

Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) refers to a number of conditions relating to the heart and blood vessels. It is the leading cause of death for both men and women and accounts for roughly \$200 billion spent on healthcare in the US each year^[6].

A major factor that impacts CV risk is diet. Many Americans eat several high-calorie meals a day, generally leading to cardiometabolic complications and chronic disease. Disease prevention or delay of disease progression focuses on avoiding major clinical events such as myocardial infarction, stroke or ischemia. By preventing these events, longevity will increase, quality of life will improve and healthcare costs will decrease.

Intermittent Fasting (IF)

Intermittent fasting (IF) is a process of planned and timed feeding restriction which can be utilized alone or in combination with a caloric deficit. There are many different variants of intermittent fasting - some examples include alternate-day fasting, limited eating windows of at most 8 hours per day, eating one large meal a day and extended fasts greater than 24 hours^[3].

Preclinical studies relying on animal models have demonstrated the disease-modifying effects of IF on a range of health disorders, including cardiovascular disease, obesity, cancer, and neurodegenerative brain disease to name a few. While the benefits seen with IF are often attributed to weight loss alone, studies have shown that more nuanced processes taking place at a cellular level are likely also responsible for the changes observed^[3,8,10].

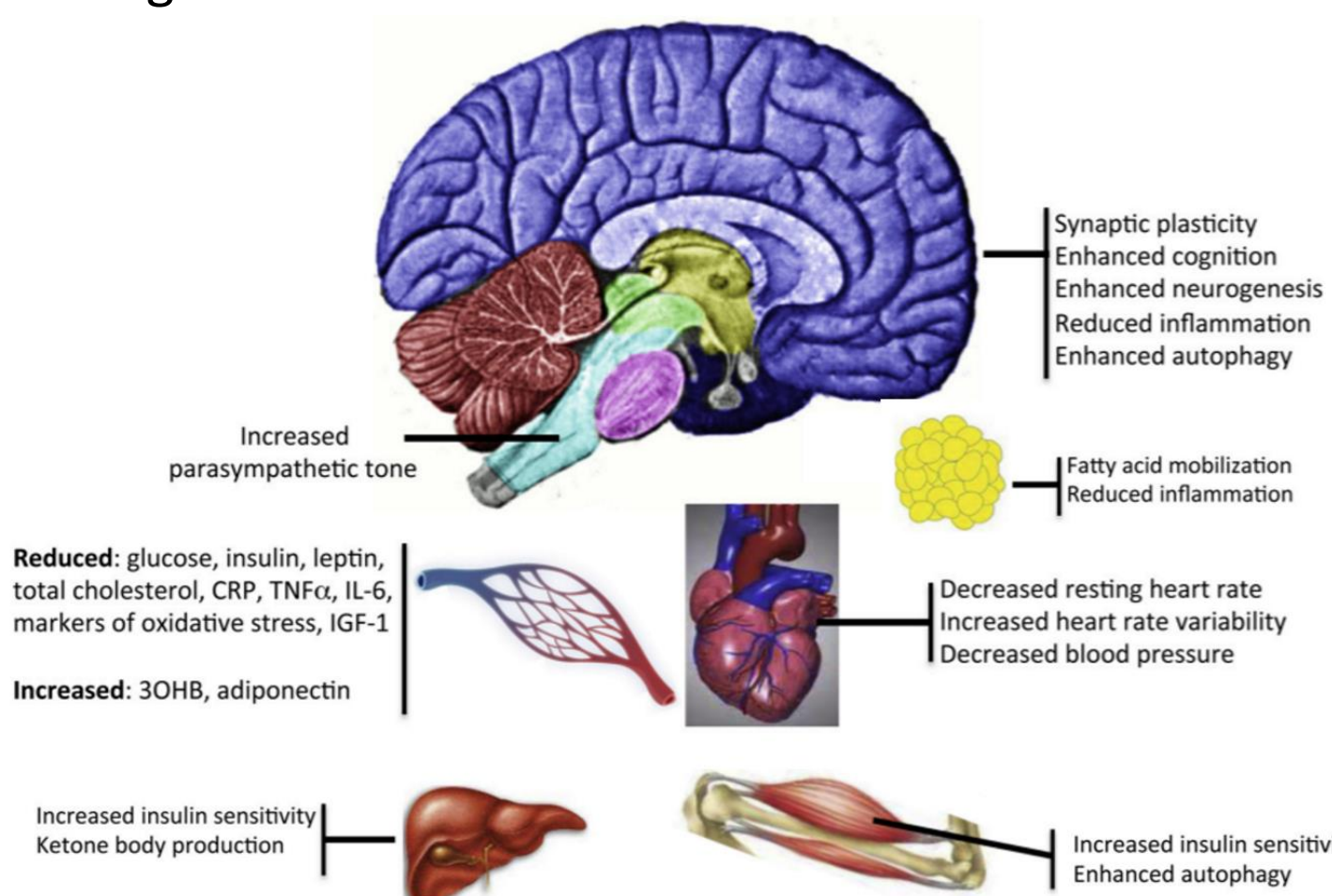


Figure 1. The effects of IF on various organ systems^[8].

During fasting, the body relies on ketones and fatty acids derived from the breakdown of adipose tissue. During eating periods, the body switches to relying on glucose as its energy source. Introducing these metabolic shifts at regular intervals is thought to improve cellular metabolic flexibility and efficiency, ultimately exerting cardioprotective effects^[9].

The cellular response that occurs with intermittent fasting has been shown to minimize anabolic processes while favoring the maintenance and repair of underlying systems. This results in the enhancement of stress resistance, improvement in the regulation of glucose and suppression of inflammatory processes^[3].

Use in Primary Care

Benefits of and evidence for the use of IF as a therapy for CVD:^[7, 12]

- Reduced resting heart rate and blood pressure
- Reduced blood glucose levels
- Reduced insulin resistance and increased insulin sensitivity
- Weight loss
- Decreased total cholesterol, LDL and triglycerides
- Reduction in certain inflammatory and oxidative stress markers such as C-reactive protein (CRP) and platelet-derived growth factor

High CRP and platelet-derived growth factor levels are associated with higher atherosclerosis and myocardial infarction risks. A chronic inflammatory state, as reflected by high CRP levels, can also contribute to atherosclerotic plaque formation. High levels of platelet-derived growth factor can lead to increased proliferation of vascular smooth muscle cells, resulting in narrowing of vasculatures^[4].

The cardiovascular protective benefits of IF can be seen within 2-4 weeks of initiating IF. One study demonstrated that even a 12% reduction in calories per day can lead to meaningful reduction in cardiovascular disease risks^[3].

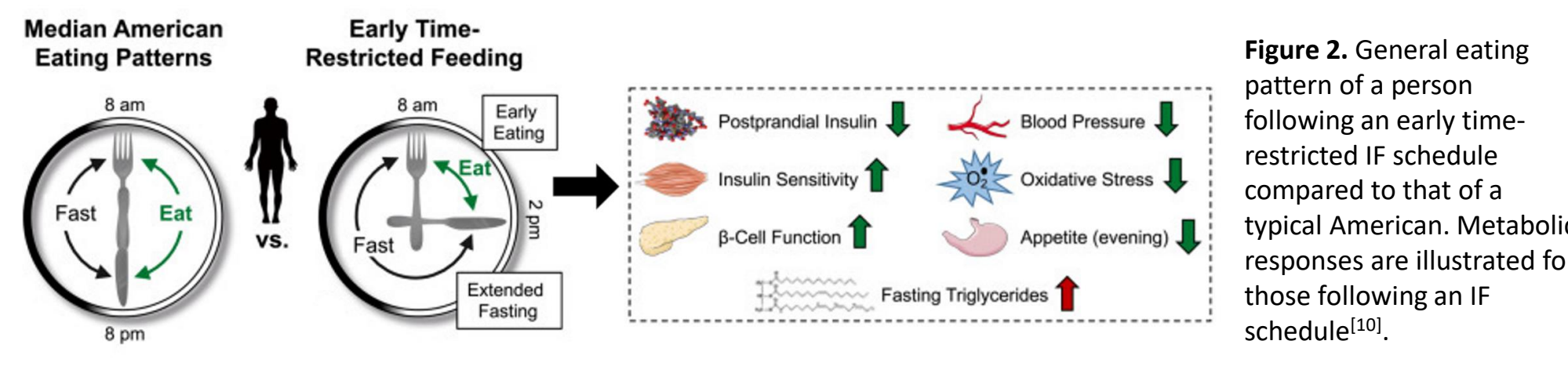


Figure 2. General eating pattern of a person following an early time-restricted IF schedule compared to that of a typical American. Metabolic responses are illustrated for those following an IF schedule^[10].

IF as a Complementary Therapy

IF can be challenging to implement initially. In the first month, there can be side effects such as irritability and reduced ability to concentrate. One method to adapt to IF is to gradually increase the fasting window over weeks or months while eating the same amount of calories, eventually resulting in a 16 to 18-hour fasting window per day. Calorie deficits can then be introduced later.

Another method is the 5:2 IF diet in which patients start off restricting calories to 900-1000 calories per day for 1 day each week. Over a period of weeks, patients gradually restrict calories to 500 calories 2 days per week^[3].

IF Benefits	Patient Education Points
<ul style="list-style-type: none"> • Easy to implement and low risk • No/low cost • No absolute contraindications • No medication changes 	<ul style="list-style-type: none"> • Different protocols provide flexibility • Initial hunger is transient but can make adherence difficult • Evaluate timing of medications

Conclusions

- Still need more research about IF, ideally human clinical trials
- Self-management tools (like IF) used in the treatment of chronic disease have been shown to produce clinically meaningful benefits while improving health outcomes in some populations as well as reducing cost^[1, 2]
- Compliance to CVD therapies can be difficult - IF can complement and simplify
- Patients should have the opportunity to talk with their provider to discuss the best plan for their needs, while considering risks and benefits of each alternative

Current CVD Therapies

For individuals between 40 - 75 years-old, the ASCVD 10-year risk-calculator is used to determine the risk of heart disease or stroke from factors such as age, comorbidities, race, smoking status, and cholesterol levels.

Non-pharmacological CVD therapies: Smoking cessation, diet modification, exercise

Pharmacologic CVD therapies: Aspirin, statins, fibric acid derivatives, bile acid sequestrants, omega-3 fatty acids, target-therapy for chronic disease management

Tobacco cessation has been proven to reduce CVD-related morbidity and mortality^[11]. With the use of low- or moderate-dose statins, there was a reduced risk of all-cause mortality, cardiovascular mortality, ischemic stroke, heart attack, and a composite cardiovascular outcome^[13].

References

1. Bodenheimer, T. (2002). Patient Self-management of Chronic Disease in Primary Care. *JAMA*, 288(19), p.2469.
2. Chodosh, J., Morton, S., Mojica, W., Maglione, M., Suttorp, M., Hilton, L., Rhodes, S. and Shekelle, P. (2005). Meta-Analysis: Chronic Disease Self-Management Programs for Older Adults. *Annals of Internal Medicine*, 143(6), p.427.
3. de Cabo, R. and Mattson, M. (2019). Effects of Intermittent Fasting on Health, Aging, and Disease. *New England Journal of Medicine*, 381(26), pp.2541-2551.
4. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc Natl Acad Sci U S A*. 2004;101(17):6659-6663. doi:10.1073/pnas.0308291101
5. Fryar CD, Chen T-C, Li X. Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999-2010. NCHS data brief, no. 103. Hyattsville, MD: National Center for Health Statistics; 2012. Accessed May 9, 2019.
6. Heron M. Deaths: Leading Causes for 2017. *National Vital Statistics Reports*. 2019;68(6). https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_06-508.pdf. Accessed February 15, 2020.
7. Klempel et al., 2012. Klempel M.C., Kroeger C.M., Bhutani S., Trepanowski J.F., and Varady K.A.: Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. *Nutr. J.* 2012; 11: pp. 98
8. Mattson, M., Longo, V. and Harvie, M. (2017). Impact of intermittent fasting on health and disease processes. *Ageing Research Reviews*, 39, pp.46-58.
9. Stekovic, S., Hofer, S., Tripolt, N., Aon, M., Royer, P., Pein, L., Stadler, J., Pendl, T., Prietl, B., Url, J., Schroeder, S., Tadic, J., Eisenberg, T., Magnes, C., Stumpe, M., Zuegner, E., Bordag, N., Riedl, R., Schmidt, A., Kolesnik, E., Verheyen, N., Springer, A., Madl, T., Sinner, F., de Cabo, R., Kroemer, G., Obermayer-Pietsch, B., Dengjel, J., Sourij, H., Pieber, T. and Madeo, F. (2020). *Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans*.
10. Sutton, E., Beyl, R., Early, K., Cefalu, W., Ravussin, E. and Peterson, C. (2018). Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metabolism*, 27(6), pp.1212-1221.e3.
11. Kirsten Bibbins-Domingo, David C. Grossman, Susan J. Curry, Karina W. Davidson, John W. Epling, Jr, Francisco A. R. Garcia, Matthew W. Gillman, Alex R. Kemper, Alex H. Krist, et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Recommendation Statement. *Aafp.org*. <https://www.aafp.org/afp/2017/0115/od1.html>. Published 2017. Accessed February 23, 2020.
12. Varady et al., 2015. Varady K.A., Dam V.T., Klempel M.C., Horne M., Cruz R., Kroeger C.M., and Santosa S.: Effects of weight loss via high fat vs. low fat alternate day fasting diets on free fatty acid profiles. *Sci. Rep.* 2015; 5: pp. 7561
13. Zbtanagar D., Huffman MD. Novel treatments for cardiovascular disease prevention. *Cardiovascular therapeutics*. Published October 2012. Accessed 2/24/2020.