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Intermittent Fasting and Time-Restricted Eating for Metabolic Syndrome: A Comprehensive Narrative Review of Mechanisms and Clinical Evidence

Jihan Alfira[1*], Veny Rachmalinda[2], Dhiya Fadhila Rahmah[3], Miftahul Jannah[4]
[1]Faculty of Health Sciences, Universitas Bina Bangsa, Indonesia
[2]Faculty of Medicine and Health Sciences, Universitas Adiwangsa Jambi, Indonesia
[3]Faculty of Health Sciences, Universitas Mohammad Natsir Bukittinggi, Indonesia
[4]Faculty of Health and Science, Universitas Internasional Batam, Indonesia
*Corresponding Author: jihan.alfira@binabangsa.ac.id

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ABSTRACT

Background: Metabolic syndrome (MetS) is a clustering of abdominal obesity, hypertension, dyslipidaemia, and dysglycaemia is now affects an estimated 1.54 billion adults worldwide and continues to rise across countries of all income levels. Intermittent fasting (IF) and time-restricted eating (TRE), which confine intake to defined fasting-feeding cycles rather than continuous caloric reduction, have emerged as popular alternatives to continuous energy restriction (CER) for MetS prevention and management. This review synthesizes mechanistic and clinical trial evidence on the principal IF protocols alternate-day fasting (ADF), the 5:2 diet, and TRE and evaluates their efficacy and safety in adults with or at risk of metabolic syndrome.
Methods: A non-systematic search was conducted in PubMed, Embase, and the Cochrane Library for landmark randomized controlled trials (RCTs), meta-analyses, umbrella reviews, and mechanistic studies published between 2016 and 2026.
Results: Fasting periods sufficient to deplete hepatic glycogen trigger a metabolic switch from glucose- to ketone-based metabolism, activating cellular stress-resistance and autophagy pathways. Across more than fifteen RCTs and several meta-analyses, IF and TRE produce modest reductions in body weight (1-8%), improved insulin sensitivity, and favourable changes in blood pressure and lipids—generally comparable to, but not consistently superior to, matched continuous energy restriction. One isocaloric trial showed fasting itself, independent of net energy restriction, can confer modest benefit.
Conclusion: IF and TRE are effective, safe, and flexible strategies for improving cardiometabolic risk factors in adults with metabolic syndrome, offering an evidence-based alternative to caloric restriction, though individualization and longer-term outcome data remain needed.

Keywords: cardiometabolic risk; intermittent fasting; metabolic syndrome; obesity; time-restricted eating

A. BACKGROUND

Metabolic syndrome (MetS) is a clustering of interrelated cardiometabolic abnormalities, including abdominal obesity, elevated blood pressure, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol, and impaired fasting glucose, that together substantially increase the risk of type 2 diabetes mellitus and cardiovascular disease[1]. Diagnostic criteria were harmonized in 2009 by a joint interim statement of the International Diabetes Federation, the National Heart, Lung, and Blood Institute, the American Heart Association, and allied organizations, which defined MetS as the presence of any three of five specific risk factors rather than requiring a single mandatory component[1]. Using this and related definitions, a recent systematic review and Bayesian modelling analysis encompassing more than 45 million adults across 198 countries estimated that global MetS prevalence more than doubled between 2000 and 2023, rising from 14.7% to 31.0% among women and from 9.0% to 25.7% among men, corresponding to approximately 1.54 billion affected adults in 2023[2]. This rising burden, driven by urbanization, sedentary behaviour, and energy-dense dietary patterns, underscores the urgent need for effective, sustainable, and broadly applicable lifestyle interventions.

Conventional dietary management of MetS has traditionally relied on continuous energy restriction (CER), in which daily caloric intake is reduced by a fixed percentage every day. However, sustained adherence to CER is often poor, prompting growing interest in intermittent fasting (IF) as an alternative paradigm. IF encompasses a family of eating patterns characterized by alternating periods of normal or unrestricted intake with periods of substantial energy restriction or complete abstinence from food, rather than uniform daily restriction[3]. The principal IF protocols studied in clinical research include alternate-day fasting (ADF), in which a near-fasting day of approximately 0-25% of energy needs alternates with an ad libitum or modestly increased intake day; the 5:2 diet, comprising five days of habitual eating and two non-consecutive fasting or very-low-calorie days per week; and time-restricted eating (TRE), in which daily food intake is confined to a consistent window of typically four to ten hours, with fasting for the remaining fourteen to twenty hours, without an explicit instruction to reduce overall caloric intake[3].

Interest in IF has been further reinforced by mechanistic research demonstrating that fasting durations sufficient to deplete hepatic glycogen stores, typically beyond twelve hours, trigger a coordinated “metabolic switch” from glucose-based to ketone-based cellular energy metabolism, accompanied by activation of pathways governing cellular stress resistance, mitochondrial efficiency, and autophagy[3]. These cellular adaptations, first elaborated through decades of animal research and increasingly substantiated in controlled human trials, provide

biological plausibility for cardiometabolic benefits that may extend beyond those attributable to caloric reduction alone. Given the substantial public interest in IF as a flexible, easy-to-follow dietary strategy, alongside an expanding and sometimes conflicting body of randomized trial evidence, an updated and comprehensive synthesis is warranted, particularly with attention to outcomes most relevant to metabolic syndrome.

This narrative review aims to: (1) describe the principal forms and proposed mechanisms of intermittent fasting; (2) synthesize randomized controlled trial and meta-analytic evidence on the effects of IF and TRE on body weight, glycaemic control, blood pressure, lipid profile, and hepatic steatosis; (3) compare the efficacy of IF with conventional continuous energy restriction; (4) evaluate safety, adherence, and special population considerations; and (5) discuss the clinical and public health implications of incorporating intermittent fasting into metabolic syndrome management strategies.

B. METHODS

This article was prepared as a narrative literature review rather than a formal systematic review. A literature search was conducted in PubMed, Embase, and the Cochrane Library for articles published between 2016 and 2026, using combinations of the keywords “intermittent fasting,” “time-restricted eating,” “time-restricted feeding,” “alternate-day fasting,” “5:2 diet,” “metabolic syndrome,” “insulin resistance,” “continuous energy restriction,” and “non-alcoholic fatty liver disease.” Priority was given to landmark randomized controlled trials conducted in dedicated metabolic research centres, large meta-analyses and umbrella reviews of randomized clinical trials, and key mechanistic publications. Articles published only as conference abstracts, non-peer-reviewed commentaries, or without available full text were excluded. Findings were thematically synthesized around mechanisms, clinical outcomes by intervention type and risk factor, comparative efficacy versus continuous energy restriction, and safety considerations, consistent with the scope of a literature-based review article intended to inform clinical and public health audiences.

C. RESULT AND DISCUSSION

1. Definitions and Classification of Intermittent Fasting Protocols

Although often discussed as a single dietary approach, intermittent fasting comprises several distinct protocols that differ substantially in fasting duration, frequency, and degree of net energy restriction. Alternate-day fasting (ADF) involves complete or near-complete fasting (typically 0-25% of estimated energy needs) on alternating days, interspersed with ad libitum

or modestly hypercaloric intake on "feast" days, such that net weekly energy intake is reduced by approximately 25-35% relative to habitual intake[4]. The 5:2 diet modifies this approach by restricting only two non-consecutive days per week to approximately 500-600 kilocalories, while permitting habitual eating on the remaining five days[5]. Time-restricted eating (TRE), in contrast, manipulates the timing rather than necessarily the total quantity of food intake, confining all caloric consumption to a self-selected or prescribed window ranging from four to ten hours per day, with extended fasting for the remaining hours; common variants include early TRE (eating concentrated in the morning and early afternoon, aligned with circadian peaks in insulin sensitivity) and standard or self-selected TRE windows[5,6].

These protocols are frequently, though imprecisely, used interchangeably in both lay and scientific discourse, despite meaningfully different physiological exposures: ADF and the 5:2 diet typically produce substantial net energy deficits through severe but infrequent restriction, whereas many TRE protocols, particularly those without explicit calorie counting, achieve more modest energy deficits primarily through spontaneous reductions in evening snacking and shortened eating opportunity[7,8]. This distinction has important implications for interpreting and comparing trial outcomes, since interventions that combine fasting-mediated and energy-deficit-mediated mechanisms may be expected to differ from those in which energy restriction is the dominant or sole active ingredient.

2. Mechanisms: Metabolic Switching, Circadian Biology, and Cellular Stress Resistance

A widely cited mechanistic framework proposes that fasting durations exceeding approximately twelve hours, sufficient to deplete hepatic glycogen reserves, initiate a coordinated "metabolic switch" in which fatty acids are mobilized from adipose tissue and converted in the liver to ketone bodies, which then serve as an alternative fuel source for peripheral tissues, including the brain[3]. This metabolic transition is accompanied by reductions in circulating glucose, insulin, and amino acid levels, and by downregulation of insulin and insulin-like growth factor 1 signalling, with consequent activation of transcription factors and kinases, including forkhead box O proteins, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, AMP-activated protein kinase, and sirtuins, that collectively enhance mitochondrial biogenesis, antioxidant defence, DNA repair, and autophagy[3,6].

A complementary mechanistic pathway relates to circadian biology. Time-restricted feeding studies in rodent models demonstrated that confining food intake to the active phase

of the circadian cycle, irrespective of total caloric intake, restores normal daily oscillations in metabolic gene expression, hormone secretion, and mitochondrial function, and protects against diet-induced obesity, dyslipidaemia, and glucose intolerance[4]. In humans, early TRE, in which the eating window is shifted to align with the morning peak in insulin sensitivity, has been specifically tested in controlled feeding trials. One such trial in men with prediabetes randomized participants to a six-hour early eating window (with dinner completed before 3:00 p.m.) versus a twelve-hour control schedule while precisely matching caloric intake to prevent weight loss; despite the absence of weight change, early TRE significantly improved insulin sensitivity, pancreatic beta-cell responsiveness, blood pressure, and oxidative stress markers, providing direct evidence that the timing of food intake, independent of caloric quantity or resultant weight loss, can confer metabolic benefit[5]. A related trial confirmed that early TRE additionally improved 24-hour glucose profiles and altered molecular markers of the circadian clock, ageing, and autophagy pathways in humans[6]. Together, these mechanistic findings lend intermittent fasting a degree of biological credibility beyond that of a simple caloric-restriction strategy applied on an altered schedule, since they demonstrate that meal timing alone can confer measurable metabolic benefit independent of weight loss.

3. Effects on Body Weight and Body Composition

Across numerous randomized trials, both ADF and TRE protocols have consistently produced modest reductions in body weight, typically in the range of 1% to 8% from baseline over intervention periods of eight to twenty-four weeks. A landmark single-arm pilot trial of ten-hour TRE in nineteen participants with metabolic syndrome receiving standard medical care, including statins and antihypertensive medication, found that compressing the daily eating window from a baseline of at least fourteen hours to ten hours produced significant reductions in body weight, waist circumference, and visceral adiposity over twelve weeks[7]. A subsequent randomized trial directly comparing four-hour and six-hour TRE windows in adults with obesity found that both regimens produced comparable reductions in body weight of approximately 3%, driven by a spontaneous reduction in energy intake of roughly 550 kilocalories per day without explicit calorie counting, alongside reductions in insulin resistance and oxidative stress markers relative to an unrestricted control group[8].

Not all trials, however, have demonstrated superiority of TRE over standard eating patterns. The Time-Restricted Eating and Other Metabolic Parameters in Women and Men with Overweight and Obesity (TREAT) randomized clinical trial, the largest TRE weight-loss trial conducted to date at the time of publication, randomized 116 adults to a sixteen-hour fast with an eight-hour ad libitum eating window (12:00 p.m. to 8:00 p.m.) or to a structured three-meals-

per-day consistent meal timing schedule over twelve weeks; while the TRE group lost slightly more weight than the control group (1.17% versus 0.75%), the between-group difference was not statistically significant, and TRE conferred no significant cardiometabolic benefit over consistent meal timing, with a marginally greater loss of appendicular lean mass observed in the TRE group[9]. This trial illustrates that the magnitude of weight loss attributable to TRE, in the absence of professional dietary counselling or explicit energy targets, may be modest and highly dependent on study design and population characteristics.

A pivotal isocaloric randomized trial conducted in lean, healthy adults sought to isolate the independent contribution of fasting per se from that of net energy restriction by comparing three groups over three weeks: continuous daily restriction to 75% of energy needs, alternate-day fasting with no net energy restriction (0% intake alternating with 150% intake, such that net weekly energy balance matched habitual intake), and alternate-day fasting with net energy restriction matched to the continuous restriction group. The trial found that alternate-day fasting without net energy restriction was ineffective at reducing body mass, and that daily continuous energy restriction more effectively reduced body fat content than an energy-matched alternate-day fasting protocol, with no evidence of fasting-specific metabolic benefit independent of net energy balance in this lean, non-obese population[1,9]. This finding contrasts with the early TRE prediabetes trial described above and suggests that the metabolic benefits of fasting timing may be most pronounced in individuals with pre-existing insulin resistance or dysglycaemia, rather than in metabolically healthy lean adults—a discrepancy that likely reflects heterogeneity in intervention design (eating-window length, timing, explicit calorie counting versus ad libitum intake) and population characteristics (lean versus obese, with versus without established metabolic syndrome) rather than a genuine contradiction in the underlying evidence[5,9].

4. Effects on Glycaemic Control and Insulin Sensitivity

Improvement in insulin sensitivity is among the most consistently reported benefits of intermittent fasting across both ADF and TRE protocols. In men at risk of type 2 diabetes, an eight-hour-eating-window crossover trial found that TRE significantly improved glucose tolerance compared with a twelve-hour control eating window, independent of weight change[10]. The ten-hour TRE pilot trial in patients with established metabolic syndrome similarly reported improvements in fasting glucose alongside reductions in blood pressure and atherogenic lipids[11]. A systematic review and meta-analysis with Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evaluation, pooling five studies with 393 participants with metabolic syndrome, found that intermittent fasting

regimens produced a statistically significant reduction in fasting blood sugar, with subgroup analyses indicating a more pronounced effect among older adults, those with higher baseline body mass index, and shorter-duration interventions[12].

Direct head-to-head comparisons of intermittent energy restriction (IER, encompassing ADF and the 5:2 diet) against continuous energy restriction have generally found comparable, and in some analyses superior, effects of IER on insulin sensitivity. A meta-analysis and systematic review of eleven randomized controlled trials comparing IER (restricted only two to three days per week) with CER in adults with overweight or obesity found that IER produced greater absolute and percentage weight loss and greater improvement in insulin sensitivity than CER, particularly in short-term interventions of two to three months[13]. A randomized trial directly comparing an energy-restriction intermittent fasting protocol with continuous energy restriction in patients with diagnosed metabolic syndrome found that both approaches produced similar reductions in body weight (approximately 7%), blood pressure, lipid profile, fasting glucose, and insulin at twelve weeks, indicating that intermittent and continuous approaches can achieve comparable metabolic improvement when matched for overall dietary quality and net energy deficit[11].

5. Effects on Blood Pressure and Lipid Profile

Beyond glycaemic outcomes, several trials have specifically reported improvements in blood pressure and atherogenic lipid fractions following intermittent fasting interventions. The ten-hour TRE pilot trial in patients with metabolic syndrome already receiving antihypertensive and lipid-lowering medication reported significant reductions in systolic blood pressure and in atherogenic lipoprotein particle concentrations after twelve weeks, suggesting that TRE may provide additive cardiometabolic benefit even in pharmacologically treated patients[7]. A pilot feasibility trial of self-selected ten-hour TRE conducted in Polish patients with metabolic syndrome similarly demonstrated meaningful reductions in the duration of the daily eating window, alongside favourable trends in cardiometabolic biomarkers and daily behavioural rhythms, supporting the feasibility of TRE implementation outside of tightly controlled research settings[12,14].

A comprehensive network meta-analysis of 99 randomized clinical trials involving 6,582 adults, comparing alternate-day fasting, time-restricted eating, and whole-day fasting against both continuous energy restriction and unrestricted (ad libitum) diets, found that all intermittent fasting strategies, as well as continuous energy restriction, produced small but significant reductions in body weight compared with an unrestricted diet[15]. Notably, alternate-day fasting was the only intermittent fasting strategy to demonstrate a small but statistically significant

additional benefit in body weight reduction compared with continuous energy restriction, and also showed modest reductions in total cholesterol, triglycerides, and non-high-density lipoprotein cholesterol compared with time-restricted eating, although no significant differences were observed between intermittent fasting strategies and continuous energy restriction for glycated haemoglobin or high-density lipoprotein cholesterol[16]. These findings, drawn from the most comprehensive network meta-analysis of intermittent fasting strategies published to date, indicate that while all approaches confer cardiometabolic benefit relative to unrestricted eating, the comparative advantage of one intermittent fasting protocol over another, or over continuous energy restriction, remains modest and protocol-specific.

6. Effects on Non-Alcoholic Fatty Liver Disease

Given the close pathophysiological relationship between metabolic syndrome and non-alcoholic fatty liver disease (NAFLD), several trials have specifically examined intermittent fasting in this population. A twelve-week randomized controlled trial of the 5:2 intermittent fasting diet in patients with confirmed NAFLD found that, compared with a usual-diet control group, the intervention group experienced significant reductions in body weight, waist circumference, fat mass, hepatic fibrosis and steatosis scores measured by transient elastography, liver enzymes (alanine and aspartate aminotransferase), triglycerides, high-sensitivity C-reactive protein, and the hepatocyte apoptosis marker cytokeratin-18[14]. These findings suggest that intermittent fasting may confer hepatoprotective benefits that extend beyond simple weight reduction, potentially through reductions in hepatic lipid accumulation, systemic inflammation, and hepatocyte injury, all of which are central to NAFLD pathogenesis and frequently co-occur with metabolic syndrome.

7. Comparative Efficacy: Intermittent Fasting versus Continuous Energy Restriction

A central question for clinical practice is whether intermittent fasting offers meaningful advantages over conventional continuous energy restriction. The alternate-day fasting trial conducted by Trepanowski and colleagues, a one-year single-centre randomized clinical trial comparing ADF, daily calorie restriction, and a no-intervention control in obese adults, found that alternate-day fasting did not produce superior adherence, weight loss, weight maintenance, or cardioprotective effects compared with daily calorie restriction, and was associated with a higher dropout rate in the ADF arm, raising questions about its long-term sustainability relative to simpler continuous restriction approaches[16].

In partial contrast, the meta-analysis of intermittent versus continuous energy restriction by He and colleagues found that IER produced modestly greater short-term weight loss and insulin sensitivity improvement than CER[13,17], while the large 2025 network meta-analysis

found alternate-day fasting specifically, among the intermittent fasting protocols studied, to confer a small additional weight-loss benefit over continuous energy restriction, though time-restricted eating and whole-day fasting did not differ significantly from continuous energy restriction[16,17]. Taken together, the cumulative evidence suggests that the comparative efficacy of intermittent fasting relative to continuous energy restriction is protocol-dependent, generally modest in magnitude, and unlikely to represent a categorically superior approach for all patients. These findings collectively indicate that intermittent fasting should not be promoted as a uniformly superior alternative to continuous energy restriction, but rather as one of several evidence-based dietary strategies whose principal clinical value lies in offering patients a structurally different, and for some individuals more sustainable, framework for achieving comparable energy deficits and metabolic improvement—particularly for those who find structured daily caloric counting difficult to sustain[15,18].

8. Safety, Adherence, and Special Population Considerations

Across the reviewed trials, intermittent fasting protocols have generally been well tolerated, with commonly reported mild adverse effects including transient headache, irritability, hunger, and fatigue, particularly during the initial one to two weeks of adaptation[15]. The umbrella review by Patikorn and colleagues, synthesizing eleven meta-analyses of randomized clinical trials and applying GRADE quality assessment, found that modified alternate-day fasting (involving 25% of energy needs on fasting days rather than complete abstinence) was associated with moderate reductions in body weight, body mass index, and several cardiometabolic risk factors in adults with overweight or obesity, supported by moderate-to-high quality evidence, representing the most robust evidence base among the IF protocols evaluated[17].

Nonetheless, important safety and applicability caveats remain. The isocaloric trial in lean, healthy adults demonstrated that alternate-day fasting without net energy restriction conferred no metabolic advantage and may be poorly suited to individuals who are not overweight or obese, given the absence of a meaningful adipose energy reserve to mobilize[19]. Trial dropout rates in some ADF protocols have been notably higher than in continuous energy restriction arms, reflecting the practical difficulty many individuals experience in tolerating near-complete fasting days[10]. Specific caution has also been raised regarding very short eating windows (four hours or less), which, while producing comparable short-term weight loss to slightly longer windows, have not been established as superior and may pose greater challenges for long-term adherence and nutrient adequacy[8,19]. Evidence regarding the comparative safety and efficacy of intermittent fasting in women, including potential effects on menstrual cyclicity

and reproductive hormone profiles, in older adults, and in individuals with a history of disordered eating remains comparatively limited and warrants dedicated future research before broad clinical recommendations can be extended to these populations[15].

More broadly, several limitations temper confidence in the current evidence base as a whole. Most published randomized controlled trials of intermittent fasting have been of relatively short duration (eight to twenty-four weeks), conducted in academic research settings with high-intensity behavioural support, and have enrolled modest sample sizes, limiting inference regarding long-term durability of effects, adherence in unsupervised real-world settings, and the precise comparative efficacy of differing eating-window durations[7-9,19]. Safety and efficacy data in women, older adults, and individuals with disordered eating histories remain comparatively sparse, and clinicians should exercise corresponding caution when extending recommendations to these populations[19].

9. Relevance to Religious and Indonesian Dietary Contexts

Indonesia's majority Muslim population observes annual Ramadan fasting, a religiously mandated form of time-restricted eating involving abstention from food and fluids from dawn to sunset for approximately twenty-nine to thirty consecutive days, which shares structural similarities with externally prescribed time-restricted eating protocols, albeit typically without modification of total caloric intake outside the fasting window[20]. Mechanistic and clinical parallels between Ramadan fasting and experimentally prescribed TRE provide a culturally relevant entry point for translating intermittent fasting research into public health guidance and clinical practice within Indonesia and other Muslim-majority populations.

From a clinical and public health perspective, intermittent fasting and time-restricted eating represent a reasonable, evidence-supported addition to the dietary armamentarium for metabolic syndrome management, particularly for patients who have struggled with adherence to conventional daily caloric restriction. Given the structural resemblance between externally prescribed time-restricted eating and the religiously mandated Ramadan fasting practiced annually by Indonesia's majority Muslim population, there exists a valuable and currently underutilized opportunity to generate locally relevant clinical evidence examining cardiometabolic outcomes of structured fasting practices among Indonesian adults with metabolic syndrome who already practice such fasting on a recurring annual basis—potentially informing culturally resonant, low-cost public health strategies for metabolic syndrome prevention and management[20,21].

D. CONCLUSION

Intermittent fasting and time-restricted eating constitute biologically plausible, generally safe, and moderately effective dietary strategies for improving body weight, insulin sensitivity, blood pressure, lipid profile, and hepatic steatosis among adults with metabolic syndrome, with mechanistic support from both metabolic-switching and circadian-alignment pathways. Comparative trial evidence indicates that intermittent fasting protocols, particularly alternate-day fasting and time-restricted eating, achieve cardiometabolic improvements broadly comparable to, though not consistently superior to, matched continuous energy restriction, with the choice between approaches reasonably guided by individual patient preference and likely long-term adherence rather than presumed differential efficacy. Future research priorities should include longer-duration trials extending beyond one year, head-to-head comparisons of differing eating-window durations and timing, dedicated investigation of safety and efficacy in women and older adults, and locally generated studies examining structured fasting, including religious fasting practices, within the Indonesian population to inform culturally appropriate, evidence-based public health guidance.

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