TRE in Humans / Intermittent Fasting vs. CR

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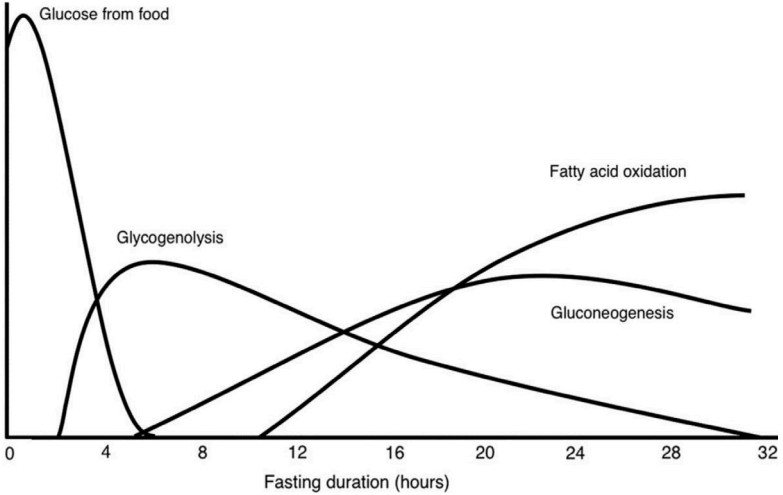
Knowledge that will change your world

Intermittent Fasting (IF)

- Definition: alternating periods of eating and extended fasting (≥14 hours)
- Median American eats over a 12-hour period[1]

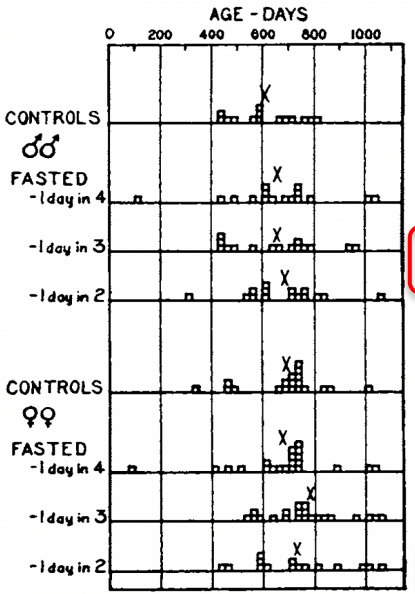


	Sun	Mon	Tue	Wed	Thu	Fri	Sat
1 Day a Week Fast							
Alternate-Day Fasting (ADF)							
Alternate-Day Modified Fasting (ADMF)							
5:2 Diet							
Fasting-Mimicking Diet (FMD)			Once a month				
Time-Restricted Eating (TRE)							

[1] Marinac et al., *Cancer Epidemiol Biomarkers Prev*, 2015

IF/TRE Extends Lifespan and Explains Much of the Effects of CR on Lifespan in Male Mice

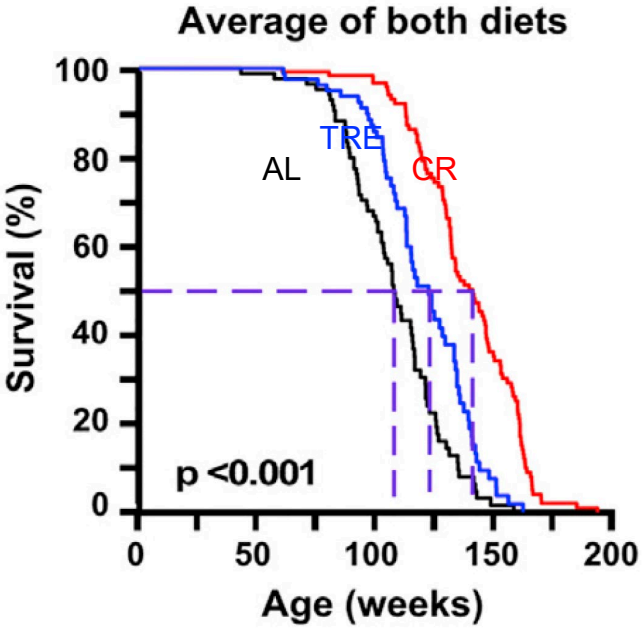
Intermittent CR extends lifespan and reduces mammary tumors in Wistar rats[1]



Development of mammary tumors in control and fasted rats.

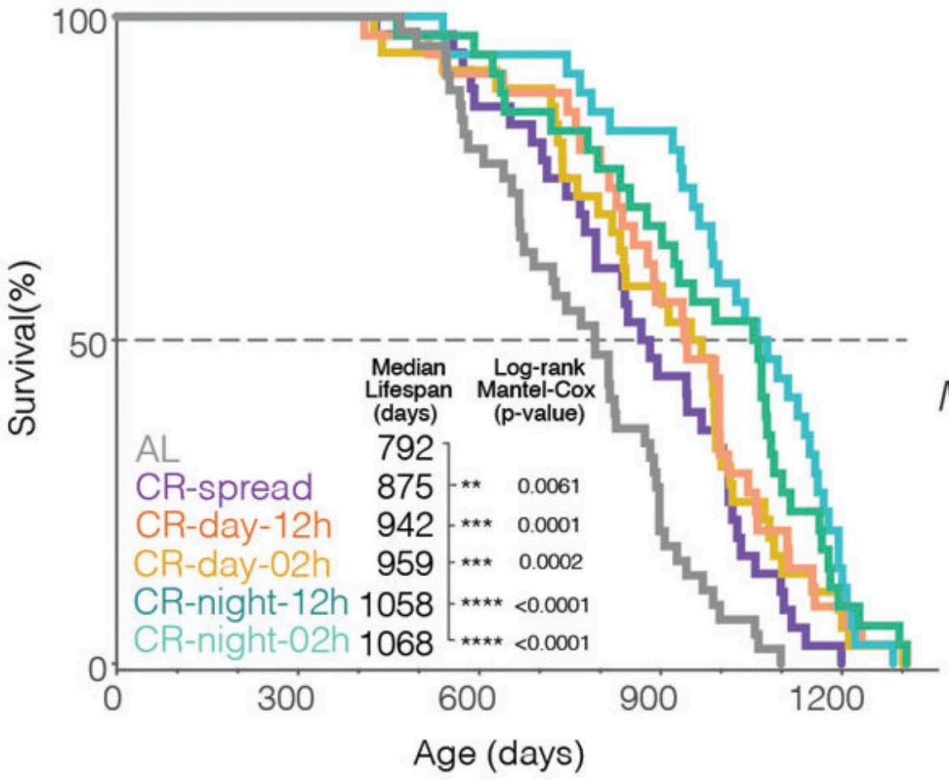
	CONTROLS	FASTED		
		1 day in 4	1 day in 3	1 day in 2
Number of females developing tumors	7	6	8	1
Per cent of females developing tumors	37%	29%	36%	7%
Earliest age at which a tumor began developing	437 days	458 days	675 days	775 days
Average age at which tumors began developing	628 days	613 days	783 days	. .
Average life span of females with tumors	760 days	760 days	871 days	977 days
Weight of largest tumor	462 gm	220 gm	140 gm	26 gm
Average weight of tumors	193 gm [1]	67 gm [1]	36 gm	. .

TRE explains ≳40% of the life-extending effects of CR[2]



[1] Carlson and Hoelzel et al., *J Nutr, 1946.* [2] Mitchell et al., *Cell Metabolism*, 2019.

Circadian-Aligned TRE Increases Lifespan More Than CR, via Nighttime Autophagy



CR Median lifespan increase vs AL

No fasting 10%

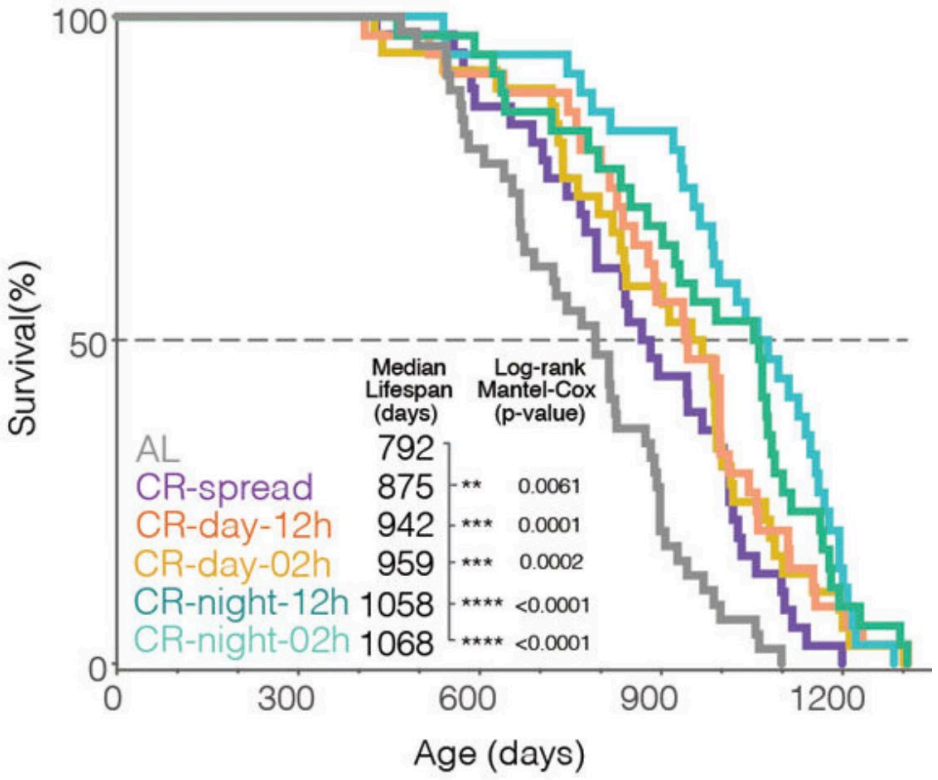
+ Fasting & Misaligned Timing 20%

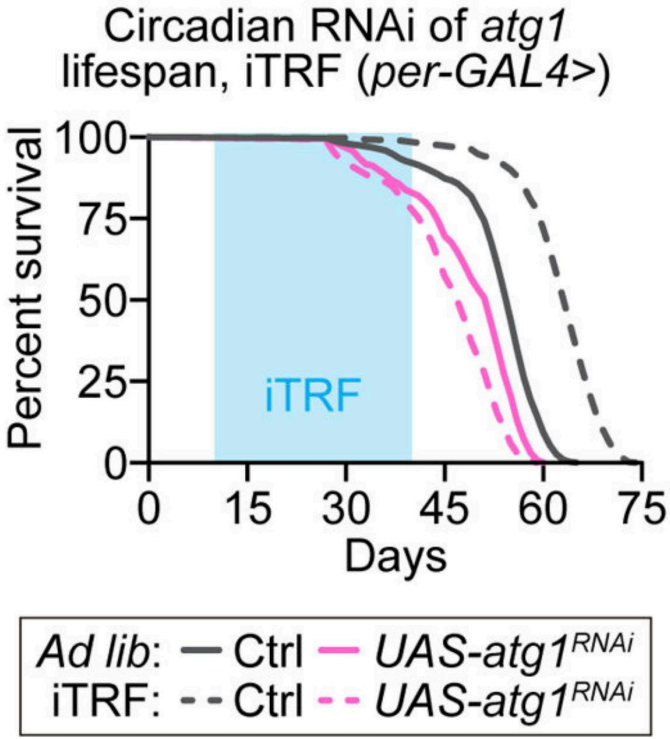
+ Fasting & Aligned Timing 35%

Independent of body weight

[1] Acosta-Rodriguez et al., *Science*, 2022. [2] Ulgherait et al., *Nature*, 2022

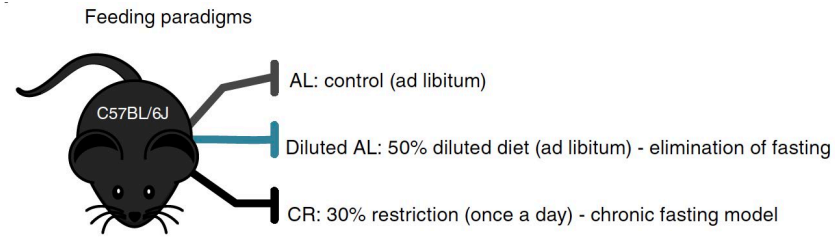
Circadian-Aligned TRE Increases Lifespan More Than CR, via Nighttime Autophagy

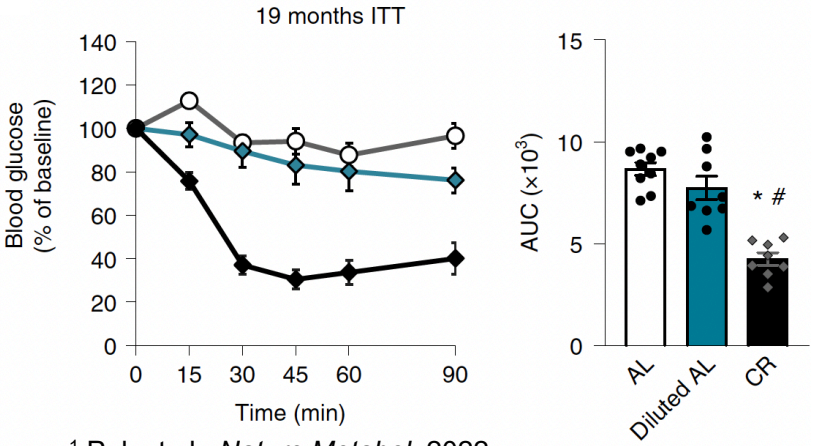


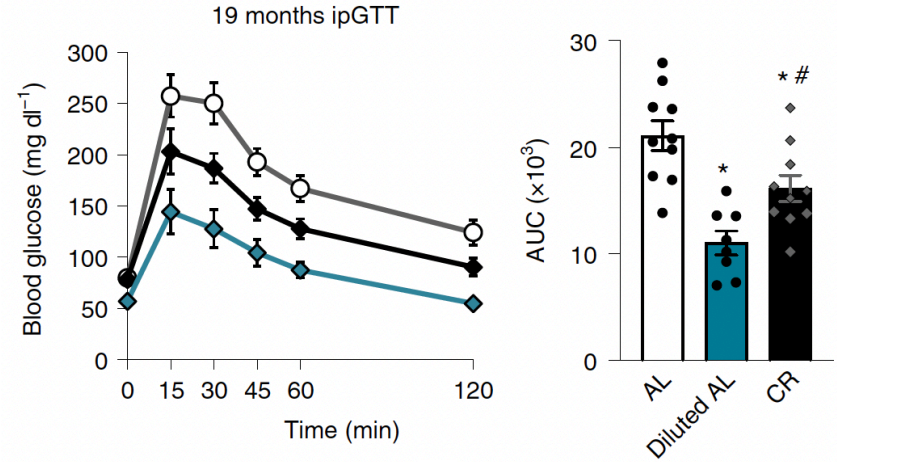


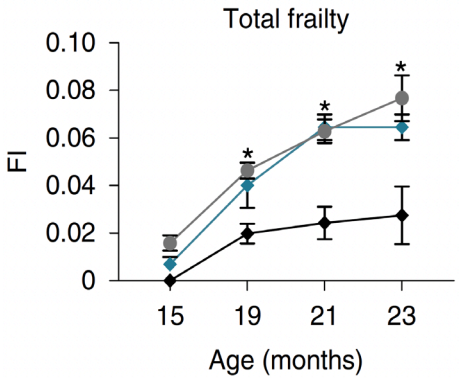
[1] Acosta-Rodriguez et al., *Science*, 2022. [2] Ulgherait et al., *Nature*, 2022

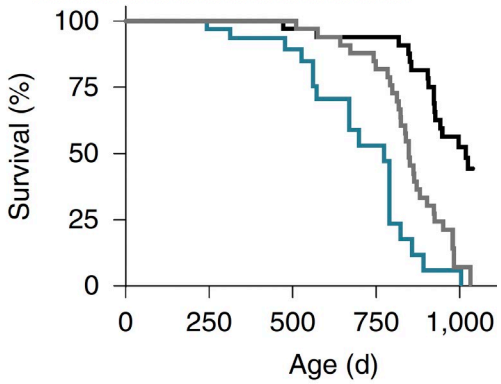
CR without Fasting Does Not Improve Insulin Sensitivity or Frailty and Decreases Lifespan





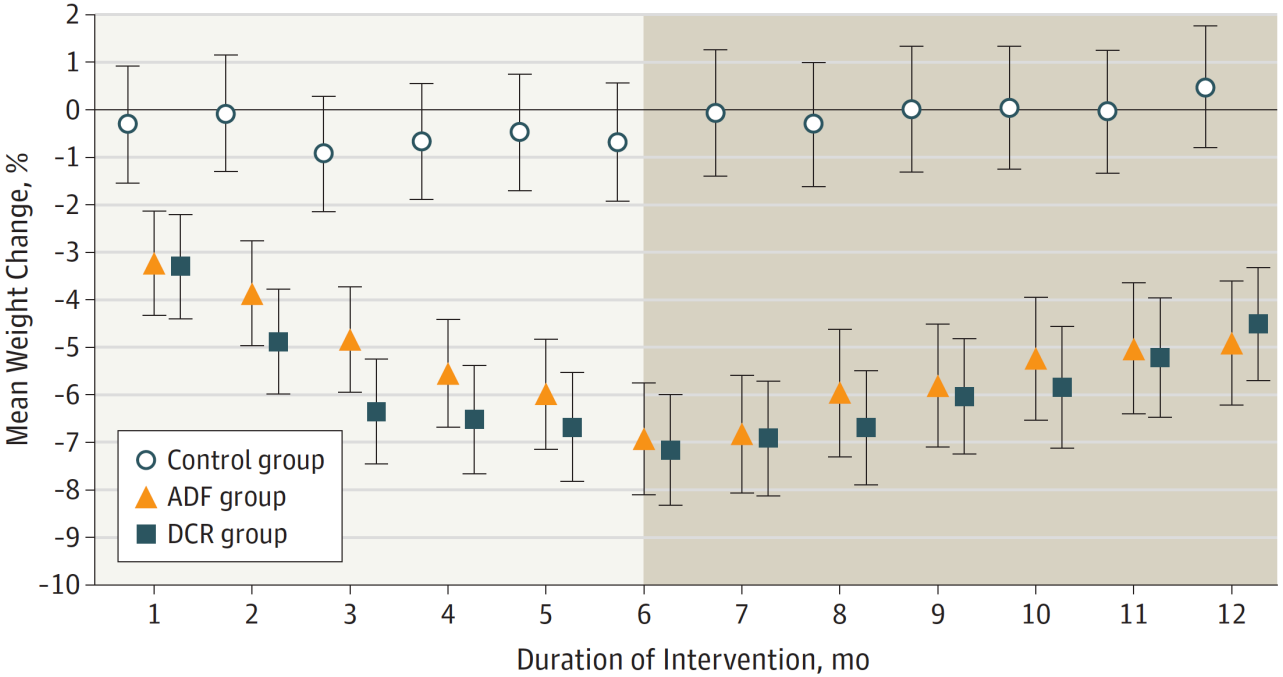






[1] Pak et al., *Nature Metabol*, 2022.

ADMF is As Effective As Continuous Energy Restriction (CER)

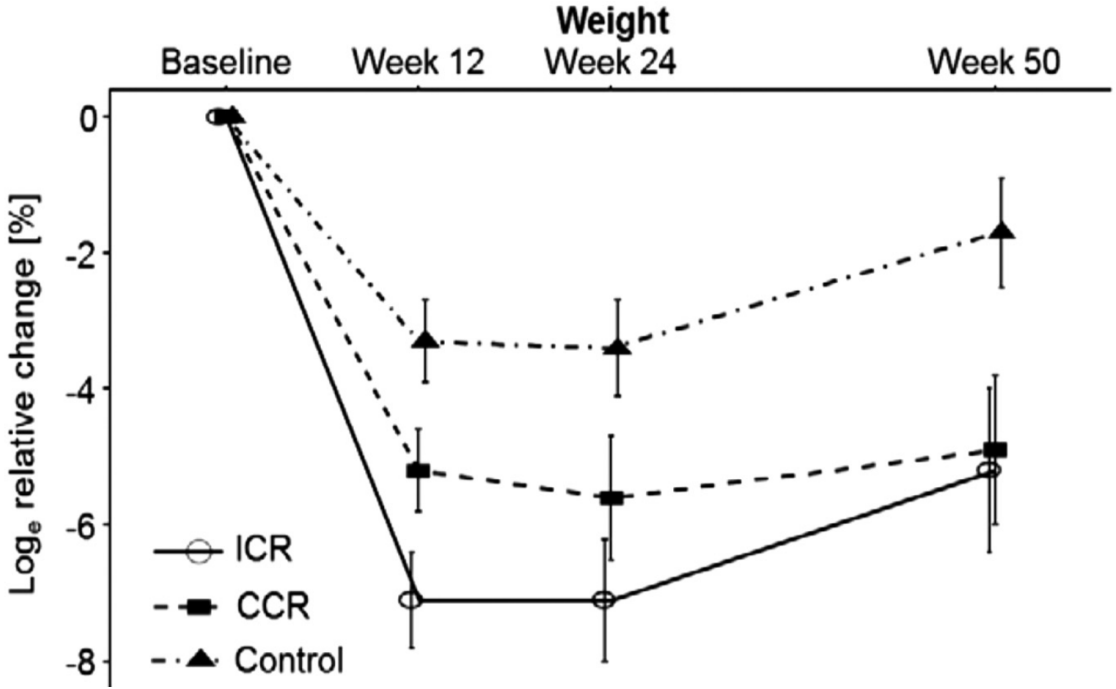


- No differences in fasting cardio-metabolic endpoints, visceral fat, and hs-CRP[1]
- Dropout rate was higher (38% vs. 29%)[1]

[1] Trepanowski et al., *JAMA Intern Med*, 2017.

5:2 Diet May Be Better for Weight Loss in the Short-Term but Not at One Year

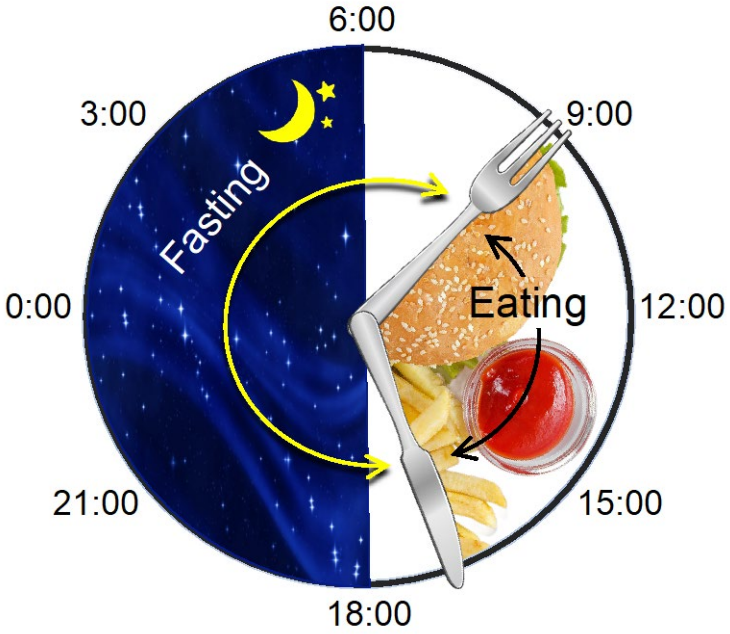
- 5 one-year RCTs with about 50-110 per group[1-6]
- Greater weight loss at 6 or 12 weeks but not at 1 year[1,6,7]
- Improved postprandial C-peptide and triglyceride levels,[8] but did not change fasting cardiometabolic risk factors[1-5]



[1] Schubel et al., *Am J Clin Nutr*, 2018. [2] Sundfør et al., *Nutr Metab Cardiovasc Dis*, 2018. [3] Carter et al, *JAMA Netw Open*, 2018. [4] Carter et al., *JAMA Network Open*, 2018. [5] Headland et al, *Int J Obes*, 2019. [6] Hajek et al, *PLoS ONE*, 2021. [7] Antoni et al., *Eur J Nutr*, 2019. [8] Antoni et al., *Br J Nutr*, 2018.

Time-Restricted Eating (TRE)

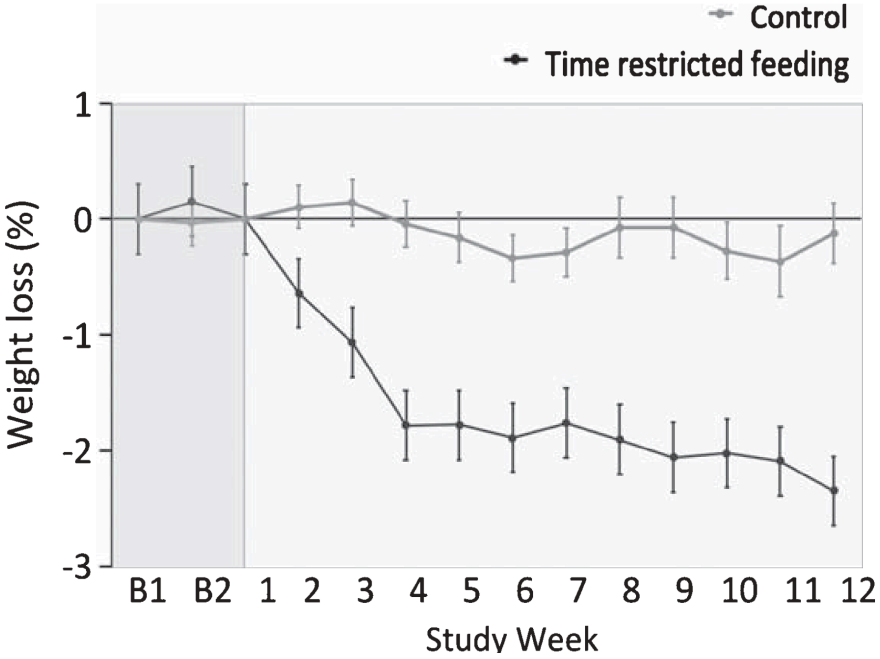
- Eat within a consistent ≤10-hour window
- Water-only fasting for the remaining 14 or more hours of the day (16:8 most popular)
- Can be practiced early vs. late in the day
- Can be practiced with or without cutting calories

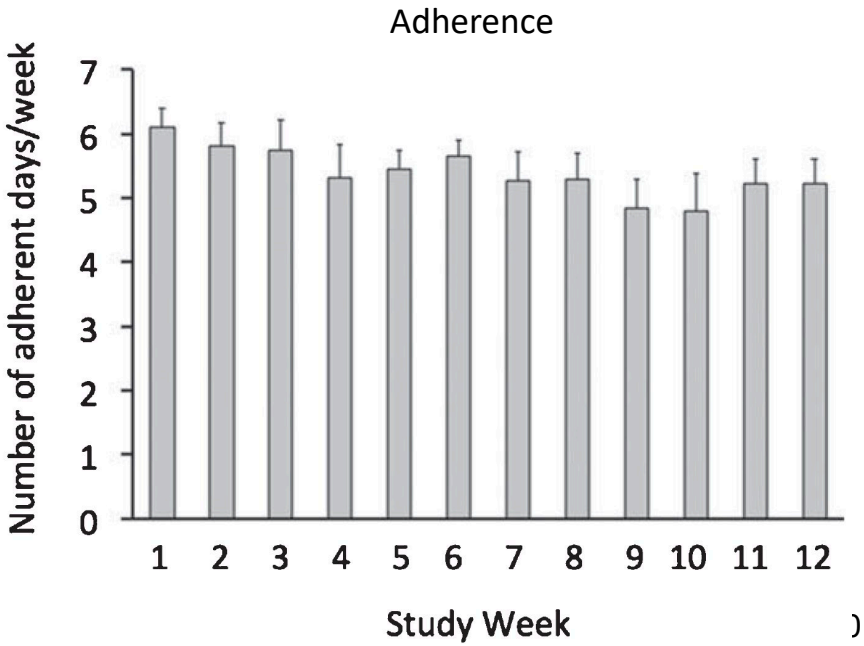


[1] Peterson, *Intermittent and Periodic Fasting, Aging and DIsease*, 2024

TRE Induces Weight Loss Without Counting Calories

- 8-hr TRE from 10 am–6 pm in 23 adults with obesity (vs. historical controls)

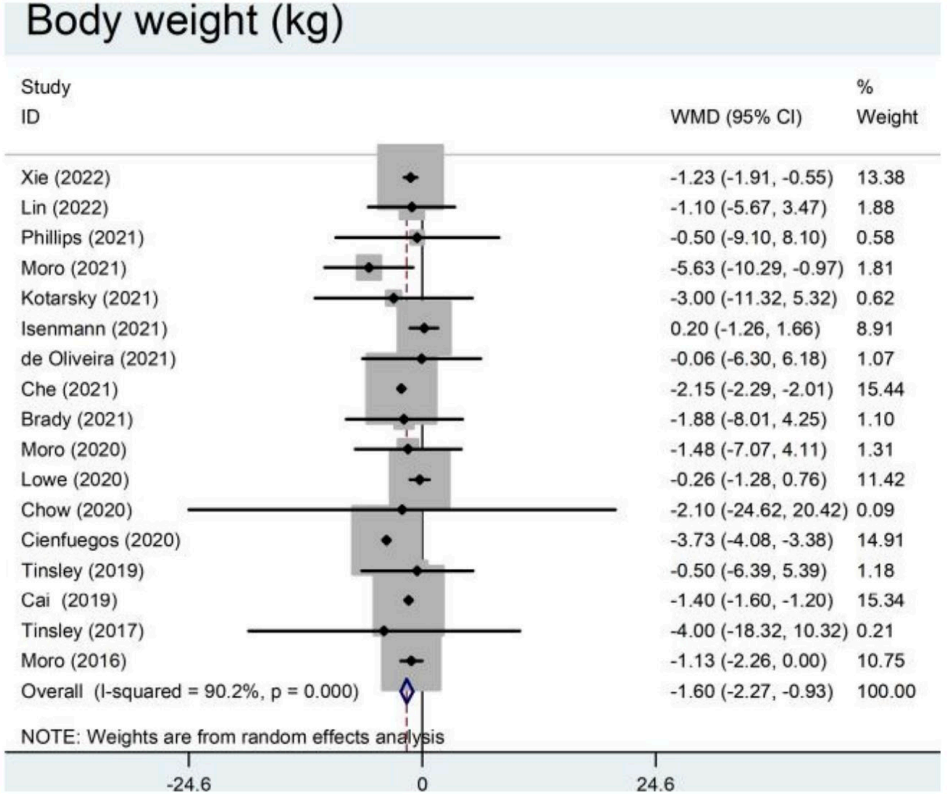




[1] Gabel et al., *Nutrition and Healthy Aging*, 2018.

Meta-Analyses of TRE on Body Weight

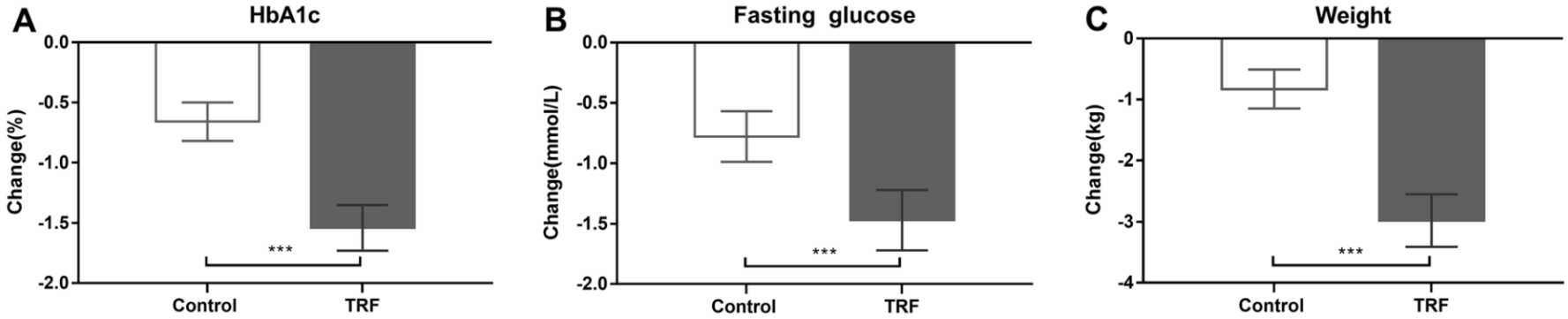
- More than 100 studies in humans (most are small)
- Meta-analysis of 17 RCTs with n=899[1]
- Weight loss of ~2% relative to control
- Calorie deficit of 214 and 350 kcal/day in ITT and PP analyses



[1] Liu et al., *JCEM,* 2022. Jamshed et al., *JAMA Intern Med*, 2022.

TRE Improves Weight Loss and Glycemic Control in Adults with Type 2 Diabetes

- 12-week trial in 120 adults with type 2 diabetes
- 10-hr TRE from 8 am–6 pm vs. unrestricted eating

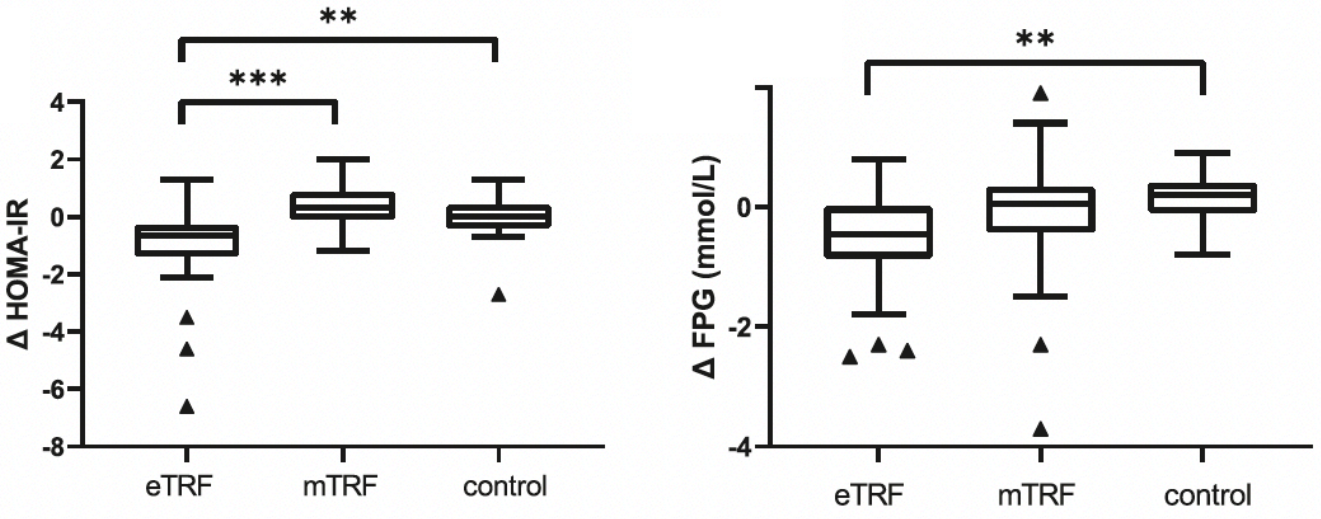


- Also reduced medication use, insulin, HOMA-IR, and lipids

[1] Che et al., *Nutr Metabol*, 2021

Effects of TRE on Glucose in Healthy Adults

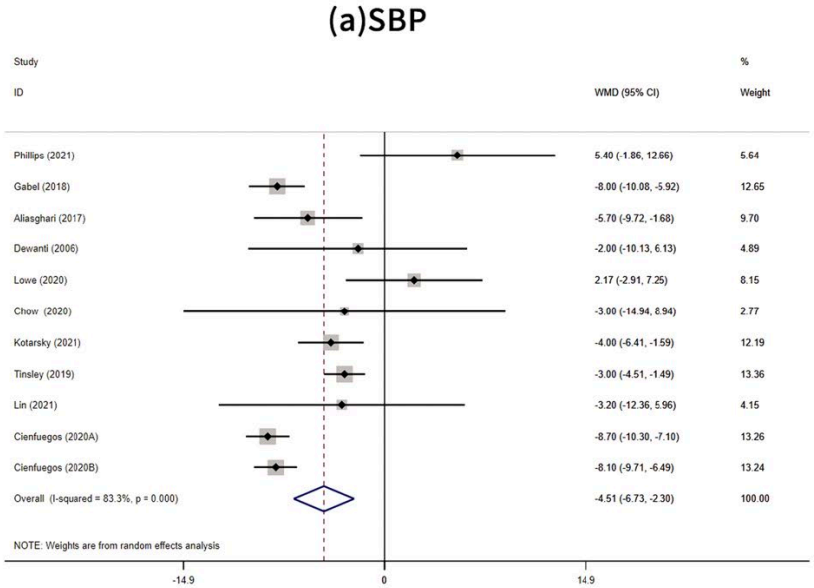
- 5-week study in 90 healthy adults without obesity
- 8-hour early TRE (by 3 pm) vs. 8-hour late TRE (after 11 am) vs. control

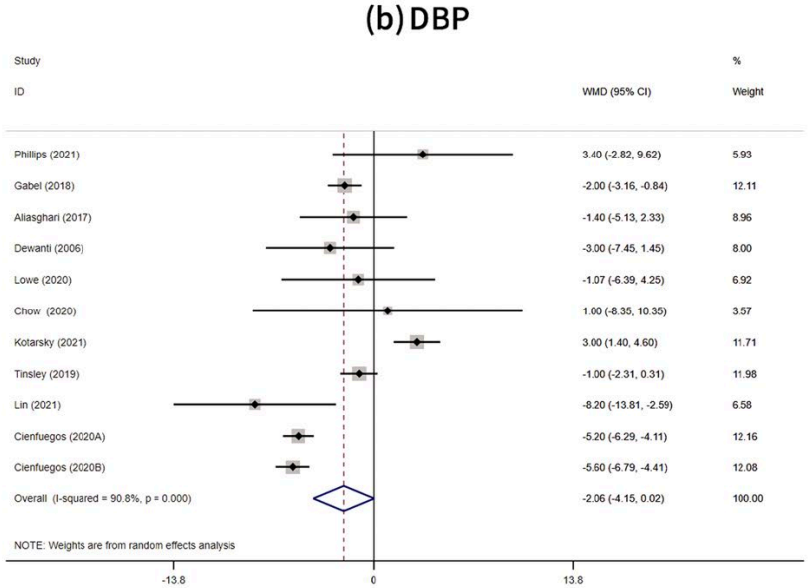


[1] Xie et al., *Nature Comm*, 2022

Meta-Analysis: Effects of TRE on Blood Pressure

- Meta-analysis of 10 trials with 694 participants (-4 mm Hg/-2 mm Hg)

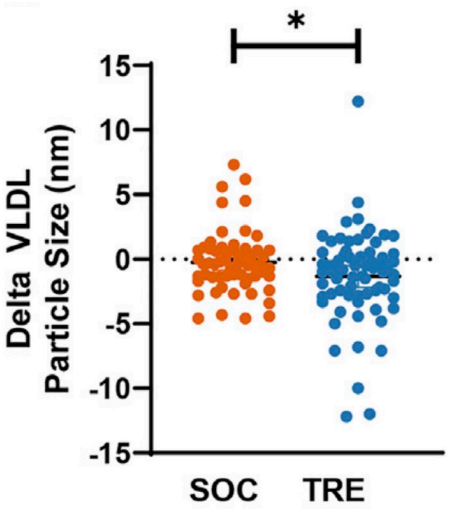


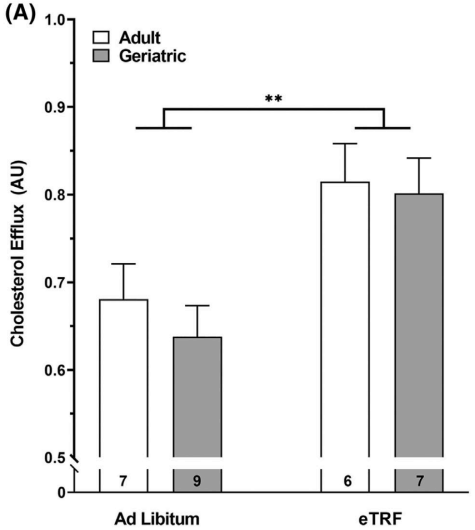


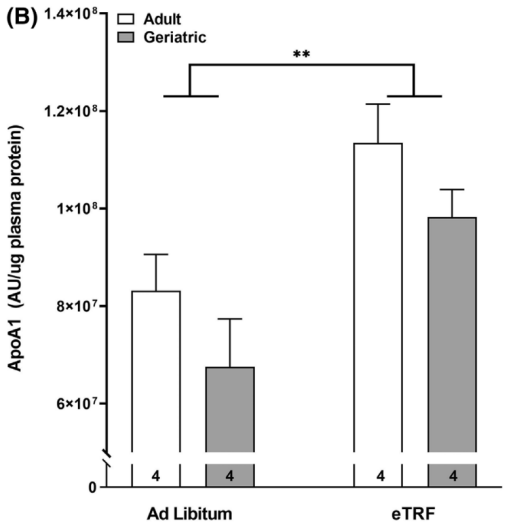
[1] Wang et al., *Nutrition and Metabolism*, 2022.

Effects of TRE on Lipids

- Most studies report no effects on lipids
- However, TRE may affect VLDL particle size (12-week human study[1]), and HDL size and content and cholesterol efflux (12-month primate study[2])



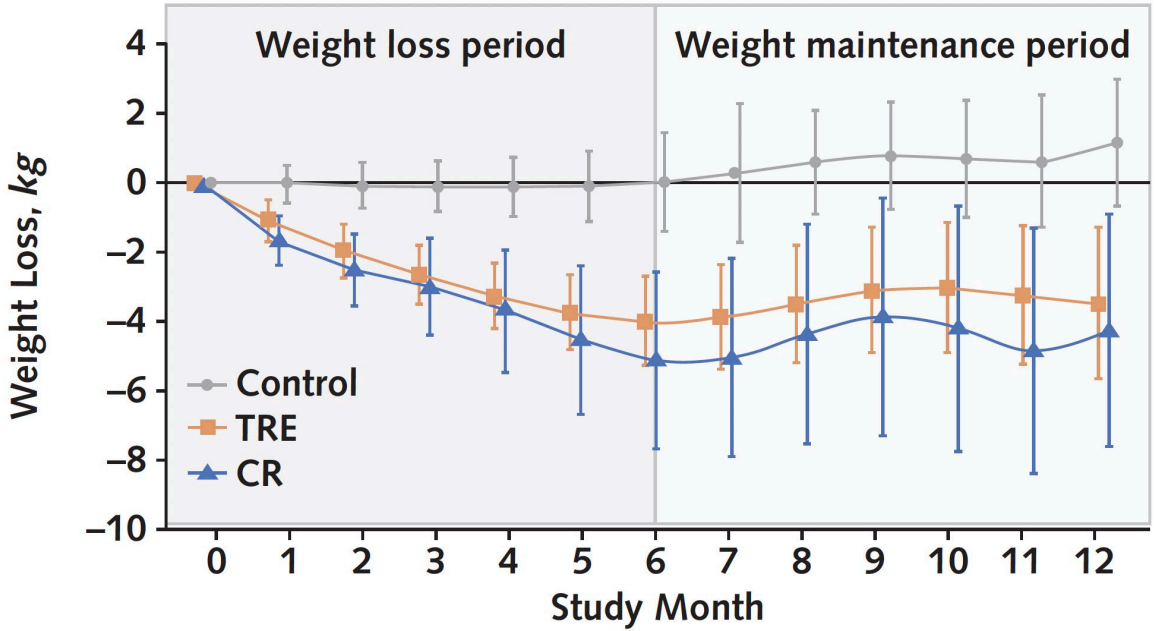




[1] Manoogian et al., *Cell Metabol*, 2022. [2] Kavanagh et al., *Obesity*, 2022.

8-Hour TRE is Equally Effective as Prescribing CR

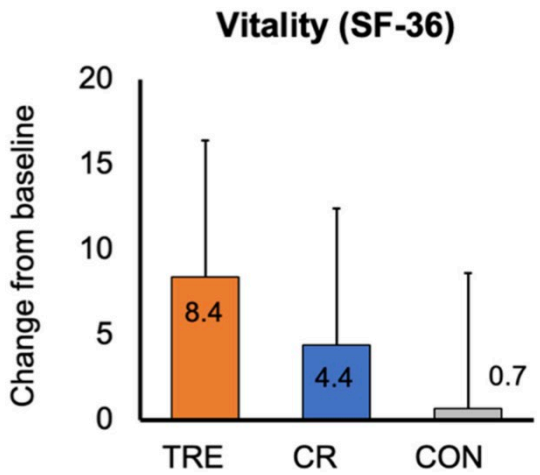
- 1-year RCT in 90 adults with obesity
- 8-hour TRE from 12-8 pm vs. 25% CR vs. weight-stable control group
- CR and TRE had similar effects on fasting CMD endpoints
- Now have 4 studies one year long, with good adherence (~6 days/week) and weight loss



[1] Lin et al., *Ann Intern Med*, 2023

Meta-analyses and Other Studies of IF vs. CR

- No difference in eating behaviors, mood, sleep quality, quality of life (QOL) and cognition[1,2]
- 8-hour TRE between 12-8 pm increased vitality more than CR[2]
- Nearly all meta-analyses find no difference in weight loss between IF and CR
- One recent meta-analysis found no difference in body weight or cardiometabolic risk factors for IF (all types combined) and CR, but did find that TRE reduced body weight more than CR[2]



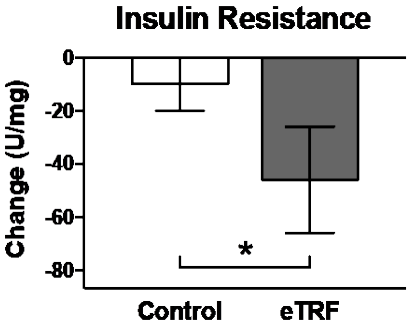
[1] Teong et al., *Nutr Res*, 2021. [2] Lin et al., Nutrients, 2023. [2] Schroor et al., *Adv Nutr*, 2023.

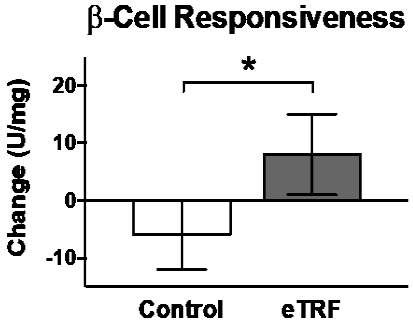
Early TRE Improves Glycemic Control and Blood Pressure Independent of Weight Loss

6-hour early TRE improves insulin sensitivity, beta-cell responsive-ness, BP, and oxidative stress

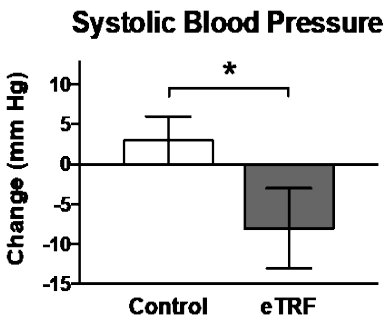
8 studies have reported benefits of TRE independent of weight loss, including by clamp

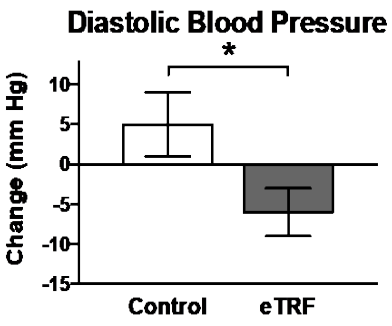
Glycemic Control

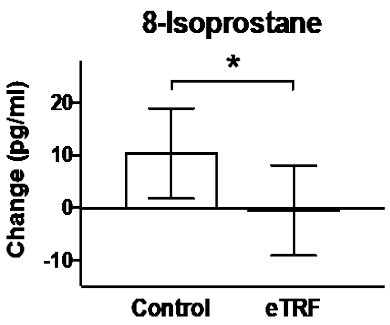


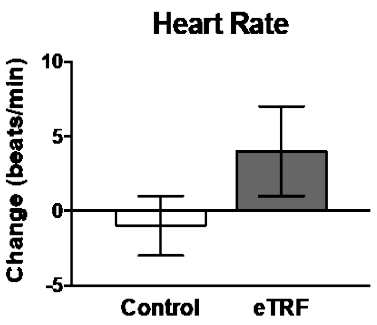


CVD Risk Factors





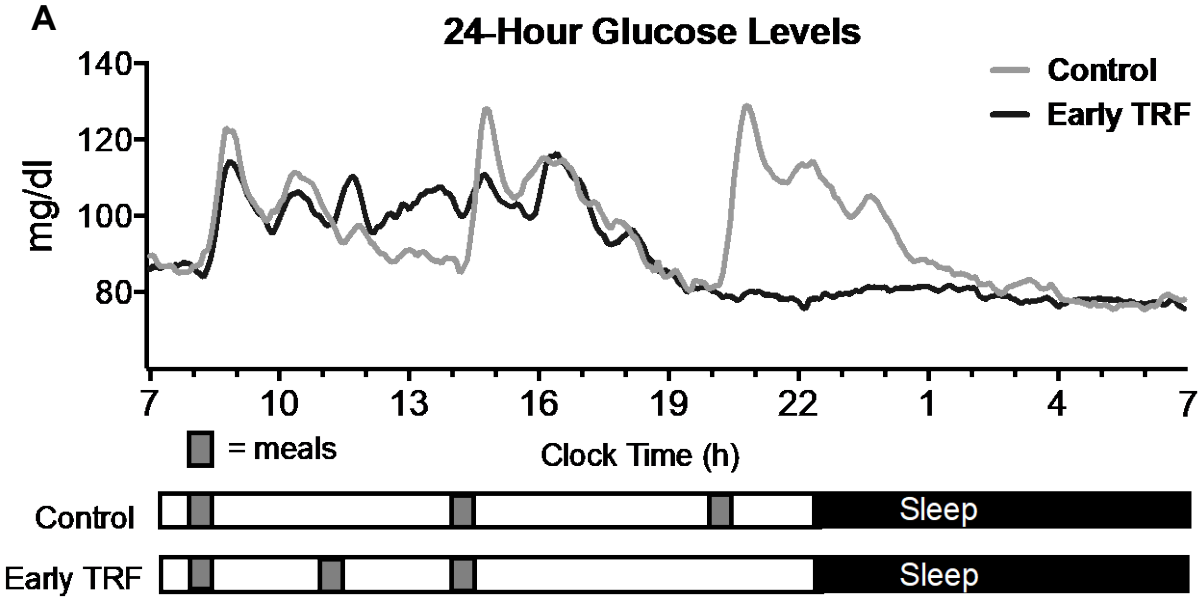


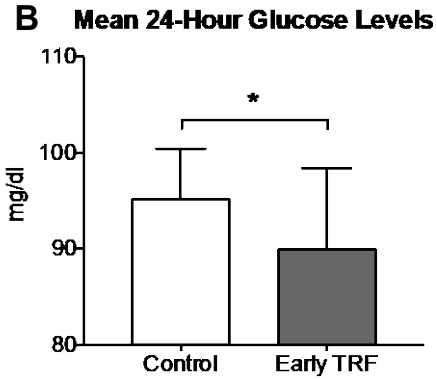


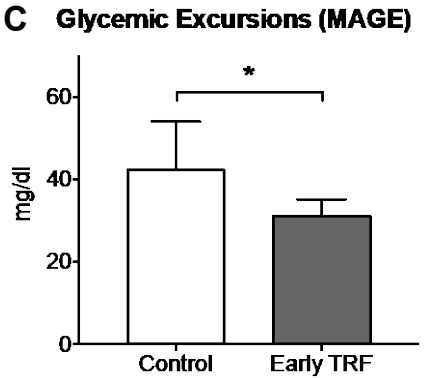
[1] Sutton et al., *Cell Metab*, 2018

Early TRE Improves 24-Hour Glucose Levels

- 4-day crossover study in 11 adults with overweight



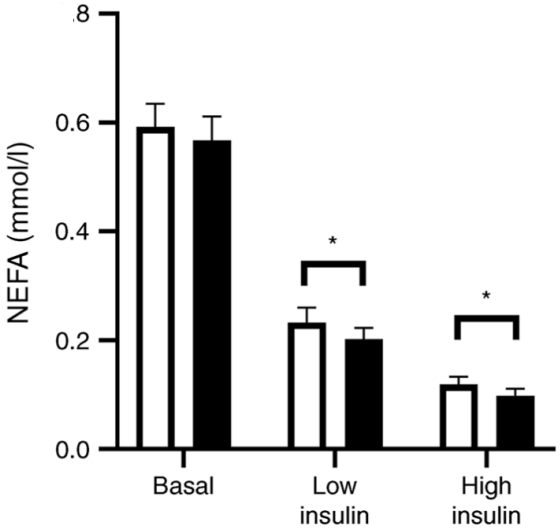


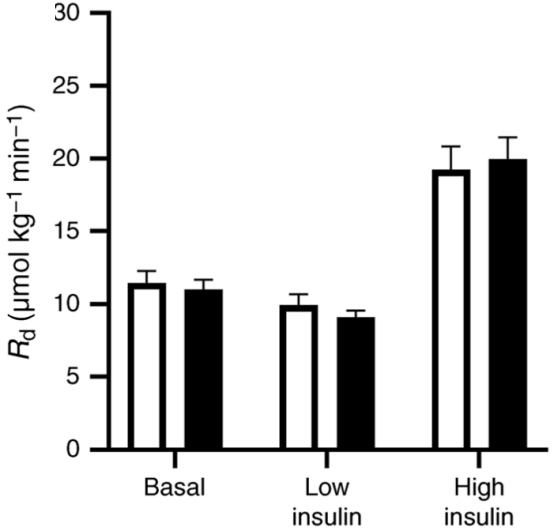


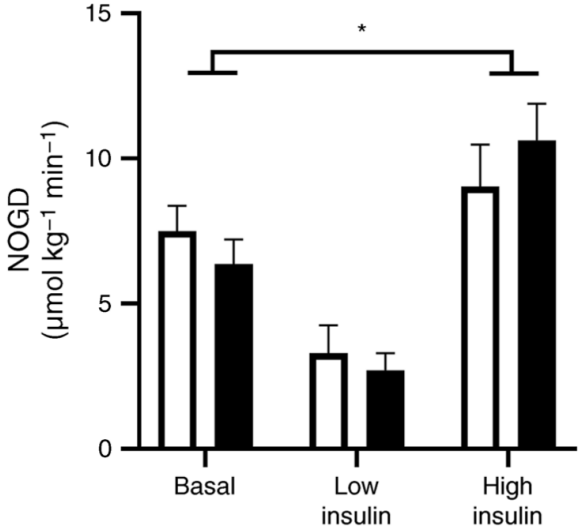
[1] Jamshed et al., *Nutrients*, 2019

10-hour eTRE Improves Insulin Sensitivity

- 3-week crossover study testing 10-hour eTRE in 14 adults with T2D
- Improves adipose tissue insulin sensitivity, tends to improve whole-body insulin sensitivity, and increased non-oxidative glucose disposal



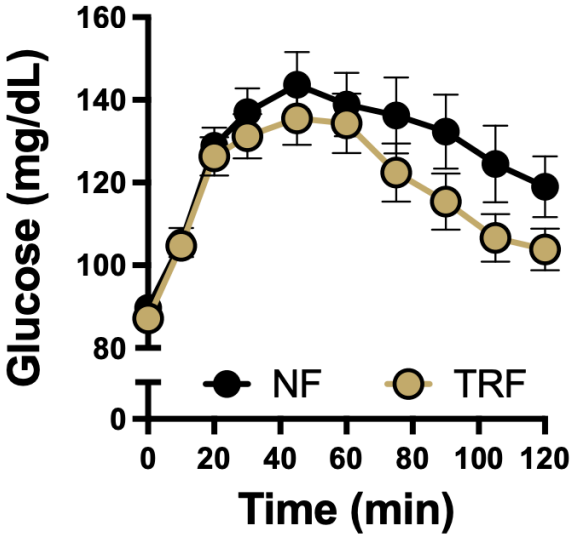


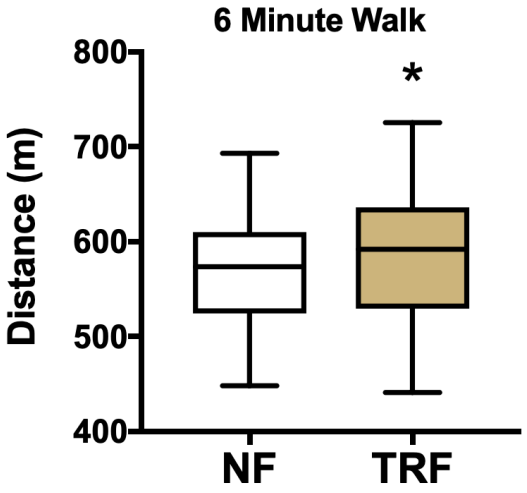


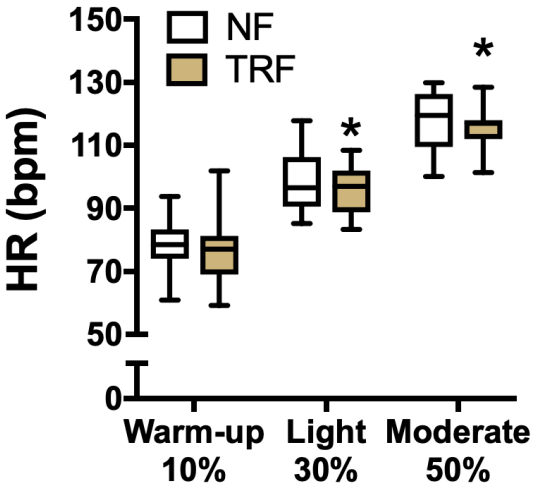
[1] Andriessen et al., *Diabetologia*, 2022.

In Older Adults, TRE Improves Glucose Tolerance and Cardiorespiratory Fitness

- Only a couple of RCTs of TRE in older adults
- Crossover study in 22 weight-stable adults aged 55-79







CALERIE Findings

- Weight loss/energy restriction
- Improved glucose tolerance, insulin secretion, and insulin sensitivity
- Increased metabolic flexibility
- Decreased lipids and BP and improvement in left ventricular function
- Lower inflammation
- Metabolic adaptation (slowed metabolic rate)
- Increased mtDNA content and mitochondrial efficiency
- Reduced DNA damage
- Reduced oxidative stress
- Reduced biological age

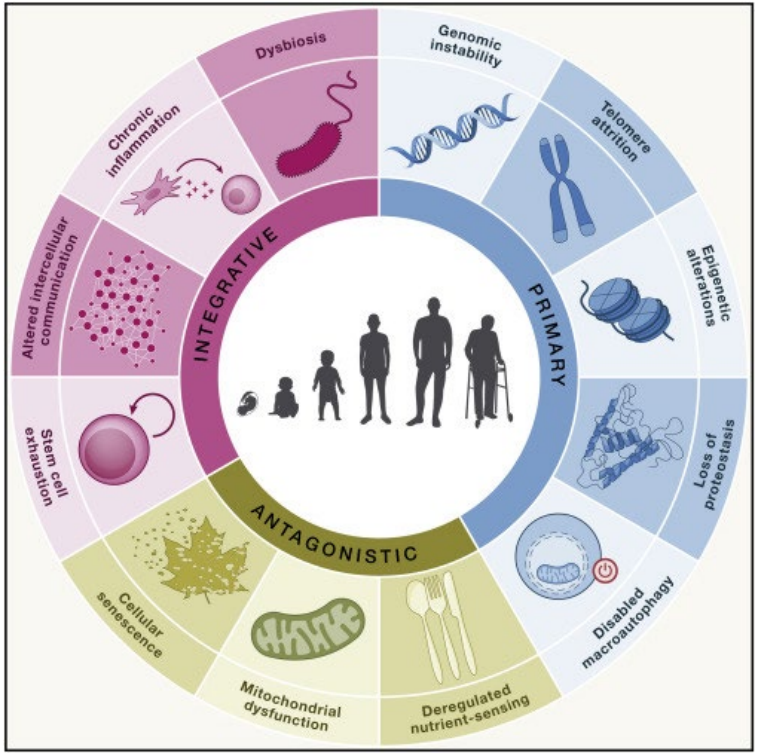
Challenges:

- Adherence
- FFM/Bone loss

Aging-Related Mechanisms of IF in the Animal Literature

- Reduced hunger → CR/weight loss
- Lower insulin/IGF-1 levels
- Autophagy
- Nutrient-sensing pathways (e.g., mTOR, SIRT1)
- Increases antioxidant capacity
- Less ROS production
- Mitochondrial function
- Neurotropic factors (e.g., BDNF)
- Hormesis/stress resistance
- Metabolic flexibility
- Optimizes circadian rhythms

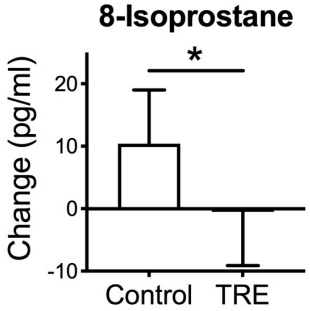
12 Hallmarks of Aging

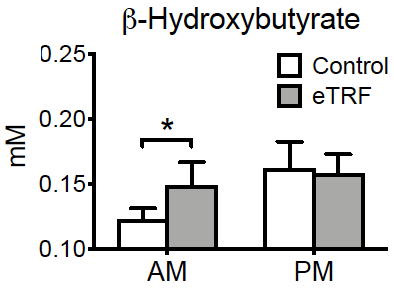


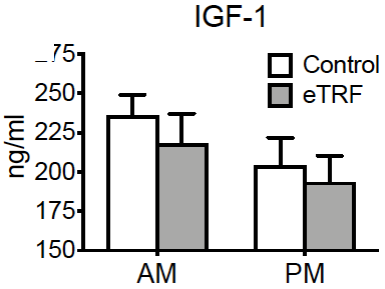
[1] López-Otin et al., *Cell*, 2022.

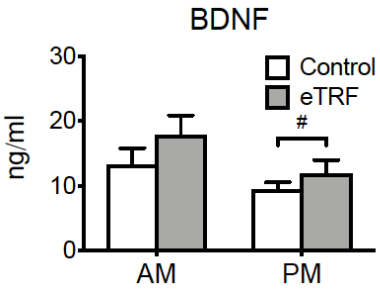
TRE Affects Several Aging-Related Molecular Mechanisms in Humans

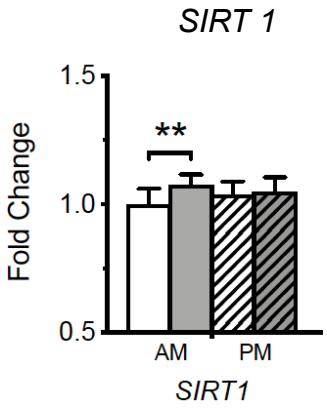
6-hr eTRE vs. 12-hr control

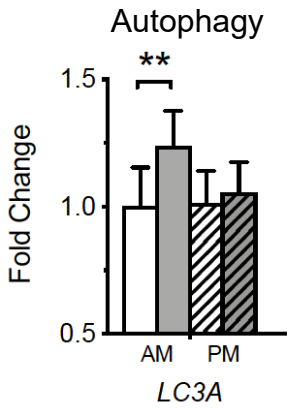


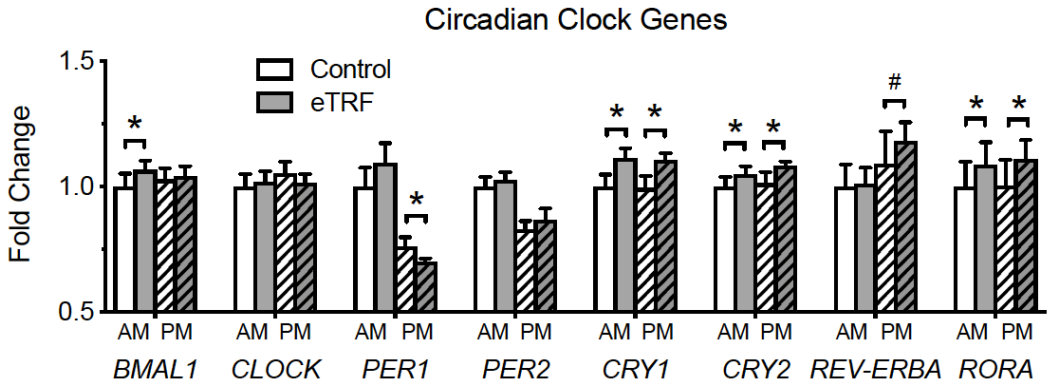












[1] Sutton et al., *Cell Metabolism*, 2018. [2] Jamshed et al., *Nutrients*, 2019

Conclusions

- DIAL Health and HALLO-P studies are comparing TRE vs. CR in younger and older adults, respectively
- Biggest gaps:
  - Need large, long-term studies of TRE
  - Need to determine the effects of the length of the eating window and time of day of TRE
  - Need studies to incorporate 24-hour/postprandial assessments
  - Need more studies comparing the molecular mechanisms (incl. hallmarks of aging) and also energetic and glycemic mechanisms

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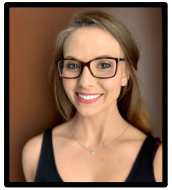
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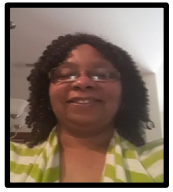
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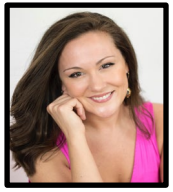
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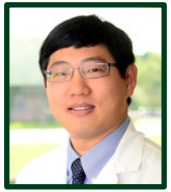
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