FASTING AND FASTING MIMICKING

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Discussion Objectives:

- Appreciate the role of diet, nutrition, and lifestyle in healthy aging
- Understand different forms of energy restriction and their differential impact on weight loss and metabolic health
- Assess practicality of implementing intermittent fasting in clinical practice - *Who are good patient candidates? How do we monitor our patients? What are potential contraindications?*

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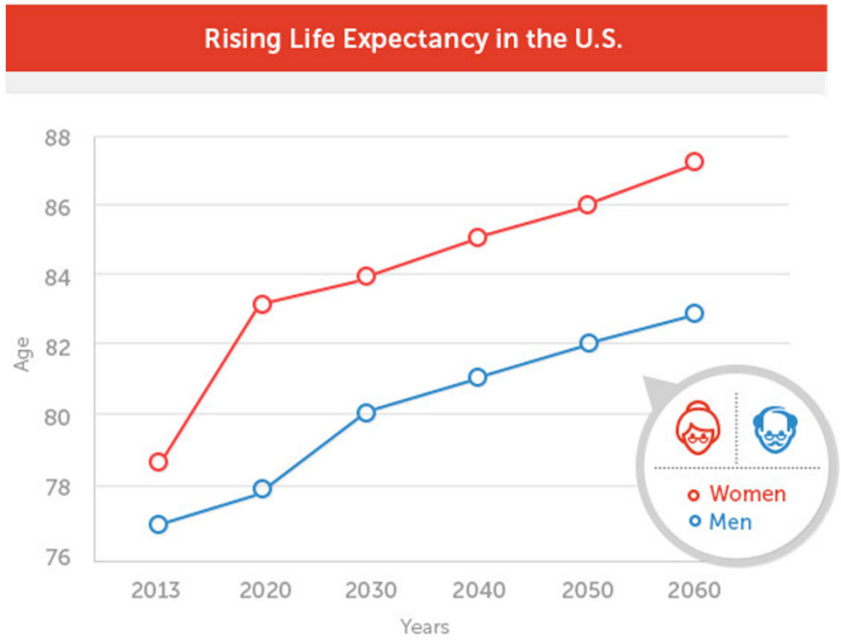
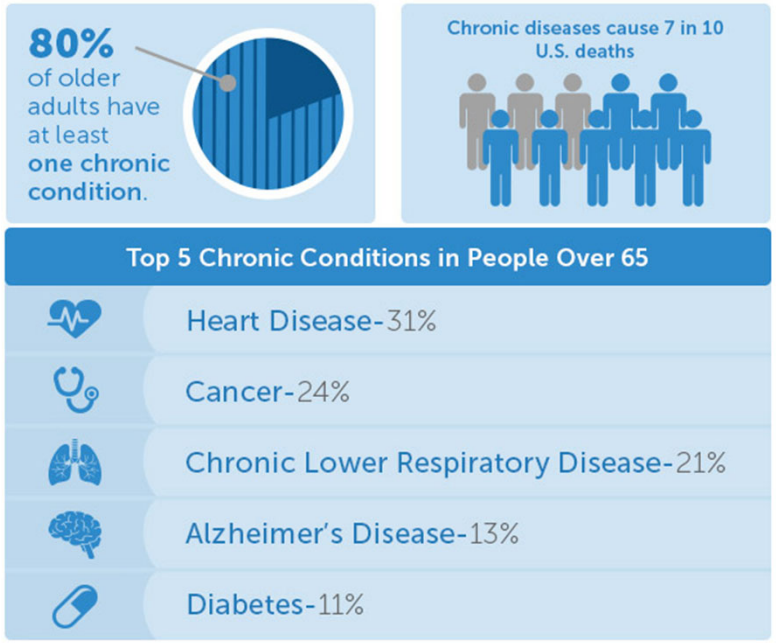
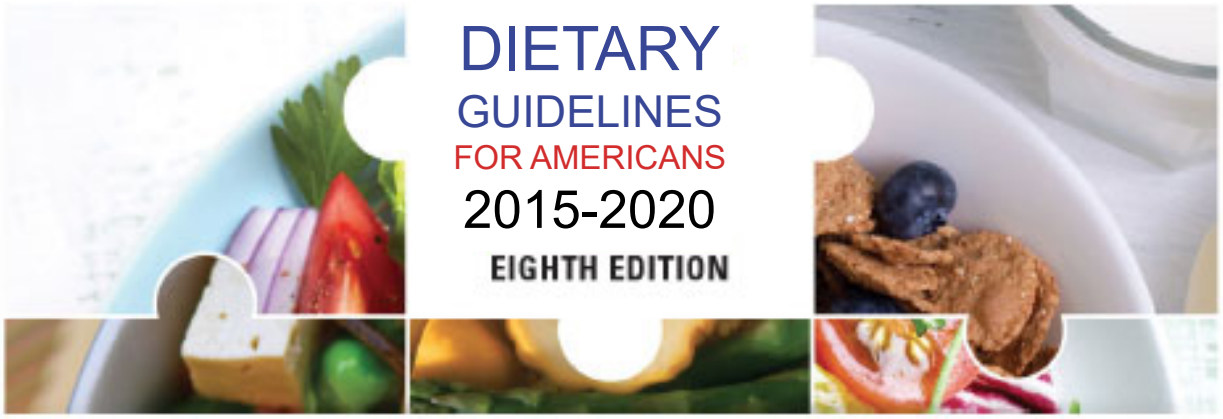
Aging & Chronic Conditions

- People are living longer than ever before
- People over 65 will comprise more than 22% of the population by 2030
- Age-associated chronic diseases & conditions are also increasing





New Dietary Guidelines: Novel Shifts Aim to Align With Improved Eating Patterns for Healthy Aging

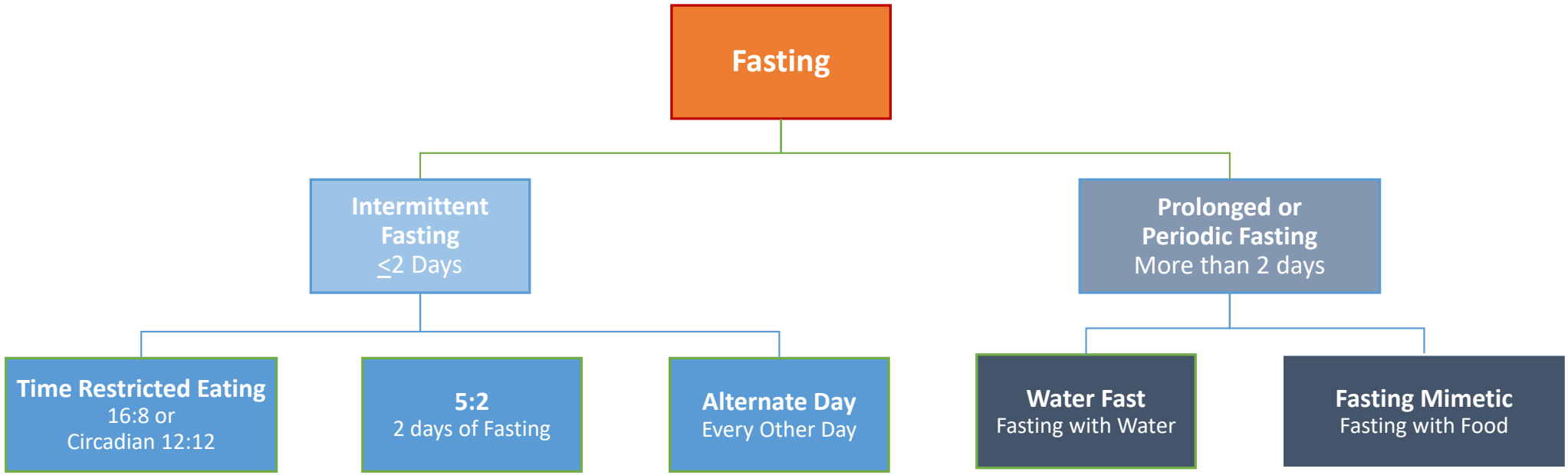


Focus on healthy eating patterns <u>across the lifespan</u>:

- All foods and beverage choices matter
- Achieve and maintain a healthy weight
- Support nutrient adequacy
- Reduce the risk of age-related chronic disease
- Shift from typical to nutrient-dense foods


What is Fasting?

TYPES OF FASTING: Not All are the Same



DEFINITIONS:

Intermittent Fasting:

An umbrella term for various eating patterns that cycle between a period of fasting and non-fasting.

Mattson MP et al. Proc Natl Acad Sci U S A. 2014;111(47):16647-16653.

DEFINITIONS:

TRE or TRF:

Involves eating only during a certain number of hours each day, typically 12 or less.

Most common types are the 16:8 and the Circadian 12:12.

Mattson MP et al. Proc Natl Acad Sci U S A. 2014;111(47):16647-16653.

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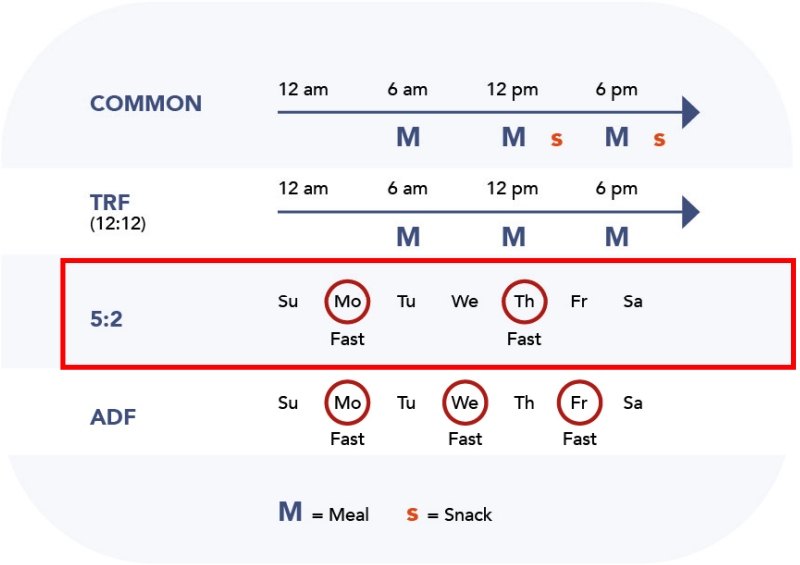
DEFINITIONS

5:2 diet:

Five days per week non-fasting and two days per week either total fasting or modified fasting (500-600 calories).



Mattson MP et al. Proc Natl Acad Sci U S A. 2014;111(47):16647-16653.

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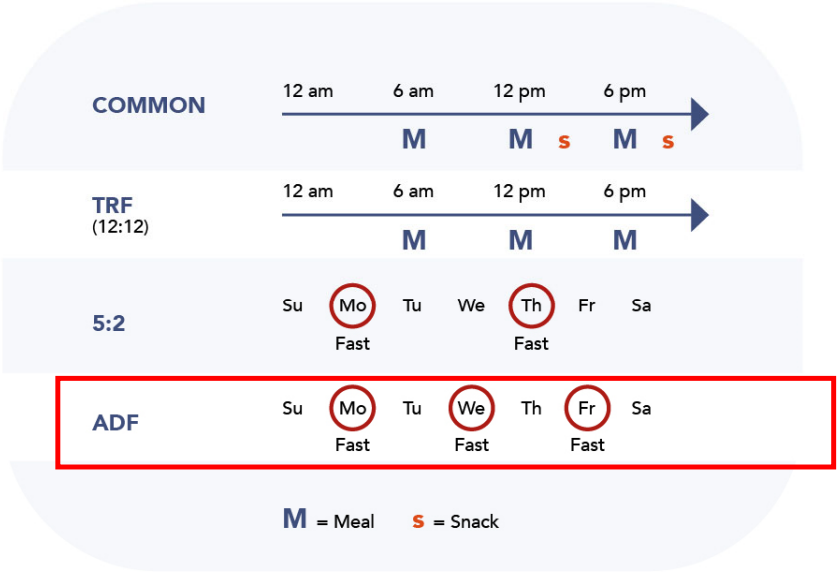
DEFINITIONS

ADF:

A 24-hour fast followed by a 24-hour non-fasting period.

Variations can include:

Alternate Day Energy Restriction:
Modified ADF that allows the consumption of approximately 500–600 calories on fasting days.



Mattson MP et al. Proc Natl Acad Sci U S A. 2014;111(47):16647-16653.

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Prolonged Water Fast: Associated Challenges

Gallstones

Dehydration

Hypotension

Adherence/Safety/Effectiveness?

Hypoglycemia

Loss of Muscle Mass

Nutrient Deficiency

Hunger

Water for 4-5 days or longer

Bolondi L et al. Gut. 1985; Wilhelmi de Toledo et al. PLoS One. 2019.

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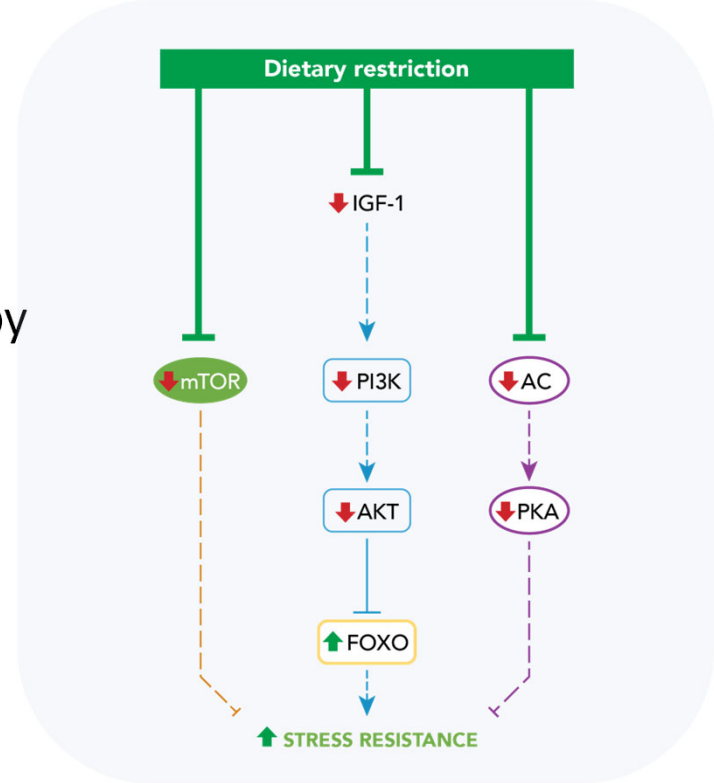
The Emergence of Fasting Mimetics

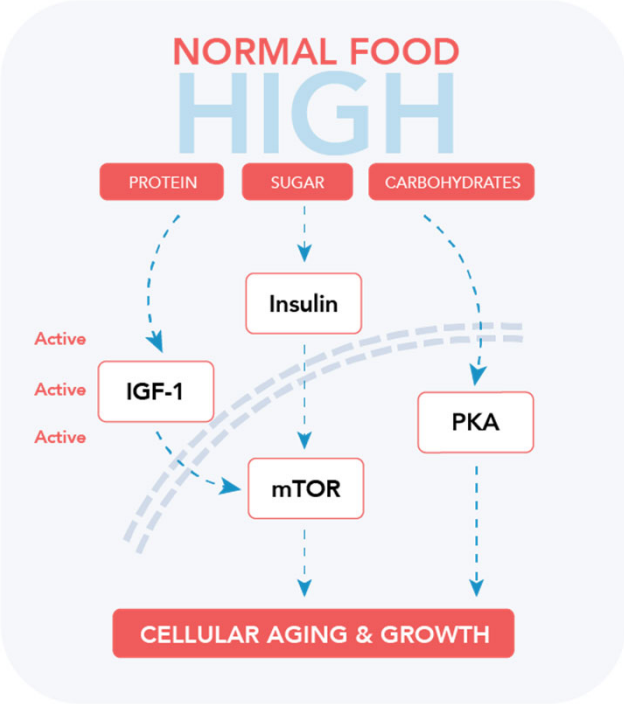
- We first need to under impact of fasting at the cellular level

- **Nutrient-sensing pathways (NSPs)** are triggered by the presence of nutrients
  - mTOR: Amino Acids Pathway
  - IGF-1: Protein Pathway
  - PKA: Carbohydrate Pathway



Wei et al, 2008; Cheng et al., 2014

How Fasting Works

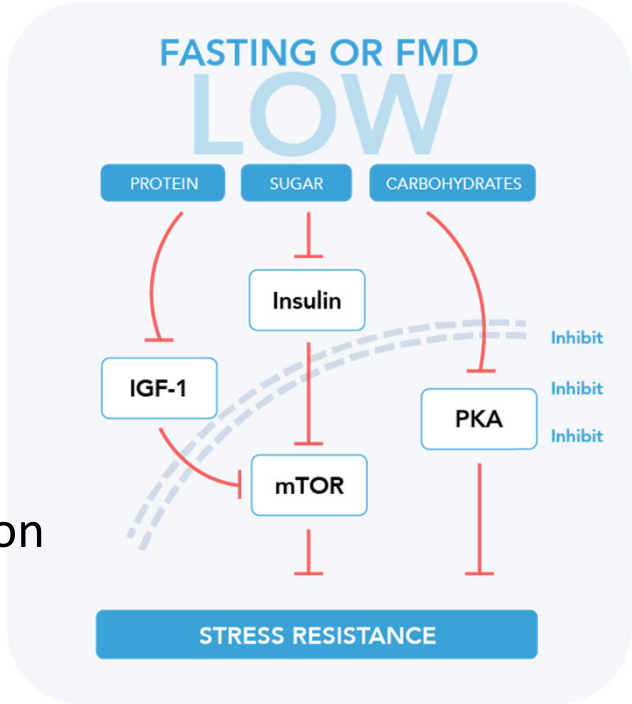


In the presence of adequate nutrients

- NSPs are up-regulated
- The cell's growth, replication, and aging mechanisms are activated (including down-regulation of longevity-promoting FOXO genes)

In a state of dietary restriction

- NSPs are down-regulated
- The cell's stress resistance functions predominate



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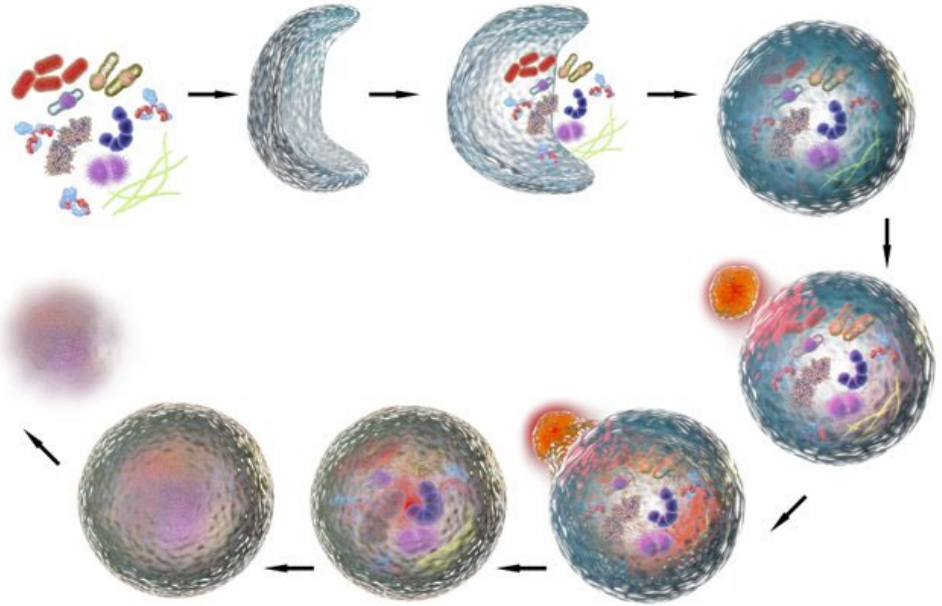
Research Background
Effect of Fasting on the Cellular Level

In addition, Inhibition of NSPs leads to activation of Autophagy

- Poorly functioning organelles - such as mitochondria, and misfolded proteins - are targeted for destruction
- Body's way of cleaning house – innate recycling
- Important in inflammation, immune function and cellular rejuvenation
- Triggered by **prolonged fasting**



NOBEL PRIZE WINNER

2016 NOBEL PRIZE : Yoshinori Ohsumi

"Discovery of Mechanisms for Autophagy"

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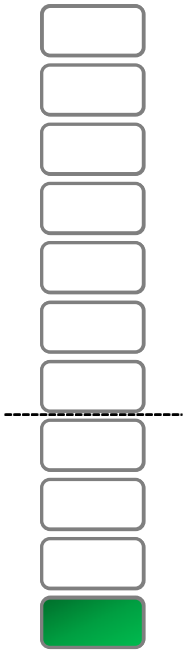
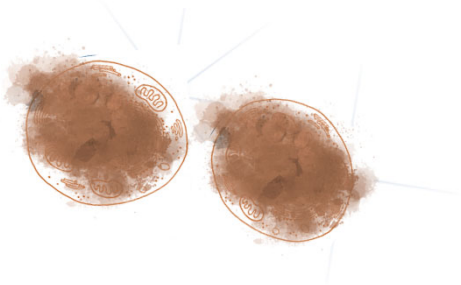
How Fasting Mimicking Diets Work

Water Fasting



Nutrient Sensing Pathway Activation Levels



Intracellular Clean-up (Autophagy)

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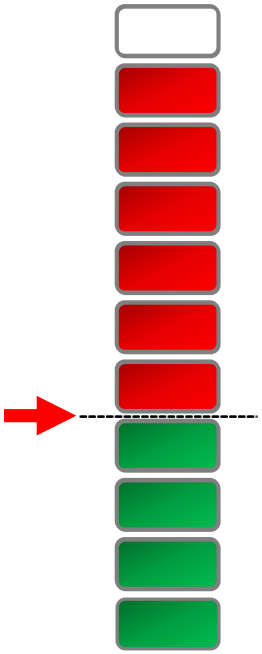
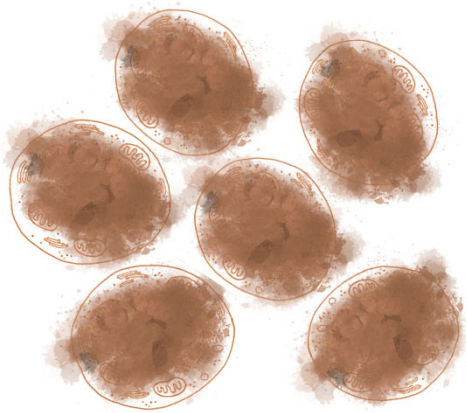
How Fasting Mimicking Diets Work

Traditional Western Diet



Nutrient Sensing Pathway Activation Levels



Old, worn-out intracellular components

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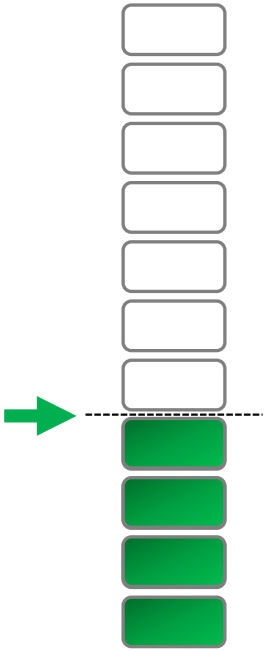
How Fasting Mimicking Diets Work

FMD



Nutrient Sensing Pathway Activation Levels

Intracellular Clean-up (Autophagy)

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COMPOSITION OF FMD: An Alternative to PF

Protein Restriction (9-11%)

Nutritious Nut-Based Fats & Omega-3 Fatty Acids (44-46%)

Complex Carbs & Fiber (43-47%)

Mild Calorie Restriction (700-1100 Kcal/day)

Mainly plant based, gluten- & lactose-free

Micronutrients & glycerol to nourish the body during fasting

Mainly Plant-based ingredients

Composition and amount of macronutrients designed to provide nutrients without significant up-regulation NSPs

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COGNITIVE PERFORMANCE	Studies discovered that intermittent fasting augments associative, spatial and working memory in animals, as well as verbal memory in adults.
CARDIOVASCULAR HEALTH	Blood pressure and resting heart rate are just two of the cardiovascular factors improved through intermittent fasting.
PHYSICAL PERFORMANCE	Young men that fast for 16 hours lost fat while maintaining muscle mass, while mice who maintained alternate day fasting displayed superior running endurance.
DIABETES & OBESITY	In animal studies, intermittent fasting prevented obesity. Six short studies of obese adults show that intermittent fasting is effective for weight loss.
TISSUE DAMAGE	In animals, intermittent fasting limits tissue damage and improves surgical outcomes.

Benefits of Fasting:

Truth or Myths?

1 INCREASED REDUCTION IN ABDOMINAL FAT

Studies published in 2013 showed that a group of women following the 5:2 intermittent fasting protocol, showed greater abdominal fat reduction and improved insulin sensitivity compared to another group of women with the same caloric intake during a week. [3]

2 FIGHTS MOST COMMON TYPES OF CANCER DIAGNOSED AMONG WOMEN

Among the 5 most common types of cancer among women, cervix, lung, breast, stomach, and colorectum, fasting was found to be have a protagonist effect, slow tumor growth, and reduce cancer risk factors and biomarkers in women. [4]

3 REDUCES PAIN ASSOCIATED WITH MUSCKOSKELETAL DISORDERS

Studies have shown that fasting helps with inflammation and reduced paint and joint stiffness related to rheumatoid arthritis and osteoporosis. Fasting has shown to positively effect the hormonal secretions thought to be beneficial in improving bone health. [4]

4 IMPROVED SLEEP AND MENTAL HEALTH

Clinical observations have shown that the early effects of fasting on depression symptoms with an improvement in mood, alertness, and a sense of peacefulness. Subjects observed also have a higher quality of sleep.[2]

5 REDUCES BLOOD PRESSURE, HEART RATE AND CHOLESTOROL

A study performed by Varady et al, confirmed the significant cardioprotective actions of IF, such as reduction in blood pressure, and heart rate; and improvements in lipid profile, with decrease in total cholesterol. [1]

6 PROMOTES REPRODUCTIVE HEALTH

A recent study conducted on women with Polycystic ovary syndrome PCOS revealed that fasting can reduce the chronic sympathetic overactivity in PCOS. [6]

7 OVERALL WEIGHT REDUCTION

Four weeks of fasting has shown to reduce total weight, body mass index, and waist circumference. Alternate day fasting has been found to contribute to weight loss by improving glucose tolerance. [5]

Unknowns:

IN ANIMALS:

Prolonged Fasting (PF) and Intermittent Fasting (IF) calorie restriction has been shown to

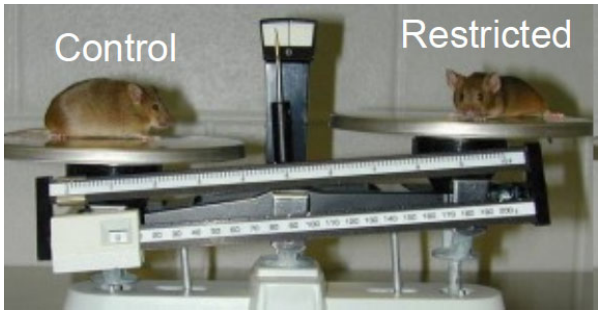
- Increase lifespan
- Improve weight loss & metabolic biomarkers
- Optimize tolerance to various physiologic stress

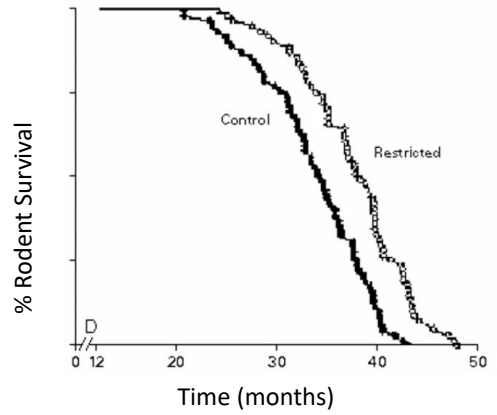
Benefits of Intermittent Fasting and Fasting Mimicking in Humans Less Clear

- *Protection against obesity?*
- *Impact on insulin sensitivity and diabetes?*
- *Improvement in cardio-metabolic risk factors and inflammatory biomarkers?*

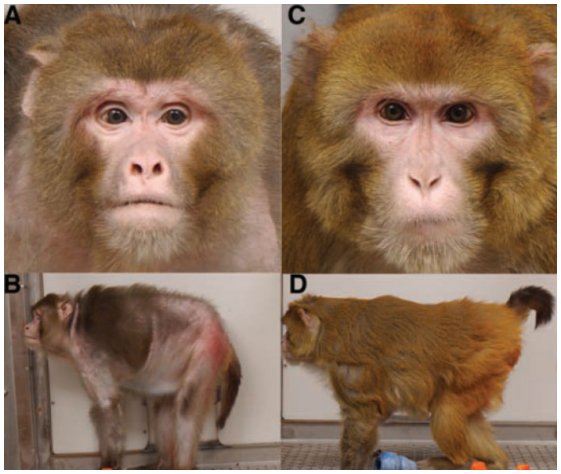
- *Impact on oxidative stress and cancer?*
- *Protection against neurodegenerative and autoimmune diseases?*
- *Extend healthspan? Longevity?*

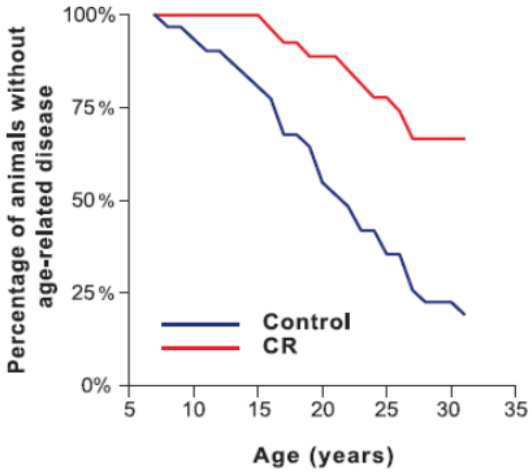
IF and IGF-1 Axis: Impact on Lifespan in Rodents and Primates





Normal Diet Caloric Restriction





Ref: Colman R, et al. Science, Vol. 324 Issue 5937, July 9, 2009.

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Cell Metabolism – Brandhorst et al (USC Longevity Institute)

A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Summary of findings:

- FMD inhibits major pro-aging genes - including those in the IGF-1, mTOR and PKA pathways
- FMD causes fat loss without reducing lean body mass
- Healthy fasting blood glucose levels were maintained and remained 5.9% lower than baseline 5 to 8 days after resuming normal diet
- Periodic FMD cycles helps to maintain healthy glucose levels, blood pressure, cholesterol, C-reactive protein, and stem cell mobilization.

Ref: Brandhorst et al. Cell Metab. 2015 Jul 7;22(1):86-99.

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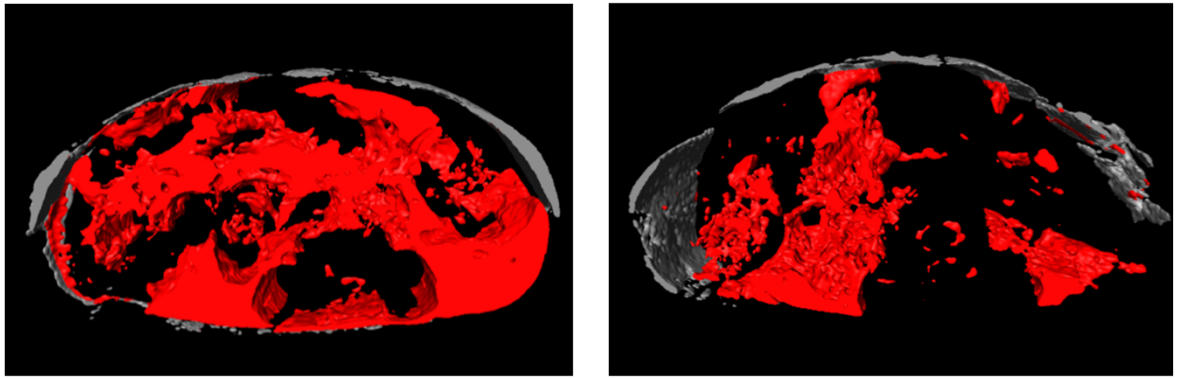
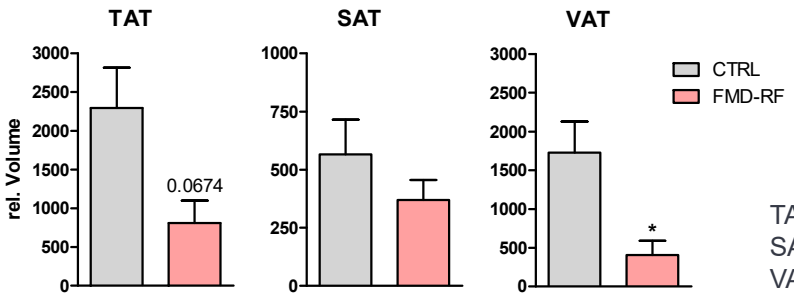
The Science of FMD

FMD and Fat

Mice: FMD lead to Reduction in visceral adipose tissue (micro-CT)



Control FMD

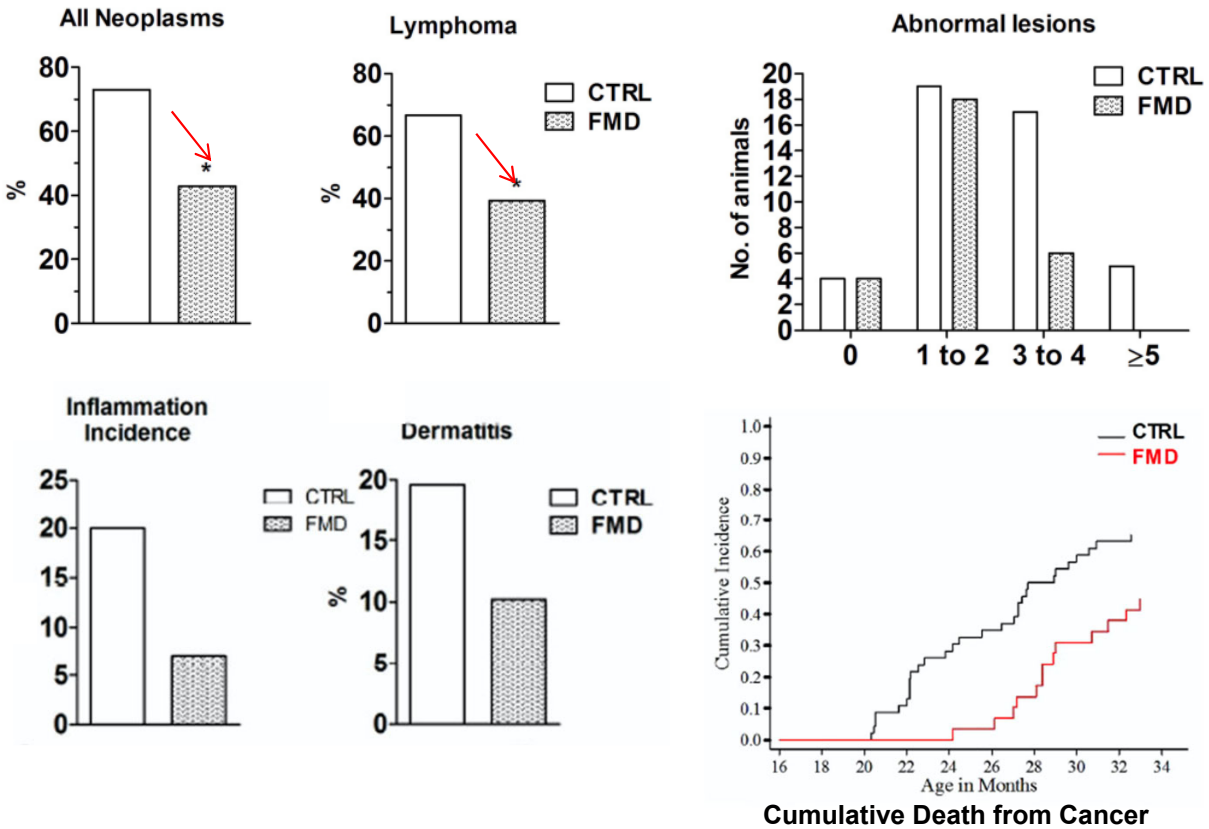


TAT= total adipose tissue
SAT= subcutaneous adipose tissue
VAT= visceral adipose tissue

Ref: Brandhorst et al. Cell Metab. 2015 Jul 7;22(1):86-99.

IF/FMD in Cancer

Fasting Mimicking Diet Cycles Reduce and Delay cancer



Cumulative Death from Cancer

- 45% reduction in total neoplasia incidence in the FMD
- Lymphomas affected ~67% of control mice, ~40% of FMD mice
- Number of animals with multiple (3 or more) abnormal lesions 3x higher control vs FMD
- ↓ Inflammation and cumulative death in FMD

Brandhorst et al. Cell Metab. 2015 Jul 7;22(1):86-99.

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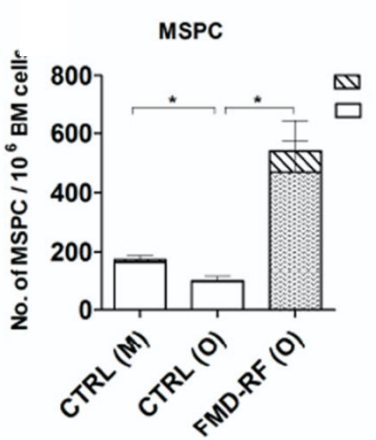
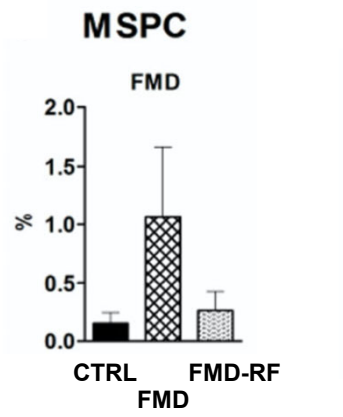
Science of FMD

FMD vs Placebo

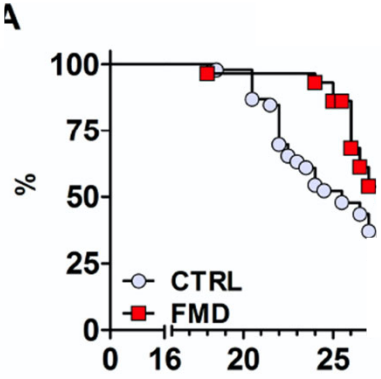
- Induction of mesenchymal progenitor stem cells (mice, human pilot trial)
- Reduction in IGF-1 level
- Reversal of age-related decline in BMD
- Control mice had a median lifespan of 25.5 months, which was extended to 28.3 months (11% extension) in the FMD group



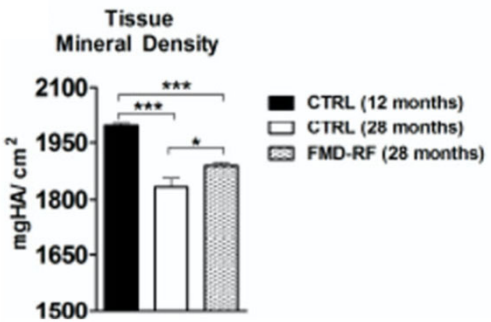
(Mice) Mesenchymal/ Progenitor Stem Cells



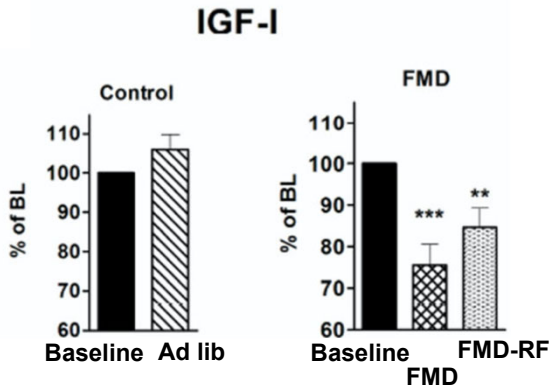
(Human) Mesenchymal/ Progenitor Stem Cells



(Mice) Survival



BMD (Mice, femur)



IGF-1 (Human)

Ref: Brandhorst et al. Cell Metab. 2015 Jul 7;22(1):86-99.

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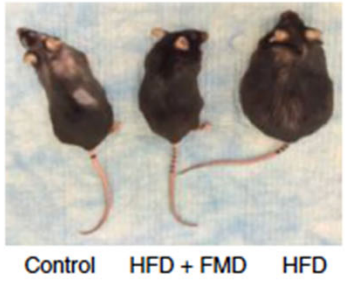
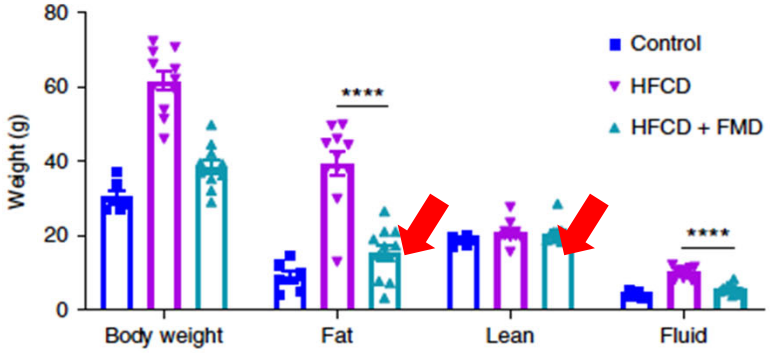
FMD prevents high-fat diet effect on cardiometabolic risk & lifespan

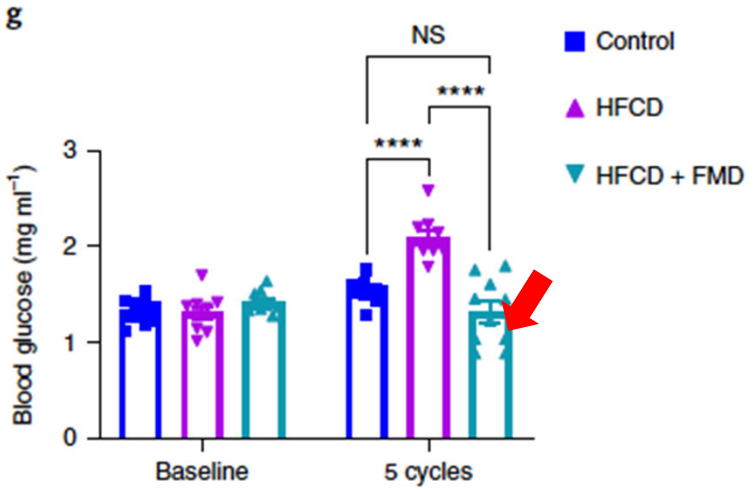
Results:

- 5-day FMD monthly for 2 years
- Ameliorates the detrimental changes caused by a high-fat, high-calorie diet (HFCD) in female mice
- FMD cycles inhibit HFCD-mediated obesity by reducing the accumulation of visceral and SQ fat without causing loss of lean body mass



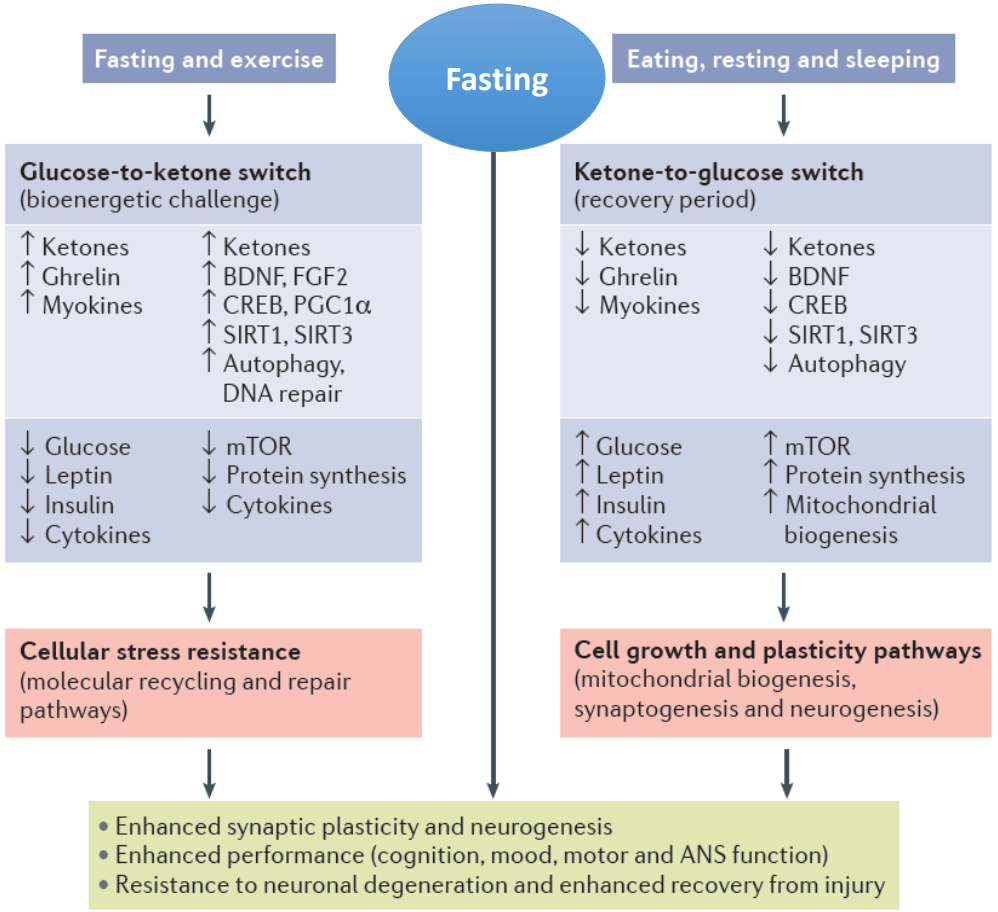


- FMD cycles:
  - Increase cardiac vascularity and function and resistance to cardiotoxins
  - Prevent HFCD-dependent hyperglycemia, hypercholesterolemia
  - Ameliorate impaired glucose and insulin tolerance



Fasting and Neuro-Cognition

- Fasting depletes liver glycogen
  - Augment fatty acid ketone production
- Ketones are transported into the brain induce expression of BDNF (brain-derived neurotrophic factor)
  - BDNF promote synaptic plasticity and cellular stress resistance
  - Enhances cognition; motor performance
- <u>Fasting in Murine models</u>:
  - Protects neurons against degeneration seen in stroke, trauma
  - Slows progression of Alzheimer disease and Parkinson disease



Ref: Mattson MP, et al. Nature Reviews Neuroscience volume 19, pages 63–80 (2018).

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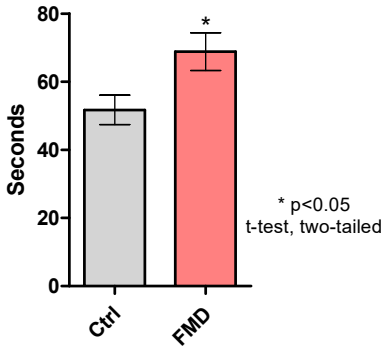
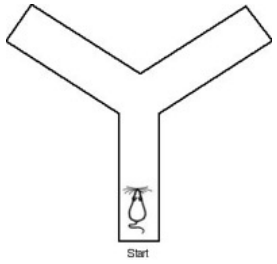
FMDs and Neuro-Cognition

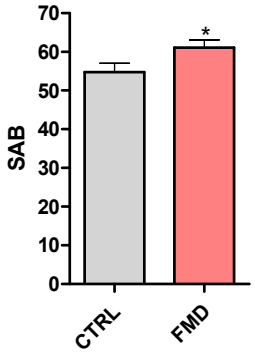
Improves cognitive performance in mice

Rotarod (Best Run)

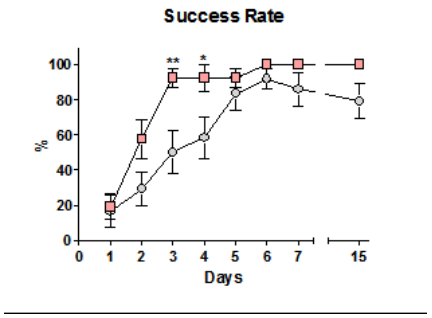


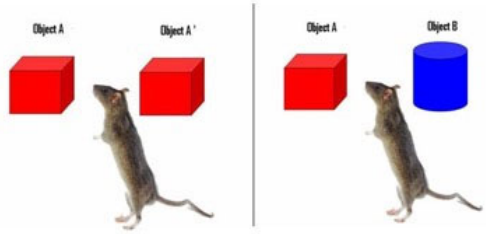


SAB

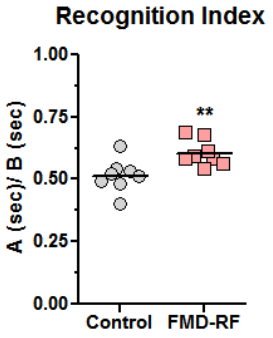


Barnes Maze



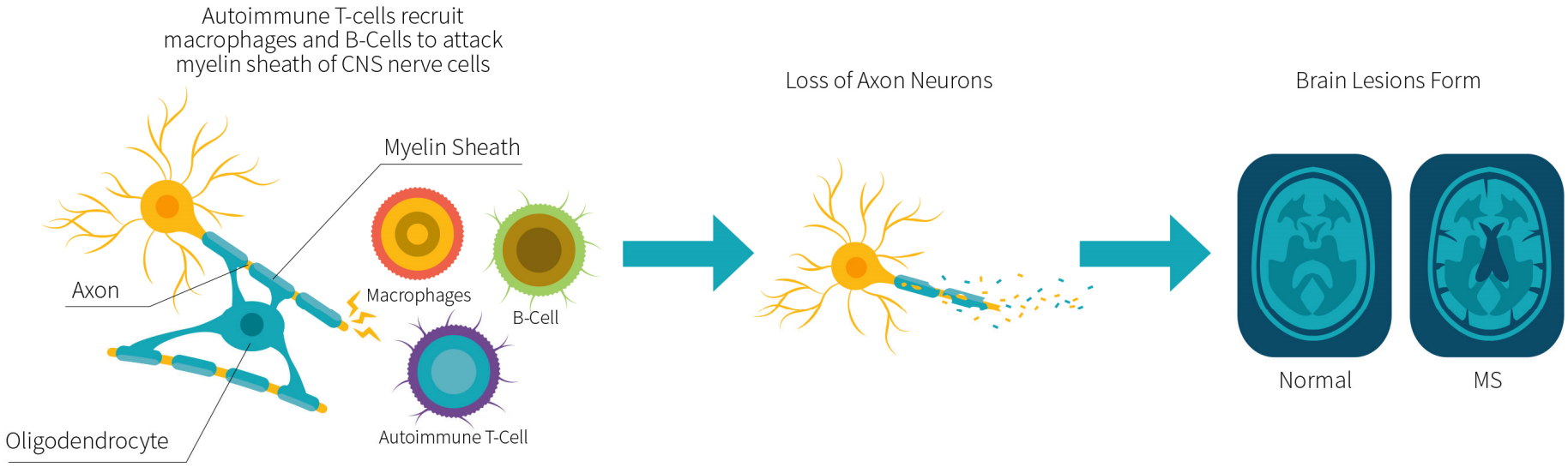


Object Recognition



Ref: O'Flanagan CH, et al (2017), BMC Med.

Fasting and Autoimmunity: Multiple Sclerosis - Pathogenesis

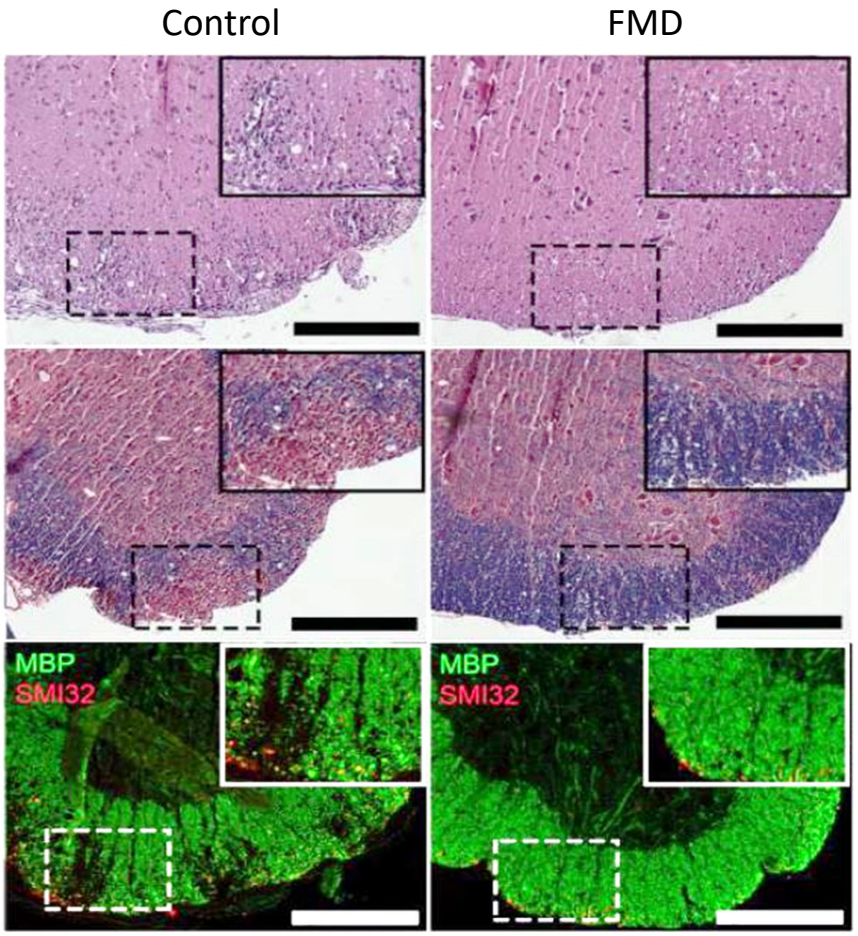


- Multiple sclerosis (MS): Autoimmune disorder characterized by T cell-mediated demyelination and neurodegeneration in the CNS
  - In MS murine model, activated myelin-specific T cells promote inflammation
- **This leads to oligodendrocyte death, demyelination and axonal damage in brain, which eventually cause neurological damage**

FMD and Autoimmunity

Reduces autoimmunity & alleviates MS symptoms

- Weekly cycles of FMD:
  - MICE: Ameliorated disability measures
- FMD reduced clinical severity in all mice
  - Complete recovery in 20% of the animals
- FMD promoted oligodendrocyte precursor cell regeneration and re-myelination in axons in mice



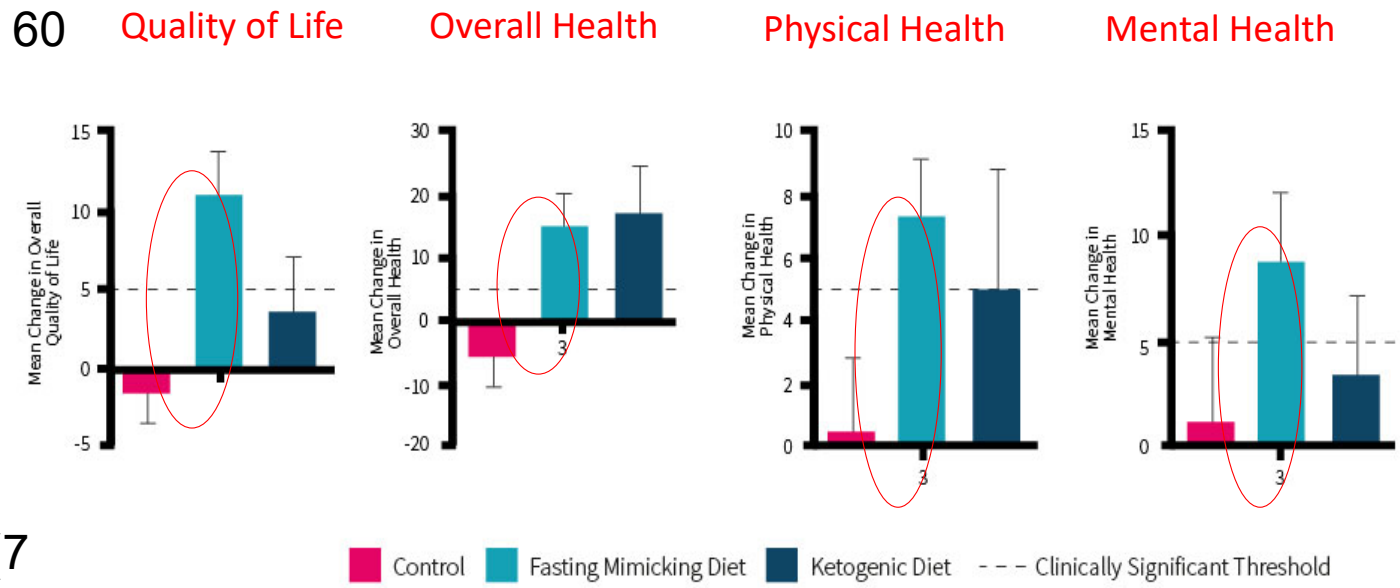
Spinal Cord Section (Mice)

Ref: Choi, Y et al. Cell Rep. 2016 Jun 7; 15(10): 2136–2146

FMD in Patients with Multiple Sclerosis

A randomized, parallel-group 3 arm pilot trial in 60 relapsing-remitting MS patients.

- Control diet (n=20)
- Ketogenic diet for 6 months (n=20)
- Single cycle of FMD (7 days; n=20) followed by a Mediterranean diet for 6 months



Ref: Choi, Y et al. Cell Rep. 2016 Jun 7; 15(10): 2136–2146

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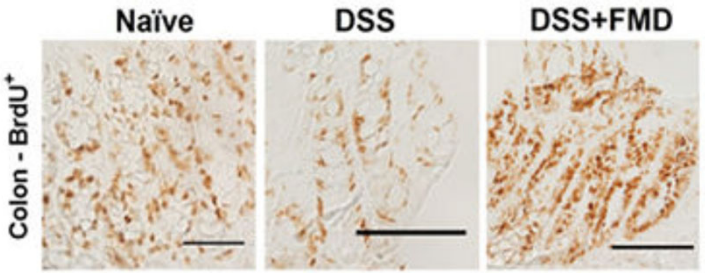
FMD: IBD

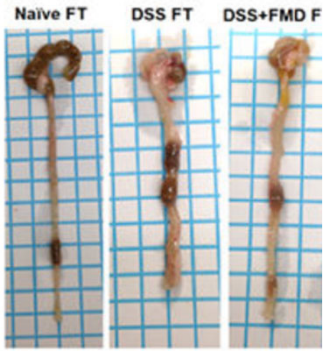
- **Murine Model of IBD**

  Dietary interventions are potentially effective therapies for inflammatory bowel diseases (IBDs)

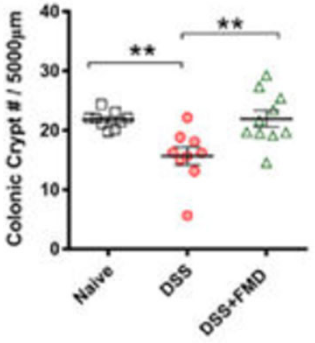
  4 days FMD vs Placebo
  - Reduced colonic inflammation
  - Increased stem cell and intestinal cell regeneration
  - Increase in protective microbial population

4-day fasting-mimicking diet (FMD) cycles on a chronic dextran sodium sulfate (DSS)-induced murine model resulting in symptoms and pathology associated with IBD

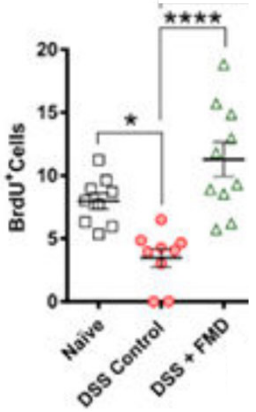




Intestinal length



Colonic Crypts #



Cellular Proliferation/ Regeneration

Ref: Brandhorst et al. Cell Metab. 2015 Jul 7;22(1):86-99.

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Human Trials: Impact on Weight Loss

Clinical Trial: Impact of ADF on Weight Loss and Weight Maintenance

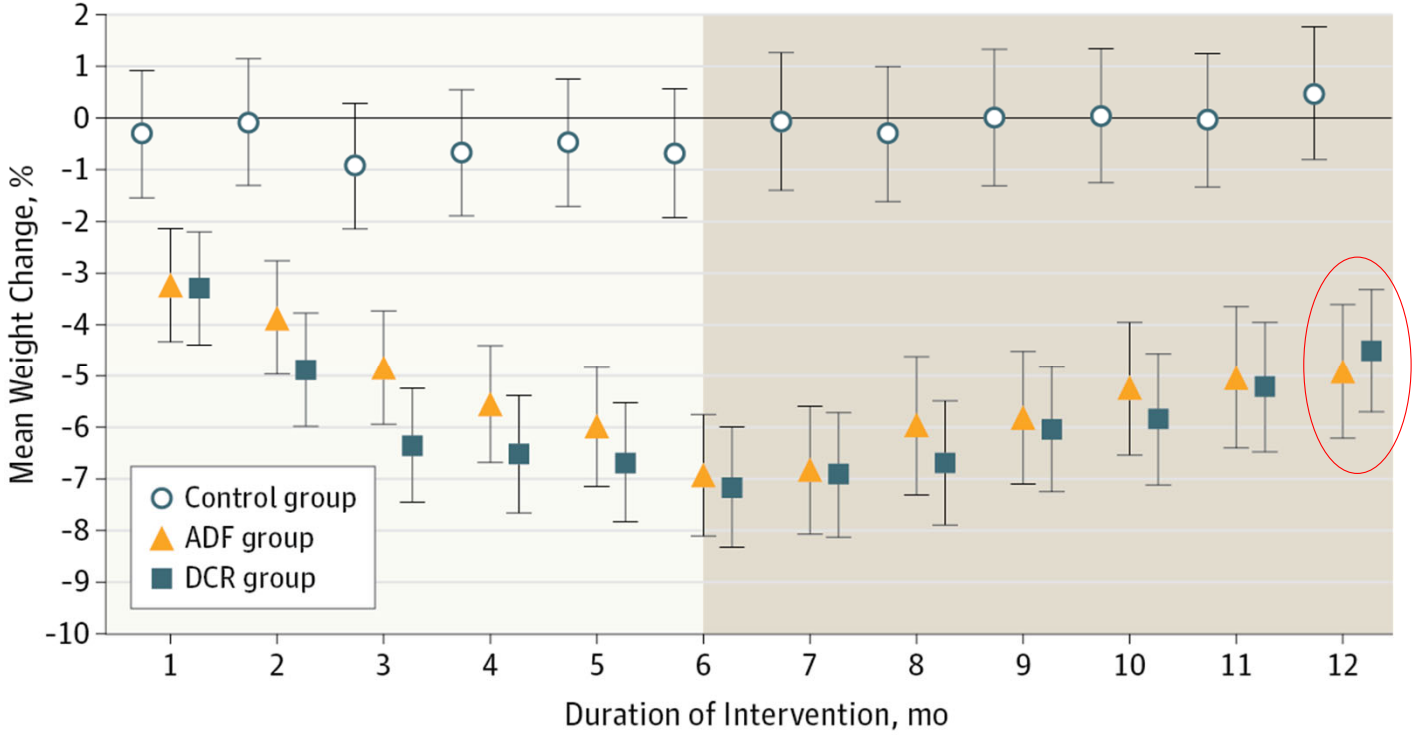
Question: Is Intermittent fasting more effective for weight loss and weight maintenance compared with daily calorie restriction?

Findings:

- 100 metabolically healthy obese adults.
- Weight loss after 1 year in the ADF group (6.0%) vs. daily calorie restriction group (5.3%)

Significance:

- ADF did not produce superior adherence, weight loss, or weight maintenance.



Ref: Trepanowski JF et al. JAMA Intern Med. 2017 Jul 1;177(7):930-938

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Overview of Studies: Effectiveness of 5:2 IF and TRF Compared to CER for Weight Loss

Age	N	BMI	Duration	Regimen	Outcome (weight loss)
30-45	107, F	24-40	26 weeks	5:2 IF	5:2 IF:11.2 kg, CER: 9.2 kg
35-65	49, M/F	25-40	12 weeks	5:2 IF	5:2 IF: 5.2 kg, CER: 5.0 kg
>18	63, M/F	>27	12 weeks	5:2 IF	5:2 IF: 6.2 kg, CER: 5.6 kg
18-55	26	>30	8 weeks	ADF	ADF: 8.8 kg, CER: 6.2 kg
18-64	100, M/F	25-40	26 weeks	5:2 IF	5:2 IF: 7.5%, CER: 7.5%
>18	135, M/F	>27	52 weeks	5:2 IF	5:2 IF: 6.8 kg, CER: 5.0 kg
55-75	24, M	>30	26 weeks	5:2 IF	5:2 IF: 5.3 kg, CER: 5.5 kg
35-65	150, M/F	25-40	12 weeks	5:2 IF	5:2 IF: 7.1 kg, CER: 5.2 kg
21-70	112, M/F	30-45	26 weeks	5:2 IF	5:2 IF: 9.0 kg, CER: 9.4 kg
35-70	88, F	25-42	10 weeks	5:2 IF	5:2 IF: 5.4 kg, CER: 3.9 kg
> 18	13, M/F	>25	10 weeks	TRF	TRF: 0.7 kg, CER: 0.5 kg
25-65	23, M/F	>30	12 weeks	TRF	TRF: 2.3 kg. CER" NC

Rynders CA et al. Nutrients. 2019 Oct; 11(10): 2442.

5:2 IF vs TRF vs CER: Weight Loss

- Overall, the available evidence suggests that 5:2 intermittent fast regimen yielded equivalent weight loss when compared to chronic energy restriction (CER)
- 9 out of 11 studies reviewed showing no significant differences in weight or body fat loss between 5:2 IF and CER groups
- Attrition rate for both IF and CER were similar
- Majority of weight loss occurred during the first 3 month, with plateau at 6 months
- Variance in % macronutrient partitioning did not result in differences in weight loss
- No gender bias observed in weight loss comparing 5:2 IF vs CER
- No significant change in weight loss seen with TRF vs CER

Rynders CA et al. Nutrients. 2019 Oct; 11(10): 2442.

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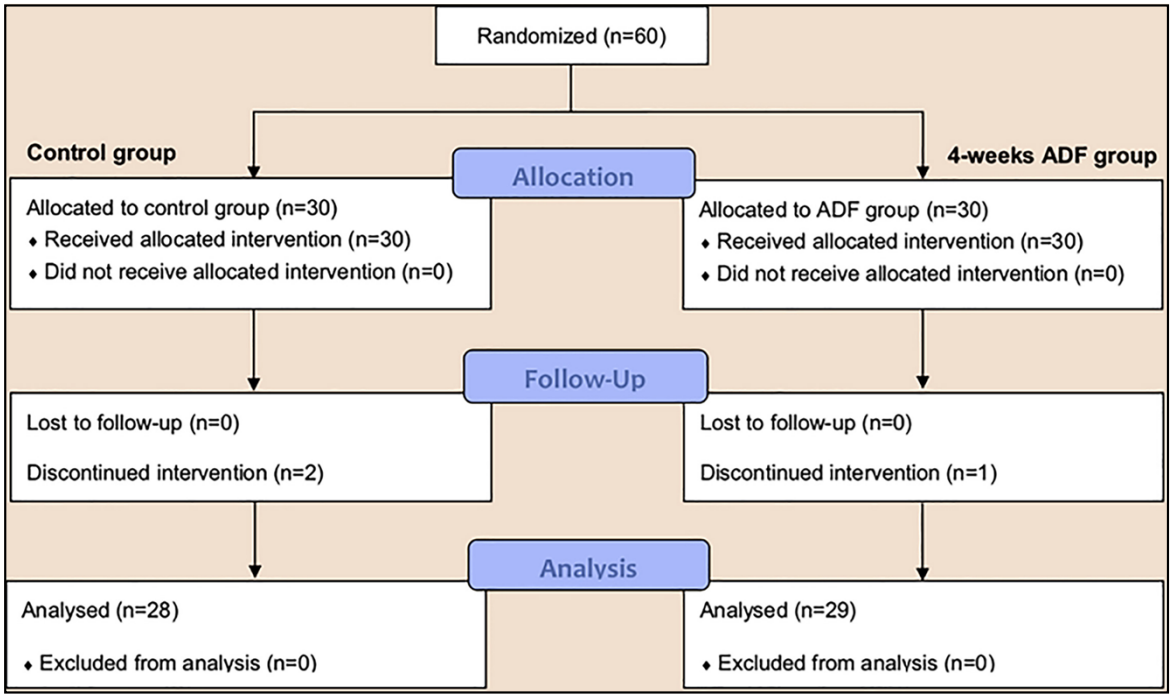
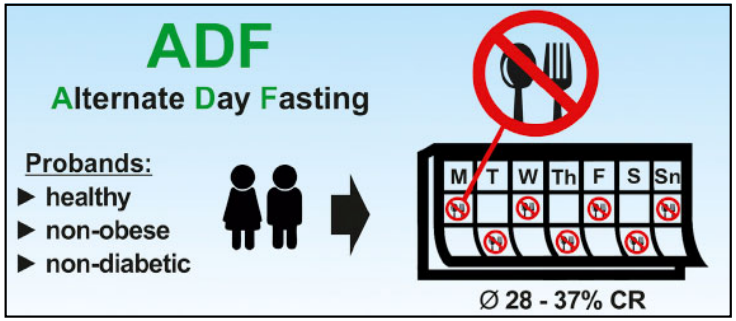
Alternate Day Fasting

Clinical Trials

Cell Metabolism (September 2019)

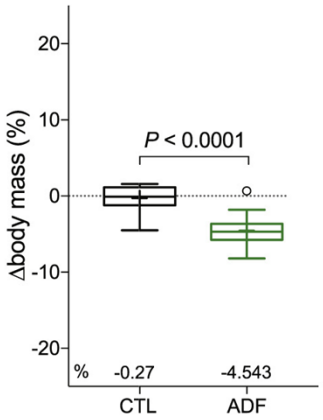
Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans



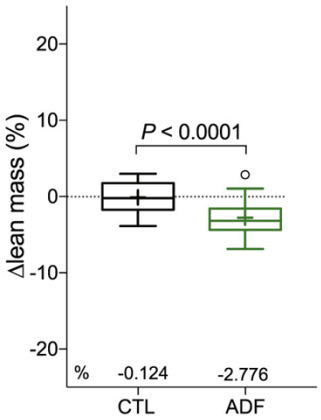


Ref: Stekovic S et al. Cell Metab. 2019 Sep 3;30(3):462-476

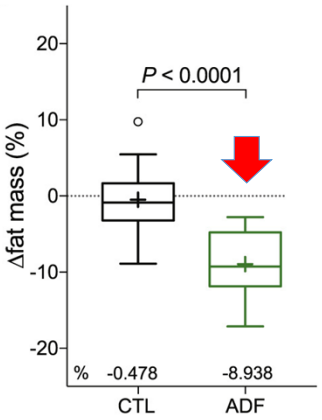
4 week ADF - Impact on Body Fat and Bone Health (Control vs ADF)



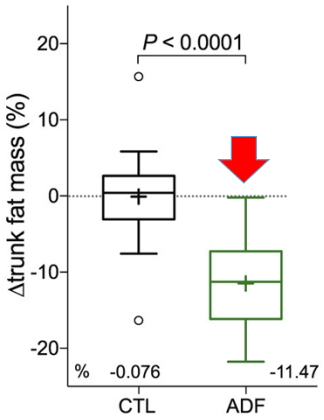
Δ Body Mass



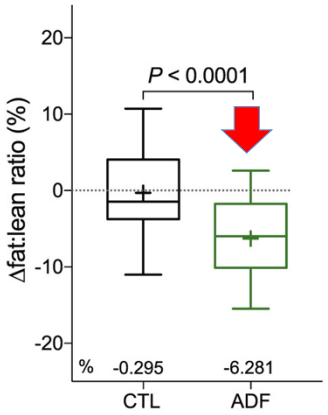
Δ Lean Mass



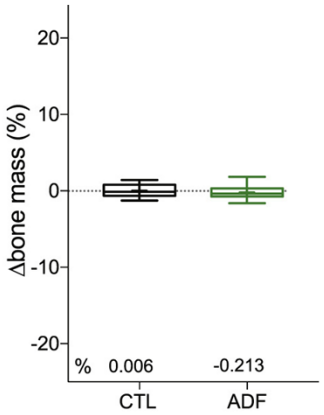
Δ Fat Mass



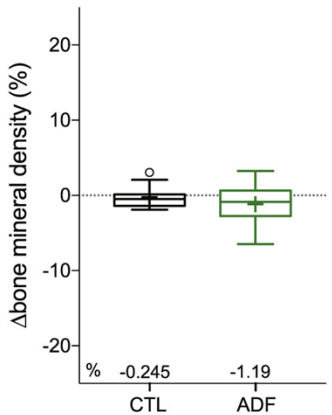
Δ Abdominal Fat



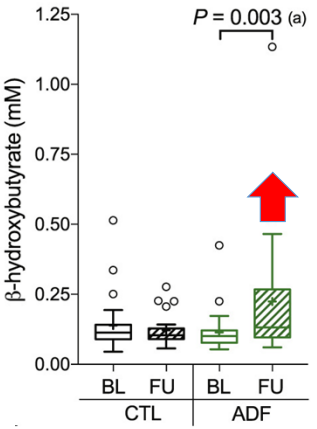
Δ Fat:Lean Ratio



Δ Bone Mass



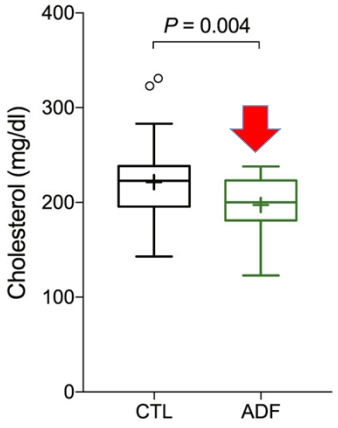
Δ BMD



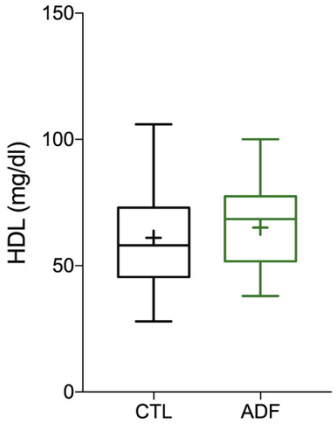
Δ ketone level: β-hydroxybutyrate

Ref: Stekovic S et al. Cell Metab. 2019 Sep 3;30(3):462-476

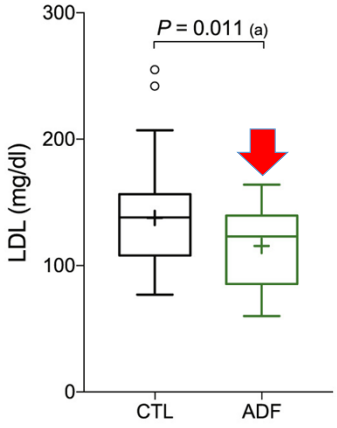
Extend ADF-6 months: Impact on Body Fat and Bone Health (Control vs ADF)



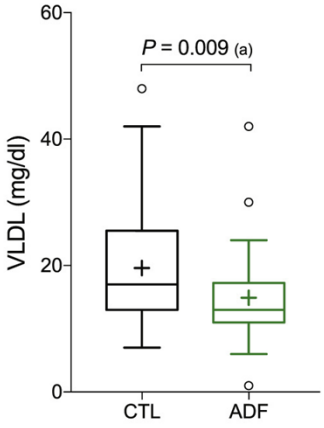
Δ Total Cholesterol



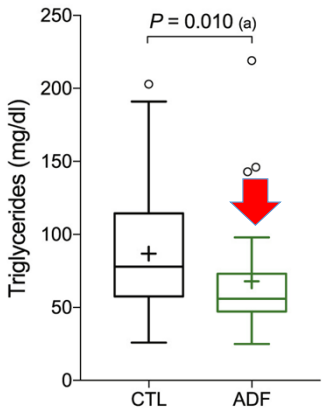
Δ HDL



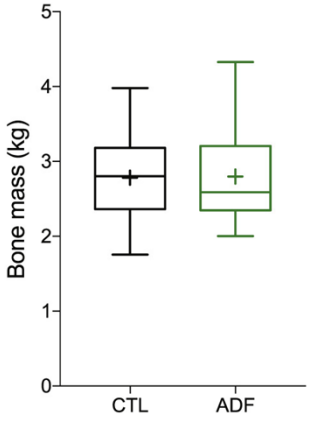
Δ LDL



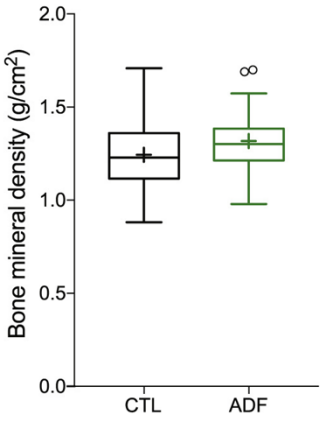
Δ VLDL



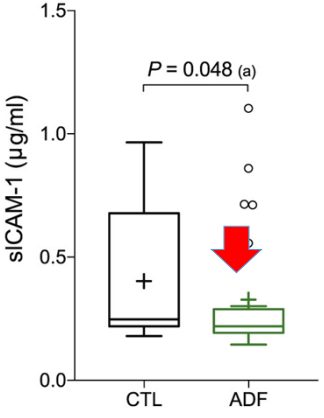
Δ Triglycerides



Δ Bone Mass



Δ BMD



Δ siCAM-1 (marker of vascular inflammation)

Ref: Stekovic S et al. Cell Metab. 2019 Sep 3;30(3):462-476

Clinical Trials

Cell Metabolism (September 2019)

Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans

Summary of Findings:

- For healthy, non-obese adults, ADF is safe to practice for several months
- 4-week ADF decreases the body weight by 4.5% and improves the fat-to-lean ratio
- Cardiovascular parameters and the CVD risk are improved upon ADF (lipids, sICAM, β-hydroxybutyrate)

Limitations

- Long term ADF may be difficult for most patients
- Selection bias - This study enrolled only healthy subjects
- While cardiovascular assessment was performed, no specific evaluation of aging markers

Ref: Stekovic S et al. Cell Metab. 2019 Sep 3;30(3):462-476

Fasting Mimicking Diet: Metabolic Health and Beyond

Clinical Trials

Science & Translational Medicine (USC Longevity Institute)

Fasting-mimicking diet & markers/risk factors for aging, diabetes, cancer, & cardiovascular disease

Summary of findings:

Three FMD cycles reduced body weight, trunk, and total body fat; lowered blood pressure; and decreased IGF-1. No serious adverse effects were reported.

BMI, blood pressure, fasting glucose, IGF-1, triglycerides, total and LDL cholesterol, & CRP were more beneficially affected in those at risk for disease than those not at risk.

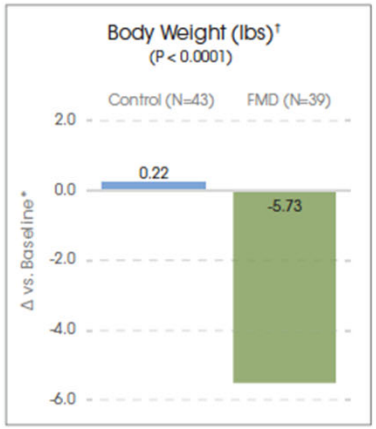
Cycles of a 5-day FMD are safe, feasible, and effective in reducing markers/risk factors for aging and age-related diseases.

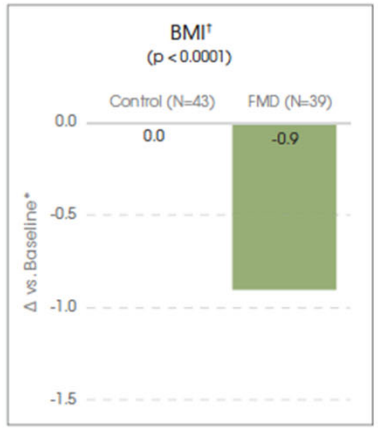
Larger studies in patients with diagnosed diseases or selected on the basis of risk factors are warranted to confirm the effect of the FMD on disease prevention

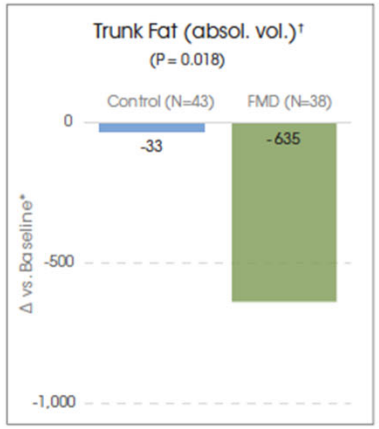
Ref: Wei et al., Sci. Transl. Med. 9, 15 February 2017

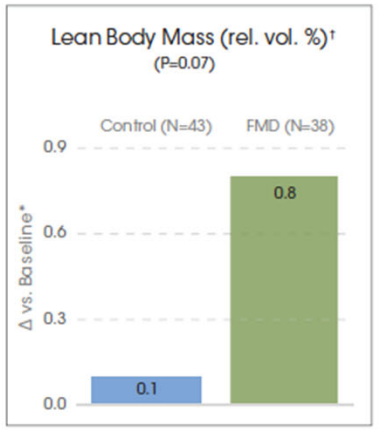
Clinical Trials

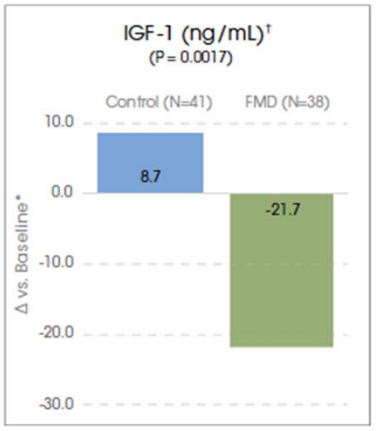
Fasting-mimicking diet & markers/risk factors for aging, diabetes, cancer, & cardiovascular disease

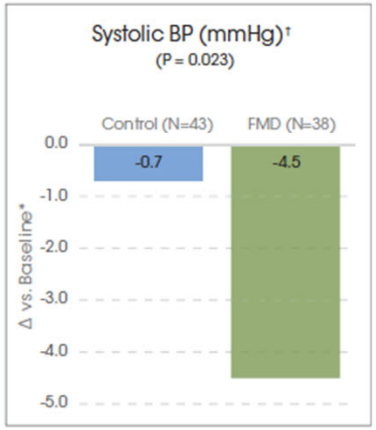


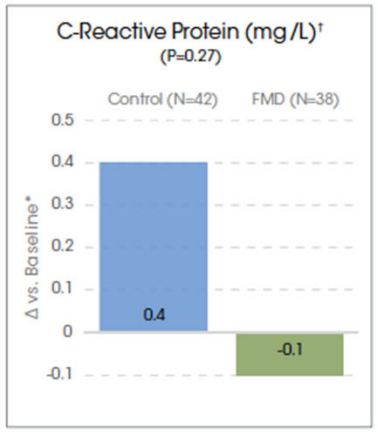










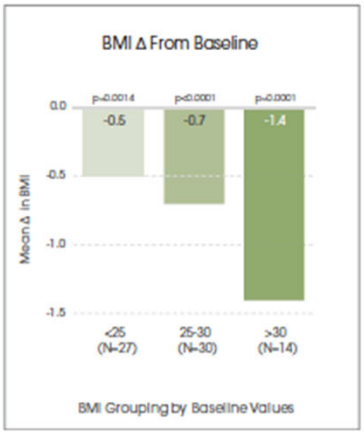


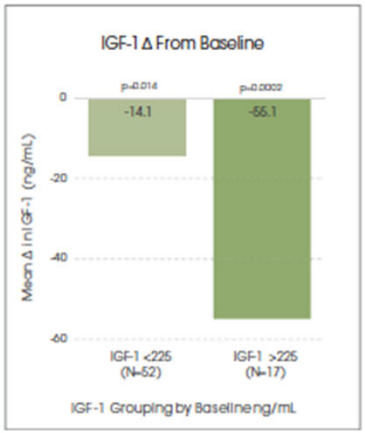
Participant Profiles:

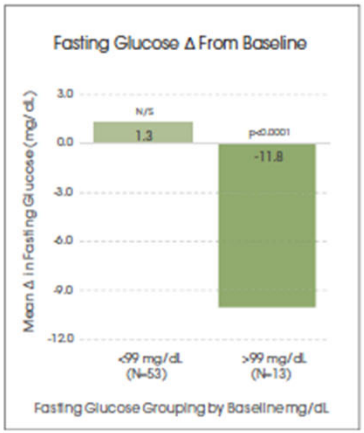
- Age of subjects at enrollment, including Arm 1 with normal diet (n=48) = 42.2 ; Arm 2 with FMD (n= 52) = 43.3
- 37% male, 63% female
- No Dx Medical Condition
- BMI mean 27.8 (control) 26.6 (FMD)
- Not taking any medication that impacts body weight

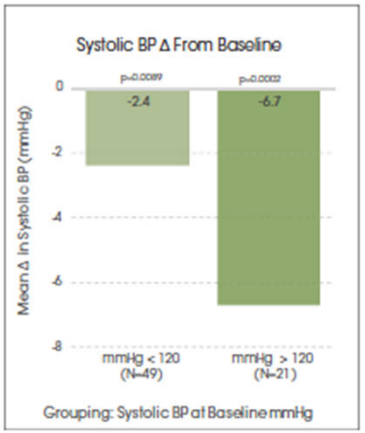
REF: Wei et al., Sci. Transl. Med. 9, 15 February 2017

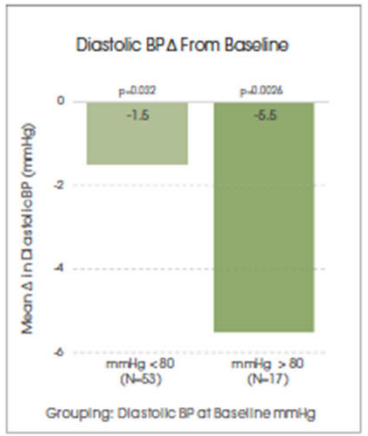
Post-hoc Data: Participants Segmented by Marker Levels

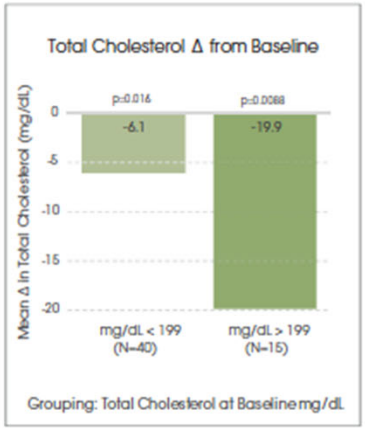


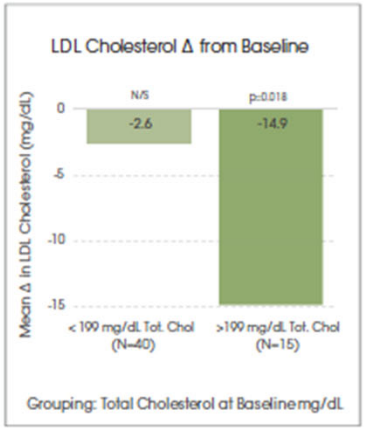


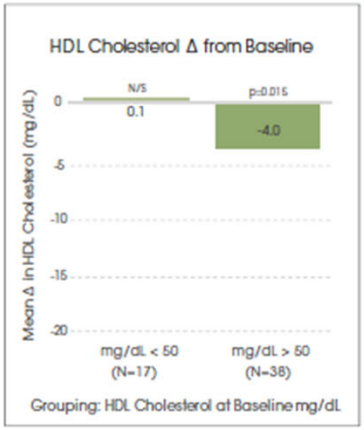


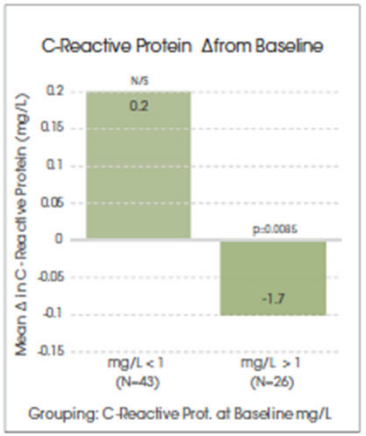












Summary:

- Greater weight loss seen in subjects with higher baseline BMI
- Greater reduction in IGF-1 in those with higher baseline IGF-1 level
- Greater improvements in metabolic profiles in those with higher baseline BP, fasting blood sugar, TC

Ref: Wei et al., Sci. Transl. Med. 9, 15 February 2017

Maintained Benefits: 3 months post FMD completion

Significant maintained changes to health factors months after completion

Weight Loss:	**60%**
BMI:	**70%**
Waist Circumference:	**60%**
Systolic BP:	**55%**
Diastolic BP:	**90%**

These factors were maintained, but not significant:

Total Cholesterol:	**60%**
LDL:	**60%**
Triglycerides:	**45%**

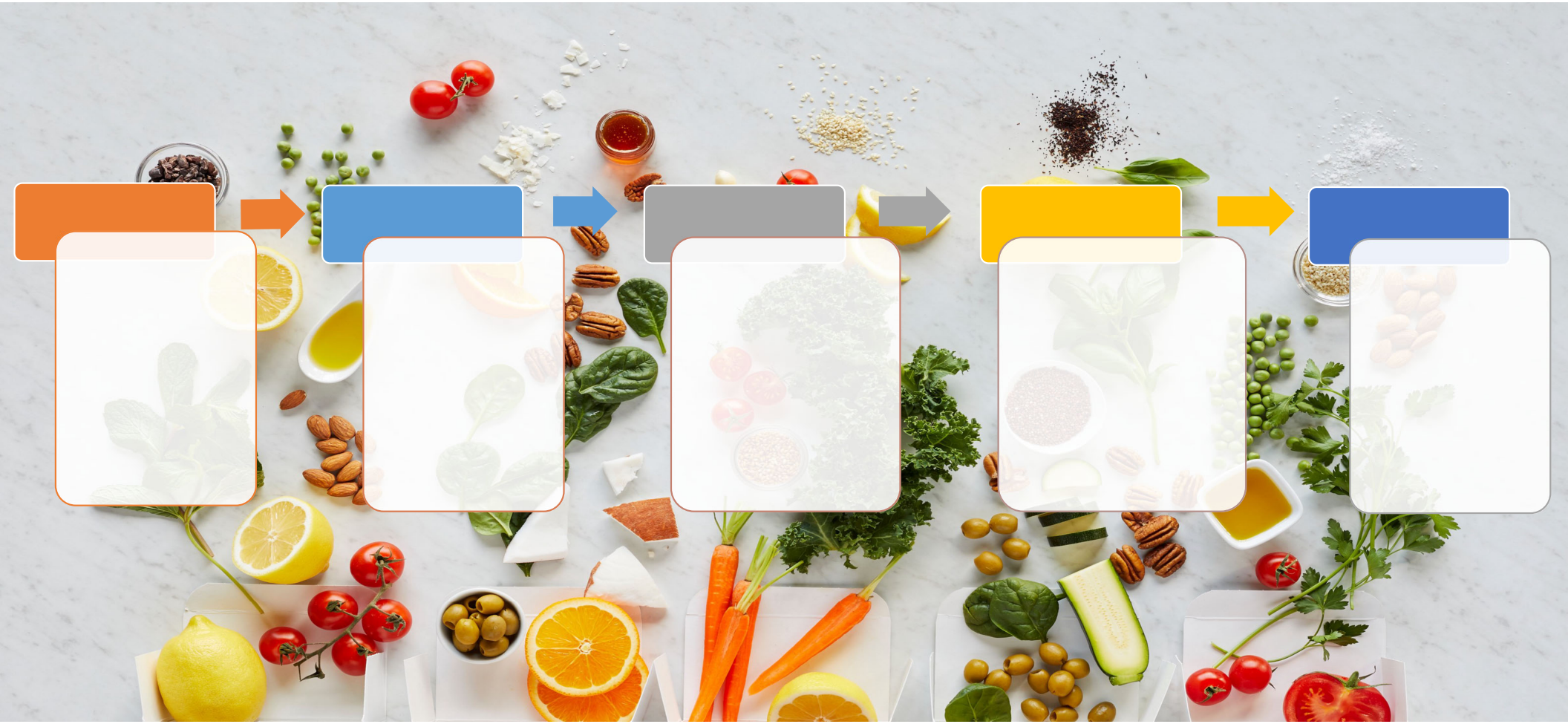
Compliance

- **71% Compliance of 3 cycles**
- **11 withdrawals**
- **2 excluded**

Reduced side effects with each cycle

Ref: Wei et al., Sci. Transl. Med. 9, 15 February 2017

The Biological Effects of IF/FMD



Patient Centric Focus – Counseling Your Patients on IF and FMD

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Patient Centric Focus

- Are all intermittent fasting regimens the same? Do they confer similar benefits?
- When would you consider intermittent fasting or FMD for your patients?
- How do you start conversations with your patients about IF or FMD?
- Which of your patients do you see as good candidates? Which are likely to have most success?
- How do you set weight loss expectations? How might you monitor patients' metabolic progress? Adverse events?
- For your patients on FMD, how many cycles per year? What should patients eat between FMD or fasting cycles?

Special Considerations:
Who Should Abstain from Intermittent Fasting?

- Active growth stage (adolescence)
- Pregnant or breastfeeding women
- Has a fever, cough, diarrhea, or signs of an active infection
- People who are underweight, have very low body mass <18.5 or suffer from chronic malnutrition
- Type 1 Diabetes
- Type 2 Diabetes (insulin dependent)
- People with advanced liver or kidney, or heart disease
- Eating disorders

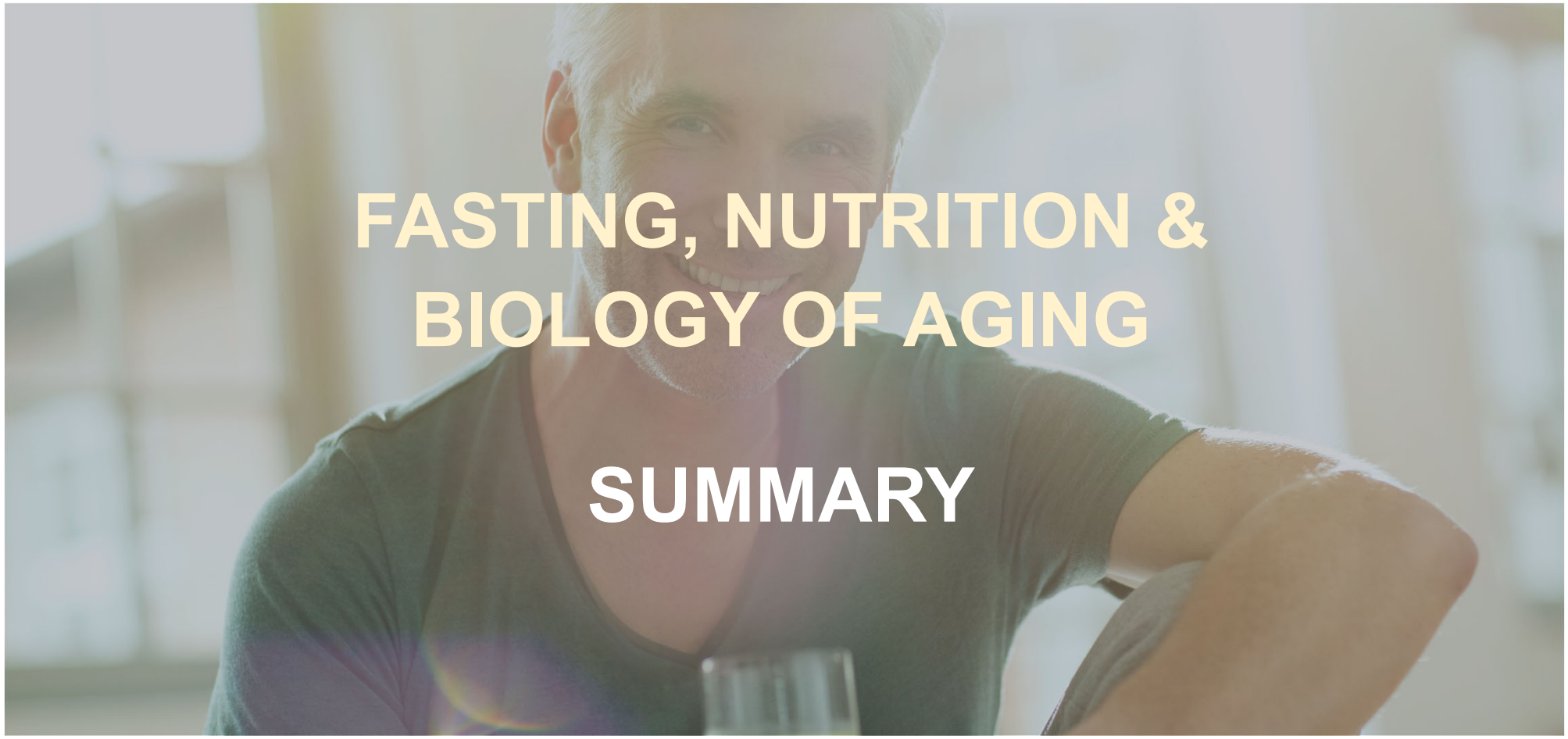
Intermittent Fasting and FMD: Patient Monitoring

Precautions

- Due to the low calorie nature of intermittent fasting and FMD, patients should drink at least 8 cups (64 fl. oz.) daily of water to minimize the risk of dehydration
- Operate motor vehicles and heavy machinery with care until it is known how IF/FMDs may affect the individual
- Avoid strenuous exercise and exposure to high temperatures (e.g. saunas, spas, Jacuzzi) or cold temperature environments and swimming
- Determine whether the patient can consume IF/FMDs in combination with any of his/her prescription or non-prescription drugs

Potential Side Effects

- **Fatigue**
- **Weakness**
- **Headache**
- **Dry mouth**
- **Menstrual irregularity**
- **Memory impairment**
- **Muscle pain**
- **Constipation**
- **Sugar cravings**
- **“Brain fog”**



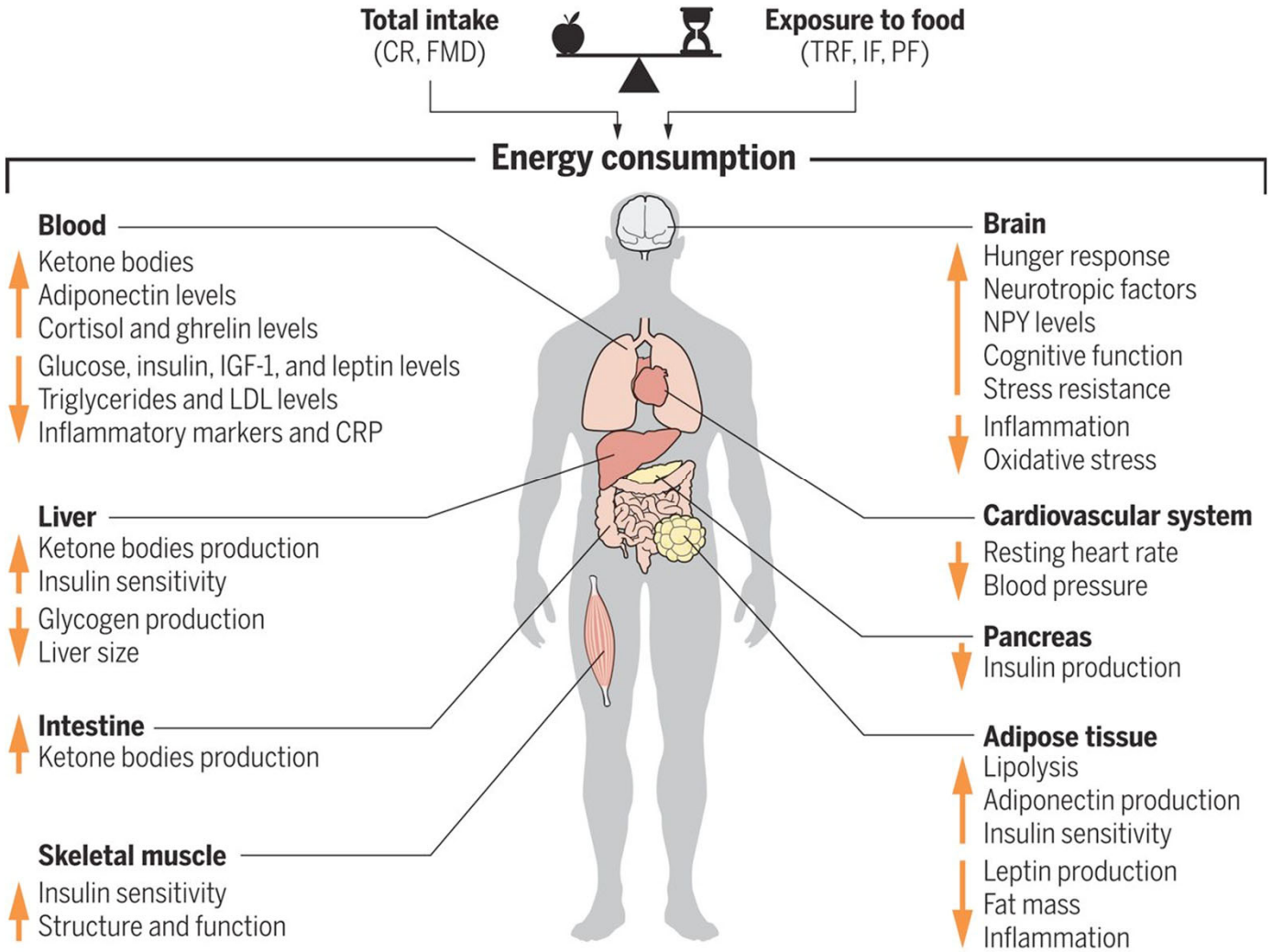
FASTING, NUTRITION & BIOLOGY OF AGING

SUMMARY

Anti-Aging Clinical Targets

Goals: Reversal of physiologic and functional declines

- Age related metabolic diseases
- Neuro-Cognitive decline
- Cancer
- Improved healthspan and quality of life



Ref: De Francesco A et al. Science 16 Nov 2018:Vol. 362, Issue 6416, pp. 770-775

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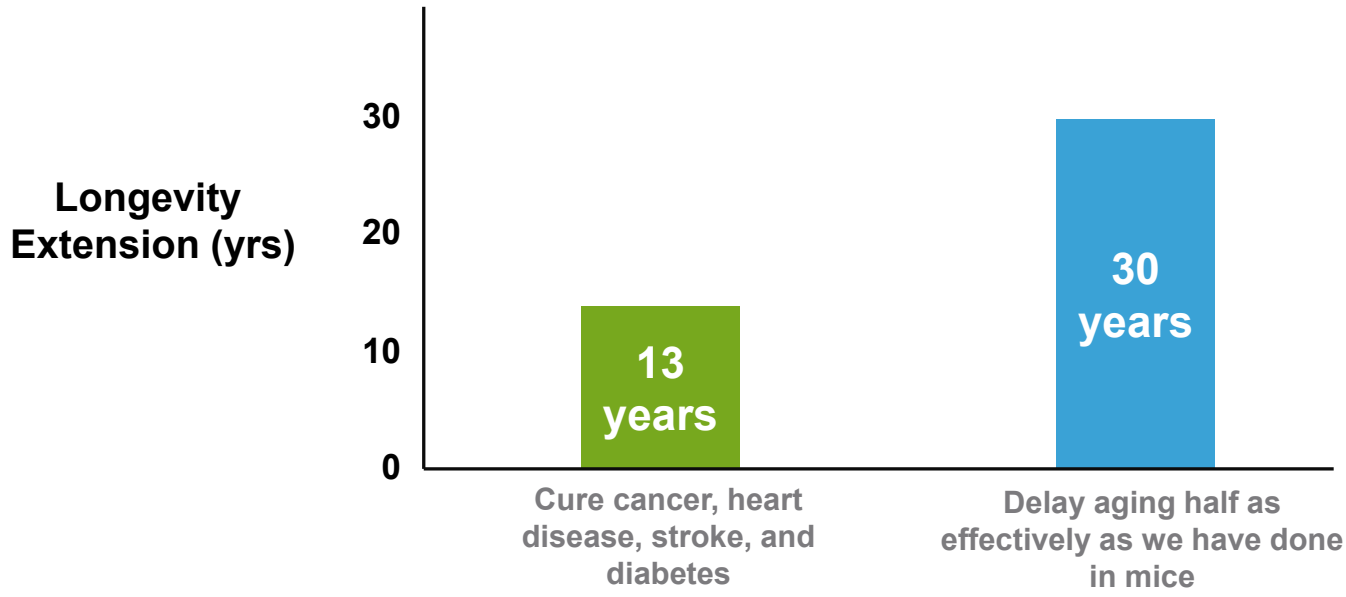
FMD and Longevity

How much longer would we live if we cured heart disease, stroke, cancer and diabetes vs delayed aging?



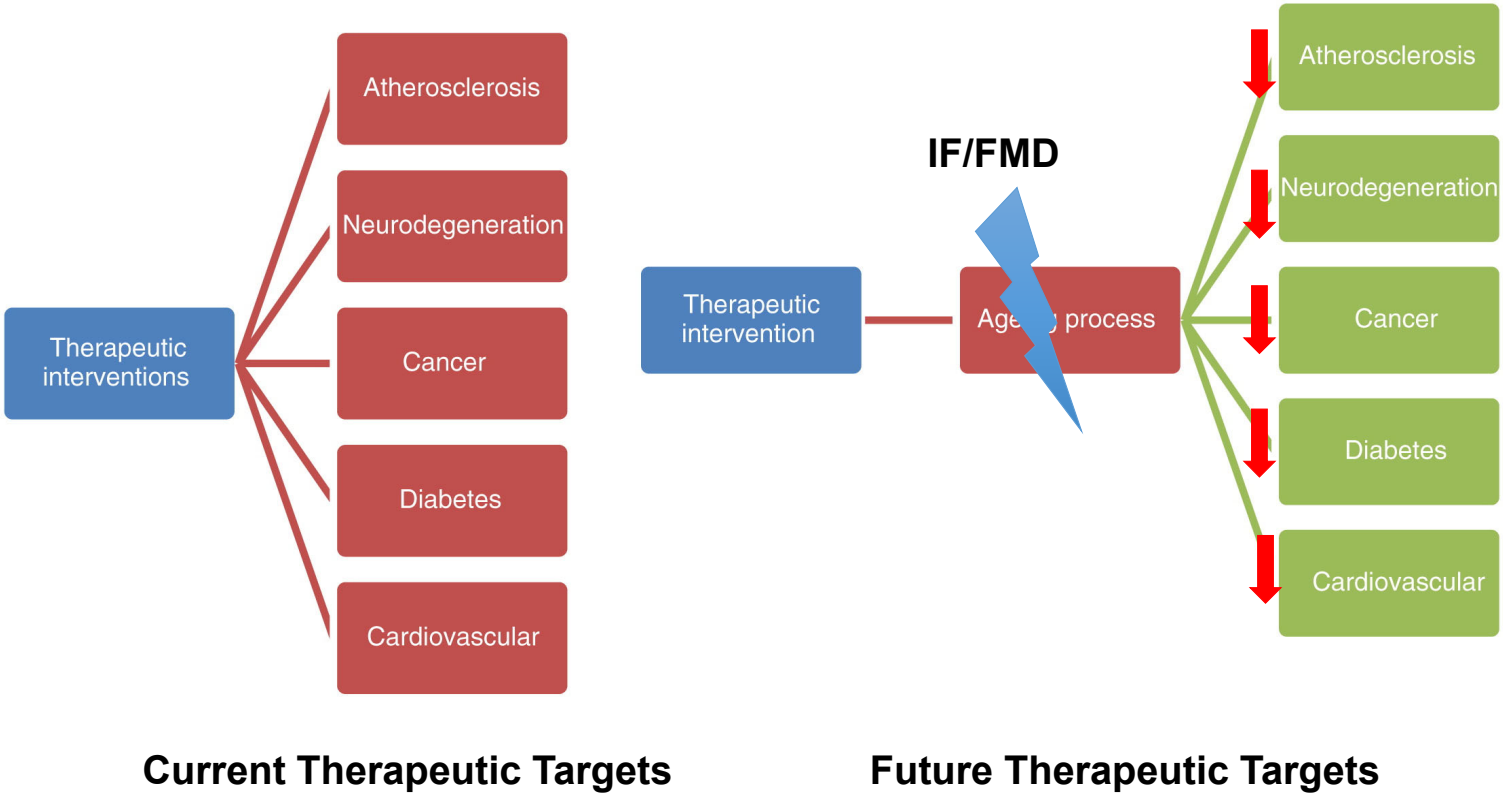
The ultimate goal is to improve biological age… that's the real frontier of fasting research

Knapton et al, Science, quoting Professor Lithgow, Buck Institute

Paradigm Shift in Target Therapeutics

Just as treating obesity leads to improvement in metabolic profile…

Targeting aging may postpone chronic diseases and **prevent age-associated conditions & improve healthspan**



Current Therapeutic Targets

Future Therapeutic Targets

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