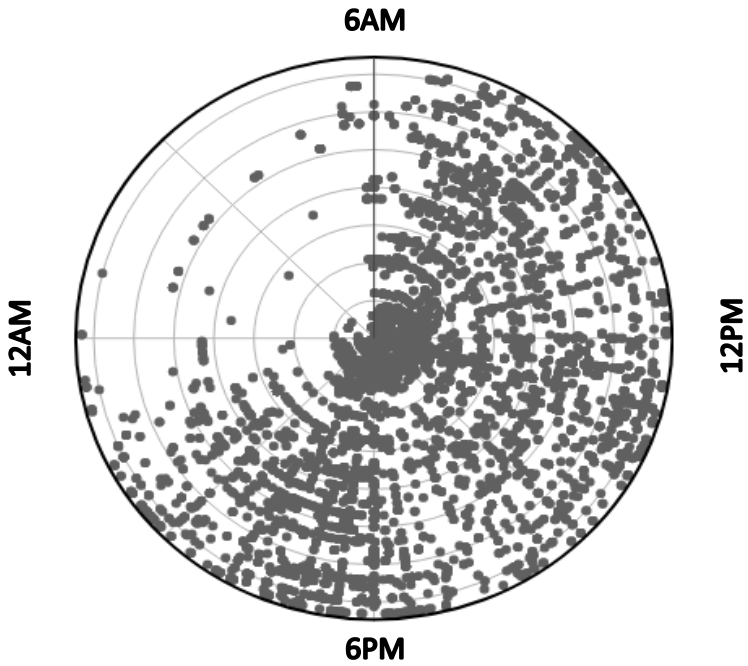
Teong et al. 2021

Modern lifestyles include erratic eating patterns characterised by prolonged daily eating and short overnight fasting



Gill et al. Cell Metab 2015

A)



Zhao et al. 2021 Nutrition

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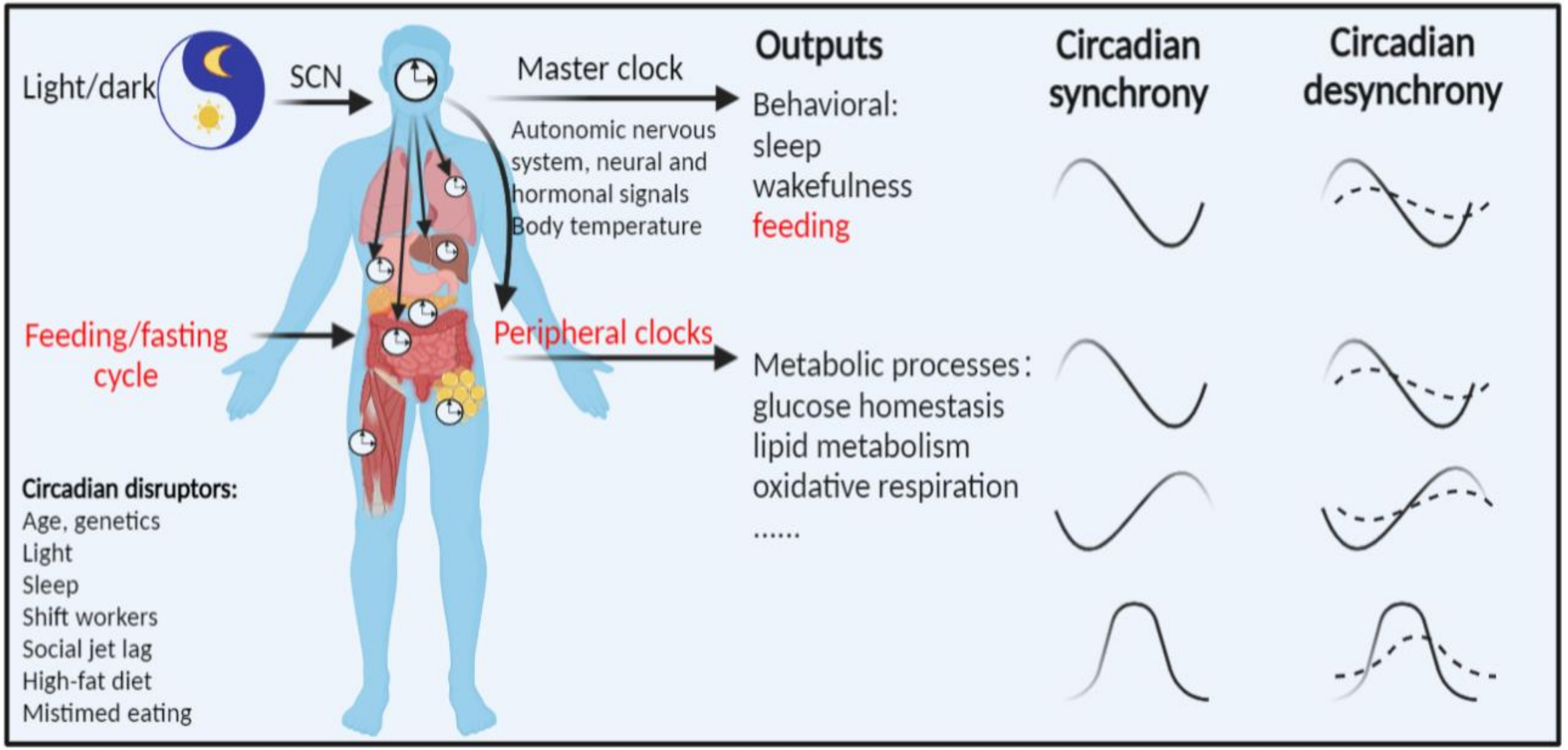
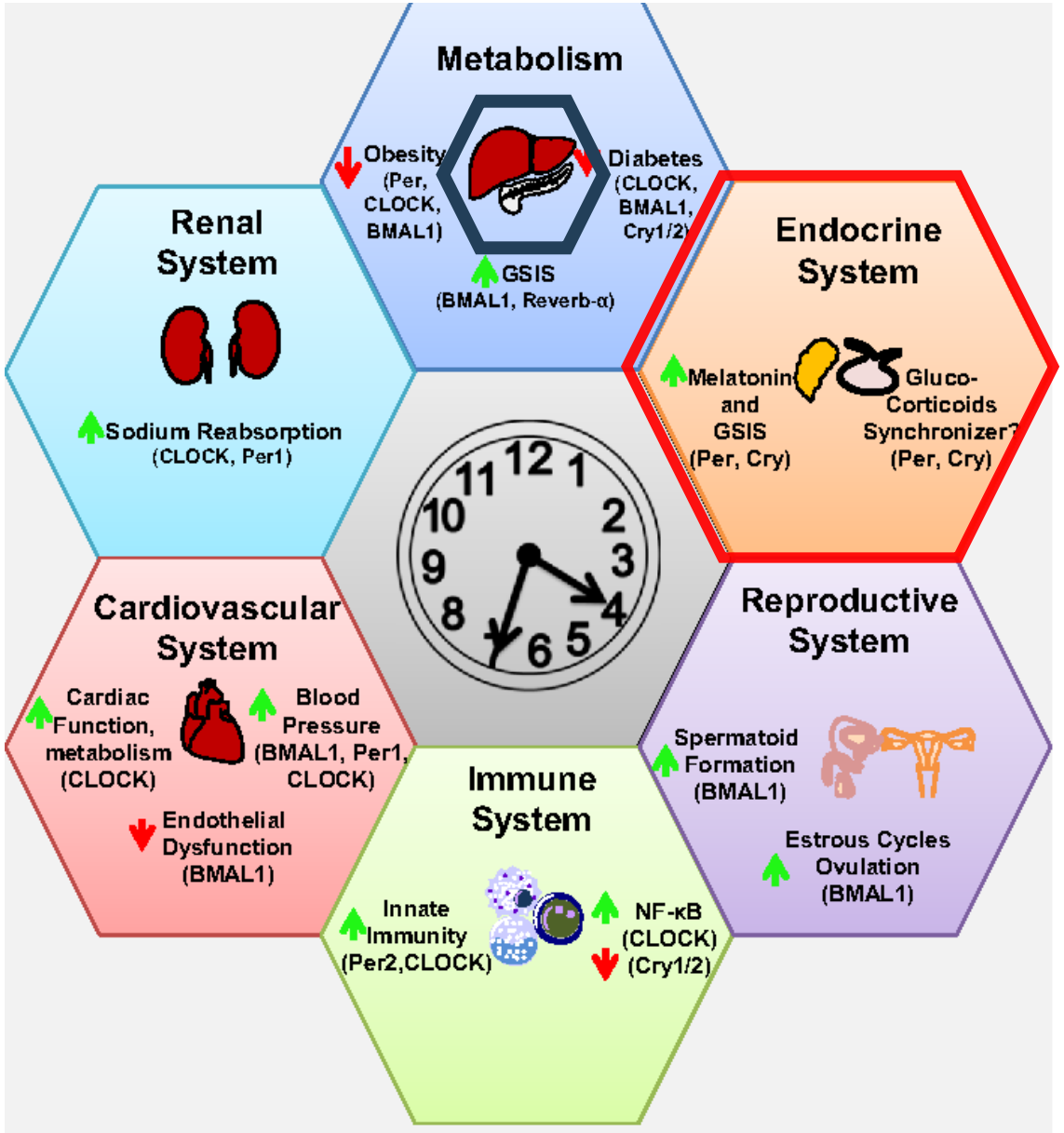
Meal timing is an entraining cue for peripheral clocks

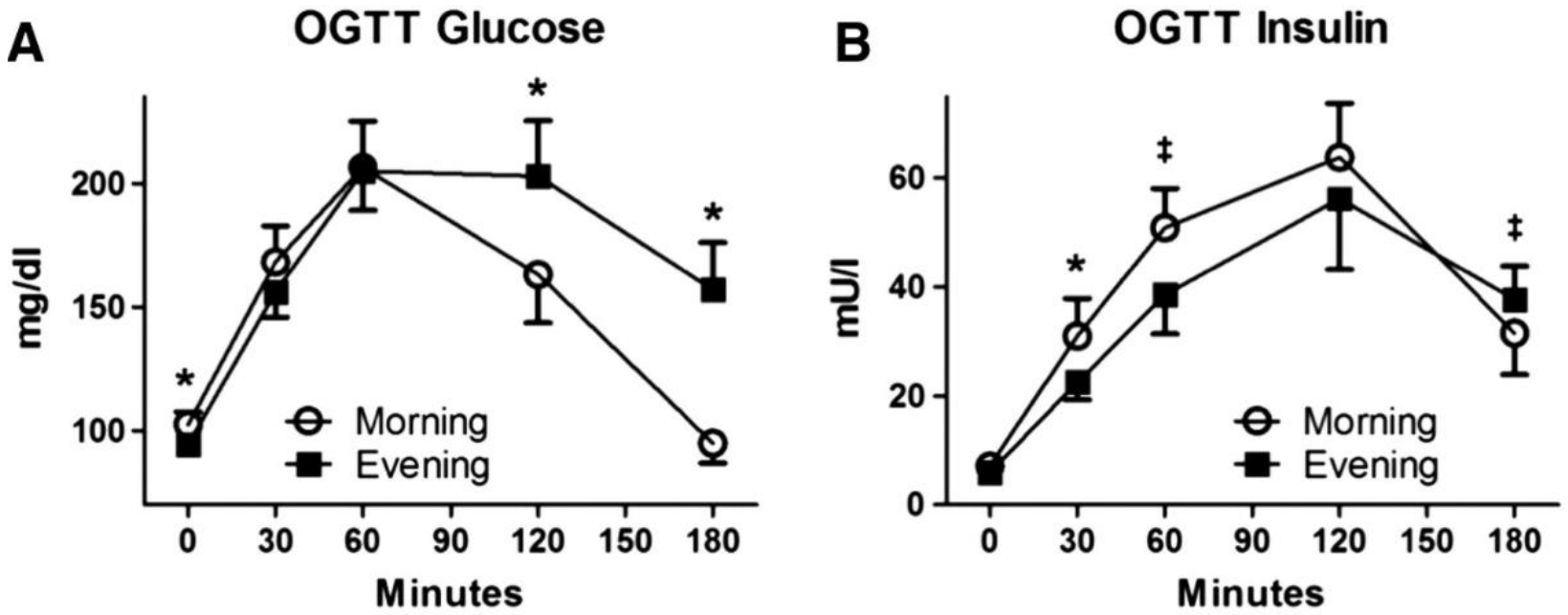


Almost every aspect of metabolism is under circadian regulation and acts in a time-of-day dependent manner



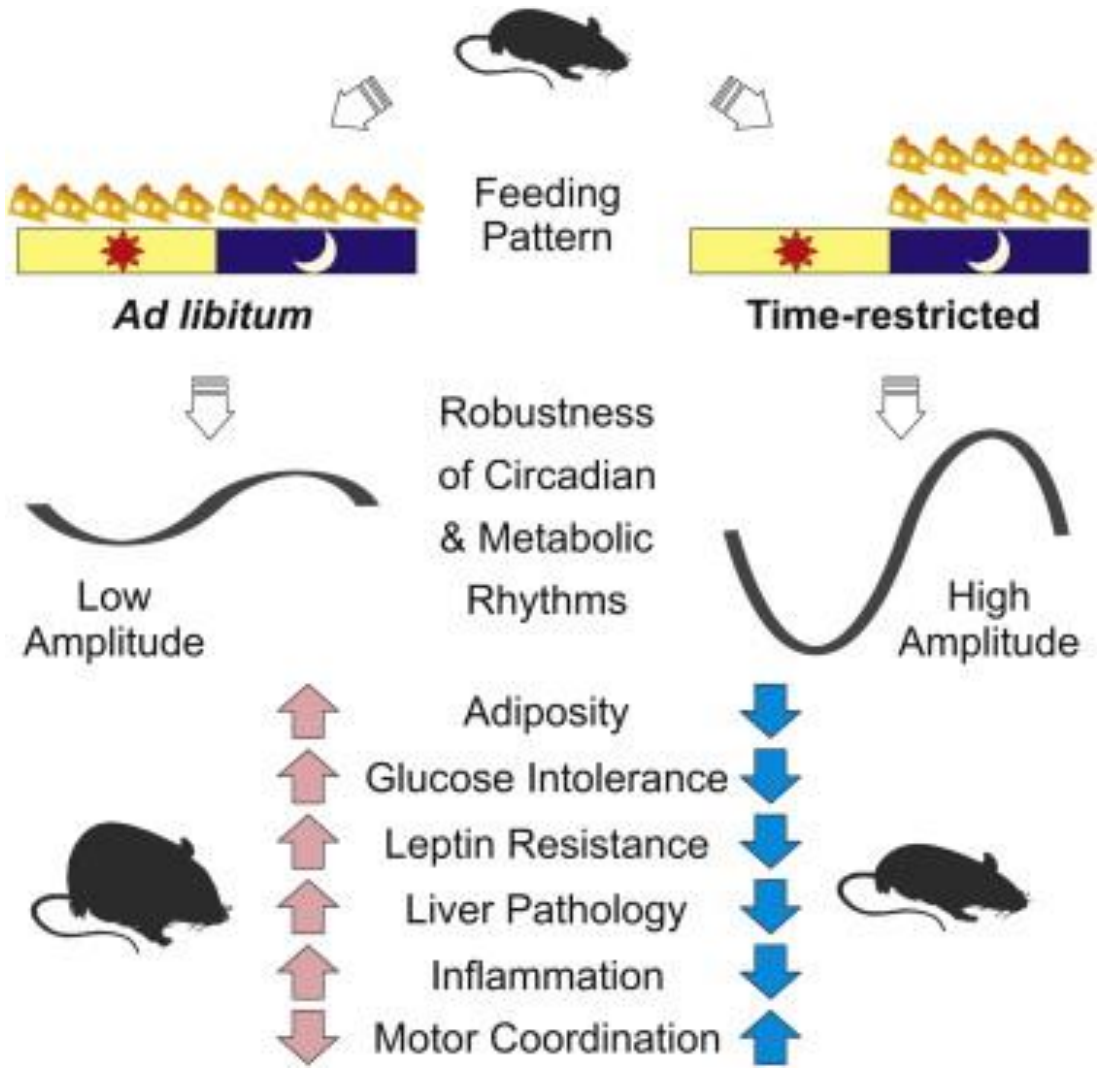
Richards et al. Am J Physiol 2013

Glycaemia is under circadian control



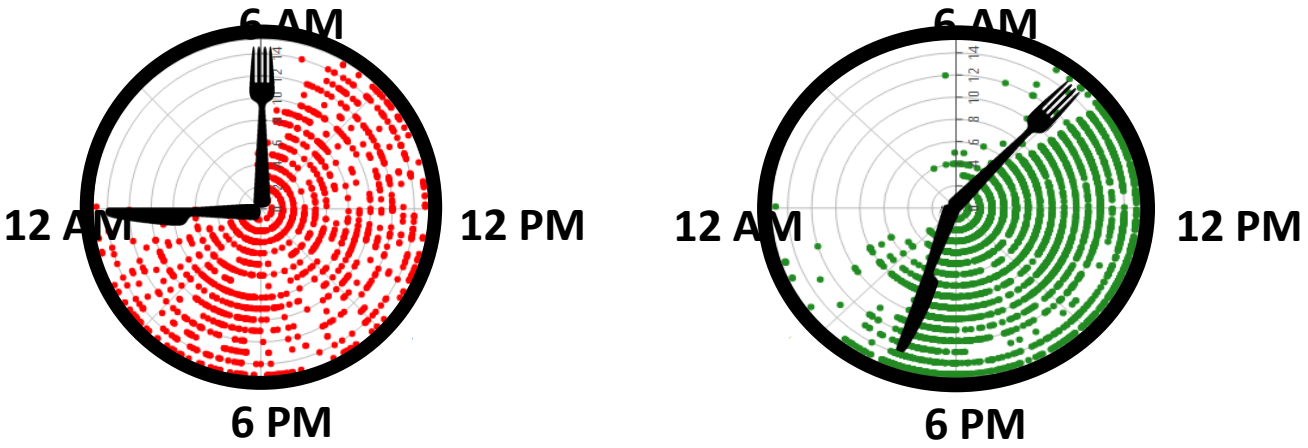
Sonnier et al., J Diab Comp 2014.

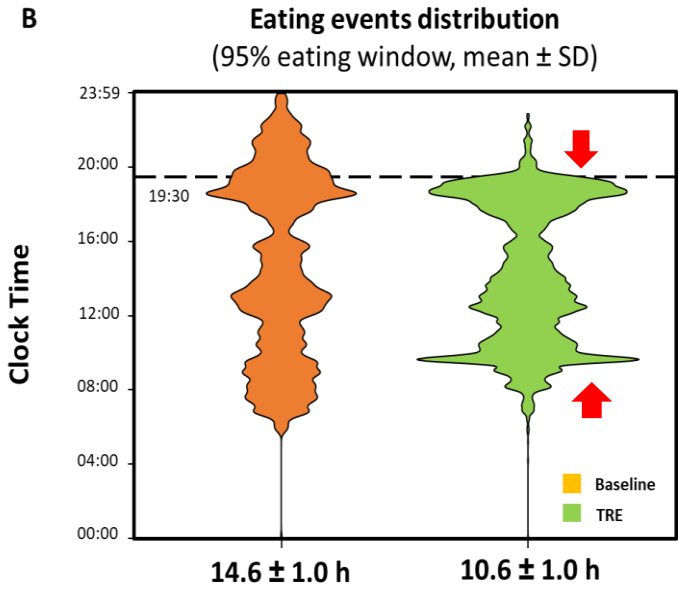
Time restricted eating improves glucose metabolism, reduces hepatic steatosis in mice with obesity.

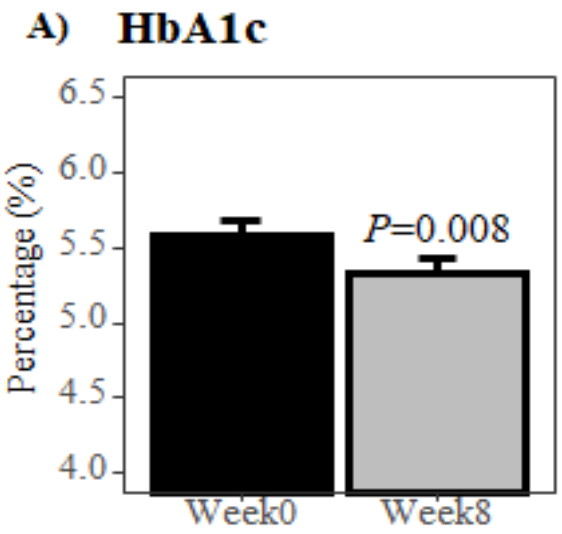


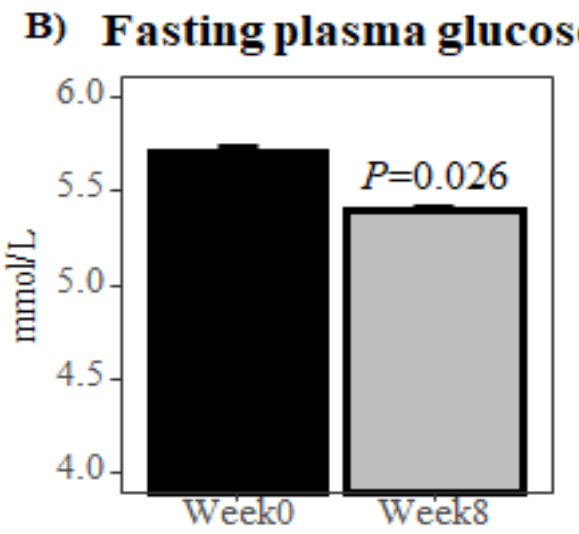
Chaaix et al. 2014

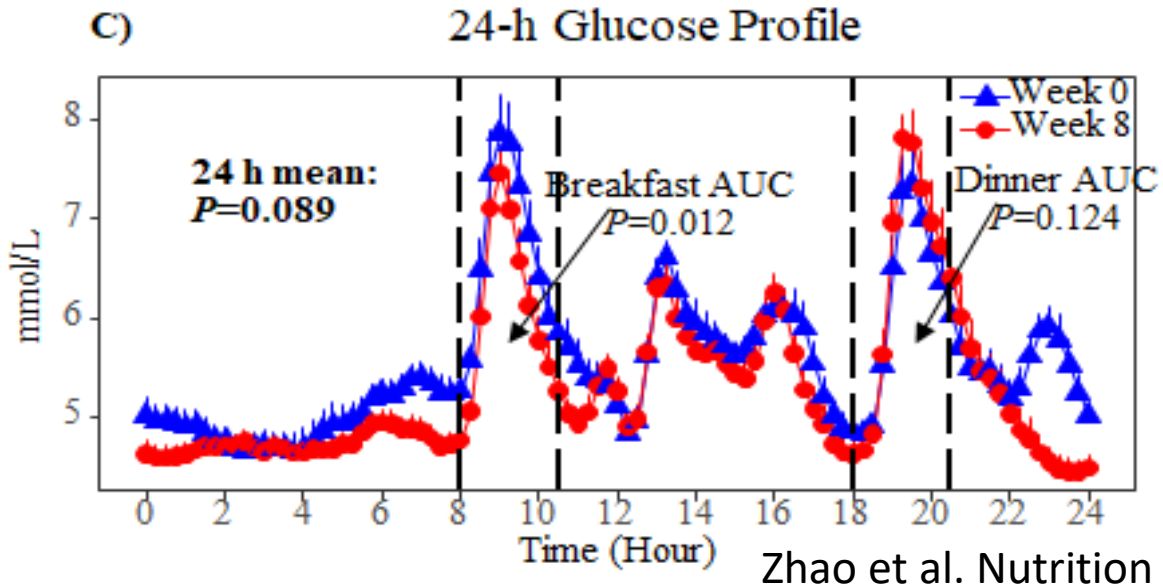
What about humans? Does TRE improve glucose control?







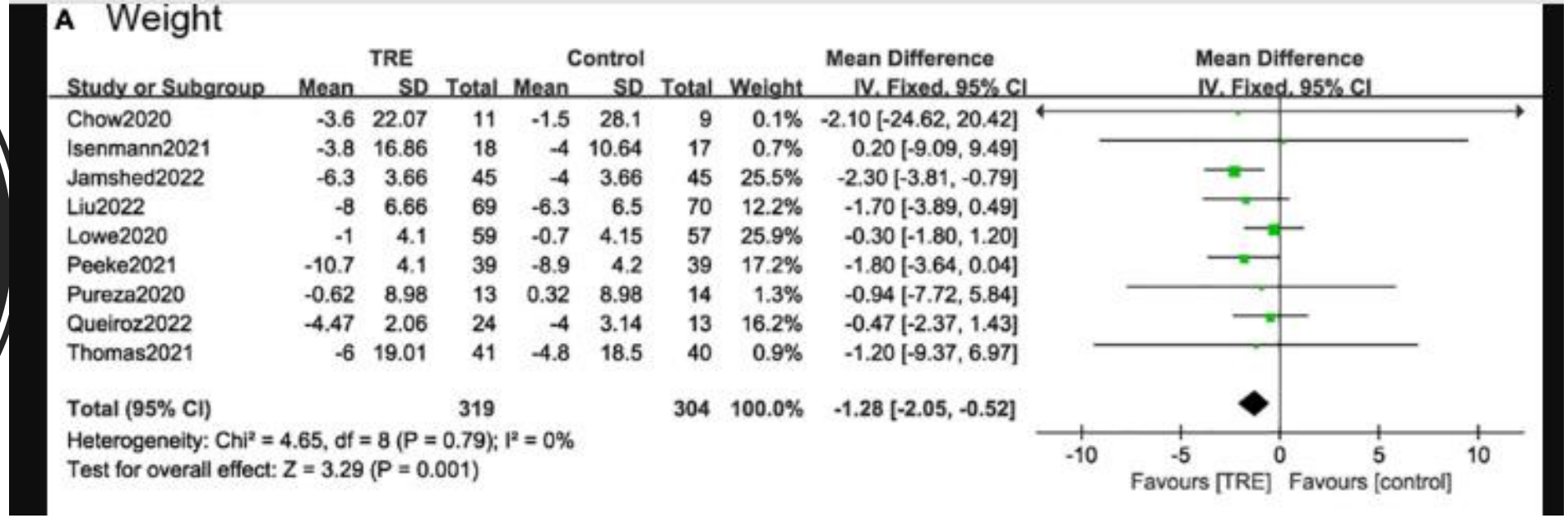




Zhao et al. Nutrition 2022

TRE is beneficial for body weight as compared to no diet control

Mixed Evidence for secondary outcomes – the shorter and earlier you go the better?



TRE results in greater improvement in HbA1c vs SOC in met. syndrome (N=108).

Table 2. Primary Outcomes: Glucose Regulation*

Outcomes	TRE	SOC	Between Groups

Table 3. Secondary and Exploratory Outcomes: Cardiometabolic Outcomes*

Outcomes	TRE				SOC				Between Groups	
	Baseline	3 mo	Δ (95% CI)	Percent Change	Baseline	3 mo	Δ (95% CI)	Percent Change	Δ TRE-SOC	Percent Change
Body composition										
Weight, *kg*	89.94 (16.98)	86.96 (17.06)	−2.98 (−4.11 to −1.84)	−3.3	89.25 (16.48)	87.93 (16.23)	−1.32 (−2.07 to −0.57)	−1.5	−1.66 (−3.00 to −0.32)	−1.8
BMI, *kg/m²*	31.50 (4.06)	30.38 (4.37)	−1.11 (−1.51 to −0.72)	−3.5	30.95 (4.03)	30.55 (4.11)	−0.39 (−0.66 to −0.13)	−1.3	−0.77 (−1.37 to −0.17)	−2.2
Body fat, %	37.70 (6.90)	36.34 (7.35)	−1.36 (−2.00 to −0.73)	−3.6	38.62 (6.62)	38.51 (6.81)	−0.11 (−0.71 to 0.49)	−0.4	−1.25 (−2.12 to −0.38)	−3.2
Trunk fat,† %	39.43 (5.88)	37.88 (6.50)	−1.55 (−7.87 to −0.90)	−3.9	40.33 (5.99)	40.18 (6.20)	−0.15 (−0.83 to 0.53)	−0.4	−1.40 (−2.37 to −0.43)	−3.5
Total fat mass, *g*	33 263.73 (8306.52)	31 023.51 (8490.32)	−2240.22 (−3044.43 to 1376.01)	−6.7	33 572.58 (7634.67)	33 163.47 (8027.05)	−409.11 (−1093.11 to 273.89)	−1.3	−1801.11 (−2871.06 to −731.16)	−5.4
Total lean mass, *g*	52 504.06 (11 954.31)	52 228.52 (12 246.54)	−275.53 (−773.69 to 222.62)	−0.5	51 544.89 (12 182.13)	50 977.86 (11 991.96)	−567.03 (−1107.95 to −26.11)	−1.1	291.50 (−434.31 to 1017.30)	+0.6
Total BMC, *g*	2458.77 (543.28)	2462.99 (551.40)	4.22 (−11.54 to 19.98)	0.0	2439.74 (548.23)	2442.64 (567.37)	2.89 (−13.55 to 19.34)	0.0	1.32 (−21.18 to 23.82)	0.0

Cardiometabolic variables

moglobin); HOMA-IR = homeostasis model assessment of insulin resistance; MODD = mean of daily differences; SOC = standard of care; TRE =

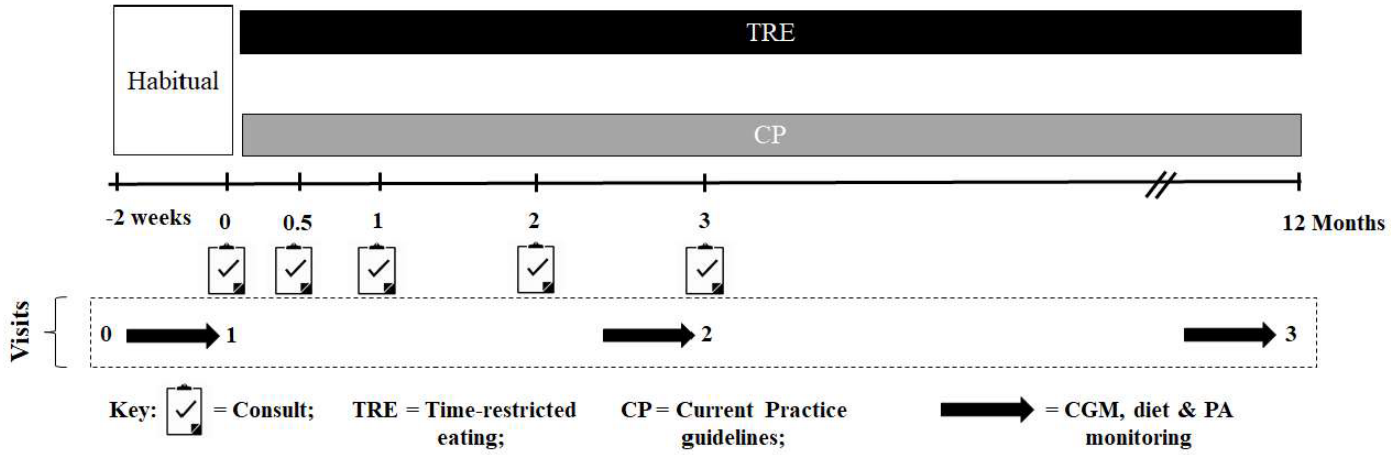
Manoogian et al. Annals 2024

What Or When to eat to reduce the risk of diabetes? (WOW)

Hypothesis: TRE is not inferior to current practice in dietetics for glycaemic control in 247 individuals with obesity, and at increased risk of diabetes.

TRE protocol: self selected window of 9h duration, but must complete eating window by 7pm.

Figure 4. Schematic of the study design. Measurements of metabolic (blood analytes, body composition), diet quality and psychological (quality of life, self-efficacy, appetite/hunger) parameters will be measured at each visit as detailed below.



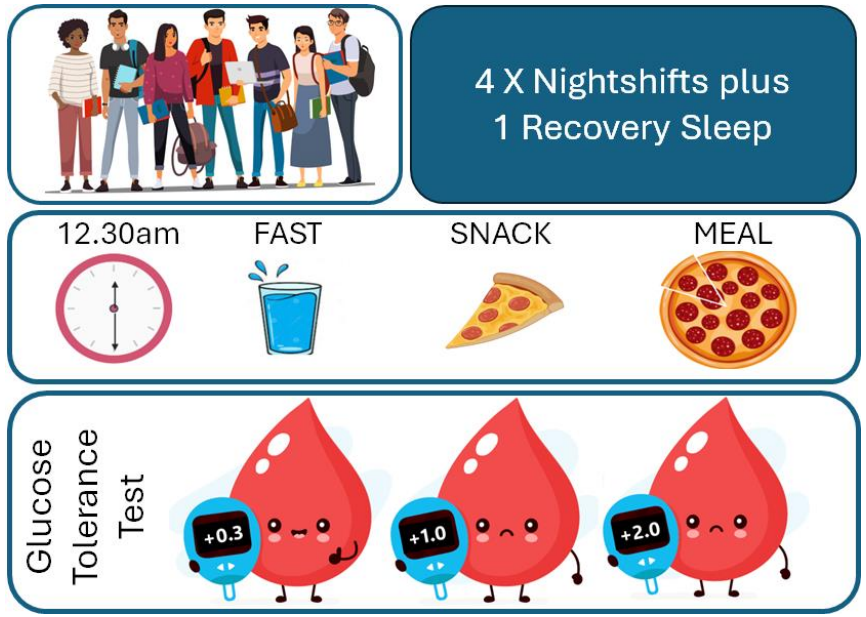
Primary Outcome: Change in glycated haemoglobin (HbA1c).

Secondary Outcomes: Change in fasting glucose, and CGM metrics, fasting insulin, CRP, blood lipids, body mass and body composition; adherence; diet quality.

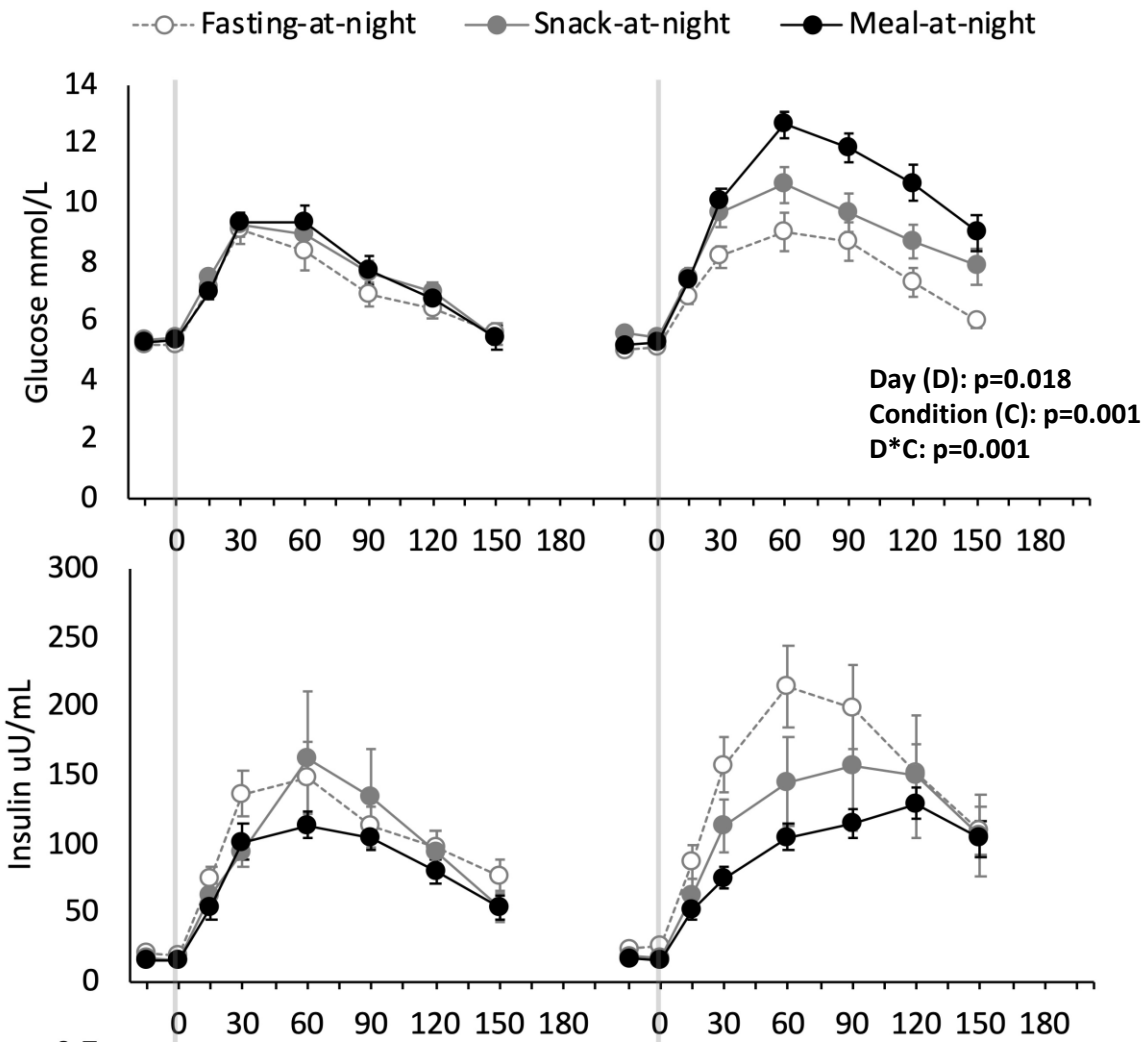
CIs Heilbronn, Hawley NCT04762251

Fasting at night prevents impairments in glucose tolerance after 5 nights of simulated shiftwork in normal weight (N=52)

Centofanti et al. Diabetologia 2024



Variable	Fasting-at-night (n=19)	Snack-at-night (n=17)	Meal-at-night (n=16)
Sex	11M, 8F	8M, 9F	10M, 6F
Age (years)	24.7±5.4	25.4±5.6	23.5±3.5
Body Mass Index (kg/m²)	23.9±2.3	23.6±1.9	24.6±3.2
Fasting Glucose (mmol/l)	5.2±0.1	5.4±0.1	5.3±0.1
Fasting Insulin (uU/mL)	18.7±2.7	17.0±2.6	16.3±5.1
Insulin sensitivity index (AU)	42.5±20.7	43.4±15.4	49.5±30.2
Insulinogenic B cell index (AU)	35.7±5.3	20.2±7.1	21.4±5.6



Does intermittent fasting plus early TRE (iTRE) extend the health benefits of CR in humans?

clinicaltrials.gov NCT03689608

- n=209
- males & females
- Age 35-75 years
- BMI 25-50kg/m^2
- AUSDRisk Score ≥12

(n=85)

Intermittent fasting plus eTRE (iTRE)

- Eat *ad libitum* on 4 non-fasting days, blood sampling after 12h overnight fast at 8am **"A"** visits at M0, M2, M6, M18
- Fast on 3 days per week following 30% energy intake 8am - 12pm (e.g. Mon, Wed, Fri).

(n=83)

Daily calorie restriction (CR)

- 70% daily energy intake prescribed with blood sampling after 12h overnight fasts on **"A"** visits at M0, M2 and M6, M18

(n=41)

Standard care (SC)

- Non-active intervention group, provided with a healthy eating guideline at M0.2.6.18.

Recruitment → Randomisation (2:2:1) → 6-month active intervention With fortnightly diet consults

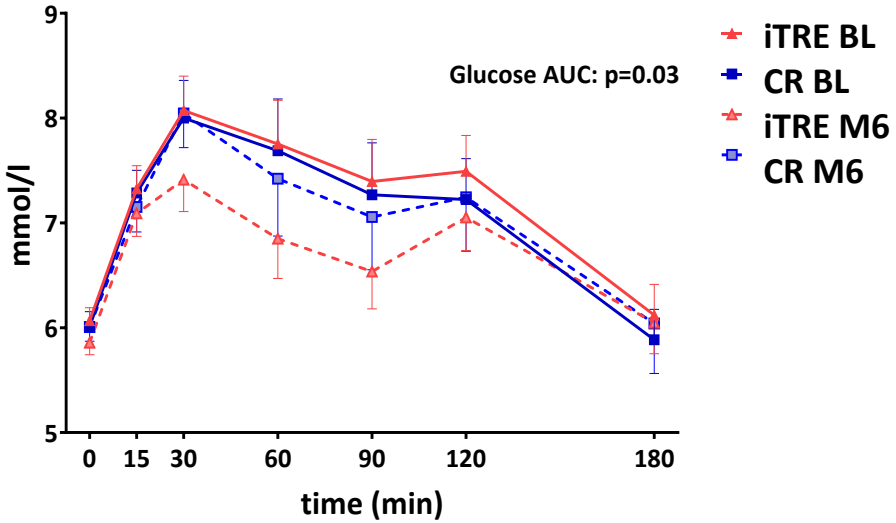
Primary outcome: Glucose AUC to liquid meal at M6 by linear regression (adj. baseline, sex, AusD risk)

Baseline characteristics

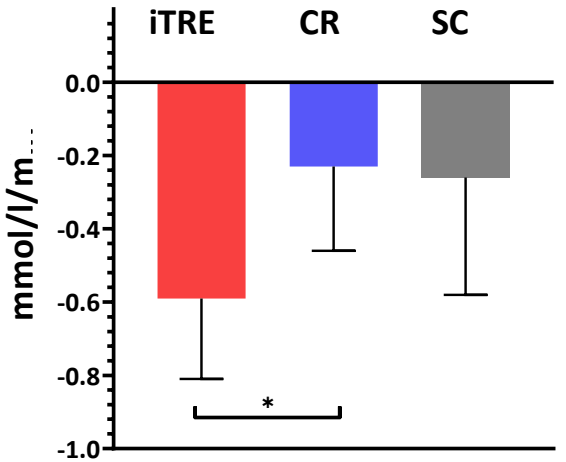
	iTRE (n=85)	CR (n=83)	SC (n=41)
Age (years)	57 ± 10	58 ± 10	59 ± 11
Females, n (%)	49 (58)	49 (59)	22 (54)
Body mass index (kg/m^2)	34.7 ± 4.6	35.0 ± 4.6	33.8 ± 4.9
Fat mass (kg)	43.8 ± 9.7	44.8 ± 11.5	42.4 ± 9.8
Waist circumference (cm)	110.4 ± 12.1	112.8 ± 11.0	109.3 ± 12.1
Systolic blood pressure (mmHg)	122.8 ± 14.0	126.6 ± 14.0	125.9 ± 17.7
Diastolic blood pressure (mmHg)	80.1 ± 8.6	80.5 ± 6.1	80.7 ± 8.8
HbA1c (%)	5.8 ± 0.4	5.9 ± 0.3	5.9 ± 0.4
Fasting glucose (mmol/l)	6.1 ± 0.6	6.0 ± 0.7	6.1 ± 0.5
Fasting insulin (mIU/L)	19.7 ± 10.0	20.4 ± 11.2	19.7 ± 9.2
Total cholesterol (mmol/l)	5.2 ± 1.1	5.1 ± 1.1	5.3 ± 1.0
High-density lipoprotein (mmol/l)	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.3
Low-density lipoprotein (mmol/l)	3.6 ± 1.0	3.5 ± 1.0	3.7 ± 1.0
Fasting triglycerides (mmol/l)	1.7 ± 1.3	1.5 ± 1.1	1.5 ± 0.9

mean ± SD

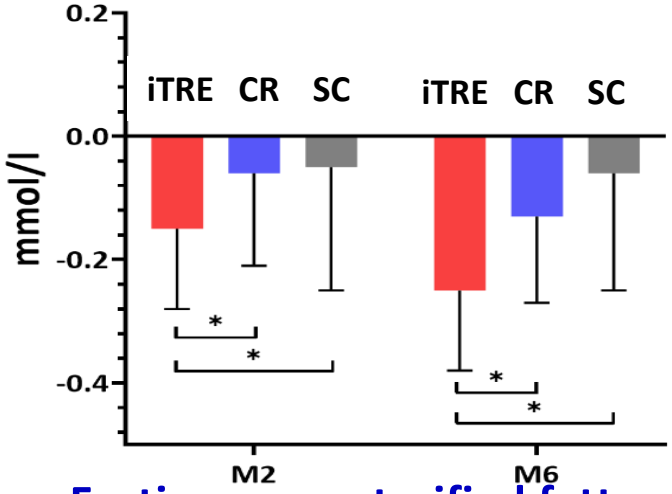
iTRE was more effective for glucose control (primary outcome)

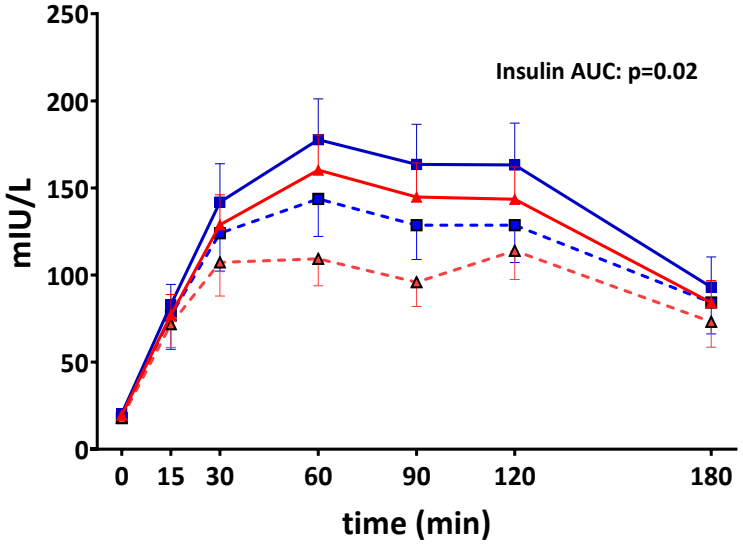


Glucose AUC

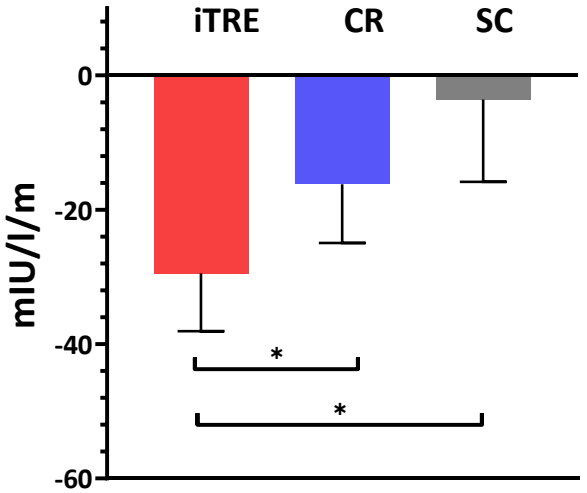


Fasting triglycerides

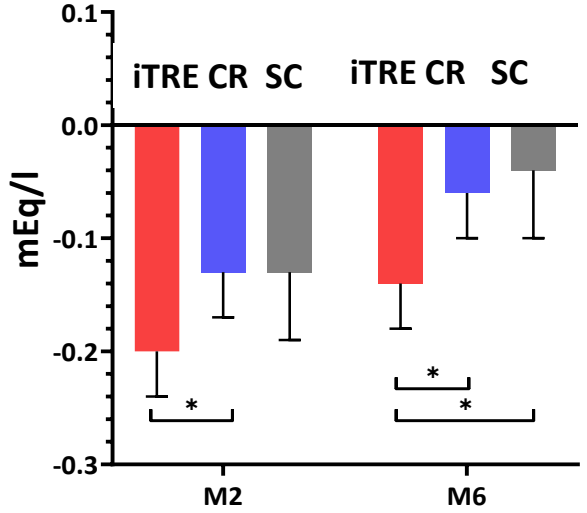




Insulin AUC

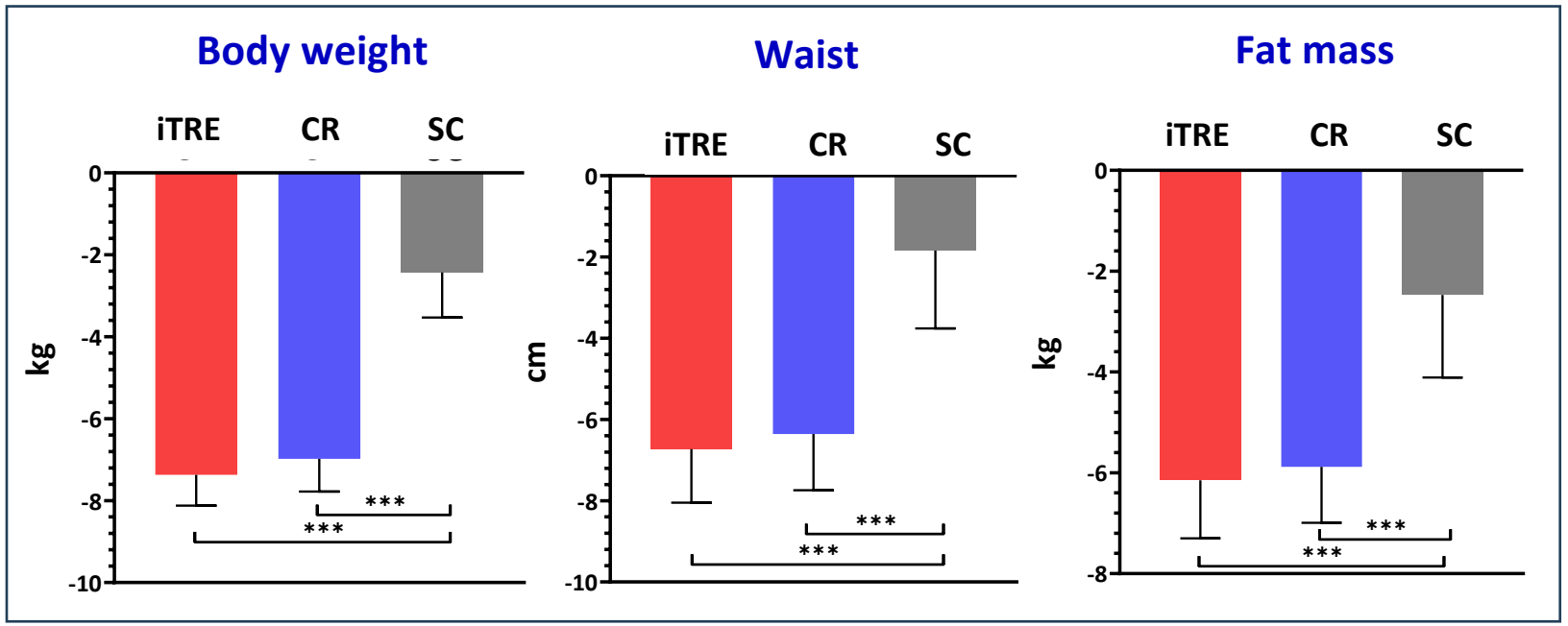


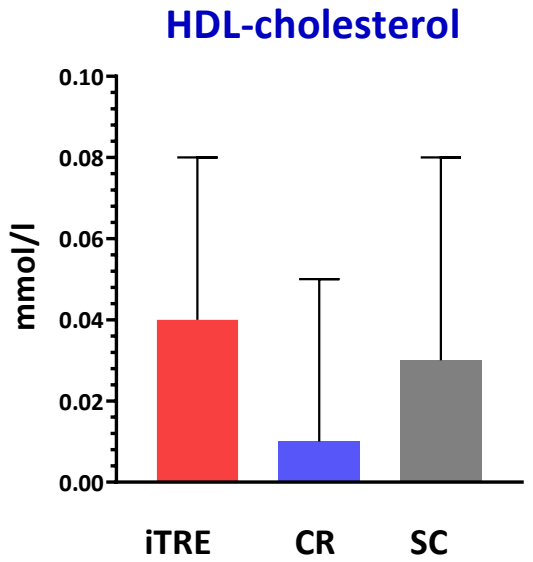
Fasting non-esterified fatty acids

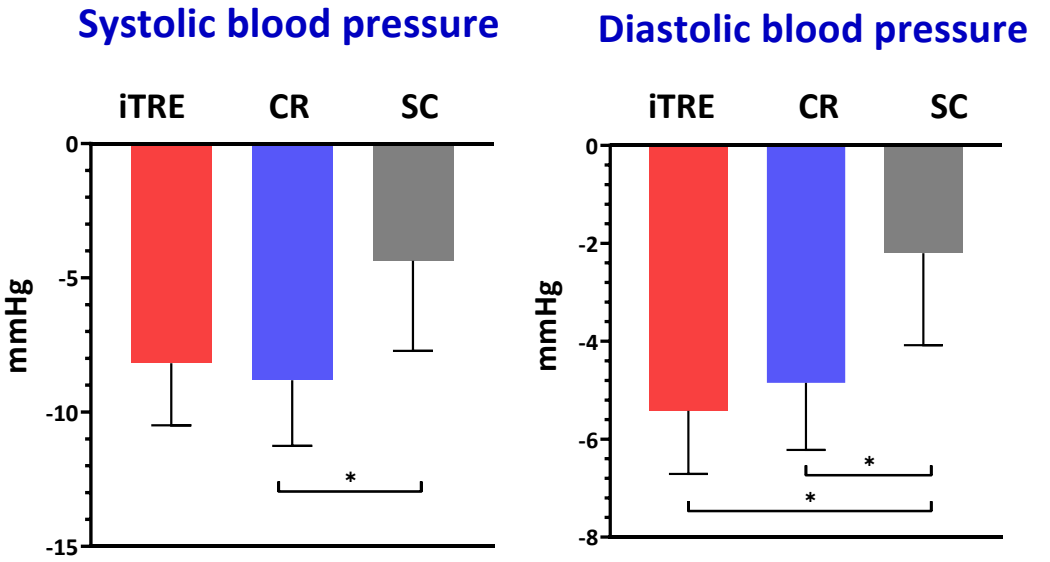


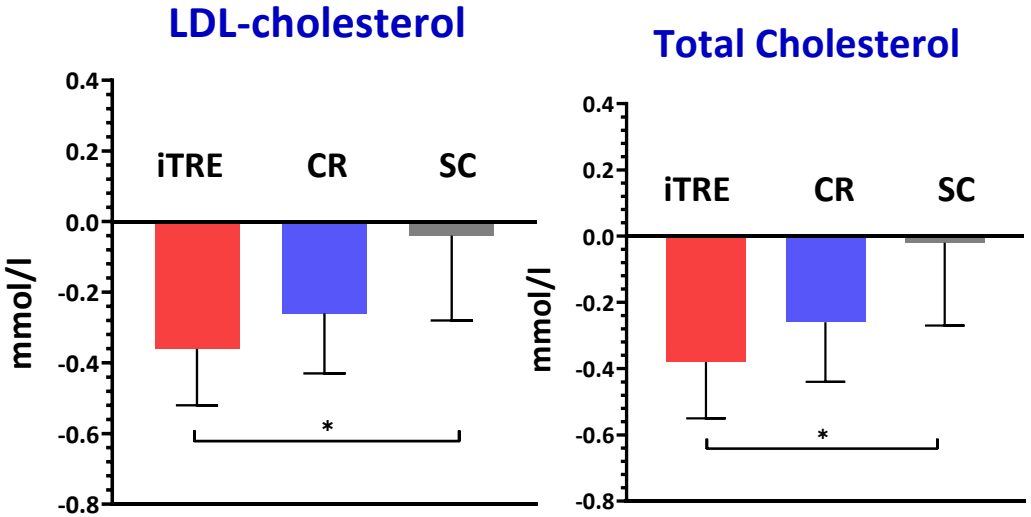
Teong et al. Nat Med 2023

Body weight and blood pressure were improved in iTRE and CR vs SC



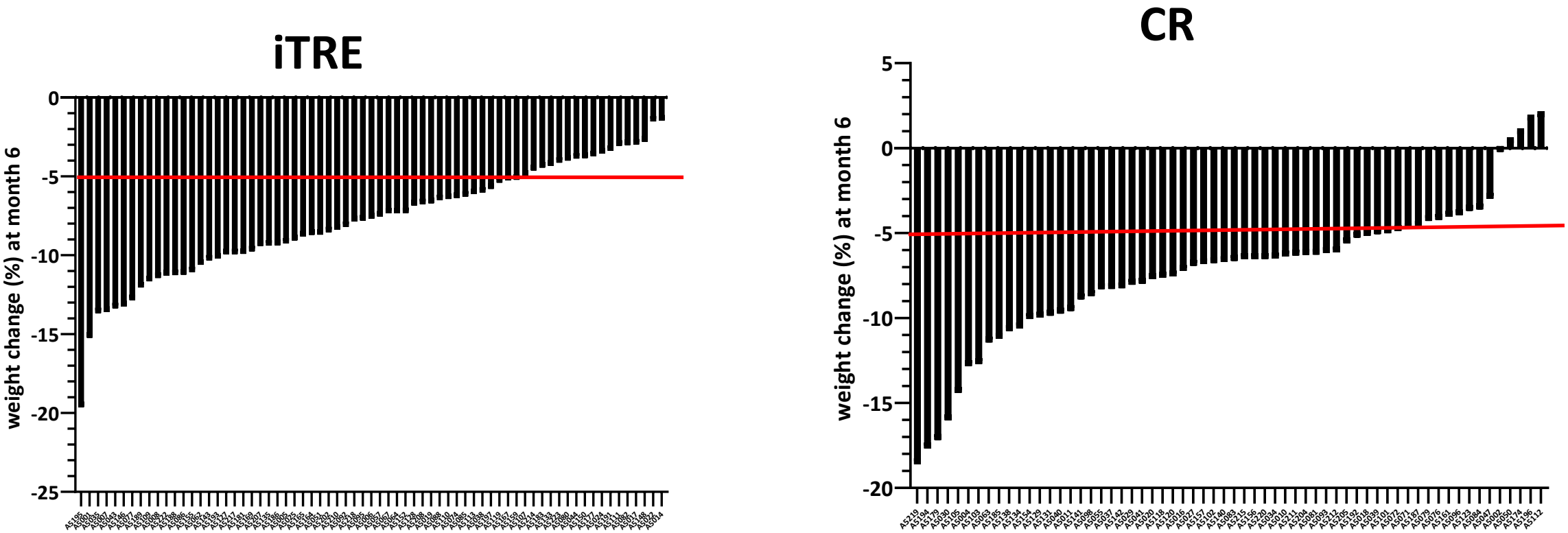




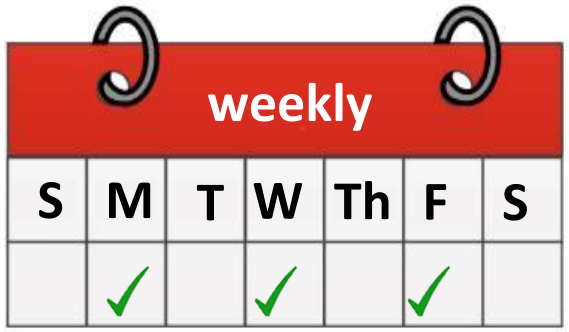


Data presented are sample means and 95% confidence intervals

Metabolic heterogeneity in weight loss in response to intervention



Can we predict who should undertake what type of diet??



Postprandial glucose

Postprandial insulin

Blood pressure

Blood lipids

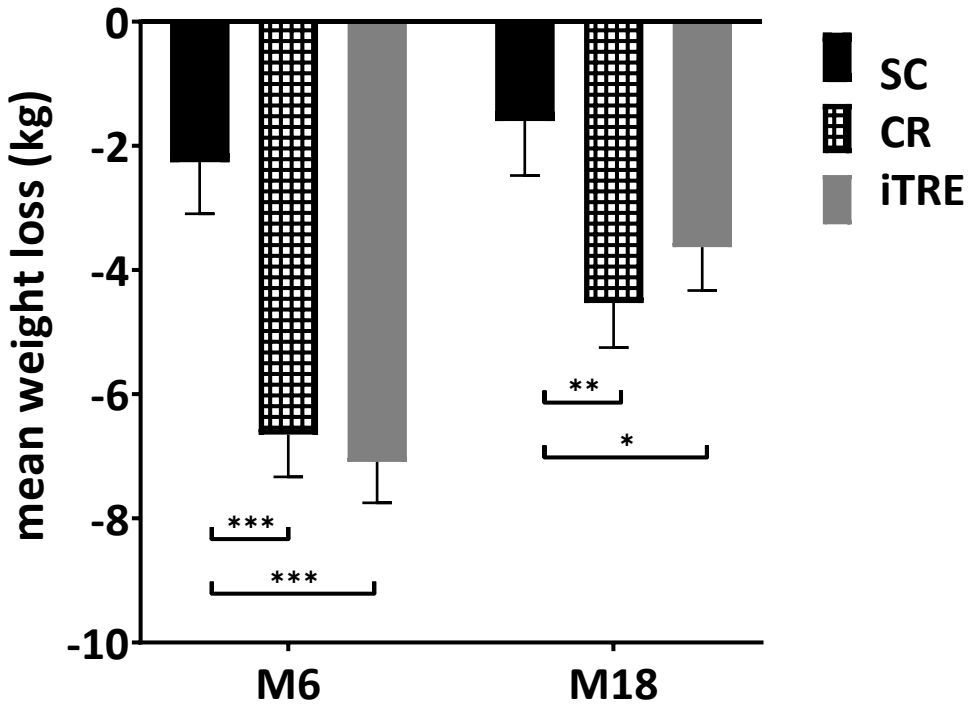
Conclusion

iTRE extends the glycemic health benefit of weight loss. The study adds to the growing body of evidence to indicate that meal timing and fasting advice might be influential in clinical practice.

What is the longevity of prescribing iTRE vs CR?

Self-reported adherence

78%	CR
42%	iTRE



Will TRE extend health benefits of CR in humans?

Calorie Restriction with or without Time-Restricted Eating in Weight Loss

- N=139 (1 year)
- Eating window 8am-4pm + 30% CR
- Primary outcome: weight
- No difference in weight or health markers

JAMA Internal Medicine | Original Investigation

Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults With Obesity
A Randomized Clinical Trial

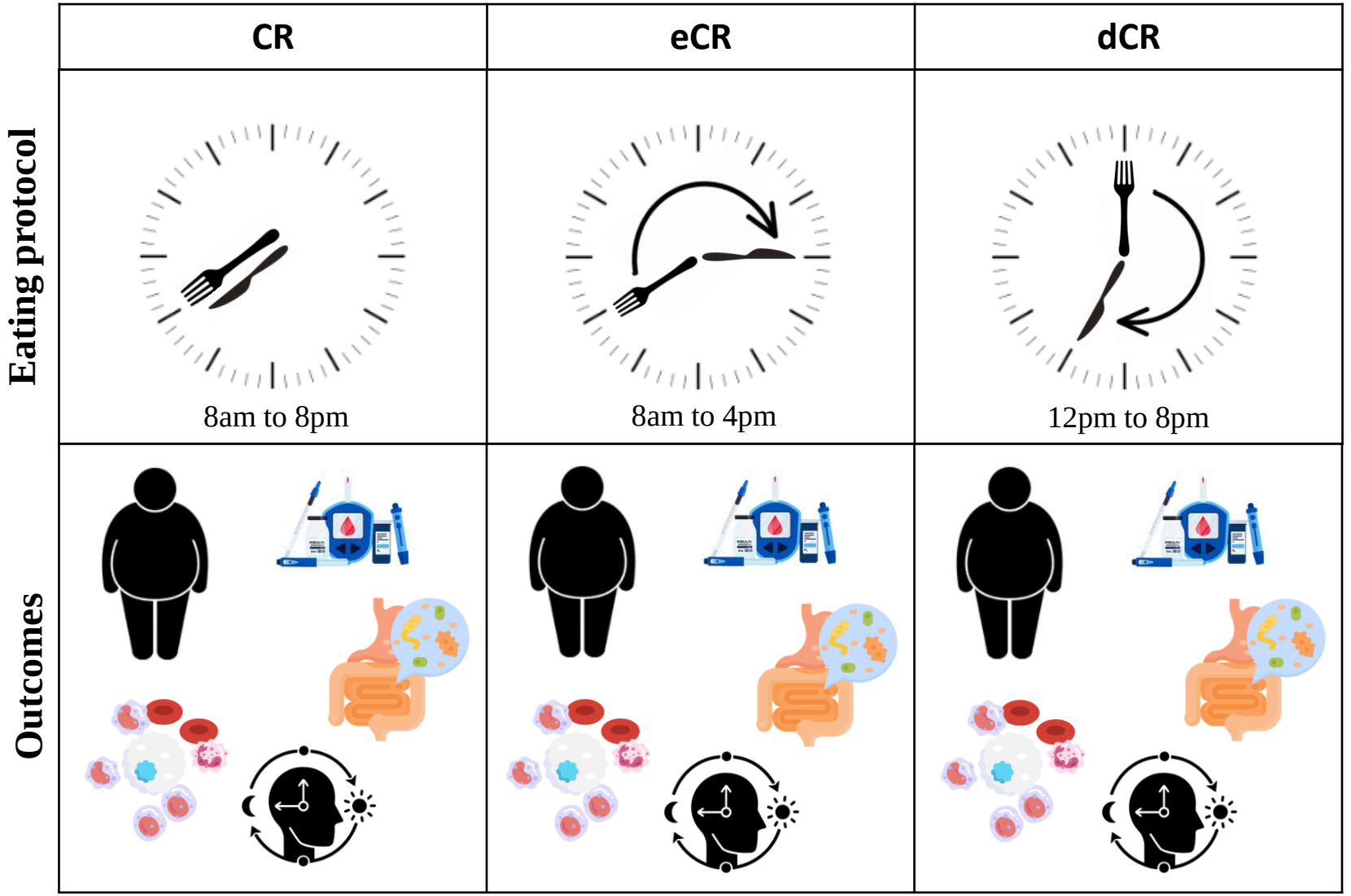
Humaira Jamshed, PhD; Felicia L. Steger, PhD; David R. Bryan, MA; Joshua S. Richman, MD, PhD; Amy H. Warriner, MD; Cody J. Hanick, MS; Corby K. Martin, PhD; Sarah-Jeanne Salvy, PhD; Courtney M. Peterson, PhD

- N=90 (14 weeks)
- Eating window 7am-3pm
- Primary outcome: weight

- ↓ body weight (-1.5%)
- ↓ diastolic blood pressure

- ↔ body fat, glucose, insulin, lipids

The OMIT study (N=114) will compare CR to early CR (eCR) and delayed CR (dCR) on glucose metabolism, blood pressure regulation, and immune cell regulation over 24 hours in humans with elevated FPG.



Conclusion

- Intermittent fasting / iTRE is a safe therapeutic lifestyle alternative to CR.
- iTRE extends metabolic health benefits of moderate CR after 6 months.
- However, once dietary support was withdrawn, the metabolic advantages were lost after 12 months follow-up.
- Fewer individuals reported following the iTRE diet than the CR diet at 12 months follow up. iTRE produced smaller changes in eating behaviours.