Obesity

# Intermittent Fasting and Metabolic Health: From Religious Fast to Time-Restricted Feeding

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Over the past 10 to 15 years, intermittent fasting has emerged as an unconventional approach to reduce body weight and improve metabolic health beyond simple calorie restriction. In this review, we summarize findings related to Ramadan and Sunnah fasting. We then discuss the role of caloric restriction not only as an intervention for weight control, but importantly, as a strategy for healthy aging and longevity. Finally, we review the four most common intermittent fasting (IF) strategies used to date for weight management and to improve cardiometabolic health. Weight loss is common after IF but does not appear to be different than daily caloric restriction when compared directly. IF may also provide additional cardiometabolic benefit, such as insulin sensitization, that is independent from weight loss. While no specific fasting regimen stands out as superior at this time, there is indeed heterogeneity in responses to these different IF diets. This suggests that one dietary regimen may not be ideally suited for every individual. Future studies should consider strategies for tailoring dietary prescriptions, including IF, based on advanced phenotyping and genotyping prior to diet initiation.

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**Study Importance**

**What is already known?**

- Interventional studies point to intermittent fasting as a weight loss approach with cardiometabolic benefits.

**What does this review add?**

- This review summarizes some of the recent studies on intermittent fasting with an emphasis on glycemic control while adding a chrononutrition perspective.

**How might these results change the direction of research?**

- Future research must consider the interaction between the timing of dietary intake and circadian biology.

## Introduction

Physiological adaptations, such as the metabolic flexibility to food availability and the priority for energy storage, were needed to survive periodic food shortages throughout human evolution (1,2). Obesity appears to be the hallmark of modernization based on many case studies documenting the adaptation of western lifestyles (2). The precise temporal feeding patterns of our ancestors are unknown, but they were likely very different than the post-industrial revolution feeding patterns characterized by increased meal frequency (3) and extended eating intervals with intake shifted to later in the day (4-6). Unfortunately, modern feeding habits often contrast with circadian physiology, which requires environmental cues (e.g., meal timing) to promote circadian synchrony (7). While circadian desynchrony has been linked to poor metabolic health and obesity, meal timing has only recently been postulated to contribute to metabolic dysfunction (8).

Intermittent fasting (IF) has emerged over the past 10 to 15 years as an unconventional approach to potentially reduce body weight and improve metabolic health beyond simple calorie restriction (CR). There are a variety of IF regimens with regards to feed-and-fast cycles, meal timing, and energy intake (9,10). Clinical trials from the most common IF regimens will be discussed. These trials share similar characteristics of prolonged periods of fasting. Alternate-day fasting (ADF) and time-restricted feeding (TRF) are characterized by extending nocturnal fasting. While ADF incorporates a complete fast every other day, TRF simply shortens the daily feeding window. Both ADF and TRF may inadvertently restrict energy intake and, therefore, cause weight loss. In contrast, most alternate-day modified fasting (ADMF) and 5:2 diet regimens utilize very low-calorie diets occurring intermittently throughout a 7-d period. These four IF regimens are summarized in Table 1. The extent that each of these feeding regimens affect total body weight, body composition, and metabolic health are discussed below.

## Religious Origins of IF

Many forms of religious fasting can be found in Christianity, Judaism, and Islam. While specific regimens vary by duration and dietary patterns, many fasts reduce animal protein, refined foods, and other indulgences while promoting intake of fruits and vegetables, increased social engagement, and prayer (11). Sunnah and Ramadan, fasts within Islam, will be discussed as these approaches bear similarities to the secular IF approaches.

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**TABLE 1** Description of different approaches in intermittent fasting

| DIET | FEED DAY Energy Allowance | FAST DAY Energy Allowance | Weekly Fast Days | Feeding Window |
|---|---|---|---|---|
| Alternate-Day Fasting (ADF) | 100% | 0% | 3-4 | Open |
| Alternate-Day Modified Fasting (ADMF) | 100% | 25% | 3-4 | 2 h* |
| 5:2 | 100% | 25%† | 2 (sometimes consecutive) | Open |
| Time-Restricted Feeding (TRF) | 100% | 100% | 7 | <10 h |

†Halberg et al. (63) and Soeters et al. (66) did not restrict calorie intake.
*Most trials have limited intake to a shortened window of time between 2 to 4 hours, and meals often occur in midday.

## Ramadan fasting

Muslims observing Ramadan traditionally are not allowed to eat, drink, smoke, or engage in any sensual activity between dawn and sunset during the Holy month (12). It is a common practice to wake early to have breakfast before dawn (12,13). Thus, energy intake is restricted to evening, nighttime, and very early morning in a bimodal pattern. Concern has been raised regarding this practice in those with diabetes (13). Here, we summarize the cardiometabolic effects of Ramadan fasting within the general adult population.

*Changes in weight, body composition, and energy metabolism.* Several meta-analyses have reported weight loss following Ramadan fasting (14-16) with initial body mass index (BMI) positively correlated with the magnitude of weight loss (17). However, complete weight regain is often observed 2 to 5 weeks after Ramadan (14,16). Several studies have reported no change in body weight (14-16), but two of these meta-analyses highlighted more pronounced weight loss in males compared with females (14,15). Considering the positive associations between the number of fasting days and the observed magnitude of weight loss (17), blunted weight loss is expected among females since fasting is not allowed during menstruation (14). As often experienced with weight loss, improvements in body composition such as decreased fat mass (16) and reduced waist circumference (18) are observed with Ramadan fasting. Decreases in fat-free mass are also observed but to a lesser degree than fat mass (16). Furthermore, recent studies report no effect of Ramadan fasting on resting metabolic rate or energy expenditure (19,20), yet increased fat oxidation and decreased carbohydrate oxidation have been reported (20,21).

*Changes in cardiometabolic health.* Meta-analyses of Ramadan fasting have reported cardiometabolic benefits among healthy individuals with inconsistencies regarding improvements in lipid profiles (15,18,22). Kul et al. (15) reported a slight decrease in total cholesterol and triglycerides, a large decrease in low-density lipoprotein (LDL) cholesterol, and no change in high-density lipoprotein (HDL) cholesterol. Faris et al. (18) similarly noted modest improvements in triglycerides and reported an increase in HDL cholesterol. Mirmiran et al. (22) included studies in athletes and pregnant women. They too reported an increase in HDL cholesterol, but were the only meta-analysis to report an increase in LDL cholesterol (22). All reviews and meta-analyses suggest sex-specific effects of Ramadan fasting, but they do not seem to agree. For example, a subgroup analysis from Kul et al. (15) indicates larger increases in HDL cholesterol in females and more pronounced decreases in triglycerides in males. Conversely, other meta-analyses indicate an increase in HDL cholesterol in males (18,22) and a decrease in triglycerides in females (18). The reason for such discrepancies is unknown, but it could stem from a disproportionately higher male sample and different criteria used for study selection. Additional subgroup analyses indicate greater health improvements relative to baseline health, age, and reduction in body weight (22). Two meta-analyses reported minimal improvements in fasting glucose among both men and women (15,18). To date, it remains unclear how Ramadan fasting may reduce fasting insulin and improve insulin resistance. Some studies have shown a reduction in insulin concentrations and an improvement in insulin resistance (homeostatic model assessment of insulin resistance; HOMA-IR) (23,24), while others report an increase in insulin and insulin resistance (25,26) or no change at all (27,28). Studies investigating the effect of Ramadan fasting on metabolic health using more robust techniques, such as the hyperinsulinemic euglycemic clamp, are warranted to further scientific understanding of the effect of Ramadan fasting on metabolic health.

## Sunnah fasting

Sunnah fasting is practiced year-round and includes fasting weekly on Mondays and Thursdays with an additional 6 days of fasting in the Shawwal month (29). Two studies by the same research group assessed 12 weeks of weekly Sunnah fasting combined with daily CR in older males from Malaysia (29,30). Sunnah fasting consisted of a small meal prior to sunrise and a full meal after sunset; additionally, participants were asked to restrict calories by 300 to 500 kcal/d and to increase intake of healthy foods (30). Both studies indicated an overall energy deficit of 18% and weight loss of ~3% (29,30). Fat mass decreased by about 6% to 8% (29,30). While fat-free mass was unchanged in one study (30), another study showed a slight decrease (-0.9%) that was not significantly different from the control group (29). Only Teng et al. (29) assessed cardiometabolic outcomes and noted decreases in both total cholesterol and LDL cholesterol by 8% and a decrease in systolic and diastolic blood pressures by 4.5% and 2.6%, respectively. There was no change in glucose, and insulin was not reported.

Additional work by Ismail et al. (31) considered whether an emphasis on faith-based dietary practices could promote health following Ramadan for 12 weeks. The control group was assigned to standard dietary advice, while the intervention group was also provided faith-based dietary advice, such as the inclusion of Sunnah fasting. The occurrence of fasting twice weekly (Monday and Thursday) was unchanged; however, fasting once weekly (Monday or Thursday) increased in the intervention group. There was no change in fasting frequency in the control group. A decrease in BMI from baseline was observed in the intervention group, but was not significantly different from the control group. The intervention group also experienced modest improvements in cardiometabolic health, such as decreases in diastolic blood pressure and increases in HDL cholesterol. However, this could also be an outcome of enhanced vegetable intake occurring in the intervention group. Together, these studies suggest that the practice of Sunnah fasting may promote cardiometabolic health. A continuation of Ismail et al. on a larger and more generalizable scale could have public health implications within Muslim communities.

## Caloric Restriction

Naturally occurring episodes of CR suggest that prolonged CR with high-quality diets may improve both health and longevity in humans. Quite a few years ago, researchers reported that the greatest number of centenarians resided on the Japanese island of Okinawa (32). Importantly, Okinawans were reported to consume 15 to 20% less energy than the average Japanese individual consumed on mainland Japan (33). These observations suggest that CR may be a physiological driver of longevity. Another study in non-obese Spanish monks showed that assignment to a CR diet (only 1 L of milk and 500 g of fruit every other day) was associated with less time in the infirmary and a non-significant decrease in death rate (34,35). Results from the Biosphere 2 experiment also provided insights into the effect of long-term CR (almost 2 years) in humans with normal weight. After experiencing a shortage of homegrown food, the 8 individuals that lived within Biosphere 2 not only lost ~15% of their body weight, but they also experienced clear improvements in physiologic, hematologic, hormonal, and biochemical health indicators (36).

Large-scale interventional studies emphasizing CR and increased physical activity (e.g., the Diabetes Prevention Program (DPP) and LookAHEAD [Action for Health in Diabetes]) have clearly demonstrated the ability to elicit weight loss and reduce diabetes risk (37,38). Even CR-induced weight loss of ~5 to 10% has definitive cardiometabolic health benefits (39). A more recent randomized clinical trial (the Comprehensive Assessment of Long-term Effects of Reducing Intake on Energy [CALERIE]) showed that CR significantly improved several cardiovascular risk factors, insulin sensitivity, and mitochondrial function (40-43). Such improvements may indeed compress mortality by delaying the incidence of aging-related chronic disease. Importantly, the health benefits of CR seem to be mediated by decreased energy expenditure, improved mitochondrial function, and decreased oxidative stress and inflammation (42). Unfortunately, maintaining CR and weight loss and their respective health benefits is challenging. Weight regain is a common occurrence during weight maintenance (44,45) and even a mild degree of weight regain may negate initial cardiometabolic benefits of weight loss (45). More specifically, a 2-year follow-up from CALERIE reported only ~50% of the initial weight loss was maintained after the intervention (46).

Much research is currently underway to better understand the inter-subject variability in weight gain and the interaction between the biology, psychology, prescribed diet, weight loss, or even more importantly, weight loss maintenance. Indeed, one diet does not fit all. As a result, IF approaches, including TRF, have been offered as alternative dietary strategies that may have beneficial effects on weight control and healthy aging.

## Intermittent Fasting: New Strategies to Improve Weight Management and Metabolic Health

In this section, we review the different IF strategies that have been studied for weight management, with added emphasis on their cardiometabolic health impact. These include the 5:2 diet, ADF, ADMF, and TRF (see **Table 1**).

### 5:2 diet

The 5:2 diet is a secular diet that shares some similarities with Sunnah fasting, as both regimens call for modified fasting to occur twice weekly. To date, all 5:2 regimens have allowed ~25% energy intake on the "fast day" rather than a complete fast. This feeding regimen, combined with *ad libitum* feeding on the remaining 5 days, may elicit a weekly energy deficit of ~20 to 25%. Meals consumed during the modified fast days are typically eaten at any time. About half of the trials permit participants to select two non-consecutive fast days, whereas others require a more aggressive approach with consecutive fast days (47-52).

*Changes in body weight, body composition, appetite, and energy intake.* All 5:2 diet studies have been designed as weight loss interventions, and many of these studies compare 5:2 versus daily CR. Short-term studies lasting ~8 weeks have reported high adherence (>90%) to 5:2 diets (51-53). Overall adherence does not appear to differ between 5:2 and daily CR (47,48,50,53). Interventions ranging from 4 to 24 weeks have reported weight loss of 4 to 8% (48-49,54-56). Weight loss of at least 5% is possible within 8 weeks (51). The efficacy of attaining at least 5% weight loss is similar between 5:2 and daily CR (51,55). Decreases in fat mass typically range from 9 to 13% with only a 1 to 4% reduction in fat-free mass and is similar to daily CR. Participants also self-report lower caloric intake during 5:2 compared to daily CR (47,51,54,57). Decreased intake could be the result of transient ketosis (58), which may partly explain the observed suppression of appetite ratings (47,48) and maintenance of baseline ghrelin concentration during 5:2 (47) a hormone which usually increases with weight loss and signals hunger. Initial ratings of hunger are higher during 5:2 compared to daily CR but appear to be mitigated by higher protein intake and normalize over time (48,55,59). Further investigation should decipher feed and fast day interactions on hunger, fullness, and satiation, while pairing perceptions with biomarkers of appetite.

*Changes in cardiometabolic health.* Similar weight loss outcomes make it possible to compare weight loss-independent cardiometabolic differences between 5:2 and daily CR. Decreases in total cholesterol, LDL cholesterol, and triglycerides as high as 13%, 15%, and 22%, respectively, have been reported with 5:2 (49,54). Modest improvements in lipids are similar between 5:2 and daily CR (48,54,60). The 5:2 diet, however, appears to have a superior insulin-sensitizing impact. Harvie et al. (47) first observed improvements in insulin sensitivity after 6 months of 5:2, which was slightly better than daily CR. Similar findings were replicated in two other studies from the same investigators (48,49). These observations could be explained by the dramatic increase in insulin sensitivity immediately following 2 days of consecutive fasting that lingered throughout the remaining feed days (47-49). Additionally, differential adipokine responses between 5:2 and daily CR could also play a role (48,49). Among individuals with type 2 diabetes, reduced medication use (i.e., insulin) and lowered hemoglobin A1c (HbA1c) were observed with 5:2 (50,59,60), thus supporting the theory that 5:2 promotes insulin sensitization. Future research should address whether baseline characteristics can predict which dietary intervention (5:2 versus daily CR) is the most effective for an individual based on their metabolic health status.

*Follow-up and weight loss maintenance studies.* Following completion of a 5:2 diet, weight regain is highly variable and similar to daily CR (48,53,54,61). Carter et al. (61) reported a 33% weight regain in returning participants upon a 2-year follow-up. In the same study, HbA1c increased, while total cholesterol and LDL cholesterol returned to baseline. Importantly, other studies curtailed weight regain while maintaining reductions in adiposity and cardiometabolic disease risk through continued engagement in weight loss maintenance programs lasting 4 to 24 weeks (48,53,54). In studies lacking continued counseling, weight regain occurred and cardiometabolic risk rebounded during follow-ups lasting approximately 6 months (53,54).

## Alternate-day fasting and alternate-day modified fasting

Both ADF and ADMF switch back-and-forth between days of fasting and feeding. Fasting days can range from ~75 to 100% CR depending on the fasting regimen, and feeding days are usually *ad libitum*. Seminal work in this field utilized either a complete fast (ADF) (62) or a 20-hour fast every other day (ADMF) (63). The extended daytime fasting has been studied less frequently due to poor tolerability of a complete fast every other day (62). Consequently, most ADMF protocols now include a single midday meal, which typically falls within a 2-hour feeding window and allocates ~25% of energy requirements.

*Changes in body weight, body composition, and appetite.* ADF and ADMF trials in humans often result in weight loss either by design or unintentionally, which is in contrast to mouse models demonstrating weight maintenance (64). Three short-term trials in male participants were successful at maintaining body weight (63,65,66). Other trials encouraged participants to consume 145 to 200% of their energy needs on the feed days, yet participants still experienced unintentional weight loss (62,67). These reports suggest that ADF and ADMF regimens may have therapeutic value as obesity treatments. Interventions lasting 4 to 16 weeks report weight loss between 3 to 13% (67-81), while trials extending to 24 weeks report weight loss of 6 to 11% (81-84). Comparisons of daily CR against ADF and ADMF demonstrate comparable decreases in body weight (70,77-78,83) and fat mass (77-79,83). Some of which report trends in favor of greater weight loss during ADF or ADMF (77,79). Other inconsistencies exist. For example, Viegener et al. (81) ADMF outperformed daily CR for weight loss for the first 4 months, but not at subsequent timepoints extending to 6 months. In other cases, ADMF elicited superior reductions in weight (67,85) and fat mass (67) compared to daily CR. Likewise, there is no consensus with respect to fat-free mass alterations. Several non-randomized trials of ADMF suggest fat-free mass retention (69,71-72,74,76,86). This effect on fat-free mass is not repeated across studies (67,75,77,79,82) and is often no different compared to daily CR (67,77-79,83). Divergent conclusions could stem from varying degrees of weight loss, duration of interventions, and discrepancies between body composition assessment methods (i.e., bioelectrical impedance versus dual-energy X-ray absorptiometry).

Despite overall high dietary adherence (69,71,72,75,85), generally good study retention (72,74,77,85), and minimal reported side effects (77,80,87), several ADF or ADMF studies have reported dropout rates greater than 20% (71,76,79,82,83). As expected, dropouts increased when the duration of the intervention was 12 weeks or longer. It also remains unclear how well-tolerated these types of IF diets actually are compared to daily CR. Small studies (<20 participants per group) appear to report similar dropout rates (70,77,79), whereas, larger studies (>40 participants) are equivocal (81,83). These findings coupled with inherent inter-individual variability in observed weight loss (88) and the growing demand for precise medical treatment, suggest that individualized weight loss approaches may be beneficial. In support of this, self-identification as a "big eater" was negatively associated with weight loss likely due to the ability to better compensate for the fast day energy deficit (62). There also appears to be differential responses among demographic groups upon pooling several ADMF studies in a secondary analysis. Caucasians and older individuals experienced larger weight loss (89), which is consistent with other daily CR studies (90-92). Reasons for these differences remain unknown, but both cultural and physiological underpinnings likely play a role (93,94).

The Varady group has explored several ADMF variations that could increase acceptability and adherence. The standard ADMF approach allows for only a single midday meal to be consumed on fasting days. Typically, a low-fat dietary pattern is recommended or provided. This may be difficult for dieters preferring to eat later in the day or those desiring higher fat meals. Hoddy et al. (75) examined meal timing and frequency during ADMF and noted no influence with respect to weight loss or changes in body composition when the fast day meal was provided at different times or split into three small meals. Additionally, providing participants with high-fat meals during ADMF also did not hinder weight loss (72). Other ADMF variations have considered whether weight loss may be enhanced by incorporating healthful behaviors, such as consuming higher dietary protein (78,82) or including exercise (71,76,95). Kalam et al.(82) noted fat-free mass retention from baseline with a high-protein diet. Another study demonstrated similar reductions in body weight, fat mass, fat-free mass, and visceral adiposity between high-protein variations of ADMF and daily CR (78). Neither study directly compared a high-protein ADMF approach to a standard ADMF approach. There have been direct comparisons between ADMF and ADMF with exercise. Bhutani et al. (71) reported that the inclusion of exercise augmented weight and fat mass loss compared to ADMF alone. Similarly, Oh et al. (76) reported improvements from baseline in body weight and body composition in both ADMF and ADMF with exercise conditions, but only the exercising ADMF group attained statistically higher fat mass loss from the control. Interestingly, exercise during ADMF appears to attenuate dropout rates (76,95). This body of work evaluating dietary and execise variations during ADMF points to the ability to tailor ADMF according to individual preferences and weight loss goals.

Appetite, which is commonly an exploratory outcome, appears to be curbed and may explain the reduced self-reported caloric intake on feed days (67,77,83). Only one study compared appetite during ADMF to daily CR and reported no difference between the diets (79). Appetitive responses to ADF or ADMF vary by study and assessment method. Three weeks of ADF enhanced daily feelings of fullness; yet, hunger remained (62). With ADMF, hunger sensations appear to subside after only 2 weeks (96). This indicates that tolerability may be enhanced with the inclusion of a small fast day meal compared with a complete fast, but this comparison has not been made experimentally. Reduced feelings of hunger and increased feelings of fullness have also been observed after longer exposure to ADF and ADMF interventions (up to 10 weeks) (67,68,74,95,96). This suggests appetite normalization with time. Responses to standardized meal tests, representing physiological appetite, have been inconsistent across studies (79,97,98). Heilbronn et al. (97) reported no change in ghrelin after 3 weeks of ADF. Conversely, hunger was unchanged following 8 to 12 weeks of ADMF and a slight increase in ghrelin was observed (79,98). Findings related to fullness and peptide YY (PYY), a gut peptide which signals fullness, are inconclusive as well. Hoddy et al. (98) observed a moderate increase in PYY (16%) coupled with increased feelings of fullness (10%) after ADMF, but Coutinho et al. (79) showed no change in PYY or fullness. ADMF and ADF may, therefore, placate appetite over time, yet the mechanisms explaining are unclear and inconsistent.

*Changes in cardiometabolic health.* ADF and ADMF have beneficial effects on overall cardiometabolic health, but disagreement exists when comparing specific outcomes. For example, fasting glucose has been shown to both increase (5%) (84) and decrease (2 to 5%) (78,85,98) during ADMF while others show no change (73,76) in trials lasting at least 6 weeks. Additionally, fasting insulin may decrease 21% to 42% in studies lasting 8 to 24 weeks (78,84,98), thus improving insulin resistance (HOMA-IR) (84). Insulin sensitivity, on the other hand, is unchanged when assessed via intravenous glucose tolerance test (IVGTT) (77) and shows differential responses to mixed meal tolerance testing by sex (97). In response to a hyperinsuliemic-euglycemic clamp after 8 weeks of ADMF or daily CR, Hutchison et al. (67) reported no difference in insulin sensitivity. The effect of ADF on lipid concentrations appears to depend on sex and may require a longer exposure period to experience benefits (62,65). Several studies lasting at least 8 weeks have also shown collective improvements in lipid profiles characterized by decreased triglycerides, LDL cholesterol, and total cholesterol (67,69,70,72,74,77-78,82). Benefits in total lipid concentrations are not universal and may not be different from daily CR. Three studies report no differences from daily CR for total or LDL cholesterol after weight loss (77-78,83), while another points to body weight independent improvements favoring ADMF (67). Importantly, the improvement in the atherosclerotic profile of lipid particles appears to consistently improve (70-71,75,99,100), and initial findings suggest it may outperform daily CR (70).

Response according to metabolic health status is perhaps more compelling. A clinical trial in participants with metabolic syndrome showed a greater decrease in fasting glucose after ADMF compared to daily CR, but no difference in insulin resistance or fasting inslulin concentrations were observed (85). Other secondary analyses provide preliminary evidence that ADMF may be more effective than daily CR for attenuating diabetes risk. Participants with the highest degree of insulin resistance experienced the greatest improvement in HOMA-IR after ADMF (101). In a different analysis of only insulin resistant participants, there were marked decrease after ADMF compared to daily CR for fasting insulin (52% vs. 14%, respectively) and insulin resistance (53% vs. 17%, respectively) (102). Long-term randomized clinical trials are needed in populations with diabetes or prediabetes to draw specific conclusions regarding disease outcomes after ADF or ADMF.

*Follow-up and weight loss maintenance studies.* Weight loss maintenance following ADF and ADMF is questionable. To date, four studies have evaluated weight loss maintenance—all employing vastly different approaches (77,78,82,83). Following 8 weeks of ADF or daily CR, Cattenacci et al. (77) reported significant weight regain (~30% of initial loss) in both diet groups during a 24-week unsupervised follow-up period. Both diet groups maintained absolute losses in fat and fat-free mass. The proportional modulations, however, in percent fat mass and percent fat-free mass were better with ADF compared to daily CR. This could be due to some particiapnts maintaining ADF during the unsupervised follow-up (77). In the longest weight maintenance comparison between ADMF (50% CR on the fast day) and daily CR, Trepanowski et al. (83) reported similar weight regain trajectories between daily CR and ADMF and no difference in body composition. Interestingly, individuals achieving at least 5% weight loss, self-selected higher protein intake throughout the trial (88). Other studies paired ADMF with daily CR during the weight loss phase while incorporating intake of higher dietary protein as part of the weight maintenance approach (78,82). Kalam et al. (82) used high-protein meal replacements on feed (1000 kcal/d) and fast (600 kcal/d) days during weight loss. During weight maintenance, the same fast day meal replacements were used while the feed days reduced reliance on meal replacements (82). Participants experienced small amounts of continued, but statistically insignificant, weight loss (<1 kg) over 12 weeks of weight loss maintenance. Cardiometabolic improvements only reached significance after weight maintenance, even though there was clinically significant weight loss (>5%) during the weight loss phase (82) Bowden et al. (78) compared ADMF with calorie-restricted feed days to daily CR alone. Following the weight loss phase, diets equally maintained weight loss by following recommendations for higher protein diets for an additional 8 weeks (78). Regardless of approach, lifestyle modifications causing a sustained energy deficit are required to achieve successful weight loss maintenance. Further research is needed to determine whether protein intake during ADF of ADMF influences compliance, appetite, or body composition.

## Time-restricted feeding

In contrast to 5:2, ADF, and ADMF regimens, TRF does not purposely impose CR. Rather, TRF extends the daily fasting period by restricting food intake to a reduced window of time. To date, dozens of animal studies have reported that TRF infers definite health benefits, including reductions in body weight, food intake, hyperlipidemia, ectopic fat, and markers of inflammation, as well as improvements in heart health, cancer outcomes, and lifespan extension (103). Recent TRF trials in humans have allowed a feeding window between 4 to 12 hours, although a window of <10 hours is thought to be optimal based on glycogenolysis, fatty acid oxidation, and gluconeogenesis modulations occurring in the absence of dietary glucose availability (104).

Single-arm TRF trials have reported 2 to 3% weight loss over 1 to 4 months (5,105). Gill and Panda (5) enrolled 8 individuals with overweight and obesity who reported an eating duration of more than 14-hour to choose a 10-hour ad libitum eating window of their choice for 16 weeks. Importantly, the participants experienced weight loss, reduced hunger at night, increased overall energy levels, and improved sleep satisfaction, which persisted for 1-year after the intervention began (5). Another recent study by Anton et al. (105) enrolled older, sedentary adults with overweight and obesity and restricted their eating to an 8-hour *ad libitum* flexible feeding window; study volunteers also experienced significant weight reduction.

In more controlled trials, eating earlier in the day ("early TRF") or in the middle of the day ("midday TRF") outperformed eating later in the day ("late TRF") for cardiometabolic health. It is possible that eating in synchronization with the natural circadian endocrine rhythm—early in the morning or around noon-time—may hold the key to naturally reduce energy intake. In just 4 days, early TRF (6-hour window: 8:00 AM – 2:00 PM) versus control (12-hour window: 8:00 AM – 8:00 PM) altered expression in 6 out of 8 circadian genes (106). This was accompanied by temporal differences characterized by a nocturnal blunting of glucose assessed by continuous glucose monitoring along with altered perceptions of appetite and body temperature (106,107). Along with this, there was an overall decrease in appetite and increased fat oxidation without impacting 24-hour energy expenditure (107). A longer 5-week crossover trial in males with overweight and prediabetes reported that early TRF (6-hour window: 8:00 AM – 2:00 PM) actually improved insulin sensitivity by 24% and β-cell function by 13% when compared to a 12-hour energy matched eating window (8:00 AM – 8:00 PM) (108). There were also impressive declines in blood pressure and oxidative stress (8-Isoprostanes) (108). Hutchinson et al. (109) directly compared early TRF (8:00 AM – 5:00 PM) with late TRF (12:00 PM – 9:00 PM) in 15 overweight males in a crossover design. TRF reduced body weight, plasma triglycerides, and postprandial glucose levels in both groups, and a decrease in fasting glucose via continuous glucose monitoring was observed only with early TRF. Midday TRF approaches have reported similar improvements in cardiometabolic health. For example, a randomized controlled study by Antoni et al. (110) found that delaying breakfast and advancing dinner by 1.5 hours each (or midday TRF) for 10 weeks reduced body fat and energy intake in a cohort of mostly female participants. Another trial of midday TRF (8-hour window: 10:00 AM – 6:00 PM) in 23 adults with obesity confirmed such improvements in cardiometabolic health, including reduced body weight, energy intake, and systolic blood pressure (111).

A few studies suggest that late TRF may worsen cardiometabolic health. Compared to consuming 3 meals/d of a eucaloric diet, consuming those same calories within a single 4-hour evening meal (1 meal/d) increased systolic blood pressure, cholesterol, hunger, early morning fasting glucose, as well as delayed insulin response (via oral glucose tolerance test) (112,113). However, one 8-week randomized controlled trial in 34 resistance-trained athletes did report that late TRF (8-hour window: 1:00 – 9:00 PM) reduced fat mass while maintaining fat-free mass, muscle area, and maximum strength when compared to consuming the same calories across the entire day (114). This trial also triggered a reduction in triglycerides, testosterone, insulin-like growth factor 1 (IGF-1), and interleukin 1 beta (IL-1β) with no changes in total cholesterol or fasting glycemic markers (114).

## Perspective and Future Directions

Our review indicates that IF approaches may provide health benefits independent of weight loss. This is in agreement with meta-analyses showing decreased fasting insulin (9,115) despite no difference in weight loss between IF regimens and CR (9-10,86,115). It is possible that one IF regimen could outperform another, but this remains to be directly tested. Furthermore, compliance to IF and daily CR is often comparable and demonstrates that one may not be superior to the other to achieve a negative energy balance. Nonetheless, repeated examples across every type of IF regimen do indicate an insulin sensitizing effect occurring almost immediately upon diet initiation. It is possible that this IF effect could be mediated through circadian biology as diurnal variations in glucose (116), energy expenditure (117,118), and substrate utilization (119) favor eating earlier in the day and fasting at night.

Importantly, the heterogeneity in the response to different IF strategies suggests that personalized approaches will improve weight loss and enhance cardiometabolic health. Therefore, the next phase of IF research should tailor dietary prescriptions based on factors related to an individual's unique physiology, current health status, dietary preferences, social influences, and built environments. This new chapter of research has the potential to identify ideal candidates for a particular weight loss treatment. Advanced phenotyping and genotyping to identify the molecular transducers of dietary interventions may one day provide the basis for better customized care (120).

Modern feeding behaviors include eating across extended periods of time (~15-hours) with the largest proportion of calories consumed in the evening (4-6). Evidence from animal models exposed to IF indicate a circadian resetting effect (121-125) that could offset chronobiological desynchrony imposed by 24-hour societies. Conversely, mistimed food intake during IF may contribute to such desynchrony (125). Continued examination of IF has the potential to clarify the interplay between diet, metabolism, and circadian physiology. Ramadan research provides insight into delayed IF in humans as energy intake is confined to predominately evening hours and has been shown to decrease sleep and disrupt circadian rhythm (25,126-128). Yet our review points to enhanced cardiometabolic health with Ramadan fasting. Limiting nighttime energy intake during simulated night shift seems to offset some of the cardiometabolic dysfunction noted in night shift workers (129,130). Such findings posit that the metabolic effect of fasting may outweigh that of circadian disruption. As such, utilizing IF as a countermeasure to known and often unavoidable circadian disruptors, including sleep restriction, social jet lag, and night shift, is an unexplored area of interventional research requiring attention. O

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