J Lipid Atheroscler. 2020 Jan;9(1):140-152
https://doi.org/10.12997/jla.2020.9.1.140
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Review

Check for updates

The Effects of Meal Timing and Frequency, Caloric Restriction, and Fasting on Cardiovascular Health: an Overview

Andrea Maugeri [1,2] **Manlio Vinciguerra** [1,3]

[1]International Clinical Research Center, St. Anne's University Hospital, Brno, Czechia
[2]Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy
[3]Division of Medicine, University College London (UCL), London, UK

OPEN ACCESS

Received: Oct 27, 2019
Revised: Dec 29, 2019
Accepted: Jan 6, 2020

Correspondence to
Manlio Vinciguerra
International Clinical Research Center, St. Anne's University Hospital, Pekařská 664/53, Brno 038975, Czechia.
E-mail: manlio.vinciguerra@fnusa.cz

Copyright © 2020 The Korean Society of Lipid and Atherosclerosis.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs
Andrea Maugeri
https://orcid.org/0000-0003-2655-8574
Manlio Vinciguerra
https://orcid.org/0000-0002-1768-3894

Funding
This work was supported by grants from the European Social Fund and European Regional Development Fund - Project MAGNET (No. CZ.02.1.01/0.0/0.0/15_003/0000492) (to Manlio Vinciguerra).

Conflict of Interest
The authors have no conflicts of interest to declare.

ABSTRACT

Cardiovascular disease (CVD), which is the leading cause of death worldwide, is strongly affected by diet. Diet can affect CVD directly by modulating the composition of vascular plaques, and indirectly by affecting the rate of aging. This review summarizes research on the relationships of fasting, meal timing, and meal frequency with CVD incidence and progression. Relevant basic research studies, epidemiological studies, and clinical studies are highlighted. In particular, we discuss both intermittent and periodic fasting interventions with the potential to prevent and treat CVD.

Keywords: Fasting; Fasting mimicking diet; Caloric restriction; Blood pressure; Cardiovascular disease

INTRODUCTION

Human aging and age-related diseases are now considered the greatest challenges and financial burdens faced by all countries, developing or developed.[1] In particular, aging has remarkable effects on the heart and arterial system, increasing the risk for cardiovascular disease (CVD), including atherosclerosis, hypertension, myocardial infarction, and stroke.[2,3] Increases in the average lifespan of humans have made CVD the top cause of death globally, with more than 17.9 million deaths in 2016.[4] Most cases of CVD could be prevented by addressing behavioral risk factors (e.g., tobacco use, unhealthy diet, obesity, sedentary behavior, and harmful use of alcohol) using population-wide strategies.[5] Although major strides have been made in the reduction of CVD mortality and morbidity through behavioral interventions and population-based surveillance programs,[6] the majority of industrialized countries still have the highest CVD rates in the world.[7] Thus, there is an increasing need to detect and manage people who suffer from CVD and those who are at an elevated risk.

In the last decades, mounting evidence began to suggest relationships between eating behaviors—in terms of timing and frequency—and CVD and cardiometabolic health markers.[8] Another concept that has attracted significant interest and debate among researchers is calorie restriction (CR), which involves a reduced daily caloric intake

Generated by xmlinkpress

Journal of Lipid and Atherosclerosis

Author Contributions
Conceptualization: Maugeri A, Vinciguerra M; Funding acquisition: Maugeri A; Supervision: Maugeri A; Writing - original draft: Maugeri A, Vinciguerra M; Writing - review & editing: Maugeri A, Vinciguerra M.

(approximately by 20%–40%) with no changes in meal frequency. Previous reviews of *in vivo* and human studies have consistently demonstrated that chronic CR can extend longevity and decrease the risk for multiple age-related diseases, including tumors, CVD, and neurodegeneration.[9-12] Results from experimental studies have also indicated that CR with adequate nutrient intake may be a suitable intervention for preventing CVD and slowing the accumulation of molecular damage.[13]

More recently, findings from well-controlled investigations in experimental animal models and emerging human studies have indicated that fasting may provide an effective strategy to reduce weight, delay aging, and optimize health.[14,15] Fasting is achieved by ingesting no food or caloric beverages for periods that typically range from 12 hours to 3 weeks. It is well known that fasting results in ketogenesis and promotes potent changes in metabolic pathways and cellular processes, such as stress resistance, lipolysis, and autophagy.[16,17]

Despite these benefits, both the duration and severity of fasting and CR regimens reduce compliance and make them unfeasible for most people, a perception that may also exist due to undesirable side effects. For this reason, experts have started to gather consensus opinions on less drastic dietary interventions and drugs that mimic the effects of fasting and CR, but that are practical, realistic, and safe.[18]

Among these, the intermittent fasting (IF) is considered to be less restrictive than traditional approaches for CR, since it consists in an adequate daily caloric intake with the use of short and strict CR.[18] In this review article, we trace the path that led researchers to hypothesize that fasting has health benefits, with a particular focus on cardiovascular health. We first summarize evidence from epidemiological studies on the effects of meal timing and frequency on CVD and its risk factors. Next, we describe the benefits of CR on cardiovascular and metabolic factors. Finally, we describe 2 types of fasting regimens—IF and a fasting-mimicking diet (FMD)—and their potential protective effects on cardiovascular health.

HOW MEAL TIMING AND FREQUENCY AFFECT CARDIOVASCULAR HEALTH

The implications of meal timing and frequency for cardiovascular health were recently illustrated in a scientific statement from the American Heart Association (AHA).[19] Specifically, the AHA stated that the state-of-art knowledge is scarce and inconclusive, and that more studies are warranted to understand the effect of meal frequency on CVD.[19]

In the last 40 years, the prevalence of eating breakfast and lunch consistently declined,[20] and many studies have provided support that total energy intake at breakfast is inversely associated with weight gain and CVD risk factors, such as elevated serum low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, and hypertension.[21-23] Interestingly, we have recently shown that skipping breakfast is a risk factor for poor cardiovascular health,[8] in accordance with the definition of the AHA.[24] Our findings, together with previous data, guided the design of several clinical interventional studies analyzing the impact of breakfast consumption on multiple CVD risk factors. However, most of those studies were 1-day interventions or had a very short duration, thus providing limited evidence.[19] The role of meal timing in regulating the circadian patterns of metabolism has been chiefly investigated in observational studies.[25,26] At the molecular/

cellular level, circadian rhythms in gene expression synchronize metabolic processes with the external environment, allowing the organism to respond in a timely and effective way to physiological challenges.[27-30] In mammals, this daily timekeeping is orchestrated by the biological clocks of the circadian timing system, composed of master molecular oscillators within the suprachiasmatic nuclei of the hypothalamus, which pace self-sustained and cell-autonomous molecular oscillators in peripheral tissues through both neural and humoral signals.[27-30] A recent study showed that skipping breakfast adversely affected the clock and clock-controlled gene expression and was correlated with an increased postprandial glycemic response in both healthy and diabetic individuals.[31] Evidence has also been found regarding the effects of evening meals on body mass index (BMI) and weight control, but current knowledge is inconclusive and controversial regarding skipping dinner. A few observational studies have pointed towards a positive association between evening high-energy intake and BMI,[32-34] with a higher risk for CVD in patients who ate late in the evening.[35] However, other studies have found no relationship[36,37] or an inverse relationship.[38] We recently found that skipping dinner increased triglyceride levels and total cholesterol-to-HDL ratio, suggesting a potential influence on CVD risk.[8] The concept of snacking is more closely related to the definition of meal frequency—a matter to be discussed in the following paragraph—but its association with CVD risk and health is also debated. Although we observed that the absence of snacking—with reduced meal frequency—might affect cardiovascular health, an analysis of data from the 2001-2008 National Health and Nutrition Examination Survey showed that snacking patterns were not linked to CVD risk factors.[39]

To the best of our knowledge, only a single prospective study has demonstrated that patients with a greater meal frequency had a lower risk of CVD than those with a lower meal frequency. Recently, our cross-sectional analysis of Czech individuals (the Kardiovize Brno 2030 study) demonstrated that eating more frequently may be an effective long-term preventive tool against weight gain and CVD risk.[8] In turn, other studies have evaluated the effects of meal frequency on risk factors for CVD, such as obesity, cholesterol levels, fasting glucose or diabetes, and hypertension. Several epidemiological analyses have demonstrated an association between higher meal frequency and a lower risk of obesity.[40-42] In contrast, a cross-sectional study of the Norfolk cohort of the European Prospective Investigation Into Cancer showed that greater meal frequency decreased total and LDL cholesterol levels, without alterations of HDL cholesterol levels.[43] Other observational studies demonstrated that greater meal frequency reduced the risk of type 2 diabetes mellitus in men, but not in women.[44] Several lines of evidence from clinical trials have raised questions on the impact of meal frequency on CVD risk. For instance, none of these trials confirmed the effect of meal frequency on body weight in the absence of CR.[45] Several studies showed that greater meal frequency affected neither HDL cholesterol nor triglyceride concentrations.[46-50]. By contrast, a study by Stote et al.[51] showed that increasing meal frequency reduced cholesterol levels, whereas decreasing meal frequency had detrimental effects. That study also demonstrated that HDL cholesterol levels were higher in patients who ate only once per day.[51]

Evidence on the impact of meal frequency on blood pressure is also controversial and inconclusive. While most studies have shown no changes in blood pressure,[48] the study by Stote et al.[51] reported that consuming 1 meal per day increased both systolic and diastolic blood pressure after an 8-week intervention.[51] Interestingly, when participants transitioned to a regimen of 3 meals per day, both systolic and diastolic blood pressure decreased.[51] With respect to fasting glucose and/or insulin levels, the current evidence is that either low or high meal frequency has no significant effects in the absence of weight loss.[46-51]

JLA Journal of Lipid and Atherosclerosis

CARDIOMETABOLIC BENEFITS OF CALORIE RESTRICTION

Previous reviews of studies on rhesus monkeys reported that CR without malnutrition extended the lifespan and reduced the risk for several diseases, including diabetes, cancer, sarcopenia, and neurodegenerative diseases.[10,11] Moreover, chronic CR ameliorated the expected age-associated alterations in autonomic function and gene expression in skeletal muscle.[10-12]

With respect to CVD, the monkey study of the Wisconsin National Primate Research Center reported that 20 years of CR reduced the incidence of CVD by 50%.[52] In human beings, long-term CR has been found to lead to several metabolic and molecular changes that protected against age-related pathologies, including changes in markers for diabetes, hypertension, CVD, cancer, and dementia.[12] Specifically, both observational and randomized clinical studies reported remarkable cardiometabolic adaptations mediated by CR.[53] For instance, well-nourished individuals who restricted their total energy intake experienced beneficial effects on several CVD risk factors, such as LDL and HDL cholesterol, triglycerides, fasting glucose, and blood pressure.[54,55] Moreover, long-term CR led to sustained improvements in intima–media thickness, left ventricular diastolic function, and heart-rate variability.[54,56-58] In the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy study, a phase 2, multicenter, randomized controlled trial conducted in young and middle-aged (21–50 years), healthy, non-obese (BMI, 22.0–27.9 kg/m^2) men and women at 3 clinical centers in the USA, it was shown that 2 years of moderate CR significantly reduced multiple cardiometabolic risk factors.[59]

THE IMPACT OF FASTING ON HEALTH: A FOCUS ON CARDIOVASCULAR DISEASE AND ITS RISK FACTORS

1. Intermittent fasting

The most potent and feasible forms of fasting include IF (including alternate-day fasting or fasting for 2 days a week, for example) and the FMD (a high-fat, low-calorie IF diet that may promote fat loss and reduce blood sugar, inflammation, and cholesterol, similar to other fasting methods). The most studied IF approaches so far are alternate days of energy restriction, with either a total fast or consumption of 25% of estimated requirements on alternate days, 2 non-consecutive days of energy restriction per week (the 5:2 approach), or time-restricted feeding, in which individuals fast for 16, 18, or 20 hours per day. Some of the health benefits of IF described in animals and humans are summarized in **Table 1**.

Table 1. Health benefits of IF

Benefits of IF	References
Reduced insulin resistance and improved glucose homeostasis	Hoddy et al.[83]; Carter et al.[84]; Arnason et al.[85]; Sutton et al.[86]
Reduced blood lipids (including triglycerides and LDL cholesterol)	Malinowski et al.[82]; Varady et al.[87]; Catenacci et al.[88]
Reduced markers of inflammation	Aksungar et al.[89]
Reduced blood pressure	Sutton et al.[85]; Malinowski et al.[82]
Reduced oxidative stress	Faris et al.[90]; Madkour et al.[91]
Reduced risk of cancer	Zhu et al.[92]
Increased cellular repair	Antunes et al.[93]
Increased fat burning	Mattson et al.[94]; Heilbronn et al.[65]
Increased metabolic rate	Webber et al.[95]
Improved memory and cognitive function	Li et al.[96]; Halagappa et al.[97]; Brandhorst et al.[74]
Reduced autoimmune diseases, protective patterns of gut flora	Cignarella et al.[98]

IF, intermittent fasting; LDL, low-density lipoprotein.

https://doi.org/10.12997/jla.2020.9.1.140

Journal of Lipid and Atherosclerosis

In vivo studies have demonstrated protective effects of IF against obesity, hypertension, glucose intolerance, insulin resistance and diabetes, inflammation, and the clinical progression of CVD in mice.[60] Plausible mechanisms underpinning these beneficial effects include improved insulin sensitivity, increased levels of fibroblast growth factor 21, reduced inflammation and oxidative stress, and enhanced cellular and molecular adaptive stress responses (e.g., mitochondrial function, proteostasis, autophagy, and endogenous antioxidant enzymatic activity).[60-62]

While *in vivo* models have been used extensively, the majority of epidemiological findings have been obtained through studies of patients who mostly fasted for religious reasons. For instance, a meta-analysis of 2 small studies within the Intermountain Heart Collaborative Study showed that participants who fasted routinely (1 time per month for 24 hours) had a lower risk of coronary artery disease and diabetes mellitus than those who did not.[63] Beyond observational studies, several clinical trials have evaluated the effect of IF on health, especially cardiovascular health. Recently, it has been observed that 4 weeks of strict IF improved markers of health in middle-aged humans, including cardiovascular parameters, inflammatory markers, LDL levels, triiodothyronine levels, fat mass (in particular, trunk fat), and the fat-to-lean ratio.[64] However, it is difficult to understand whether fasting directly affects cardiovascular markers or its benefits depend on weight loss. Indeed, it has been demonstrated that IF significantly reduced body weight after 3–24 weeks of an intervention.[65-72] The greatest benefits were observed for interventions that provided a low-calorie meal on each fast day.[65-71] Moreover, a comparison between alternate-day and periodic fasting demonstrated that the former strategy was more effective for reducing body weight.[72,73] Interestingly, the positive effects of these strategies on body weight also resulted in reductions in triglyceride levels, which decreased after IF interventions,[68,71-73] with more benefits in the studies that documented the greatest weight loss.[67]

Several lines of evidence have shown that weight loss due to IF might be also useful for lowering both systolic and diastolic blood pressure.[66,67,71,73] These studies also suggested that fasting might help prevent the progression from prehypertension to hypertension,[66,67,71,73] but further research is needed to corroborate this finding.

With respect to cholesterol levels, current evidence is controversial. Although some studies have reported that IF reduced total cholesterol levels,[67,68,71-73] no effect was observed in others.[66,69,70] It is worth noting that the benefits of fasting were significant in patients with mildly elevated cholesterol levels.[67,68,71-73] By contrast, no effect of fasting on HDL cholesterol was evident.

IF also appeared to reduce fasting glucose in patients with prediabetes, but not in healthy individuals.[67,71,72] The greatest benefits were observed in patients who fasted on alternate days.[71] Stronger evidence was reported in studies investigating the effect of fasting on insulin levels, which found that IF reduced fasting insulin levels independent of prediabetes status.[65,67,69-73] Insulin concentration seemed to be associated with the degree of energy restriction, with the greatest reduction observed in the studies with the highest CR.[65] More recently, Stekovic et al.[64] demonstrated that alternate-day fasting improved cardiovascular health by reducing blood pressure, heart rate, arterial and pulse pressure, and pulse wave velocity. Interestingly, they proposed that these changes might reduce the risk for CVD, as measured by the Framingham Risk Score.[64]

 https://doi.org/10.12997/jla.2020.9.1.140

Journal of Lipid and Atherosclerosis

2. Fasting-mimicking diet

The FMD was recently created with the goal of replicating the benefits of fasting, while still providing the body with adequate nutrition. The modifications of the FMD avoid the calorie deprivation associated with other types of fasting, which should render it more feasible for patients and increase their compliance. A 5-day FMD consists of meals and snacks that are whole-food and plant–derived. The FMD is low in carbohydrates and protein, while being high in healthy fats such as olives and flaxseed. The first day of the FMD provides approximately 1,090 kcal (10% protein, 56% fat, and 34% carbohydrates), while days 2 through 5 provide only 725 kcal (9% protein, 44% fat, and 47% carbohydrates). This corresponds to 34%–54% of normal calorie intake. The low-calorie, high-fat, low-carbohydrate content of the meals causes the body to generate energy through gluconeogenesis from noncarbohydrate sources after glycogen stores are depleted. The creators and manufacturers of the FMD 5-day plan recommend following this regimen every 1–6 months, in order to mimic the body's physiological response to traditional fasting methods, such as cell regeneration, decreased inflammation, and fat loss.

Some of the health benefits of FMD described in animals and humans are summarized in **Table 2**. In normal mice, 4 days of a FMD starting at middle age and administered bi-monthly yielded spectacular results. While FMD decreased the size of multiple organs/systems, this effect was followed upon re-feeding by an elevated number of progenitor and stem cells and regeneration.[74] FMD cycles extended longevity, lowered visceral fat, reduced cancer incidence and skin lesions, rejuvenated the immune system, and retarded bone mineral density loss.[74] In old mice, FMD cycles favored hippocampal neurogenesis and improved cognitive performance.[74] A 4-day FMD was also shown to restore insulin secretion and glucose homeostasis in both type 2 and type 1 diabetes mouse models, as well as in pancreatic islets in humans with type 1 diabetes.[75] These animal and *ex vivo* studies provide support for the use of the FMD to promote the health span.

As described for IF, the majority of findings on the benefits of FMD relate to weight loss. For instance, a previous study compared subjects who followed 3 months of an unrestricted diet to subjects who consumed the FMD for 5 consecutive days per month for 3 months. Three FMD cycles were able to reduce body weight and trunk fat, and to shrink total body fat. Moreover, FMD cycles also lowered blood pressure and decreased levels of insulin-like growth factor 1 (IGF-1), without serious adverse effects.[76] Strikingly, BMI, blood pressure, and fasting glucose, IGF-1, triglycerides, total and LDL cholesterol, and C-reactive protein levels were more beneficially affected in participants at risk for disease than in those who were not at risk.[76] This benchmark study showed that cycles of a 5-day FMD were safe, feasible, and effective in reducing risk factors for aging and age-related diseases.

Table 2. Health benefits of the FMD

Benefits of FMD	References
Modulates microbiota and promotes intestinal regeneration to reduce inflammatory bowel disease	Rangan et al.[99]
Neuroprotection in a 1-methyl-4-phenyl-1,2,3,6-tetrathydropyridine–induced Parkinson disease mouse model	Zhou et al.[100]
Improving the efficacy of chemotherapy, while inhibiting side effects	Lo Re et al.[101]; Di Biase et al.[102]; D'Aronzo et al.[103]; Safdie et al.[104]
Inhibition of diabetes progression (type I and II), regeneration of β-islets	Wei et al.[105]; Cheng et al.[75]; Brandhorst et al.[74]
Decreased markers/risk factors for aging	Wei et al.[76]; Brandhorst et al.[74]
Reduced risk of cancer in humans	Wei et al.[76]; Brandhorst et al.[74]
Reduced risk of cardiovascular disease in humans	Wei et al.[76]; Brandhorst et al.[74]
Reduced autoimmunity and symptoms of multiple sclerosis	Choi et al.[106]
Multi-system regeneration	Brandhorst et al.[74]; Cheng et al.[75]
Improves cognition	Brandhorst et al.[74]

FMD, fasting-mimicking diet.

Journal of Lipid and Atherosclerosis

Fasting has been practiced for centuries, if not for millennia, but only recently have molecular studies clarified its role in adaptive cellular responses that decrease inflammation and improve energy metabolism and cellular protection.[14] In rodents, IF and the FMD protect against diabetes, cancer, CVD, and neurodegeneration, while in humans, fasting helps to the reduce risk factors for developing these ailments. IF and the FMD have the potential to delay aging and CVD, while minimizing the side effects caused by chronic dietary interventions. Despite a wealth of proof obtained from model organisms and human pilot studies,[77,78] solid randomized clinical trials and meta-analyses are still lacking. Moreover, only a few studies have documented adverse effects in response to fasting regimens, including hunger and feeling cold, irritable, or without strength. By contrast, they reported improvements in self-confidence and positive mood, and reductions in tension, anger, and fatigue.[71,73,79-81] What is certain is that several classes of people need caution, such as children, pregnant women, those performing heavy physical work, patients with reactive hypoglycemia, and those who use antidiabetic drugs.[82]

CONCLUSION

Although both IF and the FMD are promising, a cautious note is still needed. More efforts to understand the long-term effects of fasting on cardiovascular health and disease are warranted.

REFERENCES

1. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374:1196-1208.
PUBMED | CROSSREF
2. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a "set up" for vascular disease. Circulation 2003;107:139-146.
PUBMED | CROSSREF
3. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part II: the aging heart in health: links to heart disease. Circulation 2003;107:346-354.
PUBMED | CROSSREF
4. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117-171.
PUBMED | CROSSREF
5. GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1345-1422.
PUBMED | CROSSREF
6. Cífková R, Skodová Z, Bruthans J, Adámková V, Jozífová M, Galovcová M, et al. Longitudinal trends in major cardiovascular risk factors in the Czech population between 1985 and 2007/8. Czech MONICA and Czech post-MONICA. Atherosclerosis 2010;211:676-681.
PUBMED | CROSSREF
7. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 2014;35:2929.
PUBMED | CROSSREF
8. Maugeri A, Kunzova S, Medina-Inojosa JR, Agodi A, Barchitta M, Homolka M, et al. Association between eating time interval and frequency with ideal cardiovascular health: results from a random sample Czech urban population. Nutr Metab Cardiovasc Dis 2018;28:847-855.
PUBMED | CROSSREF
9. Fontana L, Partridge L, Longo VD. Extending healthy life span--from yeast to humans. Science 2010;328:321-326.
PUBMED | CROSSREF

 https://doi.org/10.12997/jla.2020.9.1.140

Journal of Lipid and Atherosclerosis

10. Mattison JA, Roth GS, Beasley TM, Tilmont EM, Handy AM, Herbert RL, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. Nature 2012;489:318-321.
PUBMED | CROSSREF

11. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun 2014;5:3557.
PUBMED | CROSSREF

12. Cava E, Fontana L. Will calorie restriction work in humans? Aging (Albany NY) 2013;5:507-514.
PUBMED | CROSSREF

13. Fontana L. Interventions to promote cardiometabolic health and slow cardiovascular ageing. Nat Rev Cardiol 2018;15:566-577.
PUBMED | CROSSREF

14. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab 2014;19:181-192.
PUBMED | CROSSREF

15. Fontana L, Partridge L. Promoting health and longevity through diet: from model organisms to humans. Cell 2015;161:106-118.
PUBMED | CROSSREF

16. Bruce-Keller AJ, Umberger G, McFall R, Mattson MP. Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. Ann Neurol 1999;45:8-15.
PUBMED | CROSSREF

17. Hartman AL. Neuroprotection in metabolism-based therapy. Epilepsy Res 2012;100:286-294.
PUBMED | CROSSREF

18. Longo VD, Antebi A, Bartke A, Barzilai N, Brown-Borg HM, Caruso C, et al. Interventions to slow aging in humans: are we ready? Aging Cell 2015;14:497-510.
PUBMED | CROSSREF

19. St-Onge MP, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, et al. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation 2017;135:e96-e121.
PUBMED | CROSSREF

20. Kant AK, Graubard BI. 40-year trends in meal and snack eating behaviors of American adults. J Acad Nutr Diet 2015;115:50-63.
PUBMED | CROSSREF

21. Deshmukh-Taskar P, Nicklas TA, Radcliffe JD, O'Neil CE, Liu Y. The relationship of breakfast skipping and type of breakfast consumed with overweight/obesity, abdominal obesity, other cardiometabolic risk factors and the metabolic syndrome in young adults. The National Health and Nutrition Examination Survey (NHANES): 1999–2006. Public Health Nutr 2013;16:2073-2082.
PUBMED | CROSSREF

22. Purslow LR, Sandhu MS, Forouhi N, Young EH, Luben RN, Welch AA, et al. Energy intake at breakfast and weight change: prospective study of 6,764 middle-aged men and women. Am J Epidemiol 2008;167:188-192.
PUBMED | CROSSREF

23. Witbracht M, Keim NL, Forester S, Widaman A, Laugero K. Female breakfast skippers display a disrupted cortisol rhythm and elevated blood pressure. Physiol Behav 2015;140:215-221.
PUBMED | CROSSREF

24. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;121:586-613.
PUBMED | CROSSREF

25. Froy O. Metabolism and circadian rhythms--implications for obesity. Endocr Rev 2010;31:1-24.
PUBMED | CROSSREF

26. Qin LQ, Li J, Wang Y, Wang J, Xu JY, Kaneko T. The effects of nocturnal life on endocrine circadian patterns in healthy adults. Life Sci 2003;73:2467-2475.
PUBMED | CROSSREF

27. Mazzoccoli G, Laukkanen MO, Vinciguerra M, Colangelo T, Colantuoni V. A timeless link between circadian patterns and disease. Trends Mol Med 2016;22:68-81.
PUBMED | CROSSREF

28. Mazzoccoli G, Pazienza V, Vinciguerra M. Clock genes and clock-controlled genes in the regulation of metabolic rhythms. Chronobiol Int 2012;29:227-251.
PUBMED | CROSSREF

29. Tevy MF, Giebultowicz J, Pincus Z, Mazzoccoli G, Vinciguerra M. Aging signaling pathways and circadian clock-dependent metabolic derangements. Trends Endocrinol Metab 2013;24:229-237.
PUBMED | CROSSREF

30. Vinciguerra M, Tevy MF, Mazzoccoli G. A ticking clock links metabolic pathways and organ systems function in health and disease. Clin Exp Med 2014;14:133-140.
PUBMED | CROSSREF
31. Jakubowicz D, Wainstein J, Landau Z, Raz I, Ahren B, Chapnik N, et al. Influences of breakfast on clock gene expression and postprandial glycemia in healthy individuals and individuals with diabetes: a randomized clinical trial. Diabetes Care 2017;40:1573-1579.
PUBMED | CROSSREF
32. Morse SA, Ciechanowski PS, Katon WJ, Hirsch IB. Isn't this just bedtime snacking? The potential adverse effects of night-eating symptoms on treatment adherence and outcomes in patients with diabetes. Diabetes Care 2006;29:1800-1804.
PUBMED | CROSSREF
33. Wang JB, Patterson RE, Ang A, Emond JA, Shetty N, Arab L. Timing of energy intake during the day is associated with the risk of obesity in adults. J Hum Nutr Diet 2014;27 Suppl 2:255-262.
PUBMED | CROSSREF
34. Bo S, Musso G, Beccuti G, Fadda M, Fedele D, Gambino R, et al. Consuming more of daily caloric intake at dinner predisposes to obesity. A 6-year population-based prospective cohort study. PLoS One 2014;9:e108467.
PUBMED | CROSSREF
35. Cahill LE, Chiuve SE, Mekary RA, Jensen MK, Flint AJ, Hu FB, et al. Prospective study of breakfast eating and incident coronary heart disease in a cohort of male US health professionals. Circulation 2013;128:337-343.
PUBMED | CROSSREF
36. Aljuraiban GS, Chan Q, Oude Griep LM, Brown IJ, Daviglus ML, Stamler J, et al. The impact of eating frequency and time of intake on nutrient quality and body mass index: the INTERMAP study, a population-based study. J Acad Nutr Diet 2015;115:528-536.e1.
PUBMED | CROSSREF
37. Almoosawi S, Prynne CJ, Hardy R, Stephen AM. Time-of-day of energy intake: association with hypertension and blood pressure 10 years later in the 1946 British Birth Cohort. J Hypertens 2013;31:882-892.
PUBMED | CROSSREF
38. Striegel-Moore RH, Franko DL, Thompson D, Affenito S, Kraemer HC. Night eating: prevalence and demographic correlates. Obesity (Silver Spring) 2006;14:139-147.
PUBMED | CROSSREF
39. Nicklas TA, O'Neil CE, Fulgoni VL 3rd. Snacking patterns, diet quality, and cardiovascular risk factors in adults. BMC Public Health 2014;14:388.
PUBMED | CROSSREF
40. Ma Y, Bertone ER, Stanek EJ 3rd, Reed GW, Hebert JR, Cohen NL, et al. Association between eating patterns and obesity in a free-living US adult population. Am J Epidemiol 2003;158:85-92.
PUBMED | CROSSREF
41. van der Heijden AA, Hu FB, Rimm EB, van Dam RM. A prospective study of breakfast consumption and weight gain among U.S. men. Obesity (Silver Spring) 2007;15:2463-2469.
PUBMED | CROSSREF
42. Holmbäck I, Ericson U, Gullberg B, Wirfält E. A high eating frequency is associated with an overall healthy lifestyle in middle-aged men and women and reduced likelihood of general and central obesity in men. Br J Nutr 2010;104:1065-1073.
PUBMED | CROSSREF
43. Titan SM, Bingham S, Welch A, Luben R, Oakes S, Day N, et al. Frequency of eating and concentrations of serum cholesterol in the Norfolk population of the European prospective investigation into cancer (EPIC-Norfolk): cross sectional study. BMJ 2001;323:1286-1288.
PUBMED | CROSSREF
44. Mekary RA, Giovannucci E, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. Am J Clin Nutr 2012;95:1182-1189.
PUBMED | CROSSREF
45. Taylor MA, Garrow JS. Compared with nibbling, neither gorging nor a morning fast affect short-term energy balance in obese patients in a chamber calorimeter. Int J Obes Relat Metab Disord 2001;25:519-528.
PUBMED | CROSSREF
46. McGrath SA, Gibney MJ. The effects of altered frequency of eating on plasma lipids in free-living healthy males on normal self-selected diets. Eur J Clin Nutr 1994;48:402-407.
PUBMED
47. Jenkins DJ, Wolever TM, Vuksan V, Brighenti F, Cunnane SC, Rao AV, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. N Engl J Med 1989;321:929-934.
PUBMED | CROSSREF

48. Arnold L, Ball M, Mann J. Metabolic effects of alterations in meal frequency in hypercholesterolaemic individuals. Atherosclerosis 1994;108:167-174.
PUBMED | CROSSREF

49. Farshchi HR, Taylor MA, Macdonald IA. Regular meal frequency creates more appropriate insulin sensitivity and lipid profiles compared with irregular meal frequency in healthy lean women. Eur J Clin Nutr 2004;58:1071-1077.
PUBMED | CROSSREF

50. Farshchi HR, Taylor MA, Macdonald IA. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. Am J Clin Nutr 2005;81:16-24.
PUBMED | CROSSREF

51. Stote KS, Baer DJ, Spears K, Paul DR, Harris GK, Rumpler WV, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. Am J Clin Nutr 2007;85:981-988.
PUBMED | CROSSREF

52. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 2009;325:201-204.
PUBMED | CROSSREF

53. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. Ageing Res Rev 2017;39:36-45.
PUBMED | CROSSREF

54. 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;101:6659-6663.
PUBMED | CROSSREF

55. Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, et al. Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial. Am J Physiol Endocrinol Metab 2007;293:E197-E202.
PUBMED | CROSSREF

56. Meyer TE, Kovács SJ, Ehsani AA, Klein S, Holloszy JO, Fontana L. Long-term caloric restriction ameliorates the decline in diastolic function in humans. J Am Coll Cardiol 2006;47:398-402.
PUBMED | CROSSREF

57. Riordan MM, Weiss EP, Meyer TE, Ehsani AA, Racette SB, Villareal DT, et al. The effects of caloric restriction- and exercise-induced weight loss on left ventricular diastolic function. Am J Physiol Heart Circ Physiol 2008;294:H1174-H1182.
PUBMED | CROSSREF

58. Stein PK, Soare A, Meyer TE, Cangemi R, Holloszy JO, Fontana L. Caloric restriction may reverse age-related autonomic decline in humans. Aging Cell 2012;11:644-650.
PUBMED | CROSSREF

59. Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, et al. 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:673-683.
PUBMED | CROSSREF

60. Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A 2014;111:16647-16653.
PUBMED | CROSSREF

61. Planavila A, Redondo I, Hondares E, Vinciguerra M, Munts C, Iglesias R, et al. Fibroblast growth factor 21 protects against cardiac hypertrophy in mice. Nat Commun 2013;4:2019.
PUBMED | CROSSREF

62. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev 2017;39:46-58.
PUBMED | CROSSREF

63. Horne BD, Muhlestein JB, May HT, Carlquist JF, Lappé DL, Bair TL, et al. Relation of routine, periodic fasting to risk of diabetes mellitus, and coronary artery disease in patients undergoing coronary angiography. Am J Cardiol 2012;109:1558-1562.
PUBMED | CROSSREF

64. Stekovic S, Hofer SJ, Tripolt N, Aon MA, Royer P, Pein L, et al. Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. Cell Metab 2019;30:462-476.e5.
PUBMED | CROSSREF

65. Heilbronn LK, Smith SR, Martin CK, Anton SD, Ravussin E. Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. Am J Clin Nutr 2005;81:69-73.
PUBMED | CROSSREF

66. Eshghinia S, Mohammadzadeh F. The effects of modified alternate-day fasting diet on weight loss and CAD risk factors in overweight and obese women. J Diabetes Metab Disord 2013;12:4.
PUBMED | CROSSREF

67. Varady KA, Bhutani S, Church EC, Klempel MC. Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults. Am J Clin Nutr 2009;90:1138-1143.
PUBMED | CROSSREF

68. Klempel MC, Kroeger CM, Varady KA. Alternate day fasting (ADF) with a high-fat diet produces similar weight loss and cardio-protection as ADF with a low-fat diet. Metabolism 2013;62:137-143.
PUBMED | CROSSREF

69. Hoddy KK, Kroeger CM, Trepanowski JF, Barnosky A, Bhutani S, Varady KA. Meal timing during alternate day fasting: impact on body weight and cardiovascular disease risk in obese adults. Obesity (Silver Spring) 2014;22:2524-2531.
PUBMED | CROSSREF

70. Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. Obesity (Silver Spring) 2013;21:1370-1379.
PUBMED | CROSSREF

71. Varady KA, Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Haus JM, et al. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. Nutr J 2013;12:146.
PUBMED | CROSSREF

72. Klempel MC, Kroeger CM, Bhutani S, Trepanowski JF, Varady KA. Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. Nutr J 2012;11:98.
PUBMED | CROSSREF

73. Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes 2011;35:714-727.
PUBMED | CROSSREF

74. Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metab 2015;22:86-99.
PUBMED | CROSSREF

75. Cheng CW, Villani V, Buono R, Wei M, Kumar S, Yilmaz OH, et al. Fasting-mimicking diet promotes Ngn3-driven β-cell regeneration to reverse diabetes. Cell 2017;168:775-788.e12.
PUBMED | CROSSREF

76. Wei M, Brandhorst S, Shelehchi M, Mirzaei H, Cheng CW, Budniak J, et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. Sci Transl Med 2017;9:eaai8700.
PUBMED | CROSSREF

77. Abiri B, Vafa M. Dietary restriction, cardiovascular aging and age-related cardiovascular diseases: a review of the evidence. Adv Exp Med Biol 2019;1178:113-127.
PUBMED | CROSSREF

78. Mirzaei H, Di Biase S, Longo VD. Dietary interventions, cardiovascular aging, and disease: animal models and human studies. Circ Res 2016;118:1612-1625.
PUBMED | CROSSREF

79. Harvie M, Wright C, Pegington M, McMullan D, Mitchell E, Martin B, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. Br J Nutr 2013;110:1534-1547.
PUBMED | CROSSREF

80. Harvie M, Howell A. Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight and normal weight subjects-a narrative review of human and animal evidence. Behav Sci (Basel) 2017;7:E4.
PUBMED | CROSSREF

81. Johnson JB, Summer W, Cutler RG, Martin B, Hyun DH, Dixit VD, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med 2007;42:665-674.
PUBMED | CROSSREF

82. Malinowski B, Zalewska K, Węsierska A, Sokołowska MM, Socha M, Liczner G, et al. Intermittent fasting in cardiovascular disorders-an overview. Nutrients 2019;11:E673.
PUBMED | CROSSREF

 https://doi.org/10.12997/jla.2020.9.1.140

83. Hoddy KK, Bhutani S, Phillips SA, Varady KA. Effects of different degrees of insulin resistance on endothelial function in obese adults undergoing alternate day fasting. Nutr Healthy Aging 2016;4:63-71.
PUBMED | CROSSREF

84. Carter S, Clifton PM, Keogh JB. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized noninferiority trial. JAMA Netw Open 2018;1:e180756.
PUBMED | CROSSREF

85. Arnason TG, Bowen MW, Mansell KD. Effects of intermittent fasting on health markers in those with type 2 diabetes: a pilot study. World J Diabetes 2017;8:154-164.
PUBMED | CROSSREF

86. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. Cell Metab 2018;27:1212-1221.e3.
PUBMED | CROSSREF

87. Varady KA, Bhutani S, Klempel MC, Kroeger CM. Comparison of effects of diet versus exercise weight loss regimens on LDL and HDL particle size in obese adults. Lipids Health Dis 2011;10:119.
PUBMED | CROSSREF

88. Catenacci VA, Pan Z, Ostendorf D, Brannon S, Gozansky WS, Mattson MP, et al. A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity. Obesity (Silver Spring) 2016;24:1874-1883.
PUBMED | CROSSREF

89. Aksungar FB, Topkaya AE, Akyildiz M. Interleukin-6, C-reactive protein and biochemical parameters during prolonged intermittent fasting. Ann Nutr Metab 2007;51:88-95.
PUBMED | CROSSREF

90. Faris MA, Hussein RN, Al-Kurd RA, Al-Fararjeh MA, Bustanji YK, Mohammad MK. Impact of ramadan intermittent fasting on oxidative stress measured by urinary 15-f(2t)-isoprostane. J Nutr Metab 2012;2012:802924.
PUBMED | CROSSREF

91. Madkour MI, T El-Serafi A, Jahrami HA, Sherif NM, Hassan RE, Awadallah S, et al. Ramadan diurnal intermittent fasting modulates SOD2, TFAM, Nrf2, and sirtuins (SIRT1, SIRT3) gene expressions in subjects with overweight and obesity. Diabetes Res Clin Pract 2019;155:107801.
PUBMED | CROSSREF

92. Zhu Y, Yan Y, Gius DR, Vassilopoulos A. Metabolic regulation of Sirtuins upon fasting and the implication for cancer. Curr Opin Oncol 2013;25:630-636.
PUBMED | CROSSREF

93. Antunes F, Erustes AG, Costa AJ, Nascimento AC, Bincoletto C, Ureshino RP, et al. Autophagy and intermittent fasting: the connection for cancer therapy? Clinics (Sao Paulo) 2018;73:e814s.
PUBMED | CROSSREF

94. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci 2018;19:63-80.
PUBMED | CROSSREF

95. Webber J, Macdonald IA. The cardiovascular, metabolic and hormonal changes accompanying acute starvation in men and women. Br J Nutr 1994;71:437-447.
PUBMED | CROSSREF

96. Li L, Wang Z, Zuo Z. Chronic intermittent fasting improves cognitive functions and brain structures in mice. PLoS One 2013;8:e66069.
PUBMED | CROSSREF

97. Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, Laferla FM, et al. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiol Dis 2007;26:212-220.
PUBMED | CROSSREF

98. Cignarella F, Cantoni C, Ghezzi L, Salter A, Dorsett Y, Chen L, et al. Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. Cell Metab 2018;27:1222-1235.e6.
PUBMED | CROSSREF

99. Rangan P, Choi I, Wei M, Navarrete G, Guen E, Brandhorst S, et al. Fasting-mimicking diet modulates microbiota and promotes intestinal regeneration to reduce inflammatory bowel disease pathology. Cell Reports 2019;26:2704-2719.e6.
PUBMED | CROSSREF

https://doi.org/10.12997/jla.2020.9.1.140

Journal of Lipid and Atherosclerosis

100. Zhou ZL, Jia XB, Sun MF, Zhu YL, Qiao CM, Zhang BP, et al. Neuroprotection of fasting mimicking diet on MPTP-induced Parkinson's disease mice via gut microbiota and metabolites. Neurotherapeutics 2019;16:741-760.
PUBMED | CROSSREF

101. Lo Re O, Panebianco C, Porto S, Cervi C, Rappa F, Di Biase S, et al. Fasting inhibits hepatic stellate cells activation and potentiates anti-cancer activity of Sorafenib in hepatocellular cancer cells. J Cell Physiol 2018;233:1202-1212.
PUBMED | CROSSREF

102. Di Biase S, Lee C, Brandhorst S, Manes B, Buono R, Cheng CW, et al. Fasting-mimicking diet reduces HO-1 to promote T cell-mediated tumor cytotoxicity. Cancer Cell 2016;30:136-146.
PUBMED | CROSSREF

103. D'Aronzo M, Vinciguerra M, Mazza T, Panebianco C, Saracino C, Pereira SP, et al. Fasting cycles potentiate the efficacy of gemcitabine treatment in *in vitro* and *in vivo* pancreatic cancer models. Oncotarget 2015;6:18545-18557.
PUBMED | CROSSREF

104. Safdie F, Brandhorst S, Wei M, Wang W, Lee C, Hwang S, et al. Fasting enhances the response of glioma to chemo- and radiotherapy. PLoS One 2012;7:e44603.
PUBMED | CROSSREF

105. Wei S, Han R, Zhao J, Wang S, Huang M, Wang Y, et al. Intermittent administration of a fasting-mimicking diet intervenes in diabetes progression, restores β cells and reconstructs gut microbiota in mice. Nutr Metab (Lond) 2018;15:80.
PUBMED | CROSSREF

106. Choi IY, Piccio L, Childress P, Bollman B, Ghosh A, Brandhorst S, et al. A Diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. Cell Reports 2016;15:2136-2146.
PUBMED | CROSSREF