WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 3, 546-560. Review Article ISSN 2277–7105

# INTERMITTENT FASTING AS A LIFESTYLE INTERVENTION: PRACTICAL CONSIDERATION FOR IMPLEMENTATION AND LONG TERM HEALTH BENEFITS OBESITY

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Article Received on
16 Dec. 2024,

Revised on 06 Jan. 2025,
Accepted on 27 Jan. 2025

DOI: 10.20959/wjpr20253-35468

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## ABSTRACT

Obesity remains a major public health concern and intermittent fasting is a popular strategy for weight loss, which may present independent health benefits. However, the number of diet books advising how fasting can be incorporated into our daily lives is several orders of magnitude greater than the number of trials examining whether fasting should be encouraged at all. This review will consider the state of current understanding regarding various forms of intermittent fasting (e.g. 5:2, time-restricted feeding and alternate-day fasting). The efficacy of these temporally defined approaches appears broadly equivalent to that of standard daily energy restriction, although many of these models of intermittent fasting do not involve fed-fasted cycles every other 24 h sleep–wake cycle and/or permit some limited energy intake outside of prescribed feeding times. Accordingly, the intervention period therefore may not regularly alternate, may not span all or even most of any given day, and may not even involve absolute fasting. This is important because potentially advantageous physiological mechanisms may only be initiated if a post-absorptive state is sustained by uninterrupted fasting for a more prolonged duration than applied in many trials. Indeed, promising effects on fat mass and insulin sensitivity have been reported when fasting duration is routinely extended beyond sixteen consecutive hours. Further progress will require such models to be tested with appropriate controls to isolate whether any possible health effects of intermittent fasting are primarily attributable to regularly protracted post-absorptive periods, or simply to the net negative energy balance indirectly elicited by any form of dietary restriction.

**KEYWORDS:** Time restricted feeding, Obesity intermittent fasting etc.

## 1. INTRODUCTION

Obesity is a prevalent health concern throughout the world which arises due to chronic positive energy balance. Any energy surplus is stored primarily in the form of TAG within adipocytes, thus leading to adipose tissue expansion predominantly as a result of adipocyte hypertrophy.[1] If sustained over time, this hypertrophic expansion can lead to adipocyte dysfunction, hyperglycaemia, hyperlipidaemia, ectopic lipid deposition, chronic low-grade systemic inflammation and insulin resistance thereby fostering comorbidities such as type 2 diabetes and CVD. To remedy this metabolic dysfunction, interventions often seek to redress the underlying energy imbalance by reducing energy intake and/or increasing expenditure, which can improve health outcome. However, these improvements are hampered by compensatory changes in appetite and energy use, as well as poor adherence, resulting in poor long-term success rates.[2]

Strategies that exploit nutrient timing as a means of achieving weight loss and/or improving metabolic health have been the subject of considerable public interest in recent years. Intermittent fasting is an umbrella term that may be used to describe these approaches, which involve a complete or partial restriction of energy within defined temporal windows on a recurrent basis. Thus far, the therapeutic potential of intermittent fasting has been largely overshadowed by direct manipulation of the principal components of the energy balance equation.[3,4] However, advances in the understanding of circadian rhythms suggest that this could be a particularly effective approach for tackling obesity and the accompanying dysfunction, in addition to arguably being more acceptable in practice than conventional alternative. To explore this notion, this review will consider the literature on meal timing and intermittent fasting as it relates to metabolic health.

## 2. Meal timing

In Western cultures, consuming three or more meals daily is generally accepted as a societal norm. However, this typically results in an anabolic state predominating each day. The postprandial metabolic response to a mixed-macronutrient meal in metabolically healthy participants is characterised by a peak in glycaemia within the first hour followed by a steady return to fasted glycaemia over the ensuing 2h.[5]

This is paralleled by an accompanying peak in insulin secretion within the first hour followed by a decrease over the next 4 h. Conversely, plasma TAG concentrations rise steadily to a peak after 3–5 h and generally remain 50 % higher than baseline even after 6 h. When a subsequent meal is ingested approximately 5h after the first (as is common in Western diets), glucose peaks at a similar time after feeding, albeit an attenuated absolute peak. However, glucose then takes slightly longer to return to baseline as the day progresses, a pattern that is largely mirrored by insulin concentrations. Plasma TAG on the other hand does not peak until shortly after the second meal is ingested; it then falls rapidly due to the insulinaemic response to the second meal, before peaking again about 5 h after the second meal.[6,7] These responses suggest that, even with just two meals daily, plasma TAG is elevated continuously for 12 h, with this pattern then propagated when further extended to include a third meal. This is well-demonstrated by Ruge *et al*.

Who examined the 24 h circulating profiles of glucose, TAG and insulin in response to three successive meals at 10.00, 15.00 and 20.00 hours. Within this model, TAG remained elevated until 02.00 hours, along with insulin and glucose concentrations. Similarly, showed that TAG extraction by adipose tissue in response to three meals daily is elevated for over 16 h. The net effect of this is that the majority of each 24 h day is spent in a postprandial and lipogenic state, which is conducive to fat accretion. By extension, this provides fewer opportunities for net lipolysis and the predominance of lipid-derived substrates in energy metabolism, thereby favouring positive fat balance.[8]

Ultimately, this results in a scenario wherein those adhering to conventional dietary meal timing patterns are attempting to achieve energy balance using a feeding schedule that is inherently biased towards fat accretion. Conventional diet and exercise interventions aim to reduce the amplitude of postprandial excursions in order to provide more opportunities for the liberation and utilisation of endogenous lipid reservoirs. However, the imbalance between the daily fasting window and the daily feeding window remains largely unperturbed. Comparatively, the omission of meals is typically necessitated by intermittent fasting and eliminates a subset of these postprandial excursions, thereby providing greater equilibrium between fasting and feeding opportunities and a better platform for achieving energy balance.[9]

Further to this, the routine extension of fasting periods has been associated with metabolic benefits which are independent of net energy balance constituting a secondary therapeutic dimension to these strategies. Specifically, argue that the depletion of hepatic glycogen reserves and the ensuing transition towards metabolism of endogenous, lipid-derived substrates (i.e. NEFA, glycerol, ketone bodies) prompt a series of adaptive processes conducive to improved health outcomes, including improvements in body composition and insulin sensitivity. Considering that this transition does not take place in most instances until the uninterrupted fasting duration proceeds beyond 12–14 h these adaptive processes are not often invoked by the conventional meal patterns described earlier.

Based on the afore-mentioned reasoning, it is conceivable that intermittent fasting may constitute an efficacious strategy for tackling obesity and the metabolic disorders associated with excess adiposity. To date, however, studies exploring these facets of intermittent fasting are scarce and inconsistent.[10]

**3. Eating frequency**

Perhaps the most widely researched dimension of nutrient timing within the context of obesity in human subjects is eating frequency. Early work by Fabry *et al*. deployed a cross-sectional approach to explore the relationship between intake frequency and metabolic health.[11] Interestingly, in a cohort of 440 men, higher eating frequency broadly corresponded to a healthier profile of BMI, cholesterol concentrations and fasting glucose. Contrary to this, using data from the National Health and Nutrition Examination Survey, Murakami and Livingstone observed that those eating on more than four occasions daily were approximately 50 % more likely to be overweight or obese by BMI relative to those eating on less than three occasions daily. Such discrepancies are a consistent theme throughout these cross-sectional studies; a recent systematic review by Canuto *et al*. analysed data from thirty-one such studies containing a collective sample of over 130 000 participants. Of these thirty-one studies, fourteen established an inverse association, ten showed no association and seven revealed a positive association, which the authors ascribe to the spectrum of approaches employed.[12,13]

Upon shifting to prospective methodologies, the pattern appears to be largely the same; two recent systematic reviews conclude that the majority of studies reveal no association between eating frequency and subsequent obesity.[14]

The review of Raynor *et al*. makes a particularly strong case, given that these authors only included human studies in which food was provided or intake monitored in a laboratory setting. However, of the studies covered in these reviews, most evaluated the impact of increased meal frequency on metabolic health, wherein three meals daily is used as the reference for lower frequency. Therefore, upon framing these studies within the context of the 24 h metabolite profiles discussed previously, the lack of a consensus is perhaps not surprising. In fact, only one of the studies reported is likely to have resulted in the predominance of a fasting state over the course of 24 h.[15]

### 4. Intermittent Fasting

The umbrella term intermittent fasting refers to a series of therapeutic interventions which target temporal feeding restrictions, nominally categorised as: the 5:2 diet, modified alternate-day fasting, time-restricted feeding and complete alternate-day fasting. Irrespective of the rationale for each, such approaches have been subject to growing popularity in recent years, yet experimental data to support their application are comparatively spars . Bluntly, the number of diet books advising how intermittent fasting can be incorporated into our daily lives is several orders of magnitude greater than the number of scientific papers examining whether intermittent fasting should be encouraged at all.[16]

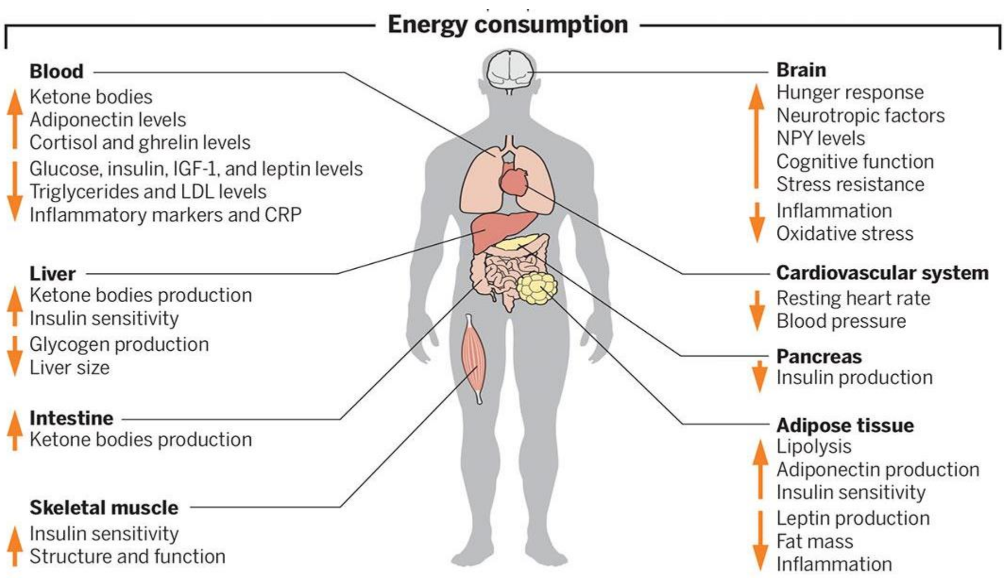


**Figure 1: Action of Components By Intermittent fasting.**

#### 4.1. The 5:2 diet

Amongst the most coveted forms of intermittent fasting is the 5:2 diet, wherein severe energy restriction is imposed on 2 d/week with *ad libitum* consumption on the remaining five. The study of Carter *et al.* (randomised sixty-three adults with overweight or obesity and type 2 diabetes to 12 weeks of either daily energy restriction or a 5:2 approach. The 5:2 group reduced their intake to 1674–2510 kJ (400–600 kcal) for two non-consecutive days per week and followed their habitual diet on the remaining five, whilst the daily restriction group simply reduced their intake to 5021–6485 kJ (1200–1550 kcal) every day. Although the extent to which prescriptions were achieved was not reported, main effects of time but not group were seen for reductions in body mass, fat mass and fat-free mass, as well as improvements in glycated Hb concentration and the use of diabetic medications. Similar conclusions were also drawn by two recent studies which compared this 5:2 approach (i.e. 1674–2510 kJ (400–600 kcal) on two non-consecutive days per week) against daily energy restriction over 6 months.[17,18]

This pattern of results indicates a broad equivalency between the metabolic impacts of the 5:2 diet and daily energy restriction, arguing against any special properties of the fasting element *per se*. However, this is not a consistent finding throughout the literature. Upon comparing the 5:2 approach (requiring two consecutive days of 75 % energy restriction per week) against daily energy restriction (requiring 25 % energy restriction every day) over 6 months, Harvie *et al*. observed differential changes in fasting insulin and fasting indices of insulin resistance.[19] Despite similar reductions in body mass and fat mass, the modest reductions in fasting insulin and insulin resistance seen in both groups were more pronounced with the 5:2 method. Although this may reflect a more potent influence of using two consecutive days of severe energy restriction (as opposed to non-consecutive), there were also greater reductions in energy and carbohydrate intake in this group, which complicate the interpretation.[20]

| | | BREAKFAST | MORNING SNACK | LUNCH | AFTERNOON SNACK | DINNER |
|---|---|---|---|---|---|---|
| | DAY 1 | | | Large mixed salad and 1 cup of Vegetable Soup (p.216) (250 calories) | | Grilled Paprika Chicken (p.246) (250 calories) |
| | DAY 2 | Mango and Passionfruit Yoatie (p.192) | Raw power snack (p.275) | Piri-Piri Chicken (p.229) | Protein pick-me-up (p.275) | Dijon Pork Chop with Apple Cabbage (p.251) |
| | DAY 3 | Poached Eggs (p.204) with 2 slices of rye toast | Raw power snack (p.275) | Tuna Niçoise (p.235) | Protein pick-me-up (p.275) | Green Thai Tofu Curry (p.268) |
| FAST DAY | DAY 4 | | | 1 cup of Minestrone Soup (p.217) and 1 oatcake (250 calories) | | Grilled Fish with Tomatoes and Olives (p.259) (250 calories) |
| | DAY 5 | Minted Quinoa Fruit Salad (p.195) | Raw power snack (p.275) | Prawn, Beetroot, Avocado and Mango Salad (p.225) | Protein pick-me-up (p.275) | Chicken and Red Wine Casserole (p.247) |
| | DAY 6 | Onion Omelette with Feta and Tomatoes (p.206) | Raw power snack (p.275) | Healthy No-Bun Burgers (p.234) | Protein pick-me-up (p.275) | Vegetable Chilli (p.271) |
| | DAY 7 | Luxury Nut Muesli with Florida Cocktail (p.198) | Raw power snack (p.275) | Asian-Style Chicken Noodle Soup (p.214) | Protein pick-me-up (p.275) | Goan Fish and Chickpea Curry (p.261) |

**Figure 2: The 5:2 Diet.**

### 4.2. Modified alternate day fasting

The majority of human studies which examine intermittent fasting have centred upon a strategy referred to as modified alternate-day fasting. It differs from the 5:2 diet in two key regards: the severe restriction is applied during alternating days (nominally 24 h, although practically more varied to accommodate sleep); and any permitted energy during fasting is provided in a single meal (thereby ensuring a tangible extension of the typical overnight fast).[21,22] Much of the work undertaken in this field originates from pioneering experiments by Varady *et al.*, in which participants were required to alternate between 24 h periods of fasting and *ad libitum* feeding, with a single 2510–3347 kJ (600–800 kcal) meal permitted between 12.00 and 14.00 hours on non-feeding days. The effects of this approach on body mass were initially explored by Varady *et al* in a single-arm trial, where twelve obese participants completed 8 weeks of modified alternate-day fasting.[23,24] Reported adherence to the fasting protocol remained high throughout, with energy intake averaging 26 % of habitual. Comparatively, intake on feeding days reached 95 % of the habitual level, resulting in a 37 % net energy restriction on average. This led to body mass losses of 5·6 kg, 5·4 kg of which was accounted for by decreases in fat mass. Total cholesterol, LDL-cholesterol and TAG were also reduced by at least 20 %, effects which were associated with improvements in adipokine profile. Subsequent work by the same group neatly demonstrates that these outcomes are similar when applied to cohorts of adults who are overweight, when meal timing on the fasting day is varied, and that concurrent macronutrient manipulation does not exert additive effects. Collectively, these data suggest that modified alternate-day fasting may be a viable means of improving cardiometabolic health in adults who are overweight or obese. However, without a comparative daily energy restriction group, it is difficult to isolate any independent effects of the fasting periods from the effects of energy restriction and/or associated weight loss. This was addressed recently by a comparison of the two methods under isoenergetic conditions relative to a no intervention control group.[25] Briefly, sixty-nine adults with obesity were randomised to undertake 6 months of modified alternate-day fasting or daily energy restriction. The alternate-day fasting diet restricted participants to a single meal containing 25 % of their measured energy requirements between 12.00 and 14.00 hours during fasting periods, but prescribed 125 % of energy requirements on feeding days. Conversely, the daily energy restriction diet prescribed a 25 % reduction in energy intake every day, resulting in an equivalent reduction in energy intake of 25 % in both groups. Macronutrient balance was preserved in both instances and the attained energy restriction was 21 and 24 % for alternate-day fasting and daily energy restriction, respectively.[26]

### 4.3. Time restricted feeding

Ironically, the adherence issues that appear common to modified alternate-day approaches may lie in the imposition of a severe restriction as opposed to a complete fast, which in being an absolute (albeit more severe) could in fact facilitate compliance.[27] Drawing from this premise, time-restricted feeding is another method of intermittent fasting which has emerged recently and requires no knowledge of food composition or restraint at eating occasions, only awareness of the time at which eating occasions are permitted at all. This approach aims to restrict food intake to a temporal window (typically ≤10 h) within the waking phase, thereby reducing feeding opportunities and extending the overnight fast to at least 14 h daily.

Work in our laboratory explored the impact of extending the overnight fast on energy balance and nutrient metabolism, thereby providing several insights regarding the effects of such strategies. Initially, thirty-three adults who were of healthy weight were randomised to 6 weeks of either consuming breakfast, defined as at least 2929 kJ (700 kcal) before 11.00 hours daily (with half consumed within 2 h of waking), or extended morning fasting up until 12.00 hours. Interestingly, improvements in anthropometric parameters and fasting health markers were not meaningfully different between interventions. In agreement, a panel of hormones implicated in the regulation of energy balance showed little change following the two interventions, although specific measures of adipose tissue insulin sensitivity suggested an improvement in the breakfast group only.[28]

These largely null findings relative to prior research could be explained by the free-living approach used to study compensatory changes in components of energy balance. The fasting group consumed less energy than the breakfast group when averaged throughout each 24 h period, but this was compensated for by lower physical activity thermogenesis. Upon applying this protocol to a cohort of adults with obesity, extended fasting resulted in a slightly greater compensatory increase in energy intake following fasting (although still not adequate to offset the energy consumed or omitted at breakfast), whilst daily fasting was again causally related to lower physical activity energy expenditure in the morning. Interestingly, in this cohort with obesity breakfast did result in improved insulinaemic responses during an oral glucose tolerance test relative to the fasting condition. However, this test was aligned for circadian cycle rather than feeding cycle, so the observed finding could simply reflect better alignment with anticipated events in the breakfast condition.[29]

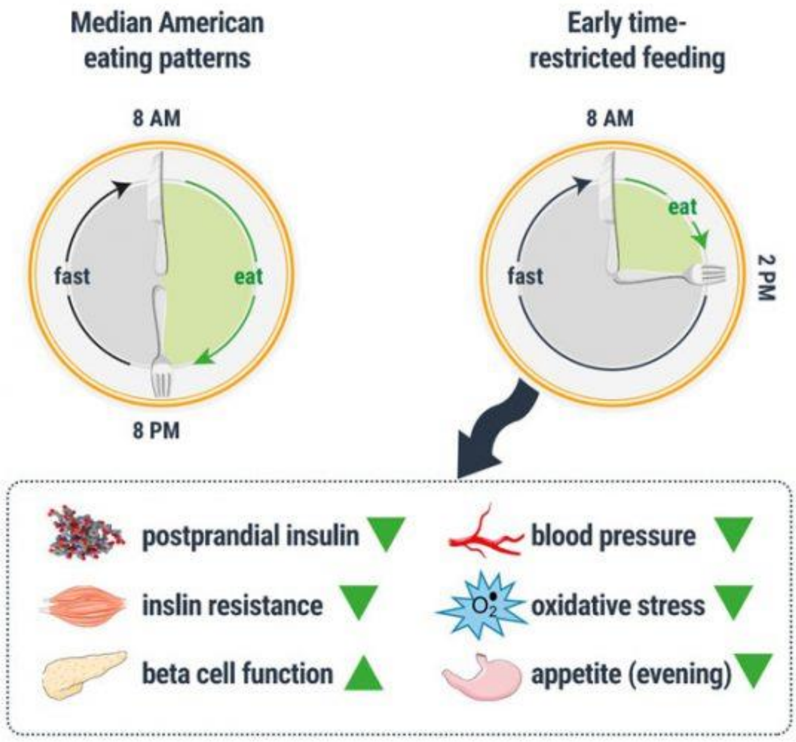


**Figure 3: Early and median feeding patterns.**

Other studies have applied time-restricted feeding under euenergetic conditions, much like the study of Stote *et al*. Focusing on energy metabolism, Moro *et al*. randomised thirty-four men to 8 weeks of time-restricted feeding or a control diet. Diets were matched for energy and macronutrient content and aimed to provide 100 % of energy requirements across three meals in both conditions. In the control condition, meals were consumed at 08.00, 13.00 and 20.00 hours, whilst in the experimental condition, meals were consumed at 13.00, 16.00 and 20.00 hours to give a 16 h fast. The time-restricted approach resulted in reductions in fat mass relative to controls, which were partnered by decreases in RER, indicating a shift towards fat oxidation. Interestingly, however, despite accompanying reductions in leptin and hypothalamic–pituitary–thyroid signalling, resting energy expenditure was maintained.[30] This reinforces the notion that nutrient timing impacts upon nutrient metabolism, whilst also highlighting that this appears to occur to a greater degree with a 16 h fast relative to a 12 h fast. Considering this in light of the typical postprandial nutrient profile discussed previously, the increase in fasting duration may provide more opportunities for the metabolism of substrates derived from endogenous lipids. This again points to the possibility that routine extension of the fasting period beyond 12–14 h may be key to these benefits, which was not necessarily achieved by the 5:2 or modified alternate-day methods discussed earlier. The pivotal question is whether these improvements are enhanced with even longer durations of complete fasting.

More prolonged and complete fasting was recently examined by Sutton *et al*., who hypothesised that circadian rhythms in energy metabolism would potentiate the effects of time-restricted feeding when eating times are confined to earlier stages of the waking phase. Using a repeated-measures crossover design, they compared the effect of consuming all daily energy within a 6 h window and a 12 h window over 5 weeks in men with pre-diabetes. The diets were prescribed based on energy requirements to maintain energy balance and were also matched for energy and macronutrient content. Compliance to the two conditions was high and the extended fasting period was accompanied by reductions in fasting insulin, peak insulin and insulin resistance during an oral glucose tolerance test. However, it appears the magnitude and persistence of any treatment effects may have required a longer wash-out interval between repeated treatments, as the impacts on insulinaemia were seemingly affected by baseline differences arising from a trial order effect. Combined with the fact that the fasting duration preceding post-intervention measurements was not standardised across trials, further investigations are warranted to verify these intriguing possibilities.[31,32]

**4.4 Complete alternate day fasting**

Thus far, the intermittent fasting strategies discussed typically permit the consumption of energy within each 24 h cycle to some degree, meaning that the fasting interval is only extended by a few hours. This is primarily to facilitate adherence but it also replenishes hepatic glycogen stores and reduces the utilisation of lipid-derived substrates (i.e. ketone bodies), which may mask several proposed benefits of intermittent fasting. Furthermore, this disruption is profoundly asymmetric, in that even a short feeding occasion immediately suppresses lipolysis and ketogenesis, which then do not return for a number of hours. It is worthy of note at this juncture that the inclusion of physical activity or exercise during the fasted period may serve to accelerate the restoration of these pathways to some degree, although the concurrent application of intermittent fasting alongside exercise interventions is beyond the scope of this review.[33] Nonetheless, the 20 h fasting interval used by Stote *et al*. is likely to have led to a greater reliance on these lipid-derived substrates over the course of 24 h, which may explain the reduction in fat mass despite euenergetic intake.Building upon this premise, Halberg *et al*. applied a 20 h fast on alternate days from 22.00 to 18.00 hours, representing an integration of the strategies employed by Stote *et al*. and Varady *et al*.

Fasting prohibited all intake with the exception of water, whilst during the intervening feeding periods, participants were told to double their habitual intake to maintain body mass. Although dietary intake was not monitored, blood samples collected in a subset of fasting periods confirmed compliance with the fasting protocol, with corresponding changes in systemic concentrations of glucose, NEFA, glycerol, adiponectin and leptin. Although both body mass and fat mass were unchanged, the glucose infusion rate during a euglycaemic–hyperinsulinaemic clamp increased in the final 30 min of the sampling period, suggesting enhanced insulin sensitivity following complete alternate-day fasting. Accordingly, this was accompanied by more rapid suppression of adipose tissue lipolysis during the insulin infusion.[34] While the lack of an effect on body mass and fat mass relative to prior studies may reflect the disparity in cumulative fasting time, the authors were nonetheless able to conclude that this approach to intermittent fasting can improve metabolic health even in the absence of detectable changes in body mass.[35]

## 5. CONCLUSION

Intermittent fasting clearly encompasses a broad spectrum of dietary interventions. The defining characteristic is the confinement of energy restriction to a specified temporal window, be that 16 h each day every other day or just 2 d per week. Across these various models, intermittent fasting can elicit reductions in body mass and improvements in metabolic health, effects which appear broadly comparable to standard daily energy restriction. However, because the therapeutic potential of these temporal strategies may lie in routinely extending catabolic periods, thereby increasing reliance on lipid-derived substrates, the similar efficacy in relation to standard approaches could instead reflect a failure to meaningfully extend the post-absorptive period. The 5:2 diet and modified alternate-day fasting rarely omit more than one meal in sequence and therefore this transition to lipid-derived substrates may scarcely be made. Conversely, if applying approaches that extend the fasting interval towards 20 h and beyond (e.g. consecutive fasting days in the 5:2 diet or time-restricted feeding), this transition to lipid-derived substrates is likely to be made more frequently, perhaps explaining the proposed superiority of these approach . Unfortunately, whilst the latter studies of complete alternate-day fasting offer amongst the longest uninterrupted fasting periods, the true effects of this are difficult to isolate due to metabolically diverse samples and the use of single-arm trials. Consequently, there remains an urgent need for well-designed, randomised-controlled trials of this commonly adopted approach.

## 6. Future Direction

Identifying more effective strategies for managing obesity and associated metabolic disorders remains a public health challenge and intermittent fasting may represent a potent tool. However, research to support this is scarce and a number of important facets have been overlooked. Further research is therefore warranted to establish whether intermittent fasting is simply an alternative means of achieving energy restriction, or a dietary strategy which offers a favourable method for maintaining/improving metabolic health.

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