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Metabolic Effects of Intermittent Fasting

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Keywords

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Abstract

The objective of this review is to provide an overview of intermittent fasting regimens, summarize the evidence on the health benefits of intermittent fasting, and discuss physiological mechanisms by which intermittent fasting might lead to improved health outcomes. A MEDLINE search was performed using PubMed and the terms "intermittent fasting," "fasting," "time-restricted feeding," and "food timing." Modified fasting regimens appear to promote weight loss and may improve metabolic health. Several lines of evidence also support the hypothesis that eating patterns that reduce or eliminate nighttime eating and prolong nightly fasting intervals may result in sustained improvements in human health. Intermittent fasting regimens are hypothesized to influence metabolic regulation via effects on (*a*) circadian biology, (*b*) the gut microbiome, and (*c*) modifiable lifestyle behaviors, such as sleep. If proven to be efficacious, these eating regimens offer promising nonpharmacological approaches to improving health at the population level, with multiple public health benefits.

Contents

INTRODUCTION

There is no shortage of information available to the public regarding various forms of intermittent fasting and the purported health benefits of such practices; in fact, an October 2016 internet search using the terms "diet fasting intermittent alternate day" had more than 210,000 hits. In contrast, there is a shortage of evidence-based support for intermittent fasting that can be used to generate recommendations for public health practice. Intermittent fasting—that is, periods of voluntary abstinence from food and drink—is an ancient practice followed in a variety of different formats by populations globally (12). The popular press includes numerous publications, blogs, news articles, and diet recommendations related to intermittent fasting and intermittent caloric restriction. For example, in 2013, Mosley & Spencer (75) published a best-selling book titled "The FastDiet," which touts the benefits of restricting energy intake severely for 2 days a week but eating normally during the rest of the week. A major online retailer lists more than 1,500 items related to intermittent fasting, including diet books, recipe collections, apps, and food supplements. There is a high level of interest in intermittent fasting and metabolic health in the scientific community, as well as among the lay public and media. The number of review articles on the general topic nearly matches the number of primary human and animal model research studies published during 2014–2016 (3–6, 8, 9, 19–23, 29, 40, 44, 48, 51, 53, 56, 58, 59, 63, 66–68, 72, 76, 84, 91, 92, 103, 104, 108, 116, 121). Together, striking evidence from animal studies and suggestive evidence from human studies strongly support the need for rigorous clinical investigation of using intermittent fasting regimens to improve health.

This review provides an overview of intermittent fasting regimens (**Table 1**), summarizes the evidence for the health benefits of intermittent fasting, and discusses physiological mechanisms by which intermittent fasting might lead to improved health outcomes. We focus on human intervention studies, but also present compelling evidence from rodent models and reviews. The bulk of scientific evidence for the health benefits of intermittent fasting primarily comes from studies of male rodent models. Human studies have largely been limited to observational studies of religious fasting (e.g., during Ramadan), cross-sectional studies of eating patterns associated with health outcomes, and experimental studies with modest sample sizes. For the purposes of this review, the health outcomes of interest are changes in weight and in metabolic parameters

Table 1 Intermittent fasting regimens hypothesized to impact health outcomes

Type of fast	Description
Complete alternate-day fasting	Involves alternating fasting days (no energy-containing foods or beverages consumed) with eating days (foods and beverages consumed ad libitum)
Modified fasting regimens	Allows consumption of 20–25% of energy needs on scheduled fasting days; the basis for the popular 5:2 diet, which involves severe energy restriction for 2 nonconsecutive days per week and ad libitum eating for the other 5 days
Time-restricted feeding	Allows ad libitum energy intake within specific time frames, inducing regular, extended fasting intervals; studies of <3 meals per day are indirect examinations of a prolonged daily or nightly fasting period
Religious fasting	Variety of fasting regimens undertaken for religious or spiritual purposes
Ramadan fasting	A fast from sunrise to sunset during the holy month of Ramadan; the most common dietary practice is to consume one large meal after sunset and one lighter meal before dawn. Thus, the feast and fast periods of Ramadan are approximately 12 hours in length
Other religious fasts	Members of the Church of Jesus Christ of Latter-Day Saints routinely abstain from food and drink for extended periods of time. Some Seventh-day Adventists consume their last of two daily meals in the afternoon, resulting in an extended nighttime fasting interval that may be biologically important

associated with type 2 diabetes, cardiovascular disease, and cancer. We also present an overview of the major physiological mechanisms hypothesized to link fasting regimens with human health: (*a*) circadian biology, (*b*) the gut microbiome, and (*c*) modifiable lifestyle behaviors, such as diet, activity, and sleep. In conclusion, we present summary points regarding the evidence base for intermittent fasting as an intervention for improving human health and propose future issues that should be addressed in rigorously designed clinical trials.

METHODS

We present a brief background of the considerable literature on intermittent fasting in animal models to provide context for the translational research that has been completed in humans. For human studies, we focus on findings from interventions that examined alternate-day fasting, modified fasting regimens, and time-restricted feeding (**Table 1**). A MEDLINE search was performed using PubMed and the terms "intermittent fasting," "fasting," "time-restricted feeding," and "food timing." In addition, we culled relevant papers from the reference lists of research papers, as well as reviews of fasting regimens (67, 84, 108). Inclusion criteria for human studies were: (*a*) randomized controlled trials and nonrandomized trials, (*b*) adult male or female participants, and (*c*) end points that included changes in body weight or biomarkers of the risk of diabetes, cardiovascular disease, or cancer. This is not a formal review or a meta-analysis: These studies cannot be combined because they are markedly dissimilar with regards to the interventions, the comparison groups (or lack thereof), sample composition, study design, and intervention duration. Intermittent fasting performed as a religious practice (e.g., during Ramadan) is reviewed separately and with less detail because these eating patterns are not motivated by health concerns and have generally been studied using observational study designs.

HUMAN INTERVENTION STUDIES

We identified 16 intervention trials in the literature (**Table 2**) that support the efficacy of intermittent fasting on human health. Most of the studies enrolled fewer than 50 participants for

Table 2 Studies of intermittent fasting interventions in humans that assessed metabolic biomarkers of diabetes, cardiovascular disease, and cancer risk

First author and year (reference number)	Sample size (*N*)	Participants	Intervention duration and type of fasting	Comparison group or condition	Weight change	Changes in fasting concentrations of biomarkers		
						Gluco-regulatory markers	Lipids	Inflammatory markers
Alternate-day fasting								
Halberg 2005 (43)	8 M	Healthy nonobese adults	15 days: alternate-day fasting (20-hour fasting intervals)	None	NS	↓ glucose NS insulin	ND	↑ adiponectin ↓ leptin NS IL-6 NS TNF-α
Heilbronn 2005 (49)	8 F 8 M	Nonobese adults	22 days: no caloric intake every other day (36-hour fasting intervals)	None	↓	NS glucose ↓ insulin	ND	ND
Horne 2013 (54)	20 F 10 M	Healthy adults	1 day: water only (28-hour fasting interval)	None	↓	↓ glucose ↓ insulin	↑ LDL ↑ HDL ↓ TGs	NS CRP NS adiponectin
Modified fasting regimens								
Williams 1998 (117)	31 F 23 M	Overweight or obese diabetic adults	20 weeks: 1 day per week fast OR 5-day consecutive fasts every 5 weeks (400–600 kcal on fasting days)[a]	1,200–1,500 kcal weight-loss diet	↓	NS glucose NS insulin	NS LDL NS HDL NS TGs	ND
Johnson 2007 (57)	8 F 2 M	Overweight adults with asthma	8 weeks: <20% of usual intake on alternate days; ad libitum diet on nonfasting days	None	↓	NS glucose NS insulin	NS LDL NS HDL ↓ TGs	NS CRP NS leptin ↓ TNF-α ↓ BDNF
Varady 2009 (109)	12 F 8 M	Obese adults	8 weeks: weight-loss diet with alternate-day modified fasting (~25% of total energy needs)	None	↓	ND	↓LDL NS HDL ↓ TGs	ND
Harvie 2011 (45)	107 F	Young, overweight adults	6 months: 25% energy restriction 2 days per week	25% energy restriction 7 days per week	NS	NS glucose ↓ insulin	NS LDL NS HDL NS TGs	NS CRP NS adiponectin NS leptin NS BDNF

(*Continued*)

Table 2 (*Continued*)

First author and year (reference number)	Sample size (*N*)	Participants	Intervention duration and type of fasting	Comparison group or condition	Weight change	Changes in fasting concentrations of biomarkers		
						Gluco-regulatory markers	Lipids	Inflammatory markers
Bhutani 2013 (10)	39 F 2 M	Obese adults	12 weeks: 25% of energy needs alternating with ad libitum intake	Usual eating habits control group	↓	NS glucose NS insulin	NS LDL NS HDL NS TGs	NS CRP
Eshghinia 2013 (28)	15 F	Overweight or obese adults	6 weeks: 25–30% energy needs on Saturday, Monday, Wednesday; ad libitum other days	None	↓	ND	NS LDL NS HDL NS TGs	ND
Harvie 2013 (46)	77 F	Overweight or obese women	3 months: 25% energy restriction 2 consecutive days per week	25% energy restriction all days of week	NS	NS glucose NS HbA1c ↓ insulin	NS LDL NS HDL NS TGs	NS adiponectin NS leptin NS IL-6 NS TNF-α
Varady 2013 (110)	22 F 8 M	Obese adults	12 weeks: weight-loss diet with alternate-day modified fasting (~25% of energy needs)	Usual eating habits control group	↓	ND	NS LDL NS HDL ↓ TGs	↓ CRP ↑ adiponectin
Hoddy 2016 (51)	50 F 9 M	Obese adults	8 weeks: weight-loss diet with alternate-day modified fasting (25% of energy needs)	None	↓	↓ glucose ↓ insulin	ND	↓ leptin
Time-restricted feeding								
Carlson 2007 (15); Stote 2007 (99)	10 F 5 M	Normal weight, middle-aged adults	8 weeks: 1 meal per day	8 weeks: 3 meals per day (crossover design)	↓	↓ glucose NS insulin	↓ LDL ↑ HDL ↑ TGs	NS leptin NS resistin NS BDNF

(*Continued*)

Table 2 (*Continued*)

First author and year (reference number)	Sample size (*N*)	Participants	Intervention duration and type of fasting	Comparison group or condition	Weight change	Changes in fasting concentrations of biomarkers		
						Gluco-regulatory markers	Lipids	Inflammatory markers
LeChemi-nant 2013 (65)	29 M	Normal weight young men	2 weeks: nightly fasting from 7:00 PM to 6:00 AM (≥11 hours)	2 weeks: usual nightly fasting interval (crossover design)	↓	ND	ND	ND
Chowd-hury 2016 (22)	16 F 8 M	Obese adults	1 day: prolonged nighttime fasting until lunch meal (≥13 hours)	1 day: breakfast and lunch meals (crossover design)	ND	↑ glucose and ↑ insulin post-lunch	↓ FFA post-lunch	↓ leptin post-lunch
Chowd-hury 2016 (21)	15 F 8 M	Obese adults	6 weeks: prolonged nighttime fasting until lunch meal at noon	Control group: inclusion of breakfast each morning	↑ in both groups; NS be-tween groups	NS glucose NS insulin	↑ total choles-terol in both groups; NS between groups; NS LDL NS HDL NS TG NS FFA	NS CRP NS IL-6 NS leptin NS adiponectin

↓ denotes a statistically significant decrease ($p < 0.05$); ↑ denotes a statistically significant increase ($p < 0.05$).
Abbreviations: BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; F, female; FFA, free fatty acid; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; M, male; ND, no data reported; NS, not statistically significant ($p \geq 0.05$); TG, triglyceride; TNF-α, tumor necrosis factor-α.
[a]There were no significant differences between fasting groups.

relatively short intervention periods, which, unfortunately, limits the statistical power of analyses of relevant outcomes.

Alternate-Day Fasting

Alternate-day fasting involves alternating fasting days, during which no calories are consumed, and feeding days, during which foods and beverages are consumed ad libitum. In 2007, Varady & Hellerstein (111) reviewed alternate-day fasting studies in rodents and concluded that this fasting

regimen was as effective as simple caloric restriction in reducing obesity-associated body weight and fasting insulin and glucose concentrations. Alternate-day fasting in rodent models of obesity has also been shown to reduce total plasma cholesterol and triglyceride (TG) concentrations, reduce liver steatosis and inflammatory gene expression, and have beneficial effects on cancer risk factors, such as cell proliferation (40, 59, 111, 121).

Four intervention studies have explored the metabolic effects of alternate-day fasting (**Table 2**) (3, 43, 49, 54). Sample sizes were modest and ranged from 8 to 30 normal weight adults and 10 overweight or obese adults (3). No information was provided about the physical activity levels of these participants. Two of three studies reported significant weight loss, although we question the clinical relevance of weight loss in a 1-day study (54). In the 22-day study of alternate-day fasting, participants experienced a mean 2.5% weight loss ($p < 0.001$) (49). Three of the studies found a significant decrease in at least one glucoregulatory marker. In contrast, the study that included overweight and obese participants did not and, in fact, reported a detrimental effect of 1-day total fasting on postprandial glucose and insulin the following day (3). This same study and another examined lipid levels with mixed results. The 1-day fasting study observed improved postprandial TGs the following day. One study observed improvements in high-density lipoprotein (HDL) cholesterol and fasting TGs, but increased low-density lipoprotein (LDL) cholesterol at the study end point. One of two studies assessing inflammation found significant improvements in inflammatory biomarkers.

One caveat of this research is that three of these four studies enrolled normal weight adults who were unlikely to show substantial improvements in metabolic risk factors. Although not a focus of this review, hunger and mental status, as well as post-fast energy intake, are important outcomes to consider with extended fasting during waking hours. Appleton & Baker (4) recently reported that in women ($n = 16$), a 2-day fast resulted in distraction, but not hunger, and was associated with lower mood and perceived work performance compared with 2 days prior to and following the fasting period. Antoni et al. (3) observed that a 1-day fast resulted in a 30% reduction in energy intake 3 days post-fast. Heilbronn et al. (49) noted that participants reported considerable hunger on fasting days, which did not decrease over time.

The sparse data on alternate-day fasting suggest that this regimen can result in modest weight loss and lead to improvements in some metabolic parameters. However, reports of extreme hunger while fasting indicate that this may not be a feasible public health intervention.

Modified Fasting Regimens

Modified fasting regimens generally specify that energy consumption is limited to 20–25% of energy needs on regularly scheduled fasting days. In these studies, the term fasting is used to describe periods of severely limited energy intake rather than no energy intake. This type of regimen, also called intermittent energy restriction, is the basis for the popular 5:2 diet, which involves energy restriction for 2 nonconsecutive days per week and unrestricted eating during the other 5 days of the week (75).

Varady et al. (112) have investigated the impacts of modified alternate-day fasting in mice. In a trial comparing 85% energy restriction on alternate fasting days to ad libitum chow, the energy-restricted condition resulted in decreased visceral fat, leptin, and resistin, and increases in adiponectin. Similar studies conducted by this research group also found that in mice these fasting regimens appear to reduce adipocyte size, cell proliferation, and levels of insulin-like growth factor 1 (113–115).

We identified nine trials of modified fasting in humans (**Table 2**) (10, 28, 45, 46, 51, 57, 109, 110, 117). Study sample sizes ranged from 10 to 107 adults, all of whom were overweight or

obese. The duration of the fasting interventions ranged from 2 to 6 months. Of the nine studies, only one instituted weekly exercise goals (117). Overall, 7 of 9 studies (78%) reported statistically significant weight loss, which ranged from 3.2% in comparison with a control group (10) during a 12-week period to 8.0% in a one-arm trial during an 8-week period (57). Three of six studies found significant decreases in fasting insulin, and one found reductions in fasting glucose. Three of eight studies found significant improvements in circulating LDL cholesterol or TGs. Three of six studies found significant improvements in inflammatory markers, including C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), adiponectin, leptin, and brain-derived neurotrophic factor (BDNF). Although Hoddy et al. (51) observed significant increases in the area under the curve of acutely measured postprandial ghrelin response to a meal tolerance test at the end of the study compared with baseline, participants' subjective hunger during this meal tolerance test was unchanged after the intervention. Interestingly, participants' feelings of fullness and levels of PYY (peptide tyrosine tyrosine) increased. Thus, although some changes in gut peptide levels associated with hunger (i.e., increased ghrelin) occur with this modified fasting regimen, there were net beneficial effects on feelings related to reduced energy intake. Half of these studies assessed some aspect of mood or other behavioral side effects in response to the fasting regimen (45, 46, 57, 110). In general, these studies reported that a small proportion (generally <15%) of participants reported negative side effects, such as feeling cold, irritable, low energy, or hunger. However, there were mean improvements in mood, including reductions in tension, anger, and fatigue, and increases in self-confidence and positive mood.

Three of the nine trials summarized above compared modified fasting regimens with simple energy restriction (45, 46, 117). As shown in **Table 2**, the weight loss regimens were either 1,200–1,500 kcal (117) or 25% energy restriction per day (45, 46). One of these studies instituted weekly exercise goals (117). In only one case did the fasting regimen result in significantly more weight loss (mean loss 9.6%) than a standard weight-loss diet (mean loss 5.5%) (117). In two of these studies, there were significantly reduced insulin concentrations compared with energy restriction, but no other differences in biomarker concentrations. The 12-week, controlled weight-loss trial found that the modified fasting regimen combined with an exercise protocol produced significantly superior weight loss results (mean loss 6.5%) compared with fasting alone (mean loss 3.2%) or exercise alone (mean loss 1.1%) (10).

Reviews and meta-analyses have compared the efficacy of fasting regimens with continuous energy restriction (6, 44, 48, 91, 107). The authors of these publications unanimously report that, given the current state of the evidence, the overall metabolic benefits of fasting regimens are not superior to those of continuous energy restriction. Furthermore, they state that studies of fasting regimen interventions that are properly powered and controlled, and of sufficient duration, are lacking and needed.

Results from the limited number of intervention trials of modified fasting regimens suggest that these eating patterns result in weight loss, with modest and mixed effects on glucoregulatory markers, lipids, and inflammatory markers.

Time-Restricted Feeding

Two recent publications have reviewed time-restricted feeding in rodent models (67, 84). We identified 13 studies that had daily fasting intervals ranging from 12 to 21 hours in numerous rodent models, with variability in coordination with light and dark phases and composition of chow. Despite the heterogeneity of published rodent studies, overall, time-restricted feeding was associated with reductions in body weight, total cholesterol, TGs, glucose, insulin, interleukin 6 (IL-6), and TNF-α, as well as with improvements in insulin sensitivity. Interestingly, positive

health outcomes occurred despite the variable effects of intermittent fasting on weight loss. Nearly all studies of rodent fasting regimens, including time-restricted feeding, have been conducted in male mice. We have published a study that recapitulates the overall metabolic benefit of time-restricted feeding as an intervention strategy in an obese, postmenopausal female mouse model (23). Thus, the time-restricted feeding intervention paradigm seems to be translational to both men and women.

Time-restricted feeding research in animals highlights the potential importance of synchronizing intermittent fasting regimens with daily circadian rhythms. Rodents fed ad libitum high-fat diet (HFD) chow eat throughout the night and the day, disrupting their normal nocturnal feeding cycle. These ad libitum HFD-fed mice become obese and metabolically dysfunctional, and can develop type 2 diabetes. It was unknown whether HFD-induced metabolic dysfunction resulted from HFD content, increased net caloric intake, disruption of circadian rhythms, or a combination of these. Interestingly, mice whose HFD feeding was restricted to 8 hours during the normal nocturnal eating time consumed equivalent energy, but were protected from obesity, hyperinsulinemia, hepatic steatosis, and inflammation compared with ad libitum HFD-fed mice (47). Time-restricted feeding also is effective as an intervention for diet-induced obesity and associated metabolic dysfunction (17, 23).

We identified only four trials in humans that investigated the impacts of time-restricted feeding interventions that prolong the duration of nighttime fasting. Two of these crossover studies found significant reductions in weight. A study in 29 normal weight men (2 weeks per study condition) prescribed a nighttime fasting interval of ≥11 hours, which resulted in a significant weight change difference between the intervention [−0.4 (SD 1.1) kg] and control [+0.6 (SD 0.9) kg] conditions, equivalent to a 2.1% weight loss (65). No biomarkers were assessed. Another crossover study reported a 4.1% weight loss effect of consuming a single meal in the afternoon each day for 8 weeks without calorie restriction compared with an isocaloric diet consumed as three meals per day (15, 99). The one meal per day condition was also associated with reductions in fasting glucose and improvements in LDL and HDL cholesterol. Although self-reported hunger was higher in the morning for those consuming one meal per day, this fasting regimen was considered acceptable because there were no mean changes in measurements of tension, depression, anger, vigor, fatigue, or confusion.

The long-term metabolic benefits associated with eating or not eating breakfast—that is, extending the nighttime fast until the lunch meal—are of great research and public interest. Focusing specifically on the omission of breakfast (equivalent to a ≥13-hour nighttime fast), Chowdhury and colleagues (21, 22) have conducted both a 1-day crossover trial and a 6-week intervention trial in obese individuals. The acute morning and post-lunch effects of omitting the breakfast meal were assessed in the 1-day study. On the day that they did not eat breakfast, participants were hungrier at lunchtime and had higher plasma levels of acetylated ghrelin compared with their levels on the breakfast day. Their post-lunch postprandial glucose and insulin levels were higher on the breakfast-free day, but they did not eat more calories at lunch. They had lower postprandial PYY, leptin, and acetylated ghrelin levels without a change in appetite later in the afternoon compared with the breakfast day. Satiety- and appetite-regulating hormones and peptides were affected by prolonged morning fasting, but these alterations did not significantly affect calorie intake. Interestingly, in their 6-week controlled trial, they observed no benefit with respect to weight change, glycemic control, lipids, or inflammatory markers for the group omitting the breakfast meal compared with the control group.

Studies in rodents have demonstrated that restricting the availability of food to the normal nighttime feeding cycle improves metabolic profiles and reduces the risk of obesity and obesity-related conditions, such as nonalcoholic fatty liver disease, and chronic diseases, such as diabetes

and cancer. Results from small clinical studies of time-restricted feeding have been mixed. However, the potential importance of aligning food intake with daytime hours for metabolic health in humans is also supported by the epidemiological evidence described in the next section.

HUMAN OBSERVATIONAL STUDIES

Religious Fasting

Fasting is an important practice in many religions, for both spiritual and physical benefits. Published research on religious practice–based fasting regimens is almost entirely observational. Therefore, we provide only an overview of these regimens.

Ramadan fasting. It is an important component of Islamic practice for healthy adult Muslims to fast from sunrise to sunset during the holy month of Ramadan. In addition, fluid intake, cigarette smoking, and medications are forbidden. Depending on the geographical location of those who are fasting during Ramadan, day fasting can vary from 11 to 22 hours. Islamic fasting during Ramadan does not require energy restriction; however, as the intake of food and fluid becomes less frequent, changes in body weight may occur.

A 2012 meta-analysis of 35 studies examined weight changes during Ramadan. Across these studies, participants' ages ranged from 18 to 58 years; just more than half (52%) of studies were conducted with both males and females, 34% were conducted with only males, and 11% were conducted with only females (86). The authors of the review found statistically significant weight loss in 21 (60%) of the studies (86). When pooled, the studies in this meta-analysis showed a 1.24 kg weight reduction [95% confidence interval (CI), −1.60 to −0.88 kg] during the month of Ramadan fasting. Across 16 follow-up studies, the mean weight regained during the 2 weeks following Ramadan was 0.72 kg (95% CI, 0.32 to 1.13 kg).

A 2013 meta-analysis of 30 cohort studies that included healthy young men and women examined whether Ramadan fasting altered biomarkers in addition to weight (62). The primary finding of this meta-analysis was that after Ramadan fasting, LDL and fasting blood glucose levels were decreased in both sexes and also in the entire group compared with levels prior to Ramadan (62). In females, HDL cholesterol levels were significantly increased. In males, there was a significant decrease in weight, total cholesterol, and TGs. Some studies have reported that Ramadan fasts are associated with significantly lower concentrations of inflammatory markers, such as CRP, IL-6, and TNF-α (1, 30). Recent studies have shown that Ramadan fasting practiced by patients with type 2 diabetes for 15–21 days leads to a statistically and clinically significant reduction in hemoglobin A1c (HbA1c) levels of approximately 0.5 points, suggesting that glycemic control is improved substantially during Ramadan fasting in this population (122). Ramadan is the most common form of time-restricted feeding, and it results in transitory weight loss, with mixed evidence for improvements in metabolic markers. However, this feeding pattern is in biological opposition to human circadian rhythms (see Health-Promoting Mechanisms Associated with Fasting, Circadian Biology) and, therefore, unlikely to be pursued as a desirable weight-loss intervention.

Other religious fasts. A study of 448 patients from hospitals in Utah found that followers of the Church of Jesus Christ of Latter-Day Saints who reported routine fasting (29%) exhibited significantly lower weight and lower fasting glucose levels, as well as lower prevalences of diabetes [odds ratio (OR), 0.41; 95% CI, 0.17 to 0.99) and coronary stenosis (OR, 0.42; 95% CI, 0.21 to 0.84) (52). Seventh-day Adventists emphasize a healthy diet and lifestyle as important expressions of their faith, and they live approximately 7.3 years longer than other white adults. This increase

in life expectancy has been primarily attributed to their healthful lifestyle, including not smoking, eating a plant-based diet, and exercising regularly (33). Seventh-day Adventists often consume the last of two daily meals in the afternoon, which results in a prolonged nightly fasting period that may be physiologically important. Although it is unknown what proportion of Seventh-day Adventists adhere to a two meals per day pattern, this pattern is typically chronic, and sometimes lifelong, which would allow sufficient time to achieve stable changes in physiology (99). However, the relationship between health and reduced meal frequency and prolonged nightly fasting among Adventists has not been studied (60).

There are considerable observational data on various forms of religious fasting, most of which suggest that these regimens result in transitory weight loss and mixed impacts on other biomarkers.

Epidemiological Studies

A large and robust literature indicates that shift-work is associated with nighttime eating and increased risks of obesity, diabetes, cardiovascular disease, and cancer (particularly breast cancer) (42, 88, 97, 98, 100). Similarly, data from trials and prospective cohort studies support the hypothesis that consuming the majority of the day's energy earlier in the day, thus prolonging the time during which little or no food intake occurs in the evening or during nighttime, is associated with lower weight and improved health (11, 14, 55, 82, 106). Using data from the National Health and Nutrition Examination Surveys (known as NHANES), we have shown that each 3-hour increase in nighttime fasting duration was associated with significantly reduced odds of elevated HbA1c (OR, 0.81; 95% CI, 0.68 to 0.97) (69) and significantly lower CRP concentrations in women who ate less than 30% of their daily calories after 5:00 PM ($p = 0.01$) (71). We recently published an analysis of the nightly fasting interval in 2,337 breast cancer survivors in the Women's Healthy Eating and Living (known as WHEL) Study (80). Our prospective data analysis indicated that cancer survivors who fasted <13 hours per night during 7 years of follow up had an increased risk of recurrence (HR, 1.36; 95% CI, 1.05 to 1.76). To our knowledge, this is the first human study to demonstrate an association of prolonged nightly fasting with a clinical outcome (70). This analysis also found that a short nightly fast was associated with significantly higher HbA1c and shorter sleep duration.

Although results from observational studies are limited, these data generally support the hypothesis that consuming energy earlier in the day and prolonging the nightly fasting interval may reduce the risk of several common chronic diseases.

HEALTH-PROMOTING MECHANISMS ASSOCIATED WITH FASTING

Figure 1 illustrates the relationships among factors hypothesized to link intermittent fasting and health outcomes. Briefly, intermittent fasting regimens are hypothesized to influence metabolic regulation via effects on (*a*) circadian biology, (*b*) the gut microbiome, and (*c*) modifiable lifestyle behaviors. Negative perturbations of these biological and physiological systems can produce a hostile metabolic milieu, which predisposes individuals to developing obesity, diabetes, cardiovascular disease, and cancer. For further detail about the molecular mechanisms potentially linking fasting with health outcomes, there are two recent comprehensive reviews (66, 67).

Circadian Biology

Organisms have evolved to restrict their activity to the night or day by developing an endogenous circadian clock to ensure that physiological processes are performed at the optimal times (77). The

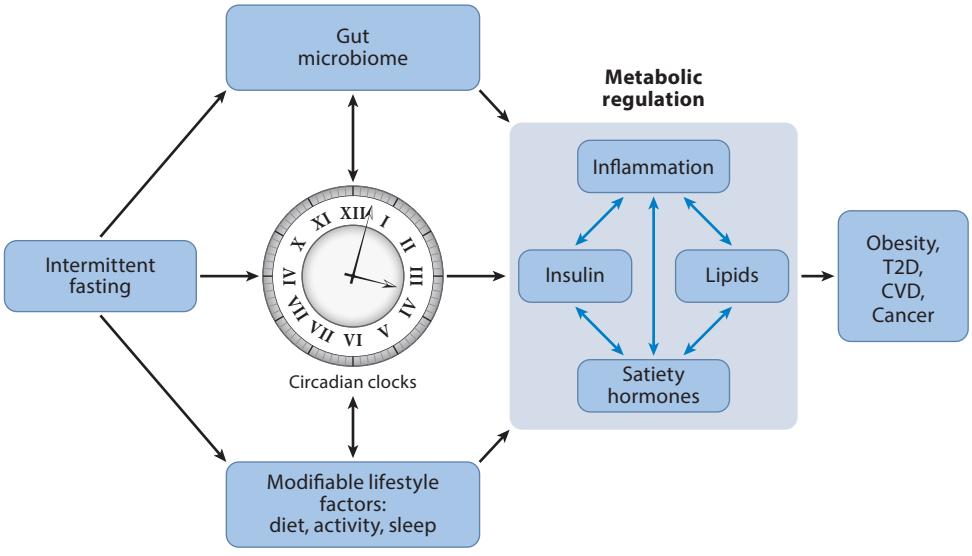


Figure 1

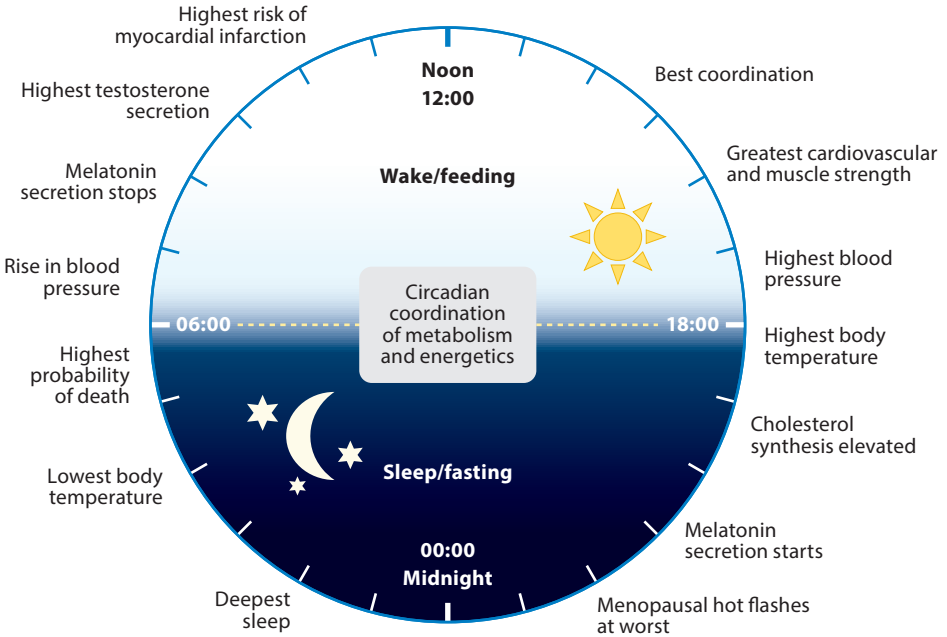
Potential mechanisms linking intermittent fasting with obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), and cancer. Figure modified from Reference 79 with permission.

time of day plays a major part in integrating metabolism and energetics, as well as physiological indices, such as hormonal secretion patterns, physical coordination, and sleep (**Figure 2**) (35). In mammals, the master biological clock is in the suprachiasmatic nucleus of the hypothalamus and is entrained to light and dark stimuli. Similar clock oscillators have been found in peripheral tissues, such as the liver, with feeding as the dominant timing cue (i.e., zeitgeber).

Circadian rhythms occur across 24-hour light–dark clock cycles and include changes in biology and behavior. Desynchronization of the suprachiasmatic nucleus master clock in the brain and peripheral circadian clocks in liver, fat, and skeletal muscle cells may increase the risk of chronic diseases (89). Feeding signals appear to be the dominant timing cue for the rhythms of peripheral clocks, including those that control metabolic pathways. Thus, consuming energy outside the normal feeding phase (i.e., late-night eating in humans) may reset some peripheral clocks and disrupt energy balance (18). The evidence that nutrient signals and meal timing are circadian synchronizers is based largely on animal research (26, 93). However, there is a large and robust literature in humans indicating that shift-work disrupts circadian rhythms and, as mentioned above, is associated with increased risks of cardiometabolic disease and cancer (42, 88, 97, 98, 100).

Circadian rhythms have an impact on metabolism across the day in humans, and these effects are malleable by behavioral intervention. Insulin sensitivity decreases throughout the day and into the night (37). This is, in part, due to the circadian rhythm of insulin secretion and the insulin-impeding action of growth hormone, the pulsatile concentrations of which increase at night. Postprandial insulin and glucose responses to meals increase across the day and into the night (32, 38, 74, 81, 85). Thus, meals consumed at night are associated with greater postprandial glucose and insulin exposure than content-matched meals consumed during the day, leading to increased HbA1c levels and risk of type 2 diabetes over time. Short-term intervention studies designed to perturb circadian rhythms in human participants have metabolic consequences. For example, inducing circadian misalignment in humans by extending the day from a 24-hour to a 28-hour

Wake/feeding	
Liver	Glycogen, cholesterol, and bile acid synthesis
Pancreas	Insulin secretion
Fat	Lipogenesis, adiponectin production
Muscle	Glycolytic metabolism



Sleep/fasting	
Liver	Gluconeogenesis, glycogenolysis, mitochondrial biogenesis
Pancreas	Glucagon secretion
Fat	Lipid catabolism, leptin secretion
Muscle	Oxidative metabolism

Figure 2

Circadian regulation of behaviors, hormones, physiology, metabolism, and energetics. Figure modified from Reference 79 with permission.

cycle causes insulin resistance after only 3 cycles (89). Fasting regimens that exclude or dramatically reduce energy intake in the evening and exclude energy intake during the nighttime synchronize food ingestion with the times of optimal postprandial hormonal response. As circadian rhythm synchronizers, it is hypothesized that fasting and time-restricted feeding regimens that actively impose a diurnal rhythm of food intake aligned with the 24-hour light–dark cycle lead to improved

oscillations in circadian clock gene expression, the reprogramming of molecular mechanisms of energy metabolism, and improved body weight regulation (47). Interested readers are encouraged to read more about these molecular outcomes in detailed reviews on the mechanisms underlying circadian biology (18, 26, 35, 77, 89, 93).

Taken together, these data strongly suggest that the timing of food intake is an important determinant of human health and disease risk.

Gastrointestinal (Gut) Microbiota

Many functions of the gastrointestinal tract exhibit robust circadian, or sleep–wake, rhythms. For example, gastric emptying and blood flow are greater during the daytime than at night and, as described above, metabolic responses to a glucose load are slower in the evening than in the morning (87). Therefore, it is plausible that a chronically disturbed circadian profile may affect gastrointestinal function and impair metabolism and health (27). The gut microbiome impacts metabolic health; its diversity is regulated by diet; and it has a circadian rhythm that is entrained by food signals (83, 102, 105, 119). Rodent studies show that the gut microbiome is highly dynamic, exhibiting daily cyclical fluctuations in compositional diversity. Intermittent fasting may directly influence the gut microbiota, which is the complex, diverse, and vast microbial community that resides in the intestinal tract. Studies suggest that changes in the composition and metabolic function of the gut microbiota in obese individuals may enable an obese microbiota to harvest more energy from the diet than a lean microbiota and, thereby, influence net energy absorption, expenditure, and storage (83, 102, 105). Diet-induced obesity dampens cyclical microbiota fluctuations. Time-restricted feeding in mice, in which food is available only during the nocturnal active phase, partially restores these cyclical fluctuations (123). Thus, cyclical changes in the gut microbiome resulting from diurnal feeding and fasting rhythms contribute to the diversity of gut microflora and represent a mechanism by which the gut microbiome affects host metabolism. An extended fasting period (i.e., gut rest) could also lead to reduced gut permeability and, as a result, to blunted postprandial endotoxemia (50, 61, 64, 73) and to blunted systemic inflammation (94, 102), which are typically elevated in obesity. Recently, investigators from the Salk Institute for Biological Studies reported that a brain–gut pathway activated in the brain during fasting acts to promote energy balance by enhancing gut epithelial integrity (95). Finally, jet-lag-induced dysbiosis in both mice and humans promotes glucose intolerance and obesity that are transferrable to germ-free mice upon fecal transplantation (101).

Fasting regimens appear to have positive impacts on the gut microbiota. Future studies characterizing the health impacts of fasting regimens on the human microbiota have the potential to make important contributions to the field.

Modifiable Lifestyle Behaviors

Fasting regimens have the potential to impact modifiable health behaviors. A study in 8 overweight young adults found that increasing the nightly fasting duration to ≥14 hours resulted in statistically significant decreases in energy intake and weight, as well as improvements in self-reported sleep satisfaction, satiety at bedtime, and energy levels (39).

Energy intake. Metabolic unit studies of alternate-day and modified alternate-day fasting have documented decreased energy consumption. As mentioned above (Human Intervention Studies, Alternate-Day Fasting), even a 1-day fast or 75% calorie restriction was shown to reduce caloric intake by approximately 30% during the subsequent 3 days (3). The Chowdhury et al. study (22)

of skipping breakfast showed no increase in food intake at lunch after the prolonged morning fast and showed no increase in post-lunch appetite. Casazza et al. (16) conducted a systematic review of obesity-related beliefs about weight loss, therein stating that evidence was lacking to support the notion that skipping breakfast independently affected obesity. Several of these authors conducted a randomized controlled weight-loss trial comparing breakfast-skipping, breakfast-eating, and control groups, finding that weight loss was not different among the groups (25). However, the influence of fasting in this study is unclear because the length of fasting across the night and into the morning was not recorded; the minimum difference in the length of morning fasting permissible in the intervention groups was only 1 hour; and the cessation of eating at night was not controlled. Studies of fasting regimens in free-living adults depend on self-reported energy intake, which correlates poorly with objective markers of energy intake (34) and confound associated analyses. Weight change offers an indirect assessment of the impact of intermittent fasting on energy intake and, as shown in **Table 2**, statistically significant weight reduction was observed in 73% of trials of intermittent fasting. Most fasting regimens reduce the total number of hours available for eating and, thereby, may reduce overall energy intake and risk of obesity. The timing of food intake with respect to the 24-hour light–dark cycle likely has an important influence on food intake, as well as on energy efficiency and weight control. Research in shift- and night-workers, who eat most of their daily calories at night and who have an increased risk for obesity, has demonstrated alterations in appetite-regulating hormones (leptin, ghrelin, xenin) that may lead to increases in total energy intake (24, 90, 118).

Energy expenditure. Animal studies indicate that the circadian clock regulates locomotion. Mice on a time-restricted, isocaloric feeding regimen have shown improved muscle coordination toward the end of the feeding period (47). Rodent studies demonstrate that time-restricted feeding regimens increase locomotion (23, 47) and improve circadian activity rhythms (47), an indicator of overall rhythmicity. However, data in humans are sparse about whether intermittent fasting regimens impact energy expenditure among free-living adults. Hoddy et al. (51) did not observe changes in physical activity—assessed by actigraphy at baseline and postintervention—during their alternate-day fasting study. Chowdhury et al. (21) did not observe differences in 24-hour physical activity in the intervention group that omitted the breakfast meal compared with the control group.

Sleep. Numerous observational studies have reported that nighttime eating is associated with reduced sleep duration and poor sleep quality (2, 120), which can lead to insulin resistance and increased risks of obesity, diabetes, cardiovascular disease, and cancer (13, 31, 36, 41, 78, 96). Specifically, eating meals at abnormal circadian times (i.e., late at night) is hypothesized to lead to circadian desynchronization (7) and subsequent disruption of normal sleep patterns. Chowdhury et al. (21) found no effect of regularly skipping the breakfast meal (i.e., prolonging the nighttime fast) on waking time, sleep time, or sleep duration compared with controls. To our knowledge, no other studies have directly examined associations between intermittent fasting and sleep in free-living adults.

The potential effects of prolonged nightly fasting on energy intake, sleep, physical activity, and circadian activity rhythm may act in concert to reduce the risks of cardiometabolic disease and cancer.

CONCLUSIONS

Even a single fasting interval in humans (e.g., overnight) can reduce basal concentrations of many metabolic biomarkers associated with chronic disease, such as insulin and glucose. For

example, patients are required to fast for 8–12 hours before blood draws to achieve steady-state fasting levels for many metabolic substrates and hormones. An important clinical and scientific question is whether adopting a regular, intermittent fasting regimen is a feasible and sustainable population-based strategy for promoting metabolic health. Further, properly powered, controlled clinical research is needed to test whether intermittent fasting regimens can complement or replace energy restriction and, if so, whether they can facilitate long-term metabolic improvements and body weight management. The Summary Points are supported by the current evidence.

Additionally, intermittent fasting regimens attempt to translate the positive effects of fasting regimens in rodents and other mammals into practical eating patterns for reducing the risk of chronic disease in humans. In the Future Issues section, we suggest issues that should be addressed in research investigating intermittent fasting and metabolic health.

This overview suggests that intermittent fasting regimens may be a promising approach to losing weight and improving metabolic health for people who can safely tolerate intervals of not eating, or eating very little, for certain hours of the day, night, or days of the week. If proven to be efficacious, these eating regimens may offer promising nonpharmacological approaches to improving health at the population level with multiple public health benefits.

SUMMARY POINTS

1. Studies in rodents and other nocturnal mammals support the hypothesis that intermittent fasting and restricting the availability of food to the normal nighttime feeding cycle improve metabolic profiles and reduce the risks of obesity and obesity-related conditions, such as nonalcoholic fatty liver disease, and chronic diseases, such as diabetes and cancer. However, data from related human studies are limited regarding the positive impacts of time-restricted feeding (i.e., eating patterns aligned with normal circadian rhythms) on weight or metabolic health.
2. Overall, evidence suggests that intermittent fasting regimens are not harmful physically or mentally (i.e., in terms of mood) in healthy, normal weight, overweight, or obese adults.
3. It appears that almost any intermittent fasting regimen can result in some weight loss. Among the 16 intervention trials included in this review, 11 reported statistically significant weight loss.
4. Alternate-day fasting appeared to result in weight loss, as well as reductions in glucose and insulin concentrations, in the three studies evaluating this regimen. However, this fasting regimen may not be practical because it leads to intense hunger on fasting days. Modified alternate-day fasting regimens result in reduced weight, with reductions ranging from 3.2%, in comparison with a control group (10) during a 12-week period, to 8.0%, in a one-arm trial during an 8-week period (57). There was limited and mixed evidence for reductions in insulin concentrations, improvements in lipids, or reductions in inflammatory factors.
5. Research has not demonstrated that alternate-day fasting regimens produce superior weight loss in comparison to standard, continuous calorie restriction weight-loss plans.
6. There are considerable observational data on various forms of religious fasting, most of which suggest that these regimens result in transitory weight loss and have mixed impacts on other biomarkers.

7. Data are lacking regarding the impacts of intermittent fasting on other health behaviors, such as diet, sleep, and physical activity.
8. There are limited data linking intermittent fasting regimens with clinical outcomes, such as diabetes, cardiovascular disease, cancer, or other chronic diseases, such as Alzheimer's disease.

FUTURE ISSUES

1. Modified fasting regimens appear to promote weight loss and may improve metabolic health. However, there are insufficient data to determine the optimal fasting regimen, including the length of the fasting interval, the number of fasting days per week, the degree of energy restriction needed on fasting days, and recommendations for dietary behavior on nonfasting days.
2. Several lines of evidence support the hypothesis that eating patterns that reduce or eliminate nighttime eating and prolong nightly fasting intervals may result in sustained improvements in human health. Although this hypothesis has not been tested in humans, support from animal research is striking, and data from human time-restricted feeding studies are suggestive. Prolonged nightly fasting (i.e., restricting food intake primarily to daylight hours) may be a simple, feasible, and potentially effective disease prevention strategy at the population level.
3. Large-scale randomized trials of intermittent fasting regimens in free-living adults are needed and should last for at least a year to properly assess whether behavioral and metabolic changes are sustainable and whether they have long-term effects on biomarkers of aging and longevity. Future studies should incorporate objective measures of energy intake, sleep, and energy expenditure; assess numerous markers of disease risk; and enroll diverse populations who disproportionately suffer from obesity and related health maladies.
4. Recommendations for weight loss frequently include advice to eat regular meals to avoid hunger. Some guidelines also advise the consumption of snacks throughout the day. However, current evidence suggests that periods of fasting do not necessarily lead to overeating.

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Errata

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