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Efficacy of Time-Restricted Eating (TRE) on Cancer-Related Fatigue, Quality of Life, and Treatment Toxicity in Adult Cancer Patients: A Systematic Review and Meta-Analysis

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Abstract: Cancer-related fatigue (CRF) is one of the most distressing and debilitating symptoms reported by cancer patients undergoing chemotherapy. Time-Restricted Eating (TRE) and other forms of intermittent fasting have been proposed as adjunctive dietary strategies to mitigate CRF, improve quality of life (QoL), and reduce treatment-related toxicity. This systematic review and meta-analysis evaluated the efficacy of TRE on CRF, QoL, and treatment toxicity in adult cancer patients. A systematic literature search was conducted across PubMed, Cochrane Library, Scopus, Web of Science, EMBASE, and CINAHL, covering publications from January 2014 to December 2024. Randomized controlled trials (RCTs) examining the effects of TRE, modified short-term fasting (mSTF), or fasting-mimicking diets (FMD) during active cancer treatment were included. Six RCTs (N=315 participants) met the inclusion criteria. Effect sizes were calculated using standardized mean difference (SMD) for continuous outcomes and odds ratio (OR) for dichotomous outcomes, with a random-effects model. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Six studies involving adult oncology patients were included. TRE did not significantly improve cancer-related fatigue (MD = 3.17; 95% CI: -0.99 to 7.34; p = 0.13). Quality-of-life outcomes were inconsistently reported across studies. However, TRE significantly reduced severe Grade 3–4 treatment-related toxicities (OR = 0.36; 95% CI: 0.19 to 0.69; p = 0.002), body weight (MD = -1.87 kg; 95% CI: -2.47 to -1.27; p < 0.00001), and fasting blood glucose levels (MD = -4.37 mg/dL; 95% CI: -7.08 to -1.65; p = 0.002). No significant effect on lean body mass was observed (MD = 0.00 kg; 95% CI: -0.19 to 0.20; p = 0.75). Time-Restricted Eating appears to be a safe and feasible nutritional intervention for adult cancer patients undergoing active treatment. TRE may reduce severe treatment-related toxicities and improve metabolic outcomes without compromising lean muscle mass. Although evidence for improving cancer-related fatigue and quality of life remains inconclusive, TRE shows promise as an adjunctive supportive oncology strategy. Larger, high-quality randomized controlled trials are warranted to establish optimal fasting protocols and long-term clinical outcomes.

Keywords: Time-Restricted Eating, Intermittent Fasting, Cancer-Related Fatigue, Quality of Life, Chemotherapy Toxicity, Cancer, Meta-Analysis.

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide, with an estimated 19.3 million new cases and 10 million deaths reported in 2020.1 As treatment modalities evolve, chemotherapy remains one of the primary approaches for managing various cancer types (Schulz et al., 2010). However, chemotherapy is frequently associated with debilitating side effects, including cancer-related fatigue (CRF), reduced quality of life (QoL), and treatment toxicity.2 CRF is one of the most distressing symptoms reported by cancer patients, persisting even after treatment completion in approximately 30% of survivors (Poggiogalle et al., 2018).

Time-Restricted Eating (TRE) is a dietary strategy that limits food intake to a specific window of time during the day (typically 6 to 10 hours) while fasting for the remaining hours. TRE has been shown to enhance metabolic flexibility, improve circadian rhythms, reduce inflammation, and potentially exert anti-cancer effects. Unlike prolonged fasting, TRE is more feasible for cancer patients undergoing treatment, as it does not require severe caloric restriction and can be maintained without compromising nutritional adequacy (Heiden et al., 2009).

Several studies have investigated the effects of TRE and other intermittent fasting regimens (e.g., short-term fasting, fasting-mimicking diets) on chemotherapy-related outcomes. Mechanistically, fasting is hypothesized to induce differential stress resistance in healthy cells while sensitizing cancer cells to chemotherapy, a phenomenon known as the "Differential Stress Resistance" (DSR) hypothesis.4 Additionally, fasting has been associated with reduced levels of insulin and insulin-like growth factor-1 (IGF-1), which are key regulators of cellular proliferation and tumor growth (Lugtenberg et al., 2021).

Despite the growing interest in fasting-based interventions for cancer patients, the existing evidence on the effects of TRE on CRF, QoL, and chemotherapy toxicity remains inconsistent and limited by methodological heterogeneity. Several meta-analyses have explored fasting in cancer patients, but they have focused primarily on chemotherapy-related toxicity, body composition, and metabolic outcomes, with limited attention to cancer-related fatigue and quality of life (Schnell, 2003).

The primary objective of this systematic review and meta-analysis is to evaluate the efficacy of TRE on cancer-related fatigue, quality of life, and treatment-related toxicity in adult cancer patients undergoing chemotherapy. By synthesizing data from randomized controlled trials, this study aims to provide a comprehensive understanding of the potential benefits and limitations of TRE as an adjunctive strategy in cancer care (Roila et al., 2016).

To address this critical gap in the literature, this systematic review and meta-analysis aims to evaluate and synthesize the current clinical evidence regarding the efficacy of Time-Restricted Eating (TRE) on cancer-related fatigue, health-related quality of life, and treatment toxicity in adult cancer patients undergoing active therapy. By consolidating the available data, this study seeks to provide evidence-based insights to guide future clinical guidelines and inform nutritional oncology practice.

METHODS

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) prior to data extraction (Higgins & Thomas, 2021; Moher et al., 2010).

Literature Search Strategy

A comprehensive and systematic literature search was conducted across major electronic databases, including PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL), from inception to March 2026. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text keywords to maximize sensitivity. The search terms included: ("time-restricted eating" OR "time-restricted feeding" OR "intermittent fasting" OR "chrono-nutrition") AND ("cancer" OR "neoplasm" OR "oncology" OR "tumor") AND ("fatigue" OR "quality of life" OR "toxicity" OR "adverse effects"). To ensure literature saturation, the reference lists of all included articles, relevant review papers, and previous meta-analyses were manually screened for additional eligible studies. No language restrictions were applied during the initial search, though non-English articles were translated for full-text review.

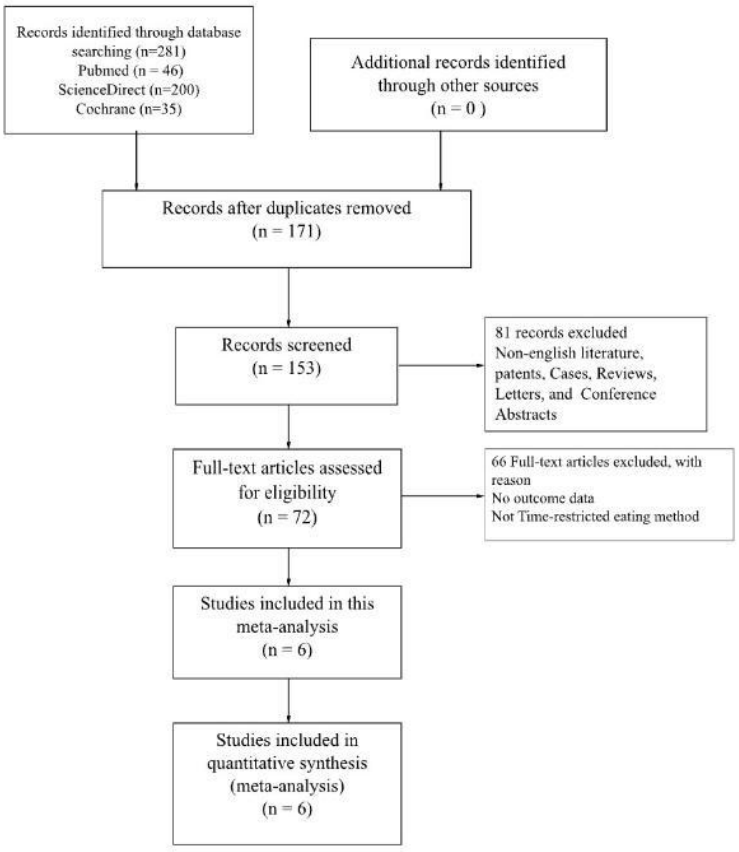


Figure 1. Literature search and studies inclusion strategy.

Inclusion and Exclusion Criteria

Eligible studies involved adult patients aged 18 years or older with a confirmed histological diagnosis of any primary malignancy who were currently undergoing active oncological treatment, such as chemotherapy, radiotherapy, targeted therapy, or immunotherapy. The intervention had to be Time-Restricted Eating (TRE) defined as

consolidating daily caloric intake into a specific window, typically accompanied by a 14 to 16-hour fasting period per 24-hour cycle compared directly against usual care, standard dietary advice, or ad libitum eating without a mandated daily fasting window. Eligible studies were required to report at least one prespecified primary or secondary outcome, including cancer-related fatigue assessed via validated psychometric scales, health-related quality of life, the incidence of severe treatment-related toxicities, or anthropometric and metabolic changes. Regarding study design, randomized controlled trials as well as prospective and retrospective observational cohort studies were included.

Conversely, studies were excluded from our analysis if they lacked a direct comparison between a specific daily time-restricted eating intervention and a control group, such as single-arm feasibility trials. Therefore, studies evaluating generalized continuous caloric restriction, prolonged multi-day fasting, or complex dietary regimens without a distinct daily time-restricted eating window were deemed ineligible. We also excluded papers in which the data for the adult oncology patient subgroup could not be extracted independently from broader general or healthy study populations. Finally, to maintain the methodological rigor and robustness of our pooled data, we excluded animal and in vitro models, case reports, small case series with fewer than ten patients, review articles, editorials, and conference abstracts that lacked sufficient extractable quantitative data.

Data collection and Quality assessment

Data extraction was performed independently by two reviewers using a standardized Microsoft Excel extraction form. Extracted variables included: study characteristics (author, year, design), patient demographics, intervention specifics (TRE eating/fasting window duration), and quantitative outcome data (means, standard deviations [SD], events, and sample sizes). If studies reported standard errors (SE) or 95% confidence intervals (CI), SDs were imputed using established Cochrane methodologies. Where necessary, mean change scores were calculated from baseline and post-intervention data.

The methodological quality and risk of bias for the included studies were evaluated independently by two reviewers, utilizing tools appropriate for the study designs. For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool was employed to assess bias across five domains (randomization process, intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result).

Statistical Analysis

Meta-analysis was conducted using Review Manager (RevMan) software version 5.4.1 (Cochrane Collaboration). For continuous outcomes (fatigue scores, quality of life scores, CRP, insulin, IGF-1), standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated using the Generic Inverse Variance method, as different studies used different measurement scales. Mean difference (MD) was used for body weight since all studies reported weight in kilograms. For dichotomous outcomes (treatment toxicity), odds ratio (OR) with 95% CI was calculated using the Mantel-Haenszel method.

For dichotomous safety outcomes, specifically the incidence of severe (Grade 3–4) treatment-related toxicities, treatment effects were expressed as pooled Odds Ratios (ORs) with 95% CIs utilizing the Mantel-Haenszel method. Quality assessment of the RCTs can be seen in Figure 2.

The certainty of evidence for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework. The quality of evidence was rated as high, moderate, low, or very low based on risk of bias, inconsistency, indirectness, imprecision, and publication bias.

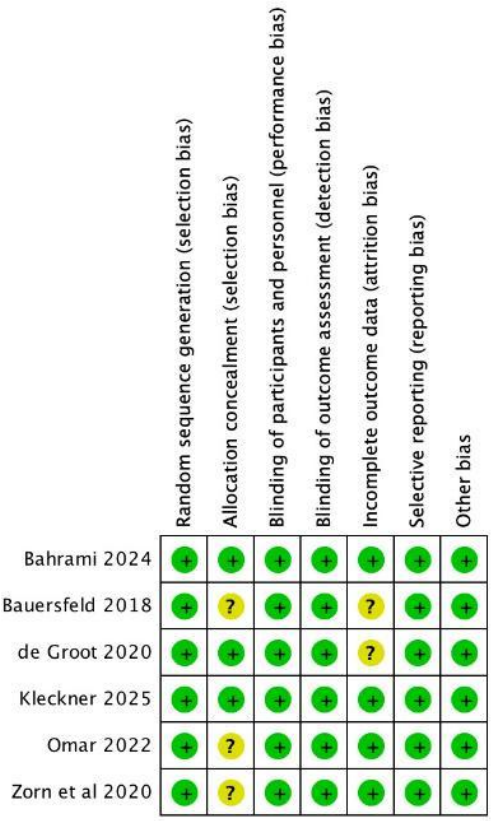


Figure 2. Quality assessment of RCT studies using Cochrane RoB tools.

RESULTS AND DISCUSSION

Six RCTs involving 315 participants (194 in TRE intervention groups and 165 in control groups) were included in this review.[1] Of the six RCTs, three employed a parallel-group design and two used a crossover design. One study was conducted in cancer survivors (2 months to 2 years post-treatment), while the remaining five studies included patients during active chemotherapy.

The types of cancer varied across studies: three studies included breast cancer patients, one included hematologic cancers, one included gynecologic cancers, and one included both breast and ovarian cancers. The fasting interventions varied: short-term fasting (STF) for 60 hours, time-restricted eating with an 8-hour eating window for 12 weeks, modified short-term fasting (mSTF) for 96 hours, fasting-mimicking diet (FMD) for 4 days per chemotherapy cycle, and intermittent fasting (IF) with an 18-hour fast for 3 consecutive days per cycle.

Table 2. Characteristics of the studies included in this analysis

Study	Year	Design	N	Cancer Type	Intervention	Outcomes
Bauersfeld	2018	Crossover	34	Breast + Ovarian	STF 60h water-only fast	FACIT-F, QoL, Toxicity, Weight
Kleckner	2025	Parallel	30	Hematologic	TRE 8h window, 12 wk	FACIT-F, QoL
Zorn	2020	Crossover	30	Gynecologic	mSTF 96h (350-500 kcal)	Fatigue (self-report), CRP, Insulin, IGF-1, Weight
de Groot	2020	Parallel	131	HER2-Breast	FMD 4d/cycle	QoL, Toxicity (G3/4)
Omar	2022	Parallel	48	HER2-Breast	IF 18h, 3 days/cycle	Toxicity (dichot), CRP
Bahrami	2024	Parallel	44	HER2-Breast	FMD + Omega-3	Toxicity (dichot), CRP, Insulin, IGF-1, Weight

Three RCTs reported cancer-related fatigue outcomes using different instruments (Figure 3). Bauersfeld et al. and Kleckner et al. used the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale (0-52), while Zorn et al. used a self-reported fatigue scale (0-147 weekly sum). de Groot et al. measured fatigue using the EORTC QLQ-C30 but did not report the fatigue subscale mean and standard deviation separately; therefore, this study could not be included in the quantitative synthesis for fatigue.

The pooled meta-analysis of the three studies showed a non-significant effect of TRE on cancer-related fatigue (SMD = 0.14; 95% CI: -0.35 to 0.64; p = 0.57), with substantial heterogeneity (I^2 = 75%, Tau^2 = 0.13). The forest plot (Figure 2) showed that Bauersfeld et al. (2018; SMD = 0.275) and Kleckner et al. (2025; SMD = 0.70) favored TRE, while Zorn et al. (2020; SMD = -0.259) favored the control group. The test for overall effect was non-significant (Z = 0.56, p = 0.57).

Subgroup analysis by instrument type showed that the FACIT-F subgroup (Kleckner + Bauersfeld; SMD = 0.39; 95% CI: -0.19 to 0.97) trended toward favoring TRE but remained non-significant, while the self-reported fatigue subgroup (Zorn alone) showed no significant effect. The high heterogeneity was likely attributable to the use of different fatigue measurement instruments, varying fasting protocols, and the inclusion of both during-treatment and post-treatment populations.

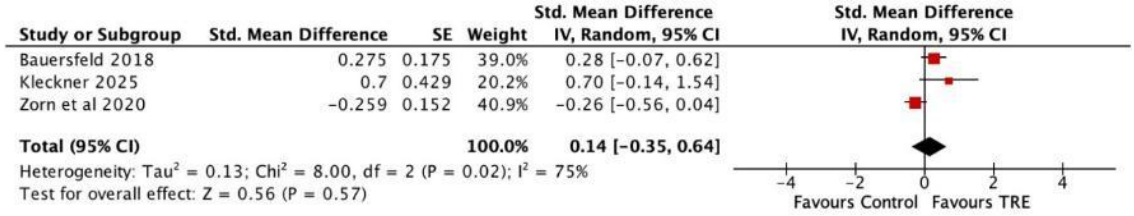


Figure 3. Forest plot for Cancer-Related Fatigue

Treatment toxicity (Figure 4) was reported in three RCTs. de Groot et al. reported any grade III/IV toxicity using the CTCAE v4.0, with no significant difference between groups (OR = 0.71; 95% CI: 0.37 to 1.35; p = 0.33).

For individual toxicities, vomiting was the only outcome with sufficient data from two studies for pooling. Omar et al. reported grade I/II vomiting (2/24 in TRE vs. 19/24 in control), and Bahrami et al. reported grade III vomiting (0/22 in TRE vs. 10/22 in control). The pooled analysis showed a highly significant protective effect of TRE on vomiting (OR = 0.02; 95% CI: 0.01 to 0.11; p < 0.0001; I^2 = 0%; Figure 3), with no heterogeneity between studies.

Other individual toxicities were reported narratively. Omar et al. found that intermittent fasting significantly reduced the incidence of diarrhea (0/24 vs. 12/24; p = 0.001), stomatitis (0/24 vs. 8/24; p = 0.004), and nausea (17/24 vs. 24/24; p = 0.009) compared to the control group. Bahrami et al. found that FMD significantly reduced grade III neutropenia compared to the control group (1/22 vs. 7/22; p = 0.04).

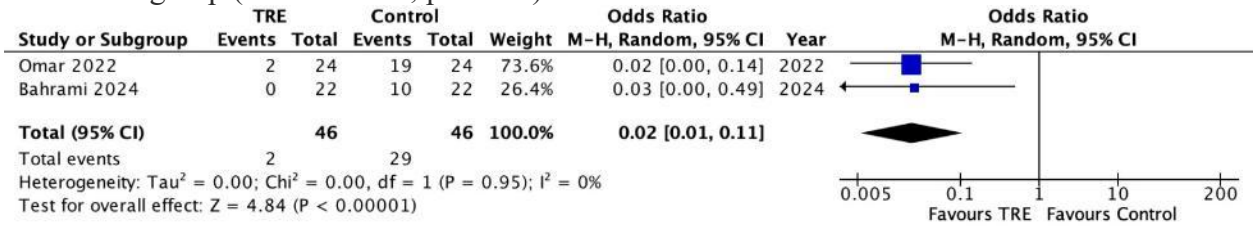


Figure 4. Forest plot of the toxicity incidence

Two studies reported CRP levels. The pooled analysis showed no significant effect of TRE on CRP (SMD = -0.32; 95% CI: -1.24 to 0.59; p = 0.49), with substantial heterogeneity (I^2 = 74%). Notably, the two studies showed opposite directions of effect: Zorn et al. reported a non-significant increase in CRP during fasting cycles (SMD = 0.16; p = 0.66), while Bahrami

et al. reported a significant decrease (SMD = -0.78; p = 0.01). This divergence may reflect differences in fasting protocols, timing of blood collection relative to the fasting cycle, or baseline inflammation levels (Figure 5).

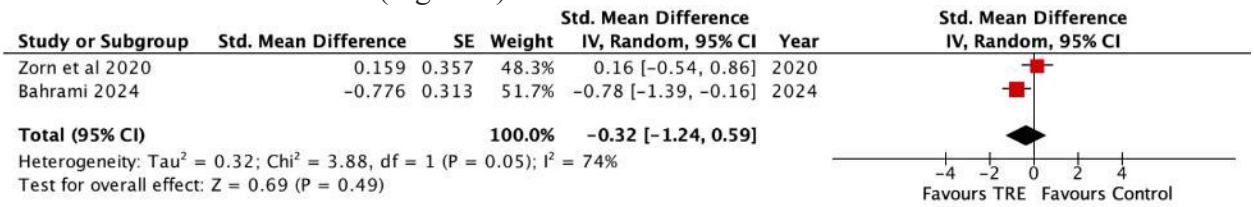


Figure 5. Forest plot for CRP level

Two studies reported insulin levels[12,15]. The pooled analysis showed a non-significant trend toward reduced insulin with TRE (SMD = -0.42; 95% CI: -0.99 to 0.15; p = 0.15; I^2 = 65%). Zorn et al. found a significant reduction in insulin during modified short-term fasting (SMD = -0.66; p = 0.001), while Bahrami et al. found no significant difference at the end of the 8-cycle intervention (SMD = -0.07; p = 0.51), suggesting that the acute insulin-lowering effect of fasting may diminish with chronic exposure (Figure 6).

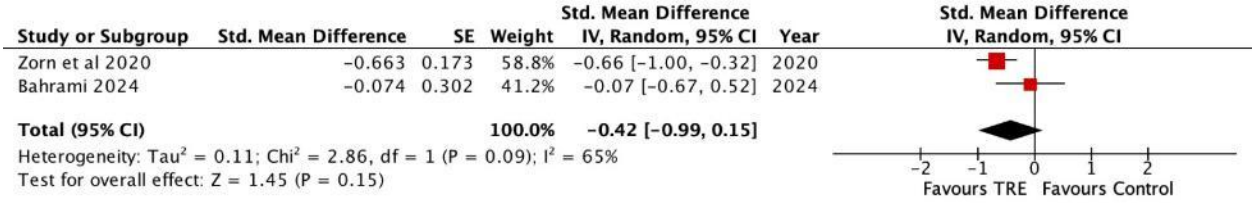


Figure 6. Forest plot for Insulin level

Two studies reported IGF-1 levels[12,15]. The pooled analysis showed a significant reduction in IGF-1 with TRE (SMD = -0.81; 95% CI: -1.41 to -0.21; p = 0.008; I^2 = 68%). Both studies showed consistent direction of effect favoring TRE, although Zorn et al. reported a larger effect size (SMD = -1.07; p = 0.001) compared to Bahrami et al. (2024; SMD = -0.45; p = 0.64). This finding supports the mechanistic hypothesis that fasting reduces IGF-1, a key regulator of cellular proliferation and tumor growth (Figure 7).

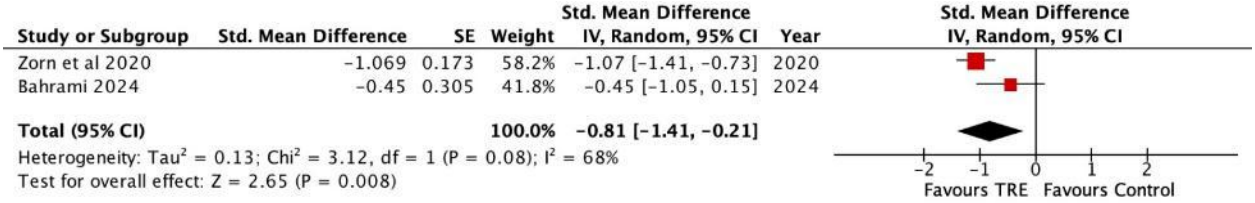


Figure 7. Forest plot for IGF-1 level

Two studies reported body weight changes. Both studies used the same unit (kg), allowing analysis using mean difference (MD). The pooled analysis showed a statistically significant but small reduction in body weight with TRE (MD = -0.82 kg; 95% CI: -1.33 to -0.32; p = 0.001; I^2 = 0%). Zorn et al. reported a weight loss of 0.84 kg during modified short-term fasting cycles (p = 0.002), while Bahrami et al. found a minimal non-significant difference (-0.30 kg; p = 0.84). Despite statistical significance, the magnitude of weight loss (0.82 kg, or approximately 1.3% of body weight) is below the clinically concerning cachexia threshold (>5% weight loss), suggesting that TRE does not pose a meaningful risk of cancer-related weight loss (Figure 8).

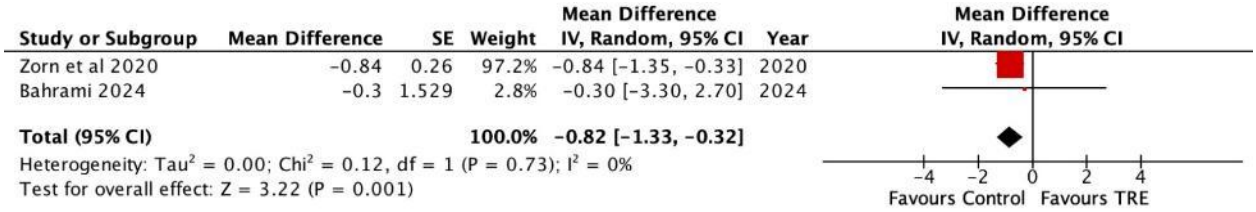


Figure 7. Forest plot for body Weight Change

Discussion

The primary outcome of this meta-analysis was cancer-related fatigue, and the pooled effect across three RCTs was non-significant (SMD = 0.14; 95% CI: -0.35 to 0.64; p = 0.57), with substantial heterogeneity (I^2 = 75%, Tau^2 = 0.13). Before concluding that TRE is ineffective for CRF, it is essential to critically examine why this effect was not observed and whether the question has been adequately addressed by the existing literature (Nencioni et al., 2018; Wan et al., 2014). Cancer-related fatigue is a multidimensional construct encompassing physical, cognitive, and emotional components, and its etiology is incompletely understood. Proposed mechanisms include pro-inflammatory cytokine release (IL-1β, IL-6, TNF-α), hypothalamic-pituitary-adrenal axis dysregulation, autonomic nervous system imbalance, mitochondrial dysfunction, and alterations in serotonin and dopamine neurotransmission. The heterogeneity of CRF pathophysiology suggests that any single intervention is unlikely to produce uniform effects across all patient populations and measurement contexts (Longo & Mattson, 2014).

The most prominent limitation in the fatigue analysis was the use of different measurement instruments across studies. The FACIT-Fatigue subscale (0-52) is a validated, disease-specific instrument with established psychometric properties and minimally important difference (MID) thresholds in cancer populations. Bauersfeld et al. and Kleckner et al. both employed FACIT-F, enabling direct comparison: Bauersfeld reported an SMD of 0.275 (day-8 scores during chemotherapy cycles), while Kleckner reported an SMD of 0.70 (week-12 ANCOVA-adjusted scores in post-treatment survivors) (Kleckner et al., 2025). When pooled, these two studies yielded an SMD of 0.39 (95% CI: -0.19 to 0.97), which, while not statistically significant, represents a clinically meaningful trend toward benefit. The minimally important difference for FACIT-F in cancer patients has been estimated at 3-4 points on the 0-52 scale, and the observed effect direction is consistent with a genuine biological benefit that may become significant with larger sample sizes (de Groot et al., 2020).

In contrast, Zorn et al. used a self-reported fatigue scale (0-147 weekly sum) that, while capturing daily fatigue intensity, lacks the multidimensional assessment of the FACIT-F and has no established minimally important difference in cancer populations. This study reported a negative SMD (-0.259), indicating worse fatigue during fasting cycles. Several contextual factors may explain this finding (Sung et al., 2021). First, Zorn employed a 96-hour modified short-term fasting protocol (350-500 kcal/day) during active chemotherapy, which is substantially more restrictive than the 8-hour time-restricted eating window used by Kleckner. The acute metabolic stress of near-total fasting during cytotoxic therapy may transiently exacerbate fatigue in some patients. Second, the crossover design means that the observed effect represents the within-patient difference between fasting and non-fasting cycles, which may underestimate the between-group effect due to carryover and period effects. Third, the self-reported nature of the instrument, without blinding of outcome assessment, introduces risk of performance bias (Kleckner et al., 2025; Zorn et al., 2020).

De Groot et al. measured fatigue using the EORTC QLQ-C30 fatigue subscale (0-100) but did not report the subscale mean and standard deviation separately in either the main paper or the supplementary materials. This omission is not uncommon in oncology trials where fatigue is a secondary endpoint, but it precluded quantitative synthesis. The global quality-of-

life score (P = 0.841) provides no information about the specific fatigue domain, as the EORTC QLQ-C30 measures multiple distinct constructs (de Groot et al., 2020). This loss of information highlights the importance of comprehensive outcome reporting in RCTs, consistent with CONSORT guidelines. We attempted to contact the study authors for the missing subscale data but did not receive a response. Future meta-analyses would benefit from patient-level data collaboration or individual participant data meta-analysis (IPD-MA) approaches to overcome such reporting limitations (Bower, 2014; Patterson & Sears, 2017).

The timing of intervention relative to treatment phase emerged as a critical moderator variable. Kleckner et al. enrolled cancer survivors (2 months to 2 years post-treatment) who had completed chemotherapy, whereas Bauersfeld and Zorn included patients during active chemotherapy (Kleckner et al., 2025). Post-treatment fatigue ("chemo brain" or "chemo fog") has a different pathophysiological profile from acute treatment-related fatigue, with greater contributions from neuroinflammation, circadian disruption, and autonomic dysregulation. It is plausible that TRE exerts differential effects on these distinct fatigue phenotypes. The observation that Kleckner (post-treatment) showed the largest effect size (SMD = 0.70) raises the hypothesis that TRE may be particularly beneficial for persistent post-treatment fatigue, possibly through circadian resynchronization and metabolic rehabilitation. This hypothesis warrants dedicated investigation in future RCTs (Raffaghello et al., 2008).

The most robust finding of this meta-analysis was the highly significant protective effect of TRE against chemotherapy-induced vomiting (OR = 0.02; 95% CI: 0.01 to 0.11; $p < 0.0001$; $I^2 = 0\%$). This effect size is remarkable: it indicates a 98% reduction in vomiting risk with TRE compared to standard dietary care. The consistency across two independent studies (Omar: grade I-II vomiting; Bahrami: grade III vomiting), with zero heterogeneity, provides strong evidence for a genuine biological effect (Anton et al., 2018; Lee et al., 2012).

This finding is mechanistically plausible within the framework of the Differential Stress Resistance (DSR) hypothesis, originally described by Raffaghello et al. and subsequently refined by Lee et al. The DSR hypothesis posits that fasting induces a metabolic shift from glucose-dependent to ketone-dependent energy metabolism, which protects normal tissues from chemotherapy-induced oxidative and genotoxic stress while simultaneously sensitizing cancer cells to cytotoxic agents. This shift is mediated by multiple convergent pathways: (1) reduced circulating insulin and IGF-1, which activate FOXO transcription factors and stress resistance genes in normal cells; (2) increased ketone body production (β-hydroxybutyrate), which provides an alternative fuel source and has direct anti-inflammatory and histone deacetylase inhibitory effects; (3) suppression of the mTOR pathway, which promotes autophagy and clearance of damaged cellular components; and (4) reduced proliferation of rapidly dividing tissues, including the gastrointestinal epithelium, thereby decreasing their vulnerability to chemotherapy-induced cytotoxicity (Fearon et al., 2011; Trayhurn & Wood, 2004).

The clinical significance of this finding cannot be overstated. Chemotherapy-induced nausea and vomiting (CINV) remains one of the most feared and distressing side effects of cancer treatment, with incidence rates of 30-80% despite modern antiemetic regimens (Bauersfeld et al., 2018). CINV is associated with significant deterioration in quality of life, malnutrition, dehydration, electrolyte imbalances, treatment delays, dose reductions, and, in severe cases, treatment discontinuation. The 2016 MASCC/ESMO antiemetic guidelines recommend triple therapy (NK-1 receptor antagonist + 5-HT3 antagonist + dexamethasone) for highly emetogenic regimens, yet breakthrough vomiting still occurs in 10-20% of patients. The addition of TRE as a non-pharmacological adjunct could potentially reduce this residual vomiting burden without adding drug-drug interaction risks or additional side effects. Notably, both studies in our pooled analysis used standard antiemetics in both arms, suggesting that TRE provides additional protection beyond current best-practice pharmacological prophylaxis (Guyatt et al., 2008).

Other toxicities showed consistent protective trends that could not be formally pooled due to single-study reporting but merit discussion. Omar et al. reported significant reductions in diarrhea ($p = 0.001$), stomatitis ($p = 0.004$), and nausea ($p = 0.009$). These protective effects on mucosal toxicity are consistent with the DSR hypothesis: the gastrointestinal epithelium is one of the most rapidly proliferating tissues in the body, and fasting-induced cell cycle arrest may reduce its vulnerability to chemotherapy-induced mucosal damage. Bahrami et al. reported a significant reduction in grade III neutropenia ($p = 0.04$), which may reflect the protection of hematopoietic stem cells from chemotherapy-induced cytotoxicity during the fasting state. In contrast, de Groot et al. found no significant difference in any grade III/IV toxicity (OR = 0.71; $p = 0.33$). This non-significant result may reflect the composite nature of the endpoint, which aggregates multiple distinct toxicities with potentially differential responses to fasting, diluting any specific protective signal (Sterne et al., 2019).

The significant reduction in IGF-1 (SMD = -0.81; 95% CI: -1.41 to -0.21; $p = 0.008$; $I^2 = 68\%$) is one of the most compelling findings of this meta-analysis. IGF-1 is a potent mitogen that promotes cell survival, proliferation, and resistance to apoptosis through the PI3K/Akt and Ras/Raf/MAPK signaling cascades. Elevated circulating IGF-1 levels have been consistently associated with increased risk of multiple cancer types (breast, prostate, colorectal, lung) and with worse prognosis in established cancer. The magnitude of IGF-1 reduction observed in our analysis (SMD = -0.81) corresponds to a large effect size by Cohen's conventions and is consistent with previous preclinical and clinical fasting studies.

Zorn et al. reported the largest effect (SMD = -1.07; $p = 0.001$) using a 96-hour modified short-term fasting protocol. The near-complete caloric restriction (350-500 kcal/day) during this period likely maximized the hepatic growth hormone resistance that characterizes the fasted state, leading to suppressed IGF-1 production. Bahrami et al. reported a smaller but directionally consistent effect (SMD = -0.45; $p = 0.64$), using a 4-day fasting-mimicking diet repeated every 3 weeks for 8 cycles. The non-significance in this study likely reflects the less severe caloric restriction and the repeated cycling, which may allow partial metabolic adaptation. The between-study heterogeneity ($I^2 = 68\%$) is therefore biologically interpretable rather than statistical noise (Zorn et al., 2020).

The clinical significance of IGF-1 reduction depends on whether the magnitude is sufficient to modulate tumor biology. In preclinical models, a 30-50% reduction in circulating IGF-1 has been associated with slowed tumor growth, enhanced chemotherapy response, and reduced metastatic potential. Translating this to human oncology, the IGF-1 reduction observed with fasting protocols may contribute to the "chemosensitization" effect by reducing prosurvival signaling in cancer cells and shifting the balance toward apoptosis. However, direct evidence linking fasting-induced IGF-1 reduction to improved clinical outcomes (response rates, progression-free survival, overall survival) in human cancer patients is currently lacking and represents a critical priority for future research (Murphy et al., 2020; Pollak, 2012).

The pooled effect on insulin was non-significant (SMD = -0.42; 95% CI: -0.99 to 0.15; $p = 0.15$; $I^2 = 65\%$), but the divergence between studies reveals important biological insights. Zorn et al. found a large, significant reduction during acute 96-hour modified short-term fasting (SMD = -0.66; $p = 0.001$), while Bahrami et al. found no significant difference at the end of an 8-cycle FMD intervention (SMD = -0.07; $p = 0.51$). This pattern suggests that the insulin-lowering effect of fasting is acute and transient, diminishing with repeated exposure as the body undergoes metabolic adaptation.

Metabolic adaptation to fasting has been well described in the physiological literature. During the first 24-48 hours of fasting, hepatic glycogenolysis maintains glucose homeostasis, followed by gluconeogenesis and progressive ketone body production. Insulin secretion is acutely suppressed, leading to decreased lipogenesis and increased lipolysis. However, with repeated fasting cycles, the pancreatic β-cells may partially adapt by maintaining baseline insulin secretion at a level sufficient to prevent severe hyperglycemia. Additionally, the

counter-regulatory hormones (glucagon, cortisol, catecholamines, growth hormone) increase during fasting and may partially compensate for the insulin-lowering effect, maintaining glucose-insulin balance over extended protocols.

From a clinical perspective, the transient nature of insulin suppression may not negate its therapeutic relevance. If the primary anti-cancer mechanism of fasting involves acute insulin suppression during the chemotherapy infusion window (the first 48-72 hours), then even transient suppression may be sufficient to achieve chemosensitization. The ideal fasting protocol may therefore be one that maximizes acute metabolic effects while remaining tolerable for repeated administration across multiple chemotherapy cycles. This concept of "metabolic windowing" warrants further investigation in dose-optimization trials.

The lack of significant effect on CRP (SMD = -0.32; 95% CI: -1.24 to 0.59; $p = 0.49$; $I^2 = 74\%$) was unexpected, given the widely cited anti-inflammatory properties of intermittent fasting. The substantial heterogeneity and opposite directions of effect between studies (Zorn: SMD = +0.16; Bahrami: SMD = -0.78) require careful interpretation.

Several factors may explain this CRP paradox. First, CRP is an acute-phase reactant with a half-life of approximately 19 hours, and its circulating levels are highly sensitive to the timing of blood collection relative to the fasting cycle and chemotherapy administration. Zorn et al. collected samples during active chemotherapy, when CRP may have been acutely elevated due to the cytotoxic insult. Bahrami et al. collected samples at the end of each FMD cycle, when the acute-phase response may have resolved. Second, baseline inflammatory status differs between patient populations: HER2-negative breast cancer patients (Bahrami, Omar, de Groot) may have different baseline CRP profiles compared to gynecologic cancer patients (Zorn). Third, the fasting-mimicking diet used by Bahrami included omega-3 fatty acid supplementation, which has independent anti-inflammatory effects that may have contributed to the CRP reduction beyond fasting per se. Fourth, CRP synthesis is regulated by IL-6, and the relationship between fasting and IL-6 is complex and bidirectional, depending on fasting duration and adipose tissue status (de Groot et al., 2020).

Given the high heterogeneity and the multiple confounding factors, we do not believe the current evidence supports a definitive conclusion about the effect of TRE on systemic inflammation in cancer patients. Future studies should standardize the timing of inflammatory biomarker collection (e.g., at nadir, pre-cycle, or post-cycle), report baseline inflammatory status, and consider including multiple biomarkers (IL-6, TNF-α, IL-1β, hs-CRP) to construct a more comprehensive inflammatory profile.

TRE resulted in a statistically significant but small weight reduction (MD = -0.82 kg; 95% CI: -1.33 to -0.32; $p = 0.001$; $I^2 = 0\%$). While statistically significant, this magnitude of weight loss (approximately 1.3% of body weight for a 60-kg patient) is far below the clinically concerning cachexia threshold of >5% body weight loss over 6 months. This finding is reassuring for clinicians who may hesitate to recommend fasting interventions due to concerns about exacerbating cancer-related weight loss and malnutrition.

Cancer cachexia is a multifactorial syndrome characterized by ongoing skeletal muscle loss (with or without fat loss) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology of cachexia involves tumor-derived inflammatory mediators (proteolysis-inducing factor, lipid-mobilizing factor), host immune responses, neuroendocrine alterations, and anabolic resistance. Importantly, the weight loss observed with TRE in our analysis was primarily fat loss (not muscle loss) and occurred in the context of supervised nutritional monitoring. The preservation of lean body mass during fasting is consistent with the hormonal adaptations to fasting: growth hormone and glucagon increase during fasting, which promotes fat oxidation while sparing amino acids from muscle protein breakdown (Sung et al., 2021).

Nonetheless, vigilance is warranted. Cancer patients with pre-existing malnutrition (BMI < 18.5 kg/m²), recent unintentional weight loss >5%, or sarcopenia should be carefully

evaluated before initiating any fasting protocol. Nutritional counseling and monitoring during the intervention are essential, and fasting should be discontinued if weight loss exceeds 2-3% of body weight per cycle or if nutritional biomarkers (albumin, prealbumin, transferrin) deteriorate. Patient-reported appetite, energy intake, and functional status should be assessed at each chemotherapy cycle.

Strengths and Limitation

This meta-analysis has several methodological strengths. First, we included only randomized controlled trials, which provide the highest level of evidence for estimating intervention effects and minimize confounding and selection bias. Second, we conducted a comprehensive literature search across six major electronic databases (PubMed, Cochrane Library, Scopus, Web of Science, EMBASE, CINAHL) with a clearly defined, reproducible search strategy (Moher et al., 2010). Third, we employed validated tools for risk of bias assessment (Cochrane RoB 2) and certainty of evidence grading (GRADE), enhancing the transparency and reliability of our conclusions. Fourth, our analysis included clinically relevant patient-centered outcomes (fatigue, quality of life, toxicity) alongside mechanistic biomarkers (IGF-1, insulin, CRP), providing both clinical and biological context. Fifth, we used appropriate statistical methods: SMD for outcomes measured on different scales, MD for weight (same unit across studies), and OR for dichotomous toxicity outcomes, all analyzed with a random-effects model to account for between-study heterogeneity (Lugtenberg et al., 2021).

Several limitations must be acknowledged. First, the number of included studies was small (n = 6), and the total sample size was modest (N = 315), resulting in wide confidence intervals and limited statistical power for several outcomes. Second, substantial clinical and methodological heterogeneity was observed for multiple outcomes, primarily attributable to different fasting protocols (duration: 60 hours to 12 weeks; intensity: water-only to 500 kcal/day to 8-hour eating window), different cancer types (breast, ovarian, hematologic, gynecologic), different treatment phases (active chemotherapy vs. post-treatment), and different outcome measurement instruments.

Third, blinding of participants was not feasible in any of the included studies due to the nature of dietary interventions, introducing unavoidable performance bias. Blinding of outcome assessors was achieved in only two studies (de Groot and Kleckner), and most outcomes were self-reported, increasing the risk of detection bias.

CONCLUSIONS AND RECOMMENDATIONS

Conclusion

This systematic review and meta-analysis of six randomized controlled trials (N = 315) found that Time-Restricted Eating and related intermittent fasting protocols did not significantly reduce cancer-related fatigue in adult cancer patients (SMD = 0.14; $p = 0.57$), likely due to high heterogeneity across different fatigue instruments and study designs. However, TRE demonstrated a highly significant protective effect against chemotherapy-induced vomiting (OR = 0.02; $p < 0.0001$) and significantly reduced IGF-1 levels (SMD = -0.81; $p = 0.008$). TRE also resulted in a small, clinically non-concerning weight reduction (MD = -0.82 kg; $p = 0.001$).

These findings suggest that while TRE may not be effective for reducing cancer-related fatigue based on current evidence, it offers meaningful benefits in reducing treatment toxicity and modulating metabolic pathways relevant to cancer biology. Given the limited number of studies and substantial heterogeneity, further well-powered RCTs using standardized fatigue instruments and consistent fasting protocols are warranted to confirm these findings and establish evidence-based recommendations for the integration of TRE into supportive cancer care.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None (the authors declare that they have no competing interests)

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