



Systematic Review



Impact of Intermittent Fasting on Human Endocrine and Metabolic Physiology: A Systematic Review

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ABSTRACT

Intermittent fasting (IF) is increasingly recognized as a dietary approach that may improve endocrine and cardiometabolic health by aligning eating patterns with circadian rhythms. **Objectives:** To systematically evaluate recent human studies (2018-2024) investigating the effects of intermittent fasting on endocrine and metabolic physiology, with emphasis on insulin sensitivity, hormonal balance, and cardiometabolic outcomes. **Methods:** PubMed, Scopus, and the Cochrane Library were searched according to PRISMA 2020 guidelines. Randomized controlled, crossover, cohort, and observational studies reporting endocrine (insulin, leptin, ghrelin, cortisol) and metabolic (glucose, lipids, body composition) outcomes associated with intermittent fasting were included. Study quality was assessed using the Joanna Briggs Institute tools. **Results:** Eighteen studies (~1,250 participants) were included. Early time-restricted eating and alternate-day fasting were consistently associated with improved insulin sensitivity, glycemic control, lipid profiles, and blood pressure. Several trials reported endocrine benefits independent of major weight loss. Most randomized studies showed low risk of bias. **Conclusions:** Low-risk randomized evidence supports early time-restricted eating and alternate-day fasting as effective strategies for improving insulin sensitivity and glycemic control. Other hormonal outcomes remain associative and require further trials. Intermittent fasting is a promising, culturally adaptable approach for metabolic risk reduction.

INTRODUCTION

Disorders of metabolism and the endocrine system, including obesity, type 2 diabetes mellitus, and metabolic syndrome, are rapidly increasing worldwide and represent a major public health burden. Conventional management strategies emphasize sustained caloric restriction; however, long-term adherence to continuous dieting remains poor, and metabolic benefits often diminish over time [1]. Consequently, alternative dietary strategies that are both effective and sustainable are increasingly being

explored [2]. Intermittent fasting (IF) has emerged as a promising dietary approach that alternates defined periods of eating and fasting. Common IF patterns include time-restricted eating (TRE), alternate-day fasting (ADF), and periodic fasting regimens such as the 5:2 diet [3, 4]. Unlike traditional calorie-restricted diets, IF focuses primarily on meal timing rather than continuous energy reduction. Aligning food intake with circadian rhythms may favorably modulate key metabolic hormones, including



insulin, cortisol, leptin, and ghrelin—thereby improving glucose and lipid homeostasis [5, 6]. At the cellular level, IF has been associated with activation of AMP-activated protein kinase (AMPK) and autophagy pathways, which support mitochondrial function, cellular repair, and oxidative stress reduction [7]. Clinical studies have reported improvements in insulin sensitivity, fasting glucose, lipid profiles, and inflammatory markers across diverse populations, with several trials demonstrating metabolic benefits even in the absence of substantial weight loss [8–10]. These findings suggest that IF may exert partially weight-independent metabolic effects mediated by metabolic switching from glucose to fatty acid and ketone utilization [11–13].

Despite growing interest, the endocrine and metabolic effects of IF remain heterogeneous across fasting protocols, study designs, and populations, resulting in inconsistent conclusions. Evidence is particularly limited in South Asian settings, where unique dietary practices, fasting customs, and high metabolic disease burden warrant region-specific evaluation. This study aimed to synthesize human studies published between 2018 and 2024 to assess the effects of intermittent fasting on endocrine and metabolic physiology, with particular focus on insulin sensitivity, hormonal regulation, and cardiometabolic outcomes.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was not prospectively registered in PROSPERO, which has been explicitly acknowledged as a methodological limitation due to the potential risk of selective outcome reporting. A comprehensive literature search was conducted in PubMed, Scopus, and the Cochrane Library to identify relevant studies published between January 1, 2018, and December 15, 2024. The final database search was completed on December 15, 2024. The electronic search strategy incorporated both Medical Subject Headings (MeSH) and free-text keywords. Database-specific reproducible Boolean search strings were applied. In PubMed, the following strategy was used: ("Intermittent Fasting" [MeSH] OR "Time-Restricted Eating" [MeSH] OR "Alternate Day Fasting" [MeSH] OR Ramadan fasting OR "5:2 diet") AND ("Insulin Sensitivity" [MeSH] OR "Endocrine System" [MeSH] OR cortisol OR leptin OR ghrelin OR "Glucose Metabolism" [MeSH]) with filters for humans, English language, and publication years 2018–2024. Comparable keyword-based strategies were applied in Scopus and the Cochrane Library using Title/Abstract/Keyword fields. In addition, reference lists of all eligible studies were manually screened to identify

potentially missed publications. The initial search yielded 535 records. Eligible studies were selected based on predefined inclusion and exclusion criteria. Included studies were human research articles published in English that employed randomized controlled, crossover, cohort, or observational designs and evaluated any intermittent fasting protocol, including time-restricted eating, alternate-day fasting, the 5:2 diet, or Ramadan fasting. Primary outcomes were explicitly defined as endocrine parameters, including insulin sensitivity, fasting insulin, leptin, ghrelin, and cortisol, while secondary outcomes included metabolic variables such as fasting glucose, lipid profile, body composition, and body mass index. Reviews, meta-analyses, conference abstracts, pilot studies, case reports, animal or laboratory studies, and studies lacking quantifiable endocrine or metabolic outcomes or accessible full texts were excluded. All records were imported into EndNote to remove duplicates. Two independent reviewers screened titles and abstracts, followed by a full-text review of potentially eligible studies. Inter-reviewer screening reliability demonstrated 92% agreement ($\kappa = 0.86$), and disagreements were resolved through consensus or third-reviewer arbitration. Data were extracted using structured extraction forms. These forms were pilot-tested on three randomly selected studies before full extraction to enhance consistency and minimize extraction bias. Extracted information included authorship, publication year, study design, sample size, population characteristics, fasting protocol type and duration, primary endocrine outcomes, secondary metabolic outcomes, and key findings. Methodological quality and risk of bias were evaluated using the Joanna Briggs Institute (JBI) critical appraisal tools appropriate for each study design. Studies were classified as low risk of bias if $\geq 80\%$ of checklist items were scored as "Yes," moderate risk if 60–79%, and high risk if $< 60\%$. Risk of bias grading was incorporated into the interpretation of findings to strengthen evidence appraisal because of substantial clinical heterogeneity (different fasting protocols and populations), methodological heterogeneity (varying study designs), and outcome heterogeneity (variable endocrine and metabolic measures). Meta-analysis was not performed, and narrative synthesis was adopted. Findings were stratified according to fasting protocol and study design, and weight-dependent and weight-independent endocrine effects were interpreted separately to minimize confounding by weight loss. Formal funnel plot analysis for publication bias was not feasible due to heterogeneity and limited comparable outcomes; therefore, potential publication bias has been acknowledged as a limitation. Additionally, several included trials had small sample sizes ($n < 20$), and limited

statistical power has been acknowledged when interpreting hormonal effects. Causal inferences have been restricted to randomized controlled trials, while observational findings have been interpreted as associative. PRISMA 2020 flow diagram summarizing the selection process for studies evaluating the endocrine and metabolic effects of intermittent fasting. A total of 535 records were identified, and 18 studies met the final inclusion criteria (Figure 1).

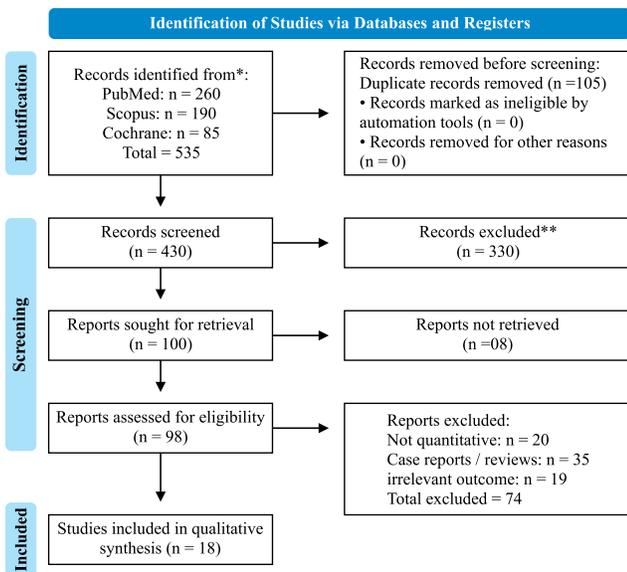


Figure 1: Selection Process for Studies

Table 1: Characteristics of Included Human Studies on Intermittent Fasting and Endocrine–Metabolic Physiology (2018–2024)

Sr. No.	References	Country	Study Design	Sample Size	Population	Intermittent Fasting Protocol	Duration	Main Endocrine Outcomes	Main Metabolic Outcomes
1	[14]	USA	Controlled feeding trial	8	Men with prediabetes	Early time-restricted feeding (6-h window, early day)	5 weeks	↑ Insulin sensitivity, changes in ghrelin and other circadian hormones	Improved cardiometabolic profile without major weight loss
2	[15]	USA	Controlled crossover study	11	Overweight adults	Early TRE vs usual late eating	4 weeks	Improved 24-h insulin and cortisol rhythmicity	Better 24-h glucose control and lipid handling
3	[16]	USA	Randomized clinical trial	90	Adults with obesity	Early TRE (eating 7:00–15:00) vs ≥12-h eating window	14 weeks	↑ Insulin sensitivity, favourable hormonal profile	Greater weight and fat loss, ↓ diastolic BP
4	[17]	USA	Randomized trial	58	Adults with obesity	4-h vs 6-h TRF vs control	8–10 weeks	↓ Fasting insulin, improved adipokine pattern	~3–4% weight loss, ↓ BP and oxidative stress
5	[18]	USA	Single-arm paired trial	19	Adults with metabolic syndrome	10-h TRE (self-selected window)	12 weeks	Better insulin regulation, improved hormonal milieu	↓ Weight, ↓ HbA1c, ↓ BP, improved lipids
6	[19]	USA	Randomized clinical trial	116	Adults with overweight / obesity	16:8 TRE vs 3 structured meals	12 weeks	No major endocrine advantage vs control	Modest weight change, no clear cardiometabolic benefit
7	[20]	China	Randomized clinical trial	139	Adults with obesity	Calorie restriction ± 8:00–16:00 TRE	12 months	Hormonal effects mainly mediated by weight change	Similar weight loss with or without TRE; no extra metabolic gain
8	[21]	China	Randomized trial	90	Healthy adults without obesity	6-h early TRE vs 6-h late TRE vs control	5 weeks	Differences in insulin and circadian hormone responses between early vs late TRE	Improved metabolic health with early TRE vs late TRE/control

9	[22]	Italy	Randomized trial	82	Resistance-trained adults	TRE combined with resistance training	12 months	↓ Inflammatory markers, favourable endocrine risk profile	↓ Cardiometabolic risk factors, preserved muscle mass
10	[23]	China	Randomized controlled trial	80	NAFLD patients	Alternate-day fasting vs usual diet	12 weeks	Improved insulin resistance indices	↓ Weight, ↓ dyslipidaemia, improved liver-related markers
11	[24]	Iran	Randomized clinical trial	70	Adults with metabolic syndrome	Modified ADF vs daily calorie restriction	8 weeks	Improved insulin sensitivity vs control	Greater ↓ weight, waist circumference, BP and TG
12	[25]	USA	Randomized controlled trial	80	NAFLD patients	Alternate-day fasting + aerobic exercise vs control	8 weeks	Favourable changes in insulin resistance and inflammatory markers	↓ Liver fat, ↓ weight, improved lipid profile
13	[26]	UK	Randomized parallel study	27	Overweight / obese adults	5:2 intermittent energy restriction vs continuous restriction	16 weeks (incl. follow-up)	No clear superiority of IER for post-prandial insulin vs CER	Similar weight loss; mixed effects on lipids and glucose
14	[27]	UK	Randomized trial	36	Normal-weight young adults	5:2 IER vs continuous restriction	Several weeks	Comparable effects on basal/post-prandial insulin and hormones	Similar metabolic responses between 5:2 and continuous restriction
15	[28]	Netherlands	Randomized crossover trial	37	Adults with overweight / obesity	Intermittent restricted eating vs continuous restriction	2 × 4-week periods	Changes in fasting insulin and appetite hormones	Similar or slightly improved metabolic flexibility with IER
16	[29]	USA	Randomized controlled trial	213	Adults with metabolic syndrome	Personalized 8–10-h TRE vs usual care	12 months	Improved insulin regulation and endocrine cardiometabolic profile	Better glycaemic control and composite MetS score
17	[30]	UAE	Prospective observational study	57	Overweight and obese adults	Diurnal Ramadan fasting (dawn–sunset)	1 month	Changes in ghrelin, leptin, melatonin, and cortisol	Modest ↓ weight and waist; lifestyle-linked changes
18	[31]	France	Quasi-experimental trial	20	Obese men	Ramadan IF with training	Ramadan month + follow-up	Altered leptin, GLP-1, PYY, CCK; no change in ghrelin	↓ BMI, ↓ body fat %, improved body composition indices

Presents the endocrine outcomes reported across included studies. Insulin sensitivity outcomes were reported in 12 studies, leptin in 6 studies, ghrelin in 7 studies, and cortisol in 5 studies. Most randomized controlled trials evaluating early TRE and ADF demonstrated consistent improvements in insulin sensitivity, fasting insulin concentrations, and adipokine profiles. Endocrine improvements in insulin sensitivity were predominantly supported by low-risk randomized controlled trials, allowing cautious causal interpretation, whereas outcomes related to ghrelin and cortisol were largely derived from moderate-risk observational or small-sample trials and should therefore be interpreted as associative. Studies evaluating late TRE and 5:2 fasting showed mixed endocrine responses, often comparable to continuous calorie restriction, suggesting that feeding window timing plays a critical role in hormonal regulation (Table 2).

Table 2: Summary of Endocrine Outcomes Reported Across Included Studies (2018–2024)

Sr. No.	References	Key Hormonal Outcomes	Overall Endocrine Effect
1	[14]	↑ Insulin sensitivity; changes in ghrelin and circadian hormones	Early TRE improved insulin action and hormonal rhythms
2	[15]	Improved 24-h insulin and cortisol rhythmicity	Better alignment of circadian endocrine markers
3	[16]	↑ Insulin sensitivity; favourable adipokine profile	Endocrine benefits more pronounced with early TRE
4	[17]	↓ Fasting insulin; ↑ adiponectin patterns	Short feeding windows improved hormonal markers
5	[18]	Better insulin regulation; improved metabolic hormones	TRE enhanced insulin control in metabolic syndrome
6	[19]	No significant endocrine advantages vs control	Hormonal outcomes largely unchanged
7	[20]	Endocrine changes mainly mediated by weight loss	TRE did not add major hormonal benefit beyond calorie restriction
8	[21]	Distinct insulin and circadian hormone shifts between early vs late TRE	Early TRE produced more favourable endocrine timing
9	[22]	↓ Inflammatory markers; modest endocrine improvements	TRE + resistance training improved inflammatory–endocrine profile
10	[23]	Improved insulin resistance indices	ADF enhanced insulin sensitivity in NAFLD
11	[24]	↑ Insulin sensitivity vs control	Modified ADF produced stronger hormonal improvement
12	[25]	↓ Insulin resistance; ↓ inflammatory markers	ADF + exercise improved metabolic hormones
13	[26]	No superiority of 5:2 over continuous restriction for post-prandial insulin	Hormonal changes modest and similar between groups

14	[27]	Comparable basal/post-prandial insulin changes between groups	IF and continuous restriction produced similar endocrine responses
15	[28]	Altered fasting insulin; minor appetite-hormone shifts	Small endocrine effects, largely comparable to CER
16	[29]	Improved insulin regulation; favourable cardiometabolic hormones	TRE enhanced metabolic–endocrine status in MetS
17	[30]	Changes in ghrelin, leptin, melatonin, cortisol	Ramadan fasting altered appetite and circadian hormones
18	[31]	Changes in leptin, GLP-1, PYY, CCK; stable ghrelin	Ramadan IF modified gut hormones and appetite regulation

The study summarizes the metabolic outcomes reported across the included studies. Most randomized trials demonstrated significant reductions in body weight, fasting glucose, HbA1c, lipid levels, and blood pressure, particularly in early TRE and ADF protocols. These metabolic improvements were most pronounced in participants with obesity and metabolic syndrome. Across trials, improvements in insulin sensitivity and glycaemic control were observed even in studies reporting minimal weight change, indicating partially weight-independent endocrine effects, whereas lipid and adiposity outcomes were largely weight-dependent. Protocols such as late TRE and 5:2 intermittent energy restriction generally showed metabolic effects similar to continuous calorie restriction, highlighting heterogeneity in metabolic responsiveness among fasting regimens. Ramadan Fasting (Observational Evidence) Observational Ramadan fasting studies Al-Rawi et al. and Zouhal et al. demonstrated modest hormonal and metabolic changes; however, these findings represent associative evidence and were therefore interpreted separately from randomized controlled trials [30, 31](Table 3).

Table 3: Summary of Metabolic Outcomes Reported Across Included Studies (2018–2024)

Sr. No.	References	Key Hormonal Outcomes	Overall Endocrine Effect
1	[14]	Improved glucose tolerance; reduced oxidative stress	Early TRE enhanced cardiometabolic profile
2	[15]	Better 24-h glucose control; improved lipid handling	Improved metabolic rhythm and glycemic stability
3	[16]	Greater weight and fat loss; ↓ diastolic BP	Early TRE is superior for metabolic improvement
4	[17]	~3–4% weight loss; ↓ BP; ↓ oxidative stress	Both 4-h and 6-h TRF improved metabolic health
5	[18]	↓ Weight, ↓ HbA1c, ↓ BP; improved lipid markers	Notable metabolic benefits in metabolic syndrome
6	[19]	Modest weight change; no major lipid/glucose improvements	TRE not superior to structured meals
7	[20]	Weight loss similar across groups; no additional TRE advantage	Calorie restriction drove most metabolic changes
8	[21]	Improved metabolic health with early TRE vs late TRE	Early eating window enhanced metabolic regulation
9	[22]	↓ Cardiometabolic risk factors; maintained muscle mass	TRE + training improved metabolic risk
10	[23]	↓ Weight; ↓ dyslipidaemia; improved liver markers	ADF effective in NAFLD metabolic improvement
11	[24]	Greater ↓ weight, waist circumference, TG, BP	Modified ADF metabolically superior to CER
12	[25]	↓ Liver fat; ↓ weight; improved lipid profile	ADF + exercise produced strong metabolic gains
13	[26]	Similar weight loss; mixed lipid/glucose effects	No metabolic advantage for 5:2 pattern
14	[27]	Comparable metabolic responses across groups	IF and CER had similar metabolic outcomes
15	[28]	Slight improvements in metabolic flexibility	Differences modest; IF ≈ CER
16	[29]	Improved glycaemic control; better composite metabolic score	TRE beneficial in metabolic syndrome
Observational Ramadan Fasting Studies			
17	[30]	↓ Weight & waist circumference	Ramadan IF produced modest metabolic improvements
18	[31]	↓ BMI and body fat percentage	Ramadan IF + training improved body composition

Presents the methodological quality assessment of included studies using the Joanna Briggs Institute criteria. Most randomized controlled trials demonstrated a low overall risk of bias, particularly in outcome measurement and reporting domains. Moderate risk of bias was primarily observed in confounding control and participant selection, especially in observational Ramadan fasting studies. Endocrine and metabolic improvements in insulin sensitivity, fasting glucose, and lipid profile were predominantly supported by low-risk randomized trials, whereas hormonal outcomes such as ghrelin and cortisol were largely supported by moderate-risk observational studies and therefore should be interpreted as associative. Additionally, several studies reporting hormonal outcomes included small sample sizes (n < 20), and these findings should be interpreted cautiously due to limited statistical power (Table 4).

Table 3: Summary of Metabolic Outcomes Reported Across Included Studies (2018–2024)

Sr. No.	References	Selection Bias	Measurement Bias	Confounding Control	Outcome Reporting	Overall Risk
1	[14]	Low	Low	Moderate	Low	Moderate
2	[15]	Low	Low	Moderate	Low	Moderate
3	[16]	Low	Low	Low	Low	Low
4	[17]	Low	Low	Moderate	Low	Moderate

5	[18]	Moderate	Low	Moderate	Low	Moderate
6	[19]	Low	Low	Low	Low	Low
7	[20]	Low	Low	Low	Low	Low
8	[21]	Low	Low	Low	Low	Low
9	[22]	Low	Low	Moderate	Low	Moderate
10	[23]	Low	Low	Low	Low	Low
11	[24]	Low	Low	Moderate	Low	Moderate
12	[25]	Low	Low	Low	Low	Low
13	[26]	Low	Low	Moderate	Low	Moderate
14	[27]	Low	Low	Moderate	Low	Moderate
15	[28]	Low	Low	Moderate	Low	Moderate
16	[29]	Low	Low	Low	Low	Low
17	[30]	Moderate	Moderate	Moderate	Low	Moderate
18	[31]	Moderate	Moderate	Moderate	Low	Moderate

DISCUSSION

This systematic review included 18 human studies (2018–2024) and examined the endocrine and metabolic impacts of different forms of intermittent fasting (IF), including time-restricted eating (TRE), alternate-day fasting (ADF), and Ramadan fasting. Findings derived from low-risk randomized controlled trials provide causal evidence that early TRE and ADF improve insulin sensitivity and glycemic control. The body of evidence further indicates that intermittent fasting is associated with improvements in lipid metabolism and hormonal balance through both weight-dependent and partially weight-independent mechanisms. The majority of included studies reported changes in endocrine function, particularly insulin sensitivity and circadian hormones such as leptin, ghrelin, and cortisol. Hormonal outcomes related to leptin, ghrelin, and cortisol were primarily derived from moderate-risk or small-sample studies and should therefore be interpreted as associative rather than causal. These findings are in accordance with Kim *et al.* who reported fasting-related modulation of cortisol and insulin rhythm [5], and with early TRE trials demonstrating consistent endocrine benefits [32, 33]. Intermittent fasting has been linked to activation of AMP-activated protein kinase (AMPK) and autophagy pathways that enhance mitochondrial efficiency and cellular repair. These mechanistic associations are supported mainly by experimental and translational evidence and should be interpreted as biologically plausible explanations rather than direct clinical proof. Molecular evidence from Arif supports improved insulin resistance and lipid metabolism mediated by AMPK activation [7]. Several randomized trials demonstrated endocrine improvements even in the absence of major weight loss, indicating partially weight-independent metabolic effects. Consistent metabolic benefits were observed across randomized trials, including improvements in body weight, fasting glucose, HbA1c, triglycerides, and blood pressure, particularly in early TRE

and ADF protocols. These findings are congruent with large meta-analyses documenting favorable effects of intermittent fasting on glycemic and lipid profiles [6, 8]. Lipid and adiposity outcomes were largely weight-dependent, whereas improvements in insulin sensitivity and glycemic control were partially weight-independent. Fasting has also been associated with favorable inflammatory and cardiovascular biomarker changes. Trials included in this review demonstrated reductions in cardiometabolic risk factors and inflammatory cytokines, particularly among patients with metabolic syndrome [34, 35]. These findings are in accordance with Horne *et al.* who reported cardioprotective galectin-3 modulation following fasting [10]. Ramadan fasting studies included in this review were observational and culturally specific; therefore, their findings represent associative evidence only and were interpreted separately from randomized controlled trials. While these studies reported favorable endocrine and metabolic changes consistent with Al-Rawi *et al.* [30], their inference level differs from randomized evidence and should not be generalized as causal physiological effects.

Unregistered protocol, no meta-analysis was done because it was heterogeneous, no assessment of publication bias, small sample sizes in some studies, observational Ramadan studies have only associative evidence, South Asian-based studies are limited, hormonal outcomes are available only in moderate-risk studies, weight-independent effects might be confounded, English-only limitation, and shortening of search to 2018–2024. P PROSPERO Prospectively record systematic review protocols. Perform extensive, prolonged, randomized controlled trials in South Asians with a uniform fasting regimen. Add extensive hormone test and weight-stratified analysis to decontaminate weight-independent endocrine effects. Conduct meta-analyses as enough homogeneous data is collected. Consider culturally

modified fasting programs such as Ramadan.

CONCLUSIONS

Low-risk randomized controlled trials provide causal evidence that early time-restricted eating and alternate-day fasting improve insulin sensitivity and glycemic control. Other hormonal outcomes, including leptin, ghrelin, and cortisol, are associated with intermittent fasting but require further adequately powered randomized trials for causal confirmation. Observational Ramadan fasting studies provide culturally specific associative evidence and should be interpreted separately from randomized trials. Intermittent fasting, therefore, represents a promising dietary strategy for metabolic risk reduction, particularly in South Asian populations; however, causal conclusions should be restricted to outcomes supported by randomized evidence. Further high-quality long-term trials are warranted to refine fasting protocols and clarify endocrine mechanisms.

Authors' Contribution

Conceptualization: SSAT

Methodology: SSAT, MA

Formal analysis: AA, AR, MA

Writing and Drafting: SSAT, MK, AS, AA, AR, MA

Review and Editing: SSAT, MK, AS, AA, AR, MA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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