Journal of Medical Science and Sports Health

JoMaSSH, 1 (1), 2025, p. 1-14

available online at https://journal.uny.ac.id/publications/jomassh
doi: 10.21831/jomassh.v1i1.1042

Type of Paper: Systematic Review with Meta-Analysis

The Impact of Ramadan Fasting on Interleukin-6, Tumor Necrosis Factor-α, and C-Reactive Protein in Overweight and/or Obese and Non-Obese Individuals: A Systematic Review with Meta-Analysis

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Article history:
Received: March 26, 2025
Revised: May 8, 2025
Accepted: May 31, 2025

How to Cite: Ridho, F.M., Alfatah, R. (2025). The Impact of Ramadan Fasting on Interleukin-6, Tumor Necrosis Factor-α, and C-Reactive Protein in Overweight and/or Obese and Non-Obese Individuals: A Systematic Review with Meta-Analysis. JoMaSSH, 1(1), 1-14. doi: 10.21831/jomassh.v1i1.1042

E-ISSN 3109-5666

Abstrak:
Pendahuluan: Puasa Ramadan (RF) diduga dapat memodulasi inflamasi. Biomarker inflamasi seperti interleukin-6 (IL-6), faktor nekrosis tumor-α (TNF-α), dan protein C-reaktif (CRP) memainkan peran penting dalam berbagai penyakit metabolik dan imun. Mengingat relevansi klinisnya, penelitian ini bertujuan untuk mengevaluasi dampak RF terhadap IL-6, TNF-α, dan CRP. **Metode:** Pencarian sistematis dilakukan pada literatur yang mengevaluasi dampak RF pada IL-6, TNF-α, dan CRP/CRP sensitivitas tinggi (hsCRP) yang diterbitkan di PubMed, ScienceDirect, Scopus, dan Google Scholar. Kualitas studi dinilai menggunakan Skala Newcastle-Ottawa. Analisis meta model efek tetap atau acak dilakukan menggunakan perangkat lunak RevMan versi 5.4. Analisis subkelompok dilakukan berdasarkan status BMI, pada individu yang kelebihan berat badan dan/atau obesitas (BMI ≥25) dan tidak obesitas (BMI ≥18,5). Analisis meta disajikan dalam *standardized mean difference* (SMD) dengan interval kepercayaan (CI) 95%. Empat belas penelitian yang melibatkan 522 partisipan diinklusikan. **Hasil:** Studi menunjukkan bahwa RF secara signifikan mereduksi IL-6 (SMD = 0,68; 95% CI = 0,50, 0,87; *p* <0,00001) dan TNF-α (SMD = 0,69; 95% CI = 0,34, 1,04; *p* = 0,0001), dengan efek yang lebih kuat pada individu yang kelebihan berat badan dan/atau obesitas untuk IL-6 (SMD = 0,71; 95% CI = 0,52, 0,90; *p* <0,00001) dan TNF-α (SMD = 0,79; 95% CI = 0,35, 1,23; *p* = 0,0005). Sementara itu, penurunan CRP/hsCRP hanya signifikan pada individu non-obesitas (SMD = 1,03; 95% CI = 0,04, 2,02; *p* = 0,04). **Kesimpulan:** RF dapat menjadi strategi alami untuk mengurangi inflamasi sistemik, terutama pada individu dengan BMI tinggi. Temuan ini memiliki relevansi klinis bagi populasi yang berisiko mengalami kondisi terkait inflamasi seperti obesitas dan sindrom metabolik. Namun, heterogenitas dalam meta-analisis ini mengharuskan interpretasi hasil dengan kehati-hatian.
Kata kunci: Interleukin-6; Peradangan; Protein C-reactive; Puasa Intermittent; Puasa Ramadan; Tumor necrosis factor

Abstract:
Introduction: Ramadan fasting (RF) has been suggested to modulate inflammation. Inflammatory biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) play pivotal roles in various metabolic and immune-related diseases. Given their clinical relevance, this study aims to evaluate the impact of RF on IL-6, TNF-α, and CRP. **Methods:** A systematic search of the literature evaluating the impact of RF on IL-6, TNF-α, and CRP/high sensitivity CRP (hsCRP) published in PubMed, ScienceDirect, Scopus, and Google Scholar was employed. Study quality was evaluated using the Newcastle-Ottawa Scale. Fixed- or random-effects model meta-analyses were performed using RevMan version 5.4 software. Subgroup analysis was performed based on BMI status, in overweight and/or obese (BMI ≥25) and non-obese (BMI ≥18.5) individuals. Meta-analysis was presented in standardized mean difference (SMD) with 95% confidence interval (CI). Fourteen studies involving 522 participants were finally included. **Results:** The finding showed that RF significantly reduced IL-6 (SMD = 0.68; 95% CI = 0.50, 0.87; *p* <0.00001) and TNF-α (SMD = 0.69; 95% CI = 0.34, 1.04; *p* = 0.0001), with stronger effects in overweight and/or obese individuals for IL-6 (SMD = 0.71; 95% CI = 0.52, 0.90; *p* <0.00001) and TNF-α (SMD = 0.79; 95% CI = 0.35, 1.23; *p* = 0.0005). Meanwhile, the reduction of CRP/hsCRP was significant only in non-obese individuals (SMD = 1.03; 95% CI = 0.04, 2.02; *p* = 0.04). **Conclusion:** RF may serve as a natural strategy to reduce systemic inflammation, particularly in individuals with elevated BMI. These findings may have clinical relevance for populations at risk of inflammation-related conditions such as obesity and metabolic syndrome. However, the heterogeneity in this meta-analysis requires the interpretation of the results with caution.
Keywords: *C-reactive protein; Inflammation; Interleukin-6; Intermittent fasting; Ramadan fasting; Tumor necrosis factor*

1. Introduction

Inflammation is a multifaceted biological reaction triggered by biological, chemical, or physical stimuli, involving cellular and molecular processes that contribute to the body's defence mechanisms. Inflammation is characterized by vascular, cellular, and molecular alterations mediated by various chemical mediators such as cytokines, chemokines, and proteins (1). Acute inflammation is protective, but inflammation that continues or is chronic is often associated with numerous diseases, including arthritis, diabetes, some cancers, aging, atherosclerosis, metabolic syndrome, and various oral diseases (2–7). Obesity, in particular, has been defined as an inflammatory condition characterized by elevated cytokines levels, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), all of which are the most studied and important inflammatory cytokines readily detected in serum and excreted in large amounts during inflammation (8–10).

Additionally, elevated IL-6 has been associated with chronic inflammatory disorders, autoimmune diseases, and certain forms of cancer (11). Another cytokine that is implicated in the development of numerous autoimmune and inflammatory diseases is TNF-α, which plays an essential role in controlling the inflammatory response. In addition, TNF-α is also known to trigger a series of inflammatory molecules such as cytokines and chemokines (12). Meanwhile, CRP is an inflammatory protein produced in the liver and secreted in high amounts during inflammatory conditions. CRP is essential in the inflammatory process and the host's response to infection, including acting a part in regulating IL-6 and TNF-α (13). In conclusion, IL-6, TNF-α, and CRP contribute synergistically to inflammation, where increases in these three biomolecules are often associated with various acute and chronic inflammatory conditions.

Fasting is a practice where an individual does not eat or drink for a certain time. Apart from being related to religious beliefs, fasting is also widely practiced in medicine. Various types of fasting have been practiced and studied for their ability to influence physiological indicators (14). Ramadan fasting (RF) is a form of intermittent fasting observed for 29–30 days during Ramadan, the holiest month for Muslims, during which individuals refrain from eating and drinking for approximately 13-18 hours per day (15). Studies showed that RF has significant health benefits, especially in reducing inflammation and oxidative stress (16,17). Furthermore, Al Zunaidy et al. (18) reported that RF can reduce body weight, increase antioxidant levels, and decrease TNF-α, indicating positive effects on metabolic health and inflammation. Furthermore, time-restricted feeding fasting, such as RF, can physiologically reset circadian rhythms and increase the rhythmic expression of a series of genes that impact systemic glucose and lipid metabolism and can modulate important neural and hormonal signals related to appetite (19). These positive effects most likely occur through autophagy mechanisms, increased insulin sensitivity, and better modulation of immune responses during the fasting period. Thus, RF is not only a form of worship but also offers significant health benefits that can contribute to the prevention of various inflammatory and metabolic diseases.

Research indicates that RF exerts beneficial effects on health, especially concerning inflammation. To date, the last meta-analysis related to the impact of RF on inflammatory biomarkers was conducted by Faris and colleagues (20) in 2018, which revealed that RF provides a protective effect against inflammation, but did not specifically evaluate the differences in its impact on overweight and/or obese and non-obese individuals. Additionally, since that publication, a growing number of new studies have investigated the impact of RF on inflammatory biomarkers that have not been systematically analyzed, which may have yielded different results. Therefore, this meta-analysis aims to update previous meta-analyses by including newer studies that assessed the impact of RF on IL-6, TNF-α, and CRP. Furthermore, this study adds a novel subgroup analysis based on BMI, which was not examined in prior reviews, to explore whether the anti-inflammatory effects of RF differ by weight status. This study's findings are expected to provide a more comprehensive insight into the impact of RF on inflammation, as well as its potential in strategies for the prevention and managing inflammatory diseases.

2. Methods

2.1. Registration

This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251013766 (www.crd.york.ac.uk/PROSPERO/view/CRD420251013766).

2.2. Focused Question

A systematic review and meta-analysis was employed in compliance with PRISMA 2020 (21). The focused question of this study was "What is the impact of RF on IL-6, TNF-α, and CRP/hsCRP in overweight and/or obese and non-obese individuals?" To answer this, the population, intervention, comparison, and outcomes (PICO) model was used, with P: individuals with overweight and/or obesity or non-obesity, without any systemic or chronic diseases; I: individuals who fasted during Ramadan; C: none; and O: IL-6, TNF-α, and CRP/hsCRP concentration pre- and post-RF.

2.3. Information Sources

A comprehensive and systematic search of studies published up to 2025 in PubMed, ScienceDirect, Scopus, and Google Scholar was conducted. The specific search terms and combinations used in each database are detailed in **Table 1**.

2.4. Eligibility Criteria

Studies were included if they met the following criteria: 1) any observational study examining the impact of RF on one or more of the biomarkers IL-6, TNF-α, and CRP/hsCRP; 2) studies involving healthy individuals with overweight and/or obesity and non-obesity as controls in case-control studies or as primary subjects in cohort studies; 3) studies using pre- (baseline) and post-RF data; 4) studies reporting numerical data; and 5) peer-reviewed studies in English. Meanwhile, we excluded papers that met the following criteria: 1) studies involving subjects with certain diseases without healthy control people who fasted during Ramadan; 2) studies providing interventions other than RF; 3) studies that did not report numerical data clearly, for example, studies with data presentation in the form of bar graphs or curves only; and 4) studies that were reviews, commentaries, editorials, short communications, case reports, and case series. Otherwise, there were no other restraints, including the year of publication.

2.5. Participants

Participants were included in this study based on the following criteria: 1) participants with overweight and/or obesity (BMI ≥25 kg/m2), and non-obesity (BMI 18.5-24.9 kg/m^2) (22); 2) participants were in good health and were not taking certain daily medications, including anti-inflammatory drugs or antidepressants, as these can affect inflammatory cytokine concentrations (23–25); 3) participants did not have a history of chronic diseases, including diabetes mellitus, infectious diseases, cancer, cardiovascular diseases, and other chronic inflammatory diseases; 4) pregnant women, breastfeeding mothers, and athletes were excluded from this study; and 5) participants were those who observe RF, abstaining from food and drink, for 28-30 days for men, while women had menstrual cycles that cannot observe RF for a whole month; therefore, female participants must fast for at least 21 days.

2.6. Quality Assessment

Two authors (FMR and RA) independently performed the study quality evaluation using the Newcastle-Ottawa Scale (NOS) (26). The overall score across all components, selection, comparability, and outcome, ranges from 0 to 9. Studies were classified as high, medium, or low quality if they received a score of 7–9, 4–6, and 0–3, respectively. Any differences of opinion during the assessment were addressed through in-depth discussion and careful conclusion drawing.

Table 1. Search terms used in each database.

Database	Search terms
PubMed	(("Ramadan"[All Fields] AND ("intermittent fasting"[MeSH Terms] OR ("intermittent"[All Fields] AND "fasting"[All Fields]) OR "intermittent fasting"[All Fields])) OR ("Ramadan"[All Fields] AND ("fasted"[All Fields] OR "fasting"[MeSH Terms] OR "fasting"[All Fields] OR "fastings"[All Fields] OR "fasts"[All Fields])) OR (("diurnal"[All Fields] OR "diurnality"[All Fields] OR "diurnally"[All Fields]) AND ("fasted"[All Fields] OR "fasting"[MeSH Terms] OR "fasting"[All Fields] OR "fastings"[All Fields] OR "fasts"[All Fields]))) AND ("inflammation"[MeSH Terms] OR "inflammation"[All Fields] OR "inflammations"[All Fields] OR "inflammation s"[All Fields] OR ("inflammatories"[All Fields] OR "inflammatory"[All Fields]) OR "immunomodulatory"[All Fields] OR ("cytokin"[All Fields] OR "cytokine s"[All Fields] OR "cytokines"[Supplementary Concept] OR "cytokines"[All Fields] OR "cytokine"[All Fields] OR "cytokines"[MeSH Terms] OR "cytokinic"[All Fields] OR "cytokins"[All Fields]) OR ("interleukin 6"[Supplementary Concept] OR "interleukin 6"[All Fields] OR "interleukin 6"[All Fields] OR "il6 protein human"[Supplementary Concept] OR "il6 protein human"[All Fields] OR "interleukin 6"[MeSH Terms]) OR ("tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor alpha"[Supplementary Concept] OR "tumor necrosis factor alpha"[All Fields] OR "tumor necrosis factor alpha"[All Fields] OR "tnf protein human"[Supplementary Concept] OR "tnf protein human"[All Fields] OR "tumor necrosis factor alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor alpha"[All Fields]) OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])) OR ("tumour necrosis factor alpha"[All Fields] OR "tumor necrosis factor alpha"[Supplementary Concept] OR "tumor necrosis factor alpha"[All Fields] OR "tumor necrosis factor alpha"[All Fields] OR "tnf protein human"[Supplementary Concept] OR "tnf protein human"[All Fields] OR "tumor necrosis factor alpha"[MeSH Terms] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor alpha"[All Fields]) OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND "factor"[All Fields] AND "alpha"[All Fields])) OR ("c reactive protein"[Supplementary Concept] OR "c reactive protein"[All Fields] OR "c reactive protein"[All Fields] OR "c reactive protein"[MeSH Terms] OR ("c reactive"[All Fields] AND "protein"[All Fields]))))
ScienceDirect	(“Ramadan intermittent fasting” OR “Ramadan fasting” OR “diurnal fasting”) AND (“inflammation” OR “inflammatory” OR “immunomodulatory” OR “cytokine” OR “interleukin-6” OR “tumor necrosis factor-alpha” OR “tumor necrosis factor-α” OR “C-reactive protein”)
Scopus	(TITLE-ABS-KEY (Ramadan AND intermittent AND fasting) OR TITLE-ABS-KEY (Ramadan AND fasting) OR TITLE-ABS-KEY (diurnal AND fasting) AND TITLE-ABS-KEY (inflammation) OR TITLE-ABS-KEY (inflammatory) OR TITLE-ABS-KEY (immunomodulatory) OR TITLE-ABS-KEY (cytokine) OR TITLE-ABS-KEY (interleukin-6) OR TITLE-ABS-KEY (tumor AND necrosis AND factor-alpha) OR TITLE-ABS-KEY (tumor AND necrosis AND factor-α) OR TITLE-ABS-KEY (c-reactive AND protein)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))
Google Scholar	"Ramadan intermittent fasting" OR "Ramadan fasting" OR "diurnal fasting" AND "inflammation" OR "inflammatory" OR "immunomodulatory" OR "cytokine" OR "interleukin 6" OR "tumor AND necrosis AND factor alpha" OR "tumor AND necrosis AND factor α" OR "C reactive OR protein"

2.7. Data Extraction

One author (RA) read the article thoroughly and extracted data in a table. The study characteristics table consists of reference, country, study design, sample size, age, examined biomarkers, and quality assessment results in the form of NOS scores. Then, another author (FMR) performed data extraction in the form of a summary of changes in inflammatory biomarkers pre- and post-RF with a table consisting of reference/author(s), sample size, biomarkers, baseline (pre-RF), and post-RF. We ensured that the extracted data met the inclusion criteria, where numerical data must be available. Data was extracted using Microsoft Excel 2019 software.

2.8. Statistical Analysis

Statistical analyses were conducted using RevMan version 5.4 software for meta-analysis and Stata version 17.0 software for formal analysis of publication bias. This meta-analysis evaluated pre- (baseline) and post-RF data in one group of overweight and/or obese and non-obese individuals. The heterogeneity test (I^2) was conducted to evaluate data variation among studies, with the provision that heterogeneity was low if the I^2 value was <50% and high if the I^2 value was ≥50%. Fixed-effects model meta-analysis was used if heterogeneity was low, whereas random-effects model was used otherwise. Sensitivity analysis using the leave-one-out method was performed by omitting studies one by one and recalculating the remaining studies. Meta-analysis was performed in each category based on inflammatory biomarkers, IL-6, TNF-α, and CRP/hsCRP, and subgroup meta-analyses were performed by stratifying overweight and/or obese individuals and non-obese individuals. A funnel plot was used when the meta-analysis included a minimum of 10 studies (27), followed by formal analysis in the form of Egger's test (28) and Begg's test (29) to confirm the visualization results of the funnel plot. The findings were presented with a forest plot with effect sizes in the form of standardized mean differences (SMD) with 95% CI. Effect sizes were considered small if SMD was <0.40, medium effects if SMD was 0.40-0.70, and large effects if SMD was >0.70. If *p*-value <0.05, the statistical results were considered significant.

3. Results

3.1. Study Selection

The literature search identified 380 articles, after removing 68 duplicates. Initial screening successfully excluded 228 inappropriate articles, the remaining 152. We then screened the titles and abstracts, resulting in the exclusion of 64 reports. The remaining 88 papers were evaluated for eligibility. Based on the results of the eligibility assessment, we excluded 75 studies for the following reasons: abstract only (n = 2), irrelevant aim (n = 9), incomplete data (n = 7), athlete subjects (n = 3), people with diseases (n = 32), not a pre-post study (n = 2), reviews (n = 11), case report (n = 1), language (n = 1), using the same dataset (n = 1), and in vivo study (n = 6). In addition, a search using other sources, citation searches, was also performed, identifying one study. Finally, 14 studies were included in this meta-analysis (see **Figure 1**).

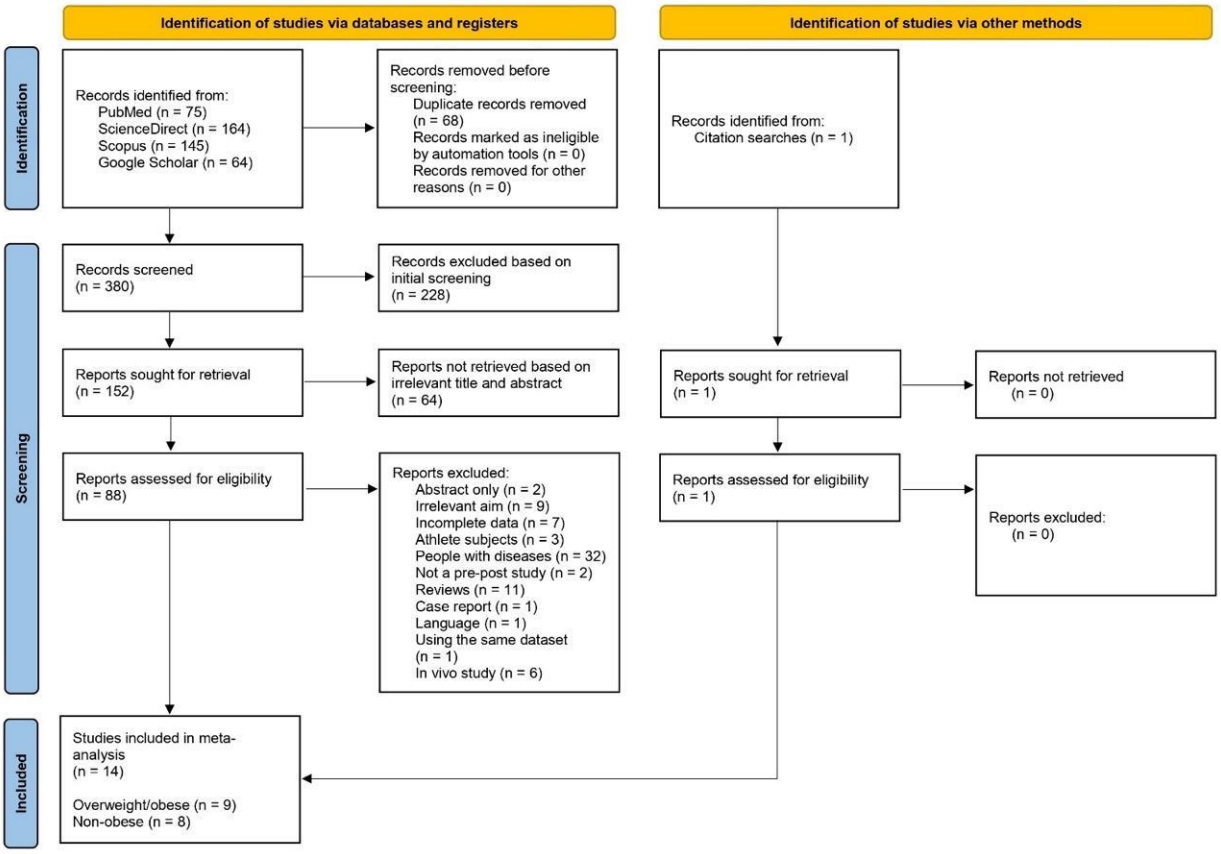

Figure 1. PRISMA flowchart.

3.2. Characteristics of Included Studies

A total of 14 studies involving 522 participants aged ≥18 years were finally included. Studies were conducted in Saudi Arabia (18,30), Iran (31,32), Jordan (33), United Arab Emirates (34,35), Germany (36), Denmark (37), Indonesia (38,39), Pakistan (40), Turkey (41), and Tunisia (42), and used a variety of study designs, including prospective observational (30–34,38,41), prospective cohort (18,35,36), non-randomized, crossover, intervention (37), randomized controlled trial (42), cross-sectional (40), and experimental (39). Based on the type of biomarkers, eight studies examined IL-6 (32–35,37,39,41,42), eleven studies examined TNF-α (18,33–42), and five studies examined CRP/hsCRP (30–32,41,42). It is important to note that the number of studies analyzing CRP/hsCRP was relatively small compared to IL-6 and TNF-α, which may limit the generalizability of the findings related to this biomarker. The quality assessment results indicated that all studies were high quality based on their NOS scores. All details regarding the study characteristics are presented in **Table 2**.

Table 2. Characteristics of included studies.

Reference	Country	Study design	Sample size (*n*)	Age (mean or range) (years)	Examined biomarker	NOS score
Ajabnoor et al. (30)	Saudi Arabia	Prospective observational	23	23.16 ± 1.2	hsCRP	8
Al Zunaidy et al. (18)	Saudi Arabia	Prospective cohort	62	21-68	TNF-α	9
Askari et al. (31)	Iran	Prospective observational	14	37.5 ± 7.86	hsCRP	9
Faris et al. (33)	Jordan	Prospective observational	50	18-51	IL-6, TNF-α	9
Faris et al. (34)	United Arab Emirates	Prospective observational	57	36.2 ± 12.5	IL-6, TNF- α	9
Ghashang et al. (36)	Germany	Prospective cohort	25	26.12 ± 0.98	TNF- α	9
Harder-Lauridsen et al. (37)	Denmark	Non-randomized, crossover, intervention	10	25.2	IL-6, TNF- α	9
Lahdimawan et al. (38)	Indonesia	Prospective observational	27	20.26 ± 1.13	TNF- α	7
Madkour et al. (35)	United Arab Emirates	Prospective cohort	57	38.42 ± 11.18	IL-6, TNF- α	9
Mohammadzade et al. (32)	Iran	Prospective observational	30	29.44 ± 7.4	IL-6, CRP	8
Mushtaq et al. (40)	Pakistan	Cross-sectional	110	20-40	TNF- α	8
Ünalacak et al. (41)	Turkey	Prospective observational	20	27.4 ± 5.2	IL-6, TNF- α, CRP	9
Zekri et al. (39)	Indonesia	Experimental	23	19-29	IL-6, TNF- α	7
Zouhal et al. (42)	Tunisia	Randomized controlled trial	14	24 ± 3.4	IL-6, TNF- α, CRP	9

3.3. Summary of Changes in Inflammatory Biomarkers Pre- and Post-RF

We subsequently extracted all data on changes in inflammatory biomarkers examined by each study. Data were extracted from studies if they reported baseline or pre-RF data, which were recorded on the first day before RF or a maximum of one week before RF, and post-RF data, which were recorded in the last week of RF or the end of RF. **Table 3** summarized changes in inflammatory biomarkers in overweight and/or obese individuals, while **Table 4** reported data in non-obese individuals.

Table 3. Changes in inflammatory biomarkers from baseline (pre-RF) and post-RF in overweight and/or obese individuals.

Study	Sample size (*n*)	Biomarker	Baseline (mean ± SD)	Post-RF (mean ± SD)
Al Zunaidy et al. 2024	31	TNF-α	123.43 ± 9.71	117.19 ± 2.13
Faris et al. 2012	40	IL-6	155.85 ± 121.18	67.42 ± 51.25
	48	TNF-α	179.62 ± 129.56	52.22 ± 57.25
Faris et al. 2019	57	IL-6	70 ± 69	32 ± 24
		TNF-α	23 ± 21	13 ± 11
Madkour et al. 2022	57	IL-6	29.86 ± 16.75	18.21 ± 1.29
		TNF-α	28.17 ± 4.40	21.24 ± 1.49
Mohammadzade et al. 2017	30	IL-6	1.09 ± 1.63	0.79 ± 0.26
		CRP	1.72 ± 1.67	1.99 ± 1.45
Mushtaq et al. 2019	20	TNF-α	25.36 ± 10.34	22.16 ± 9.30
	60	TNF-α	36.08 ± 10.71	30.20 ± 10.17
Ünalacak et al. 2011	10	IL-6	4.13 ± 1.20	3.76 ± 0.99
		TNF-α	10.56 ± 3.84	7.57 ± 2.60
		CRP	2.83 ± 1.39	2.70 ± 1.29
Zekri et al. 2016	23	IL-6	8.38 ± 4.90	7.57 ± 2.80
		TNF-α	1523.48 ± 462.61	1686.96 ± 588.82
Zouhal et al. 2020	14	IL-6	49.1 ± 4.2	44.0 ± 3.1
		TNF-α	4485.7 ± 575	4028.5 ± 610.7
		CRP	18.02 ± 1.7	18.20 ± 1.8

Table 4. Changes in inflammatory biomarkers from baseline (pre-RF) and post-RF in non-obese individuals.

Reference	Sample size (*n*)	Biomarker	Baseline (mean ± SD)	Post-RF (mean ± SD)
Ajabnoor et al. 2014	23	hsCRP	1.68 ± 0.47	0.97 ± 0.22
		hsCRP	1.33 ± 0.32	1.13 ± 0.35
Al Zunaidy et al. 2024	31	TNF-α	194.45 ± 8.02	183.30 ± 9.65
Askari et al. 2016	14	hsCRP	2.08 ± 0.52	1.24 ± 0.29
Ghashang et al. 2024	25	TNF-α	4.45 ± 1.48	3.67 ± 0.31
Harder-Lauridsen et al. 2017	10	IL-6	0.3 ± 0.14	0.3 ± 0.08
		TNF-α	4.6 ± 0.7	4.4 ± 0.4
Lahdimawan et al. 2013	27	TNF-α	15.46 ± 7.15	19.61 ± 6.09
Mushtaq et al. 2019	30	TNF-α	19.66 ± 6.07	17.13 ± 5.36
Ünalacak et al. 2011	10	IL-6	4.03 ± 0.30	3.56 ± 0.78
		TNF-α	10.87 ± 2.60	7.70 ± 2.52
		CRP	1.85 ± 1.51	2.41 ± 1.98

3.4. Impact of RF on IL-6 in Overweight and/or Obese and Non-Obese Individuals

Fixed-effects model meta-analysis showed that RF statistically significantly reduced IL-6 levels (SMD = 0.68; 95% CI = 0.50, 0.87; p <0.00001). This effect was observed to be stronger in overweight and/or obese individuals (SMD = 0.71; 95% CI = 0.52, 0.90; p <0.00001) than in non-obese individuals (SMD = 0.36; 95% CI = -0.27, 1.00; p = 0.26). No heterogeneity was observed overall (I^2 = 44%; p = 0.08) (see **Figure 2**).

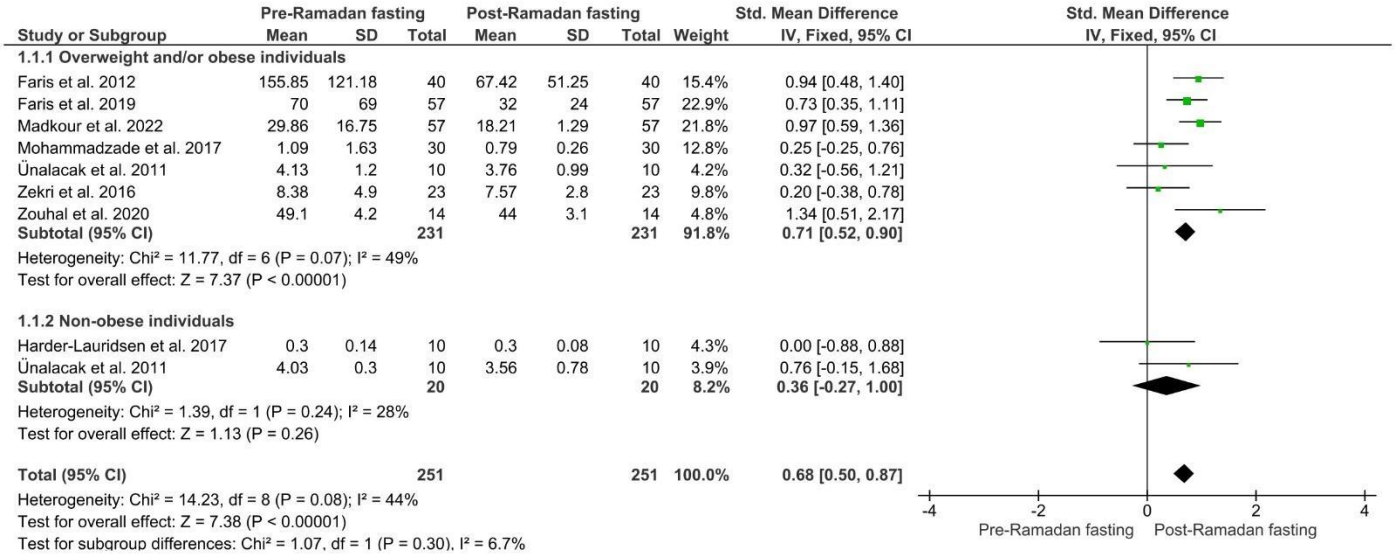

Figure 2. Forest plot of the impact of RF on IL-6.

3.5. Impact of RF on TNF-α in Overweight and/or Obese and Non-Obese Individuals

Random-effects model meta-analysis demonstrated that RF significantly reduced TNF-α (SMD = 0.69; 95% CI = 0.34, 1.04; p = 0.0001). A stronger reduction effect was observed in overweight and/or obese individuals (SMD = 0.79; 95% CI = 0.35, 1.23; p = 0.0005) than in non-obese individuals (SMD = 0.53; 95% CI = -0.06, 1.12; p = 0.08). The findings need to be interpreted with caution because the studies were heterogeneous (I^2 = 83%; p <0.00001) (see **Figure 3**).

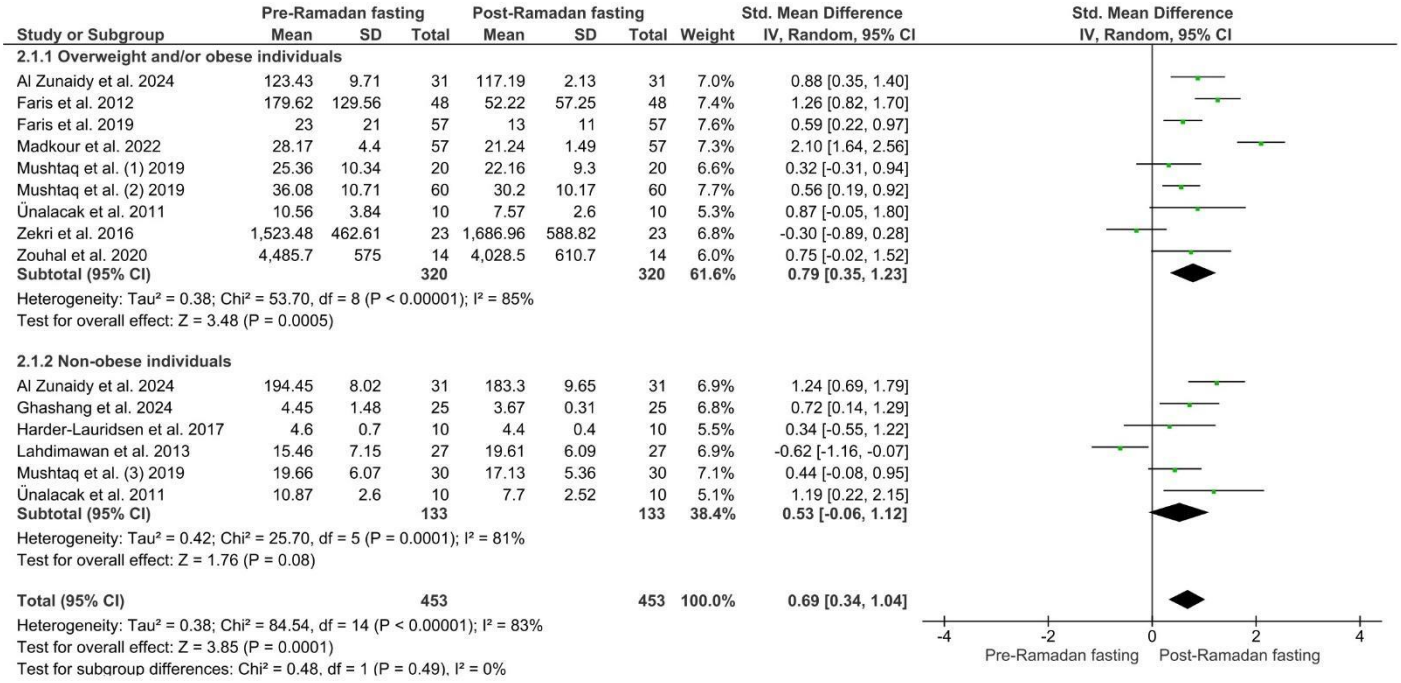

Figure 3. Forest plot of the impact of RF on TNF-α.

Since the number of studies was more than 10, a formal analysis for publication bias was performed. Funnel plot visualization results indicated an asymmetric distribution, indicating the potential for publication bias (see **Figure 4**). However, to confirm this, we further conducted Egger's test and Begg's test, the results of which were p = 0.53 and p = 1.00 respectively, indicating that no publication bias was finally observed (p >0.05).

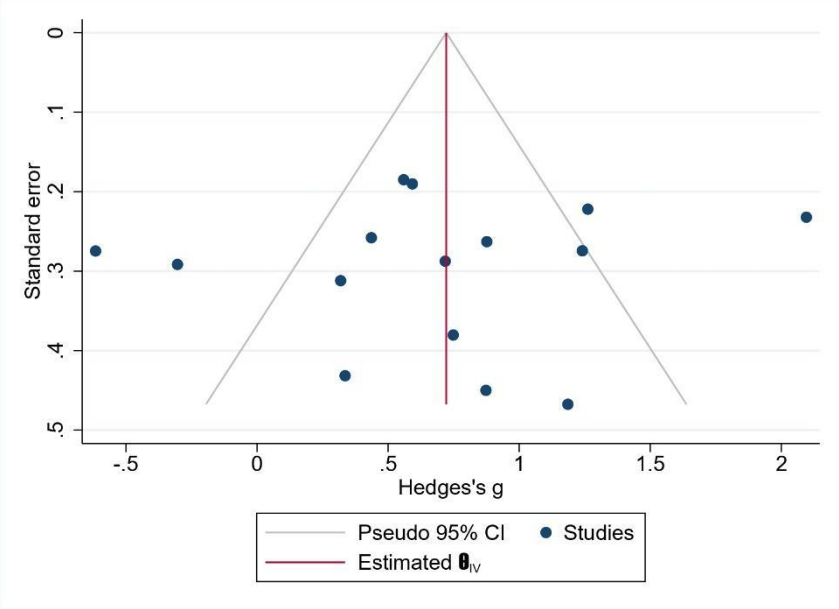

Figure 4. Funnel plot in the meta-analysis of the impact of RF on TNF-α.

3.6. Impact of RF on CRP/hsCRP in Overweight and/or Obese and Non-Obese Individuals

Random-effects model meta-analysis revealed that RF insignificantly reduced CRP/hsCRP levels in any individual (SMD = 0.55; 95% CI = -0.13, 1.23; $p = 0.11$). However, a large and significant reduction effect was observed in non-obese individuals (SMD = 1.03; 95% CI = 0.04, 2.02; $p = 0.04$), although RF did not have a reduction effect on CRP/hsCRP in overweight and/or obese individuals (SMD = -0.10; 95% CI = -0.48, 0.28; $p = 0.59$). This meta-analysis should be interpreted with caution because high heterogeneity was observed in both the non-obese individuals ($I^2 = 85\%$; $p = 0.0001$) and the combined groups ($I^2 = 84\%$; $p < 0.00001$) (see **Figure 5**).

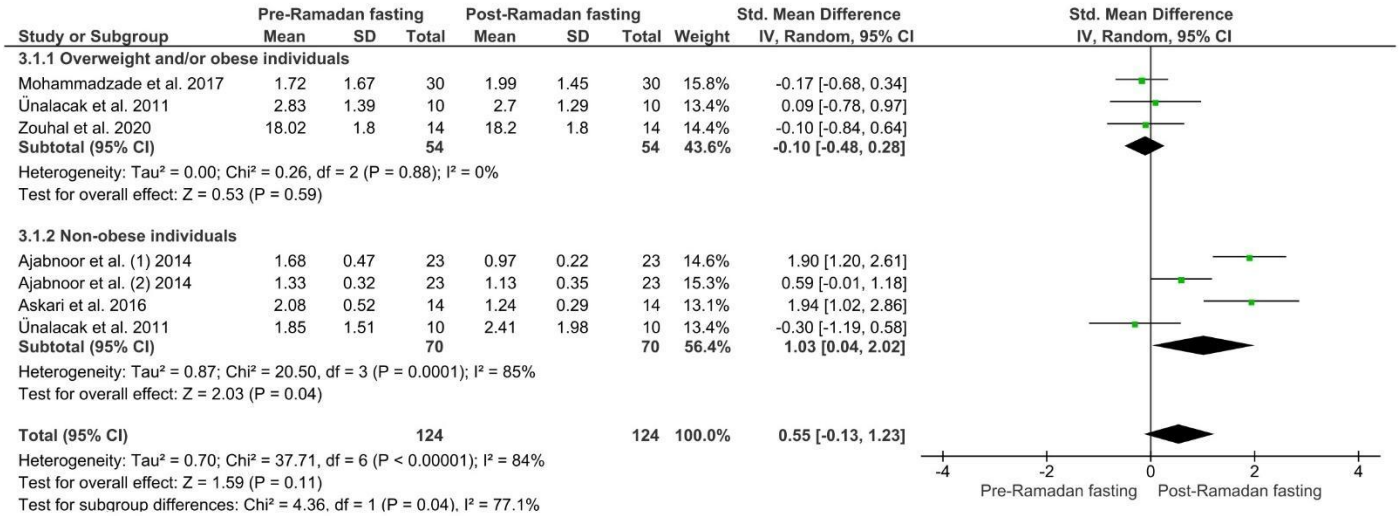

Figure 5. Forest plot of the impact of RF on CRP/hsCRP.

3.7. Sensitivity Analysis

To assess the robustness of this study, we employed the leave-one-out sensitivity analysis. The meta-analysis results remained stable in studies measuring the impact of RF on IL-6 and TNF-α, showing no significant changes in SMD and 95% CI, as well as *p*-value. However, the meta-analysis of studies measuring the impact of RF on CRP/hsCRP changed significantly when Ajabnoor et al. 2014 (30) and Askari et al. 2016 (31) were removed (see **Table 5**).

Table 5. Sensitivity analysis using leave-one-out method.

Omitted study	SMD and 95% CI of remaining studies	*p*-value
IL-6		
Overall	0.68 (0.50, 0.87)	<0.00001
Overweight and/or obese individuals		
Faris et al. 2012	0.64 (0.44, 0.84)	<0.00001
Faris et al. 2019	0.67 (0.46, 0.88)	<0.00001
Madkour et al. 2022	0.60 (0.40, 0.81)	<0.00001
Mohammadzade et al. 2017	0.75 (0.55, 0.94)	<0.00001
Ünalacak et al. 2011	0.70 (0.52, 0.89)	<0.00001
Zekri et al. 2016	0.74 (0.55, 0.93)	<0.00001
Zouhal et al. 2020	0.65 (0.47, 0.84)	<0.00001
Non-obese individuals		
Harder-Lauridsen et al. 2017	0.68 (0.49, 0.87)	<0.00001
Ünalacak et al. 2011	0.65 (0.46, 0.84)	<0.00001
TNF-α		
Overall	0.69 (0.34, 1.04)	0.0001
Overweight and/or obese individuals		
Al Zunaidy et al. 2024	0.67 (0.30, 1.05)	0.0005
Faris et al. 2012	0.64 (0.27, 1.01)	0.0006
Faris et al. 2019	0.70 (0.31, 1.09)	0.0004
Madkour et al. 2022	0.58 (0.29, 0.86)	<0.0001
Mushtaq et al. (1) 2019	0.72 (0.35, 1.09)	0.0002
Mushtaq et al. (2) 2019	0.70 (0.31, 1.09)	0.0004
Ünalacak et al. 2011	0.68 (0.31, 1.05)	0.0003
Zekri et al. 2016	0.76 (0.42, 1.11)	<0.0001
Zouhal et al. 2020	0.69 (0.32, 1.05)	0.0003
Non-obese individuals		
Al Zunaidy et al. 2024	0.65 (0.28, 1.02)	0.0006
Ghashang et al. 2024	0.69 (0.31, 1.06)	0.0003
Harder-Lauridsen et al. 2017	0.71 (0.34, 1.08)	0.0001
Lahdimawan et al. 2013	0.79 (0.47, 1.11)	<0.00001
Mushtaq et al. (3) 2019	0.71 (0.33, 1.08)	0.0002
Ünalacak et al. 2011	0.66 (0.30, 1.03)	0.0004
CRP/hsCRP		
Overall	0.55 (-0.13, 1.23)	0.11
Overweight and/or obese individuals		
Mohammadzade et al. 2017	0.69 (-0.08, 1.45)	0.08
Ünalacak et al. 2011	0.63 (-0.15, 1.40)	0.11
Zouhal et al. 2020	0.65 (-0.11, 1.44)	0.09
Non-obese individuals		
Ajabnoor et al. (1) 2014	0.31 (-0.27, 0.89)	0.29
Ajabnoor et al. (2) 2014	0.55 (-0.29, 1.39)	0.20
Askari et al. 2016	0.34 (-0.31, 1.00)	0.31
Ünalacak et al. 2011	0.69 (-0.06, 1.43)	0.07

4. Discussion

This meta-analysis revealed that RF resulted in a significant decrease in IL-6 and TNF-α in any individuals. When the analysis was stratified by BMI status, larger effect and more significant reduction in IL-6 and TNF-α were observed in overweight and/or obese individuals, and CRP/hsCRP in non-obese individuals. The results of the impact of RF on IL-6 and TNF-α were robust, but less stable on CRP/hsCRP, based on sensitivity analysis. The results of the formal analysis of publication bias in the impact of RF on TNF-α indicated no potential publication bias. In

addition, this meta-analysis should be interpreted with caution, especially in the analysis of the impact of RF on TNF-α and CRP/hsCRP due to the high heterogeneity of the test results.

However, it is important to acknowledge that the included studies were mostly observational studies, which inherently limits the ability to establish causal relationships due to potential confounding factors and bias. Observational studies are susceptible to various forms of bias that may affect the validity of the findings. Therefore, the results should be interpreted with caution and further well-designed RCTs are needed to confirm these findings and establish causality. Furthermore, variability in participant factors such as dietary intake, sleep patterns, and physical activity levels during RF may influence inflammatory markers and contribute to heterogeneity among studies. Future research should aim to control for these variables to better understand their impact on outcomes.

In a previous meta-analysis carried out by Faris et al. (20), their study concluded that RF exhibited a small significant effect on decreasing IL-6, a non-significant effect on TNF-α, and a very small non-significant effect on CRP/hsCRP. Meanwhile, our updated meta-analysis revealed results where the effects of reducing IL-6 and TNF-α were observed to be medium and significant, and the effects increased in overweight and/or obese individuals, and a large and significant effect on reducing CRP/hsCRP in non-obese individuals. This is because previous meta-analyses included very few studies and did not perform subgroup analyses based on BMI status. Therefore, our study represents the most comprehensive and up-to-date to date.

Reduced levels of IL-6, TNF-α, and CRP levels after RF suggest that this form of intermittent fasting has significant anti-inflammatory effects. The immunological response to chronic inflammation and metabolic stress is regulated by IL-6 and TNF-α (43,44). Our study indicates that RF can reduce systemic inflammatory conditions, which are often increased in overweight individuals. Additionally, a more significant decrease in CRP in non-obese individuals suggests that RF may provide a protective effect against inflammatory conditions in individuals without overweight. These anti-inflammatory effects are relevant for the prevention of chronic metabolic and inflammatory ailments, such as cardiovascular diseases and diabetes (45).

Several biological mechanisms explain the decrease in inflammatory biomarkers after RF. One of the main mechanisms is the induction of autophagy (46), where the body naturally clears damaged cells and reduces the production of inflammatory cytokines. RF, furthermore, has been shown to have no negative impact on inflammatory, biochemical, and hematological parameters, which have beneficial and protective effects against inflammation in healthy individuals (47). In addition, RF is known to increase insulin sensitivity (48); thus, the body's cells are more effective in absorbing glucose and keeping blood sugar levels stable, which is linked to a reduced risk of insulin resistance and metabolic diseases such as diabetes mellitus (49). Increased adiponectin during fasting was also observed (40). Adiponectin, secreted by adipose tissue, is an adipokine that has antidiabetic, anti-inflammatory, and antiatherogenic properties (50). Adiponectin plays a part in inhibiting the pro-inflammatory cytokines, IL-6 and TNF-α, and leptin. In obese individuals in particular, increased adiponectin activates AMP-activated protein kinase (AMPK) signaling and suppresses the IκB kinase (IKK)/NF-κB/phosphatase and tensin homolog (PTEN) signaling, which further shows the effects of decreasing IL-6 and TNF-α levels (51–53). These effects are more pronounced in overweight and/or obese individuals because they generally have higher levels of inflammation prior to fasting in Ramadan. Therefore, RF not only affects energy balance but also regulates the immune system and inflammation in the body as a whole.

Our study carries significant clinical implications for the prevention and management of chronic inflammatory diseases. Decreased IL-6, TNF-α, and CRP due to RF suggest that a one-month intermittent fasting-based intervention may be a potential strategy for reducing systemic inflammation. Given that RF significantly reduces inflammatory biomarkers, this approach may be recommended as part of non-pharmacological therapy for individuals with mild to moderate inflammatory conditions. Additionally, the findings from this study provide a foundation for further investigation into the application of intermittent fasting outside of Ramadan as a long-term strategy to control inflammation and improve metabolic health. It should be noted, however, that although this meta-analysis suggests potential promising effects on inflammation, the observational design of the included studies and variability in participant behavior highlights the need for careful interpretation of the results. Further studies, particularly RCTs with standardized protocols and long-term follow-up, are needed to confirm these findings and elucidate the underlying mechanisms.

This meta-analysis has several strengths. First, this study is an update of previous meta-analysis by incorporating more recent literature and a larger number of studies; thus, providing a more comprehensive understanding of the impact of RF on inflammation. Second, the subgroup analysis conducted based on BMI status allowed the identification of differences in inflammatory responses between overweight and/or obese and non-

obese individuals, which had not been explored in previous meta-analyses. Third, this study used rigorous statistical methods, including sensitivity analysis and formal analysis of publication bias, to ensure the robustness of the findings. Fourth, this meta-analysis only included studies with observational designs that had pre- and post-RF data, thus increasing the accuracy in exploring the effects of RF on inflammation without the influence of other factors. Furthermore, only healthy participants without chronic diseases, inflammatory conditions, and long-term use of medications that can affect inflammatory cytokines were included; thus, the results are more valid without being influenced by other inflammatory factors. With these strengths, the present paper makes a significant contribution to understanding the impact of RF on systemic inflammation and its potential as a preventive strategy for inflammatory and metabolic diseases.

However, we acknowledge some limitations of our study. First, the limited studies, especially for the analysis of CRP/hsCRP, may affect the strength of our conclusions. Second, high heterogeneity in some analyses, particularly for TNF-α and CRP/hsCRP, suggests significant variation between studies that may be due to differences in population characteristics, fasting duration, or methods of measuring inflammatory biomarkers. Third, most of the included studies used observational designs, which although useful in understanding biomarker changes pre- and post-RF, cannot fully control for potential confounding factors that may influence the results. Fourth, the grouping of overweight and/or obese individuals and non-obese individuals was obtained from the average data presented in, only a portion of, the included articles, and not the raw data from each individual. In addition, none of the studies analyzed underweight individuals. This, in turn, may have impacted our final findings. Fifth, differences in dietary patterns, physical activity levels, and sleep duration and quality during Ramadan were not analyzed in depth in each study, even though these factors may potentially modulate the inflammatory response. Sixth, this study did not evaluate the long-term effects of RF on inflammation; therefore, further research may be warranted to assess whether the observed anti-inflammatory benefits persist after the RF period ends. Considering these limitations, interpretation of the results should be done with caution, and additional studies with more robust methodology are needed to strengthen the findings obtained.

5. Conclusions

In conclusion, RF significantly reduces IL-6 and TNF-α levels, as well as reduces CRP/hsCRP in non-obese individuals. However, studies with more robust methodological designs, larger samples, and long-term evaluation of the effects of RF on inflammation may be warranted to clarify the mechanisms and clinical implications of these results. Overall, the findings of this meta-analysis may support the potential role of RF as a complementary approach to modulate inflammation, especially in individuals with elevated BMI. However, these conclusions should be interpreted with caution due to major limitations in the current evidence base, including the small number of studies for certain biomarkers, especially CRP/hsCRP, high heterogeneity, and reliance on observational designs.

Acknowledgments: This research received no external support.

Author Contributions: FMR and RA contributed equally to this study. All authors have read and agreed to the published version of the manuscript.

Funding: None.

Conflicts of Interest: None declared.

Informed Consent Statement: Not applicable.

List of Abbreviations

AMPK	AMP-activated protein kinase
CRP	C-reactive protein
hsCRP	High-sensitivity C-reactive protein
IKK	IκB kinase
IL-6	Interleukin-6
PTEN	Phosphatase and tensin homolog
RF	Ramadan fasting
TNF-α	Tumor necrosis factor-α

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