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REVIEW

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The effectiveness of fasting regimens on serum levels of some major weight regulating hormones: a GRADE-assessed systematic review and meta-analysis in randomized controlled trial

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Abstract

A current investigation was performed to review and summarize the results of randomized clinical trials (RCTs) studies that have assessed the effectiveness of fasting regimens (FRs) including intermittent fasting (IF), time-restricted feeding (TRF), alternate day fasting (ADF) and fasting-mimicking diet (FMD) on some weight regulation hormones included; leptin, adiponectin, ghrelin, and resistin in healthy, overweight and obese adults recently. Four databases have been reviewed until June 2024 using keywords related to the subject of the study. Overall, 16 documents were considered in this study. Based on Pooled effect sizes, the FRs marginal significantly increased the level of adiponectin (weighted mean differences (WMD): 0.41 µg/ml, 95% confidence interval (CI): − 0.07 to 0.89, *P*: 0.09) and also significantly decreased the level of leptin (WMD: − 2.65 ng/ml, 95% CI: − 3.86 to − 1.44, $p < 0.001$) and ghrelin (WMD: − 0.57 ng/ml, 95% CI: − 1.01 to − 0.03, *P*: 0.01). There was no significant effect of this regimen approach on resistin levels. In general, according to this evaluation, FRs have a beneficial impact on weight-regulating hormone levels, still the long-term effects of these dietary approaches should also be evaluated in future studies.

Keywords Fasting regimen, Hormone, Obesity, Meta-analysis

Introduction

The definition of overweight and obesity is an accumulation of abnormal or excessive fat resulting in potential health risks. According to the definition of the World Health Organization (WHO), overweight is noticed as a body mass index (BMI) above 24.9 to 29.9, and values above 30 are considered as obesity [1]. Global estimates suggest that 3.3 billion adults may be affected by high BMI by 2035, which represents a 12% increase compared to 2020 [2]. Obesity can elevate the risk of chronic disease developing like heart disease, type 2 diabetes, and certain types of cancer, and can generally decrease the quality of life [3].

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As obesity rates rise, dietary interventions like calorie restriction have gained importance as a strategy for weight loss [4]. Recently, FR has been recommended instead of continuous calorie restriction, which frequently involves calorie intake restriction for a certain period and free consumption of calories at non-fasting times [5]. FRs have various models such as FMD in which the amount of energy, protein, and sugar intake has been reduced [6]. In ADF pattern as a type of FRs people experience calorie restriction on fasting days while allowing unrestricted eating on feeding days. In contrast, TRF permits individuals to consume food within a designated time frame each day [5]. the hypothalamus plays a vital role in food intake regulation by sending hormonal and nerve signals related to satiety and eating behaviors [7]. Modifying the abnormal secretion of hormones could be beneficial in the management of obesity [8]. Some hormones that play a role in weight control such as; ghrelin which promotes food intake and reduces energy expenditure, leptin which has the reverse effect on appetite, and adiponectin which appears to facilitate weight loss mainly by enhancing energy expenditure and also helps to reduce insulin resistance [9]. Based on study results; around obese individuals, serum levels of ghrelin and adiponectin decrease while leptin levels increase [10–12]. Studies have shown that high levels of resistin are associated with insulin resistance and obesity, and recent research shows a positive relationship between resistin levels and visceral fat and BMI in obese adults [13]. In recent years, most evidence has assessed the effectiveness of FRs effects on hormone secretion but the findings were contradictory. In an study on obese mice, IF increased adiponectin and decreased leptin levels, and improved adipose tissue pro-inflammatory profile [14]. In a clinical trial conducted by Trepanowski and colleagues, after 24 weeks of ADF, and another clinical trial conducted by Zhang and colleagues after an 8-week intervention with TRF, leptin levels decreased [15, 16]. In one study performed on type 2 diabetes, IF decreased adiponectin and increased leptin levels in diabetic people [17]. In another study IF decreased leptin and also ghrelin levels [18]. In an RCT conducted on obesity, FMD increased ghrelin levels significantly [19].

Considering the mentioned content and the existence of contradictions among the reports of different studies, we performed a systematic review and meta-analysis study in RCT studies to evaluate the effects of FDs such as; IF, TRF, ADF, and FMD on some weight-regulating hormones.

Methods

This systematic review and meta-analysis addressing the efficacy of FRs around leptin, adiponectin, ghrelin, and resistin levels, around overweight, obese, and healthy adults had been done based on the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline [20].

Registration

This study protocol was registered prior in PROSPERO (CRD42024596085).

Search strategy

The online medical databases, such as SCOPUS, Web of Science, PubMed, and Google Scholar were systematically searched until June 2024. MESH (Medical Subject Heading) and non-MESH keywords were recruited to specify relevant articles were: ((“time restricted feeding”[All Fields] OR “time restricted diet”[All Fields] OR “time restricted eating”[All Fields] OR “intermittent fasting”[All fields] OR “intermittent energy restriction”[All Fields] OR “alternate day fasting”[All Fields] OR “fasting diet”[All Fields] OR “intermittent calorie restriction”[All Fields] OR “time restricted fasting”[All Fields] OR “time restricted meal”[All Fields] OR “time restricted”[All Fields]) AND (“Appetite”[MeSH] OR “hunger”[MeSH] OR “food intake”[MeSH] OR “acylated ghrelin”[All fields] OR “satiety”[All fields] OR “satiation”[All fields] OR “Leptin”[MeSH] OR “Adiponectin”[MeSH] OR “Resistin”[MeSH] OR “hormones”[MeSH] OR “total ghrelin”[All Fields] OR “appetite hormones”[MeSH] OR “Gastrointestinal Hormones”[MeSH] OR “gut hormone*”[All Fields] OR “gut peptide*”[All Fields] OR “obesity hormone*”[All Fields] OR “weight regulation hormone”[All Fields] OR “fasting mimicked diet”[All Fields])). We did not impose any language or time restrictions on the chosen of articles. moreover, we carried out a hand-search of related studies references to refrain missing any studies that had been eligible. In this study, we did not include unpublished information, gray literature, and conference abstracts.

Study selection

At first, two reviewers (AT and BPG) screened the titles and abstracts of identified studies; ultimately, full-text reports of eligible studies were assessed for data extraction.

Inclusion criteria

Population (P): Studies were done on 18-year-olds and older overweight, obese, and healthy adults without any limitation of gender, race, or geographic region.

Intervention (I): FRs including IF, ADF, TRF, and FMD.

Comparison (C): usual intake or energy-restricted intake.

Outcome (O): weight-regulating hormone levels including adiponectin, leptin, ghrelin and resistin.

Exclusion criteria

We excluded studies that: (a) were done on children, adolescents, pregnant or lactating women; (b) with no control group (c) studied any other intervention along with FR; (d) Studies that examined the effect of fasting conditions acutely and over 24 h, not over days; we excluded studies that examined the acute or short-term effects of fasting diets on hormone levels because our study aimed to consider fasting as a dietary pattern and examine its effects in the long term, rather than examining fasting conditions that have been studied in the short term.

Data extraction

The current data were extracted by two independent reviewers (AT and MB) according to a standardized data collection form: the first author's last name; date of publication; the country of the study; study design; participants' gender, range of age and health status; the number of persons in two groups (intervention and control); intervention duration; mean ± standard deviation (SD) or changes of hormone levels and intervention and control groups details.We standardized the units of hormone levels by using the unit reported by most studies as the reference and converted the remaining studies that reported different units for hormone levels to the reference unit, using μ/ml for adiponectin and ng/ml for leptin and ghrelin. Regarding dispersion indices, we considered the reference SD and if a study reported a different index, we converted them to SD using the following formulas:

If a standard error was reported: SD = SE*$\sqrt{}$number of people in the target group.

If interquartile range (IQR) was reported: SD = (upper limit—lower limit)/1.35.

If it was necessary, any mismatches were improved by a third independent researcher (PZ).

Quality assessment of studies

We used the Cochrane Risk of Bias Review Tool (RoB 2) for risk of bias assessment (Table 1) [21]. Two researchers independently (AT and FT) investigated the following methodological areas: (1) blinding of participants and personnel, (2) blinding of outcome assessment, (3) allocation concealment, (4) random sequence generation, (5) selective reporting, (6) incomplete outcome data and (7) other probable sources of biases. Based on information from the Cochrane Handbook, studies were classified as low risk, high risk of bias, or unclear. (Table 1).

Table 1 Risk of bias for randomized controlled trials, assessed according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Publications	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
1.Bhutani etal.2013	L	S	L	L	L	L
2.Varady et al.2013	L	S	L	L	L	L
3.Catenacci etal.2016	L	H	L	L	L	S
4. Moro etal.2016	L	L	L	L	L	L
5. F. Trepanowskia etal.2017	L	L	L	L	L	L
6.T. Stratton etal.2020	L	S	L	L	L	L
7.Pureza M.S. etal.2020	L	S	L	L	L	L
8. Moro etal.2020	S	H	L	L	L	S
9. Moro etal.2021	L	L	L	L	L	L
10.Templeman etal.2021	L	L	S	L	L	L
11. Sadeghian et al.2021	L	S	L	L	L	L
12.Castela et al.2022	L	S	L	L	L	L
13.Zhang etal.2022	L	L	S	L	L	L
14.Çelik et al.2023	L	H	L	L	L	L
15.Czerwi ´ nska-Ledwig etal.2024	L	L	L	L	L	S
16.Keawtep et al.2024	L	L	L	L	L	L

L, Low risk of bias; H, High risk of bias; S, Some concerns

Statistical analysis

We used Mean differences ± SDs of leptin, adiponectin, ghrelin, and resistin levels to assess the effect size as mean differences in changes in the intervention and control groups. in studies where change differences were not clear, we computed them using initial and final values. To calculate between-study heterogeneity, we used the Random effects model with the method of DerSimonian and Laird [22]. To measure the content of interstudy heterogeneity with amounts larger than 50% (studies by a medium to high heterogeneity), I^2 testing was used. when we found a considerable between-study heterogeneity, a sub-group analysis was performed according to gender (both, male, and female), duration of intervention (≤ 12 or > 12 weeks), country (US/non-US), and number of study participants (≤ 50 or > 50). we did a sensitivity analysis to assess the effect of each piece of evidence on the overall effect size. with visual evaluation of funnel plots and using the Egger test, we assessed quantitatively any publication bias by considering $P > 0.05$ in the Egger test as each study did not perform any bias. All of the analysis was performed by Stata software, version 17 (Stata Corp. College Station, Texas, USA). *P*-values below 0.05 were noticed as statistically and below 0.1 were noticed as marginal significant notable.

Certainty assessment

The certainty of the studies was assessed according to the guidelines of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group (gradeworkinggroup.org) for outcomes which was significantly affected by FRs. Based on the assessment criteria, the quality of the investigation was subsequently classified into four groups: high, moderate, low, and very low.

Results

Study selection

Flow diagram of the study is shown in Fig. 1. In our initial screen, 6492 articles were obtained, of which 63 articles entered the next stage for full-text evaluation. For the following reasons, 46 studies were excluded: studies with inadequate data for the outcomes (n = 36), irrelevant investigations (n = 10), and conference abstracts (n = 1). Finally, sixteen RCTs were included in the current quantitative analysis.

Study characterizes

The general characteristics of the investigations included in this meta-analysis are shown in Table 2. RCT articles were only included in this study and these papers were published between 2013 and 2024 and were implemented in the USA [15, 23–26],

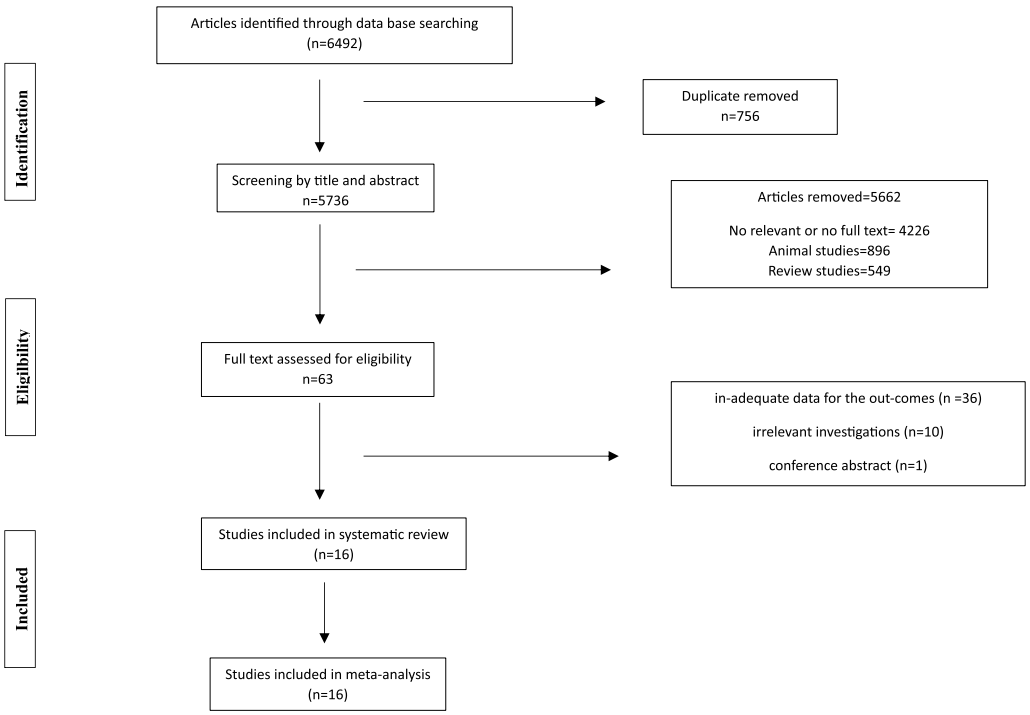

Fig. 1 flow chart for study search

Table 2 Demographic characteristics of the included studies

Code first author(year)	Location	Study design	Health status	Gender	Sample size	Duration(week)	Range age(year)	Intevention group	Comparator group	Out come
1. Bhutani etal.2013	USA	RCT	Obese	Both	32	12	25–65	ADF	Usual intake	Adiponectin/Leptin
2.Varady et al.2013	USA	RCT	Normal and overweight	Both	30	12	35–50	ADF	Usual intake	Adiponectin/Leptin/Resistin
3.Catenacci etal.2016	USA	RCT	Obese	Both	26	8	18–55	ADF	Energy restricted	Leptin/Ghrelin
4. Moro etal.2016	Italy	RCT	resistance-trained males	Both	34	8	18–20	TRF	Usual intake	Adiponectin/Leptin
5. F. Trepanowskia etal.2018	USA	RCT	Overweight and obese	Male	65	24	18–65	ADF	Usual intake	Adiponectin/Leptin/Resistin
6.T. Stratton etal.2020	USA	RCT	Healthy	Male	26	6		TRF	Usual intake	Adiponectin/Leptin/Ghrelin
7.Pureza M.S. etal.2020	Brazil	RCT	Obese	Female	58	3	19–44	TRF	Energy restricted	Leptin
8. Moro etal.2020	Italy	RCT	resistance-trained males	Both	16	4	18–20	TRF	Usual intake	Adiponectin/Leptin
9. Moro etal.2021	Italy	RCT	resistance-trained males	Both	20	12	18–20	TRF	Usual intake	Adiponectin/Leptin
10.Templeman etal.2021	UK	RCT	Healthy	Both	24	3	18–65	ADF	Energy restricted	Adiponectin/Leptin
11. Sadeghian et al.2021	Iran	RCT	Obese	Female	60	8	18–55	FMD	Energy restricted	Leptin/Ghrelin
12.Castela et al.2022	Norway	RCT	obese	Both	28	12	45–59	IF	Energy restricted	Adiponectin/Leptin/Resistin
13.Zhang etal.2022	China	RCT	Obese	Both	30	8	18–30	eTRF	Usual intake	Adiponectin/Leptin
14.Zhang etal.2022	China	RCT	Obese	Both	49	8	18–30	ITRF	Usual intake	Adiponectin/Leptin
15.Çelik et al.2023	Turkey	RCT	Overweight	Female	23	64	19–32	TRF	Energy restricted	Adiponectin/Leptin
16.Czerwi ´ nska-Ledwig etal.2024	Poland	RCT	Obese	Female	25	6	21–85	TRF	Usual intake	Leptin/Resistin
17.Czerwi ´ nska-Ledwig etal.2024	Poland	RCT	Obese	Female	25	8	21–85	TRF	Usual intake	Leptin/Resistin
18.Keawtep et al.2024	Thailand	RCT	Overweight and obese	Female	41	12	45–59	IF	Usual intake	Adiponectin

Abbreviations: USA, United States of America; RCT, Randomized controlled trial; ADF, Alternate Day Fasting; TRF, Time Restricted Feeding; IF, Intermittent Fasting. FMD, fasting mimicking diet

Brazil [27], Italy [28–30], UK [31], Iran [19], China [16], Norway [32], Turkey [33], Poland [34] and Thailand [35]. the parallel study design was approved for all evidence including a non-intervention group (usual intake or energy-restricted). Overall, 593 persons, aged 18 to 85 years were considered in this investigation. the duration of the studies was between 3 and 64 weeks. The health status of the included studies was as follows: the participants in 7 studies were obese [16, 19, 23, 25, 27, 32, 34], 2 were overweight and obese [15, 35], 1 was overweight [33], 1 was normal weight and overweight [24], 2 were healthy [26, 31] and 2 were resistance-trained persons [28–30]. The intervention in Bhutani et al. [23], Varady et al. [24], Catenacci et al. [25], F. Trepanowskia et al. [15], Templeman et al. [31], studies were ADF and in T. Stratton et al. [26], Pureza M.S. et al. [27], Moro et al. [30], Moro et al. [28], Moro et al. [29], Zhang et al. [16], Çelik et al. [33] and Czerwi ´ nska-Ledwig et al. [34] investigations were TRF, in Sadeghian et al. [19] the study was FMD and in Castela et al. [32] and Keawtep et al. [35] studies were IFD.

Meta-analysis

Effects of FRs on leptin levels

By Pooling 16 effect sizes from 14 articles, including 463 participants, this result was obtained that FRs reduced leptin levels (WMD: −2.65 ng/ml, 95% CI: -3.86 to −1.44, $p < 0.001$).

compared with the control group. The result of the analysis showed that there is heterogeneity between the studies (I^2: 87.1%, $P < 0.001$) (Fig. 2). Subgroup analysis was conducted according to gender, country, number of participants, and study duration to specify the source of heterogeneity. The results revealed that gender (*P*:0.001) might be a source for heterogeneity: FRs had a significant effect on leptin levels in both sexes (WMD: −1.03 ng/ml, 95% CI: −1.08 to −0.66, I^2: 85.4%, $P < 0.001$) and female (WMD: −0.02ng/ml, 95%CI: −0.61 to 0.56, I^2: 71.1%, *P*: 0.008) but no such effect was found in those had done on male (WMD: −2.39, 95% CI: −4.5 to −0.28, I^2: 52.3%, *P*: 0.14) and also duration of studies ($P < 0.001$) might be a source of heterogeneity; FRs had significant effect on leptin levels in both studies with < 12 weeks duration (WMD: −0.81, 95% CI: −1.02 to −0.61, I^2: 79.3%, $P < 0.001$) and ≥ 12

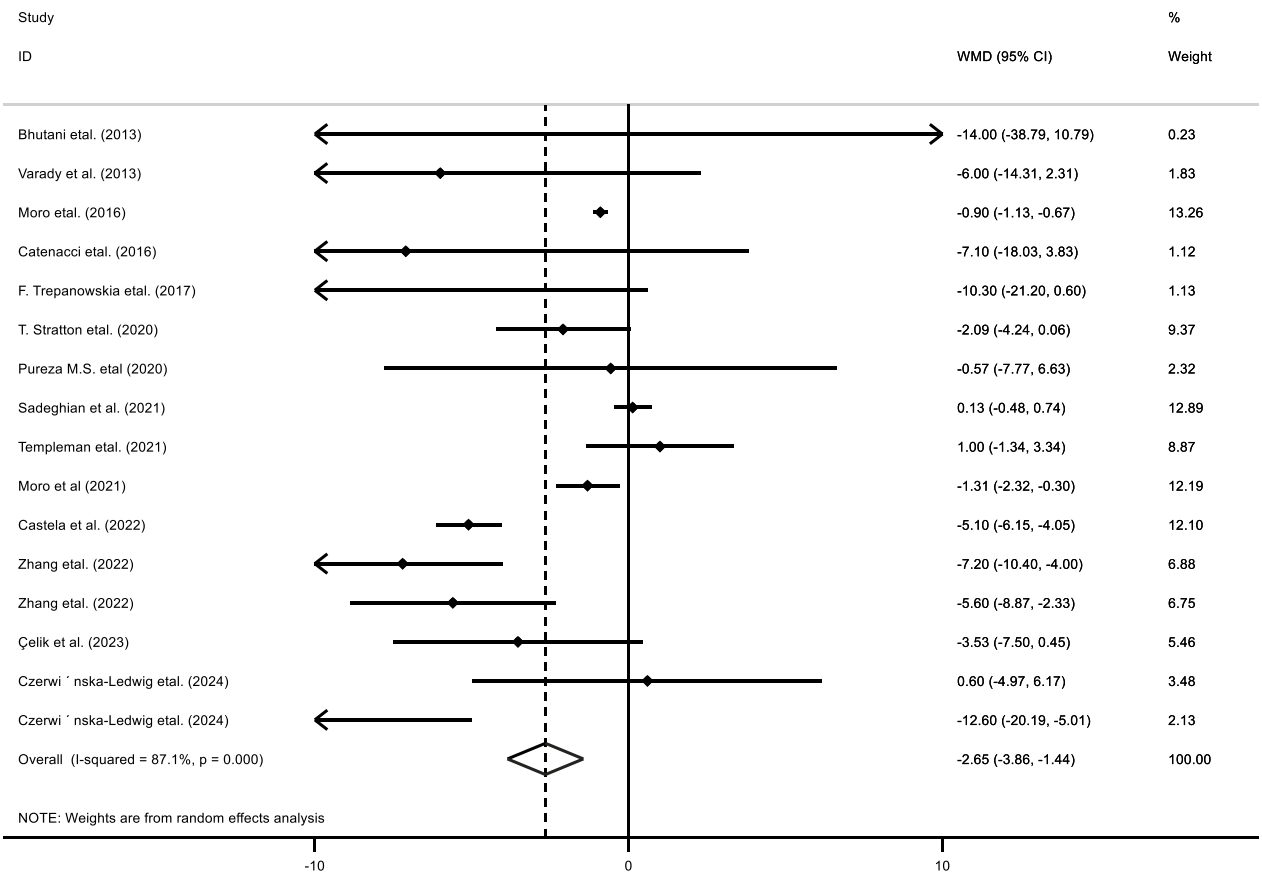

Fig. 2 Forest plot detailing weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of fasting regimen on leptin levels

Table 3 Subgroup analysis of included randomized controlled trials in meta-analysis of the effect of fasting regimen on hormone levels

Group	No.of.studies	WMD (95%CI)	*P* value	I^2(%)	P-heterogeneity	P for between subgroup heterogeneity	P for meta-regression
Adiponectin							
Duration							
< 12 week	5	0.04(-0.33 to 0.42)	0.82	48.1	0.08	**0.02**	0.18
≥ 12 week	6	0.76(0.27 to 1.25)	0.002	43.5	0.1		
Country							
US	4	0.41(-0.11 to 0.94)	0.12	49.5	0.11	0.64	0.86
Non-US	7	0.26(-0.1 to 0.62)	0.15	58.5	0.01		
Gender							
Male	1	0.28(-0.32 to 0.88)	0.36	< 0.001	0.51	**0.05**	0.5
Female	1	1.7(0.52 to 2.88)	0.005	56.5	0.13		
Both	9	0.19(-0.17 to 0.55)	0.29	52.7	0.03		
Number of participants							
≤ 50	10	0.28(-0.03 to 0.61)	0.08	56.5	0.008	0.73	0.99
> 50	1	0.43(-0.32 to 1.18)	0.26	0	0		
Leptin							
Duration							
< 12 week	8	-0.81(-1.02 to -0.61)	< 0.001	79.3	< 0.001	**< 0.001**	0.12
≥ 12 week	6	-3.2(-3.98 to -2.57)	< 0.001	82.8	< 0.001		
Country							
US	4	-2.84(-4.84 to -0.83)	0.005	4.4	0.38	0.07	0.4
Non-US	10	-0.99(-1.19 to -0.79)	< 0.001	90.8	< 0.001		
Gender							
Male	1	-2.39(-4.5 to -0.28)	0.02	52.3	0.14	**0.001**	0.85
Female	4	-0.02(-0.61 to 0.56)	0.92	71.1	0.008		
Both	9	-1.13(-1.34 to -0.91)	< 0.001	87.1	< 0.001		
Number of participants							
≤ 50	11	-1.15(-1.36 to -0.94)	< 0.001	87.8	< 0.001	**< 0.001**	0.41
> 50	3	0.09(-0.5 to 0.69)	0.76	43.5	0.17		
Ghrelin							
Country							
US	2	-0.51(-0.63 to -0.39)	< 0.001	61.8	0.1	**0.02**	0.39
Non-Us	1	-1.02(-1.43 to -0.6)	< 0.001	0	0		
Gender							
Male	1	0.06(-0.64 to 0.76)	0.86	0	0	**0.01**	0.67
Female	1	-1.02(-1.43 to -0.6)	< 0.001	0	0		
Both	1	-0.53(-0.64 to -0.4)	< 0.001	0	0		
Number of participants							
≤ 50	2	-0.51(-0.63 to -0.39)	< 0.001	61.8	0.1	**0.02**	0.39
> 50	1	-1.02(-1.43 to -0.6)	< 0.001	0	0		

Abbreviations: US, United States

weeks duration (WMD: − 3.2, 95% CI: − 3.98 to − 2.57, I^2: 82.8%, $P < 0.001$). we also did meta-regression and did not find any significance about these items. We have bolded the P-value of these items in Table 3.

Effects of FRs on adiponectin levels

Pooling 13 effect sizes of 12 studies, including 369 persons have shown the marginal significant positive effect of FR on adiponectin levels compared with the control

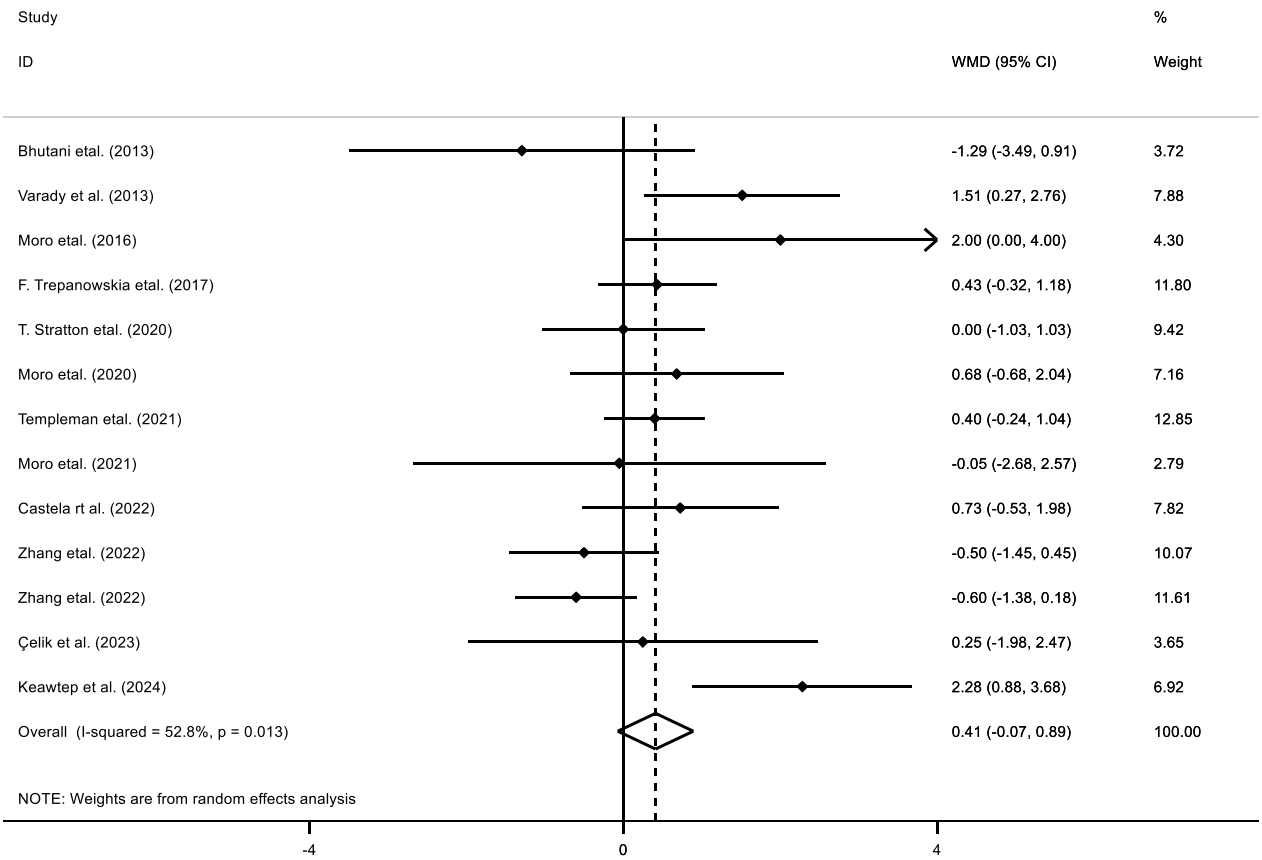

Fig. 3 Forest plot detailing weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of fasting regimen on adiponectin levels

diet (WMD: 0.41 µg/ml, 95% CI: −0.07 to 0.89, *P*: 0.09) and it seemed there was heterogeneity between investigations (I^2: 52.8%, *P*: 0.01) (Fig. 3). subgroup analysis was performed based on gender, country, number of participants, and duration of the study. Analysis revealed that the duration of studies might be a source of heterogeneity (*P*: 0.02) and a marginally significant effect of the FR on adiponectin levels within < 12-week period (WMD: 0.04, 95% CI: −0.33 to 0.42, I^2: 48.1%, *P*: 0.08) was conducted. Gender might be a source because it resulted in a marginal significant effect of FRs on adiponectin levels in gender subgroups (*P*: 0.05). In meta-regression, no significance was found about these items. We have bolded the P-value of these items in Table 3.

Effects of FRs on ghrelin and resistin levels

About ghrelin, we pooled 3 effect sizes of 3 documents (112 participants) and found a significant effect of FR on ghrelin levels, which decreased the levels of ghrelin (WMD: −0.57 ng/ml, 95% CI: −1.01 to −0.03, *P*: 0.01) and there was significant heterogeneity between studies (I^2: 74.9% *P*: 0.01) (Fig. 4). We conducted subgroup analysis and concluded that FRs had a significant effect on ghrelin levels in gender (*P*: 0.01), country (*P*: 0.02), and number of participants (*P*: 0.02) subgroups. Also, we conducted meta-regression and found no significance about these items. We have bolded the P-value of these items in Table 3. About resistin, we pooled 5 effect sizes from 4 studies (148 participants) that resulted in no significant effect of FR on resistin levels (WMD: −3.9 pg/ml, 95%CI: −7.9 to 1.72, *P*: 0.2) and also no significant heterogeneity between these documents (I^2: 53.5%, *P*: 0.07). (Fig. 5).

Sensitivity analysis

In this regard, the overall effect size of the effect of FR on the levels of leptin (WMD: −1.74 ng/ml, 95%CI: −2.63 to −0.85), adiponectin (WMD: 0.008 ng/ml, 95%CI: −0.001 to −0.06), ghrelin (WMD: 38.85 pg/ml, 95%CI: 3.6 to 74.1) and resistin (WMD: −3.09 pg/ml, 95%CI: −7.91 to 1.72) did not depend on single study.

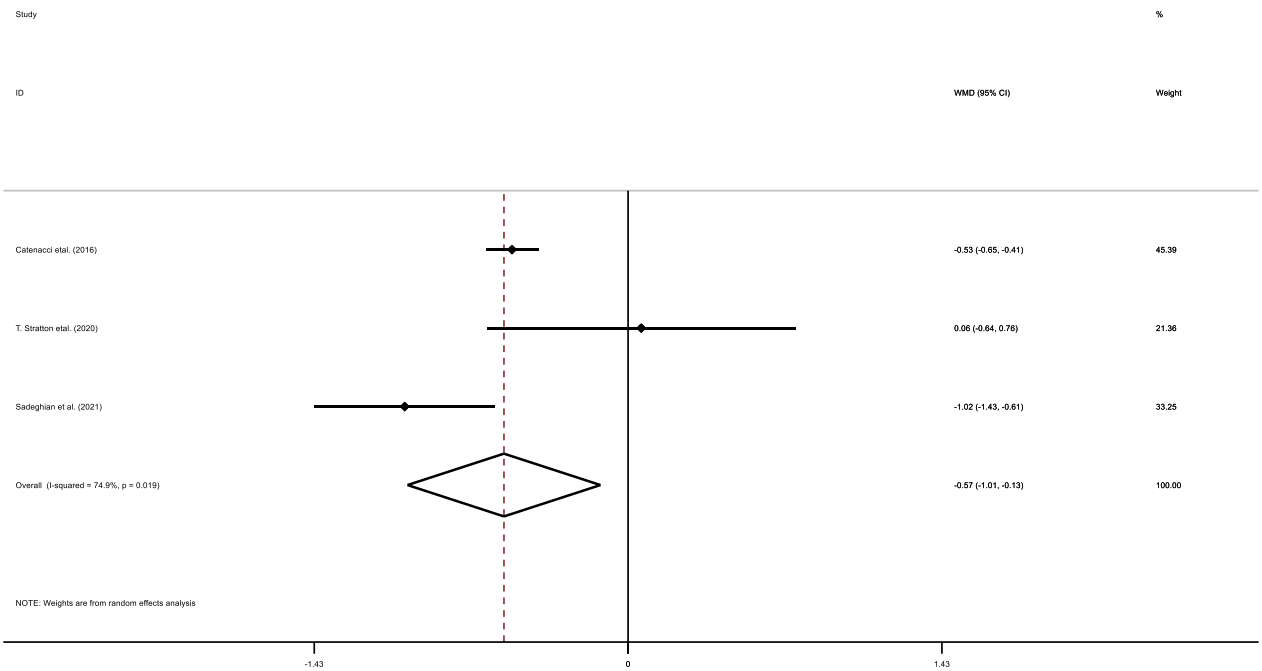

Fig. 4 Forest plot detailing weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of fasting regimen on ghrelin levels

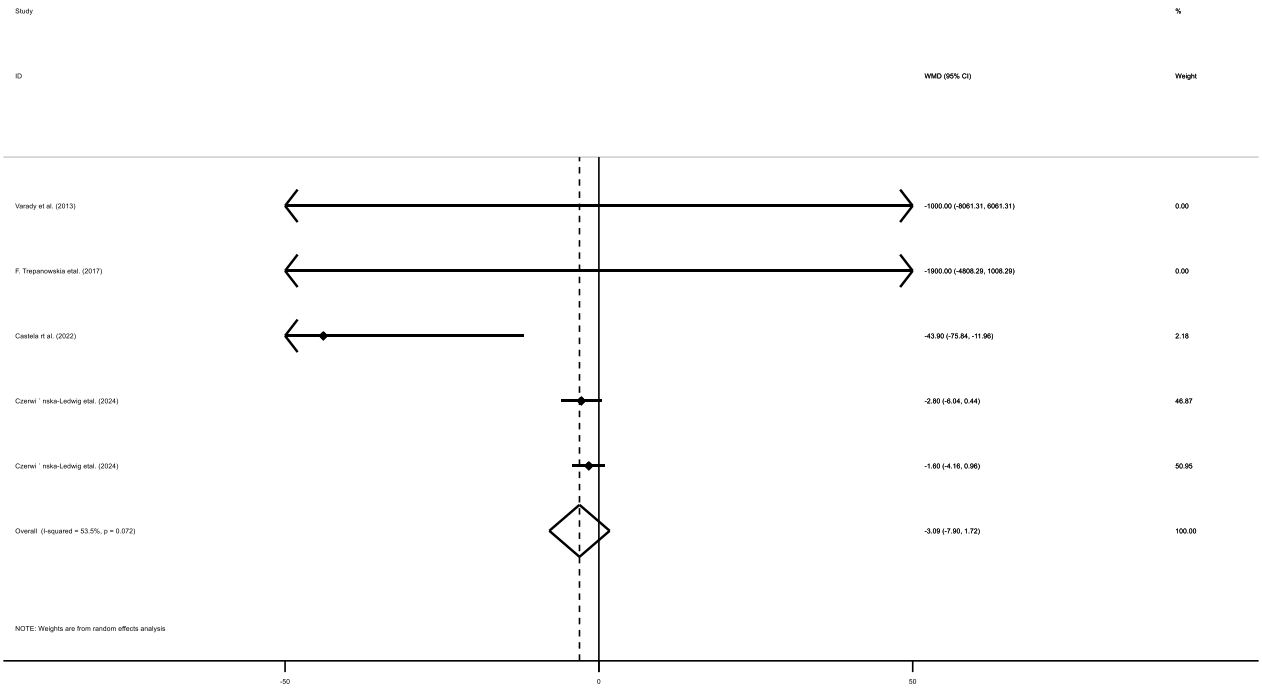

Fig. 5 Forest plot detailing weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of fasting regimen on resistin levels

Publication bias

Funnel plots visual evaluation obtained from SEs of effect sizes (WMD) showed that there was no asymmetry in this meta-analysis. These claims were approved by Egger's linear regression: leptin (*P*: 0.06), adiponectin (*P*: 0.66), ghrelin (*P*: 0.9), and resistin (*P*: 0.1). We have bolded the P-value of these items in Table 4.

Grading of evidence

The GRADE protocol was approved for assessing the evidence's certainty (Table 5). The studies on adiponectin and leptin were identified as high and ghrelin was recognized as moderate quality. The explanations for each component are as follows: For risk of bias, according to our reviews using the Rab2 tool, most studies scored low risk, and in a small number of them moderate, so we considered this component in the non-serious grade tool. Regarding inconsistency, the results for ghrelin showed high heterogeneity, which despite finding the source of heterogeneity, was not very credentialed due to the low number of studies, so we considered a serious score. Still, regarding adiponectin and leptin, there was high heterogeneity, the source of which was also identified, and the number of studies was sufficient for citation, so we considered a non-serious score. Regarding indirectness, all items, namely information related to interventions, study population, outcome, and comparison group, were correctly reported in all studies, so we considered a non-serious score. Regarding imprecision, a serious score was considered for all three variables due to the insufficient sample size of studies. The effect sizes have been bolded in Table 5.

Discussion

The present systematic review and meta-analysis of sixteen available RCTs evaluated the effects of various FRs, including IFD, ADF, TRF, and FMD on key weight-regulating hormones: leptin, adiponectin, ghrelin, and resistin. The results provide valuable insights into how these fasting approaches influence metabolic health and hunger regulation.

Summary of results

The findings revealed that FRs significantly reduced leptin levels, indicating a decrease in satiety signaling. For adiponectin, the pooled analysis indicated a marginally significant positive effect, suggesting a potential improvement in insulin sensitivity and anti-inflammatory responses. Ghrelin levels, associated with hunger, were significantly decreased, while resistin levels showed no significant change.

It is important to note that although significant effects of leptin and ghrelin were observed, subgroup analyses revealed substantial heterogeneity among studies. There are several factors that influence the pooled results, including the gender of the participants, the duration of the study, and geography. According to subgroup analyses, leptin reductions were greater in females in comparison to males, possibly due to hormonal interactions with estrogen that amplify the response of leptin to caloric restriction [36]. Additionally, adiponectin levels showed significant heterogeneity linked to study duration, with shorter interventions eliciting only marginal increases. Moreover, variations in geographic regions may be related to differences in dietary habits and genetic predispositions. These factors collectively underscore the multifaceted nature of fasting-induced hormonal changes and their dependence on individual and contextual variables. Specifically, leptin reductions were more pronounced in females and in studies lasting longer than 12 weeks, suggesting that both sex-specific hormonal interactions and prolonged fasting regimes may have an impact on results. Similarly, adiponectin levels demonstrated heterogeneity linked to study duration, with marginal increases predominantly observed in shorter-term interventions. There were also gender and country specific variations in the response of ghrelin to fasting regimens, reflecting the complex interplay between individual characteristics and fasting regimens.

The findings from this meta-analysis primarily focus on adults with overweight or obesity, and their applicability to other populations, such as those with metabolic disorders or different ethnic backgrounds, remains uncertain. Future studies should address these gaps in order to improve the generalizability of these findings. Moreover, practical guidance for implementing fasting regimens in clinical or public health settings is essential [37, 38]. For instance, recommendations could focus on the appropriate selection of fasting patterns, such as time-restricted eating versus alternate-day fasting, tailored to the metabolic needs and preferences of specific populations [39].

Table 4 publication bias assessment through Egger linear regression

	t	95%CI	*P*-value
Adiponectin	0.85	− 1.41 to 3.2	**0.66**
leptin	− 2.08	− 3.13 to 0.04	**0.06**
Ghrelin	− 0.05	34.63 to 34.34	**0.9**
Resistin	− 2.27	− 5.94 to 1	**0.1**

CI: Confidence Interval

Table 5 Certainty assessment

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients		Effect		Certainty	Importance
							fasting regimens	energy restricted or usual intake	Relative (95% CI)	Absolute (95% CI)		
Adiponectin (follow-up: range 4 weeks to 64 weeks; assessed with Kit)												
12	randomised trials	not serious	not serious	not serious	serious[a]	all plausible residual confounding would reduce the demonstrated effect	211	197	-	MD **0.41** **0.41 higher** (0.07 lower to 0.89 higher)	⊕⊕⊕⊕ High[a]	CRITICAL
Leptin (follow-up: range 3 weeks to 64 weeks; assessed with: Kit)												
15	randomised trials	not serious	not serious	not serious	serious[b]	strong association all plausible residual confounding would reduce the demonstrated effect	292	284	-	MD **2.65** **2.65 lower** (3.86 lower to 1.44 lower)	⊕⊕⊕⊕ High[b]	CRITICAL
Ghrelin (follow-up: range 6 weeks to 8 weeks; assessed with: Kit)												
3	randomised trials	not serious	serious[c]	not serious	Serious[d]	very strong association all plausible residual confounding would reduce the demonstrated effect	57	55	-	MD **0.57** **0.57 lower** (1.01 lower to 0.03 lower)	⊕⊕⊕⊕ moderate[c,d]	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations

[a] In some studies sample size were lower than estimated optimal sample size. [b]some studies had lower sample size in compare with evaluated optimal sample size. [c]about this variable, the number of studies were low and heterogeneity was high although the source of heterogeneity was investigated, it cannot be relied upon due to the small number of studies.[d]some studies' sample sizes were below of optimal sample size

Question: Fasting regimens compared to energy-restricted or usual intake for management of weight-regulating hormones

Setting: Normal-weight or obese adults

Practical recommendations for implementing fasting regimens in clinical or public health settings should also be developed [40, 41]. It may be necessary to provide guidelines for the duration, timing, and intensity of fasting protocols tailored to each individual's metabolic profile and lifestyle.

Comprehensive analysis of results, clinical implications, practical guidance, and influencing factors

The present meta-analysis highlights several factors that may have influenced the observed results, providing a nuanced understanding of the impact of FRs on appetite-regulating hormones. The observed hormonal changes have significant clinical implications, particularly for obesity management and metabolic health [42, 43]. Reductions in leptin levels and increases in adiponectin levels may enhance insulin sensitivity and promote weight loss [44]. However, the observed decrease in ghrelin, while potentially beneficial for reducing hunger signals in the short term, raises concerns for long-term adherence to fasting regimens. Increased levels of ghrelin play an important role in hunger signaling, and their suppression might make it more difficult to maintain a regular fasting schedule over the long term [45]. Effective strategies to counterbalance potential challenges related to ghrelin modulation, such as combining fasting with behavioral or dietary interventions, should be considered. These factors include variations in baseline metabolic health, differences in fasting protocols (e.g., duration, caloric intake, and timing), and participant demographics such as gender and age. For example, the pronounced effects on leptin in females might reflect hormonal interactions with estrogen, while shorter-duration fasting regimens appear to have a more transient impact on adiponectin levels [46]. Geographic differences may also play a role, as dietary habits, genetic predispositions, and cultural factors could modulate hormonal responses to fasting. Furthermore, the variability in ghrelin levels may be partly attributed to individual differences in gut microbiota composition, which is increasingly recognized as a critical factor in energy homeostasis and hunger regulation [47]. By considering these factors, this analysis underscores the complexity of fasting-induced hormonal changes and the need for tailored approaches to optimize metabolic outcomes.

Comparison with other studies

In general FR, as a diet approach that has an increasing reputation, consists of two periods of fasting and feeding, each of which can change in different forms of this regimen [48]. The results of this meta-analysis align with previous studies showing that IF reduces leptin levels. For example, studies by Heilbronn et al. [49] and Varady et al. [50] reported similar reductions in leptin under fasting conditions, suggesting that FR reduces energy intake and body fat mass, resulting in less leptin production. In 2024, Kazeminasab et al. conducted a systematic review and meta-analysis on 153 participants to evaluate the effects of IF combined with exercise on serum leptin and adiponectin in adults with or without obesity. This study suggested that IF combined with exercise training reduced leptin significantly, but did not change adiponectin levels when compared to exercise only [51]. In contrast, the marginal increase in adiponectin levels observed in this analysis has been inconsistent in the literature. Some studies, such as those by Klempel et al. [52], found no change in adiponectin following intermittent fasting, suggesting that variations in study design, participant characteristics, and fasting protocols may influence the outcomes [53]. However, the result of a systematic review and meta-analysis by Kord et al. [54] on Ten RCTs, show that that fasting and energy restriction, to $\leq$ 50% of normal required daily energy intake, resulted in significantly increased concentrations of adiponectin.

The reduction in ghrelin levels contrasts with the expected increase associated with fasting, as described by Cummings et al. [55]. This divergence may reflect specific adaptations in hunger-regulating mechanisms unique to the fasting protocols analyzed. The observed ghrelin reduction might indicate a compensatory mechanism to improve adherence to fasting regimens by mitigating excessive hunger signals [56]. However, the lack of a significant change in resistin is also congruent with other studies that found little to no effect of fasting on resistin, which is typically more closely linked to inflammatory states than dietary patterns [57, 58]. This study highlights that resistin levels are more closely linked to inflammation rather than changes in diet, which supports the observation that intermittent fasting may not significantly alter resistin levels [57].

Mechanisms

Several physiological mechanisms can explain the observed effects of FR on these hormones. First, leptin, secreted by fat cells in direct proportion to the amount of body fat, plays a central role in energy homeostasis. When fat stores or adipose tissue decrease, as occurs during caloric restriction or fasting, leptin levels drop. This decrease signals the hypothalamus to stimulate hunger and reduce energy expenditure to maintain energy balance and prevent further fat loss [59, 60]. The body's response to reduced leptin levels reflects an adaptive mechanism aimed at conserving energy during times of caloric deprivation. [61, 62].

Adiponectin, which is involved in enhancing insulin sensitivity and reducing inflammation, may increase

during fasting as a compensatory mechanism to improve metabolic efficiency in the face of reduced caloric intake [63, 64]. Elevated adiponectin levels could help counteract insulin resistance and support glucose homeostasis, particularly in populations at risk of metabolic disorders [65, 66]. Adiponectin plays a crucial role in regulating glucose levels and fatty acid breakdown in the body [67]. Higher levels of adiponectin are associated with improved insulin sensitivity, which helps in preventing type 2 diabetes [68]. Moreover, it possesses anti-inflammatory properties that can protect against cardiovascular diseases and other metabolic conditions [69]. The marginal effects observed in shorter-duration studies suggest that prolonged fasting may be necessary to elicit more robust changes in adiponectin levels.

Ghrelin, often termed the "hunger hormone," is primarily secreted by the stomach and functions to stimulate appetite and regulate energy homeostasis. Typically, ghrelin levels rise during fasting as a physiological signal to promote food intake and maintain energy balance [55]. However, the observed decrease in ghrelin levels in this meta-analysis may reflect adaptive mechanisms specific to prolonged fasting protocols. One plausible explanation is the downregulation of ghrelin secretion due to alterations in gastric hormone dynamics triggered by sustained caloric restriction. This could also involve changes in the gut-brain axis, where decreased ghrelin signaling may reduce hunger perception and facilitate dietary adherence [70]. Moreover, some studies suggest that fasting-induced shifts in the gut microbiota composition may influence ghrelin regulation, further contributing to reduced hunger signals. These mechanisms collectively underscore how fasting regimens may suppress ghrelin as part of a complex adaptive response aimed at optimizing energy utilization and promoting metabolic stability during extended periods of caloric deprivation.

The lack of significant change in resistin suggests its primary role as an inflammatory marker rather than one influenced by short-term dietary interventions. This finding underscores the limited impact of fasting regimens on inflammatory pathways linked to resistin. The stability of resistin levels across diverse fasting protocols suggests that its regulation may be more closely tied to chronic inflammation rather than acute dietary changes [71, 72].

Strengths and weaknesses of this study

One strength of this meta-analysis is its inclusion of a wide range of studies from various countries, participant demographics, and fasting protocols, enhancing the generalizability of the findings. The robust sensitivity analysis and lack of publication bias further strengthen the credibility of the results. It also provides many clues about the impact of this diet on hormone levels to conduct further studies to achieve more solid results. Additionally, the integration of the GRADE framework to evaluate evidence certainty highlights the reliability of findings, with leptin and adiponectin studies classified as high quality, enhancing confidence in the results. However, the moderate quality of ghrelin studies indicates areas for improvement, such as increasing sample size and addressing heterogeneity across studies, to strengthen the overall evidence base.

However, several limitations should be acknowledged. The substantial heterogeneity observed across studies, stemming from differences in design, participant characteristics, and fasting protocols, limits the precision of pooled estimates. Furthermore, the relatively small number of studies included for certain hormones, such as ghrelin and resistin, may reduce the statistical power and limit the ability to draw definitive conclusions about these hormones. Another potential limitation is the lack of long-term data, as most studies had a relatively short duration, making it difficult to assess the long-term hormonal effects of intermittent fasting. Further research must be conducted to close these gaps by standardizing fasting protocols, including larger and more diverse RCTs and also cohorts, and extending the duration of studies. Additionally, future research should also explore the potential interactions between fasting regimens, gut microbiota composition, and genetic factors to better understand the underlying mechanisms driving hormonal changes.

Conclusion

In conclusion, FRs significantly reduced leptin and ghrelin levels and marginally increased adiponectin, while resistin remained unaffected. These findings underscore the potential of fasting regimens to modulate appetite-regulating hormones, contributing to metabolic health benefits. However, observed heterogeneity highlights the need for personalized approaches to fasting interventions. The sex-specific and temporal variations observed in hormonal responses suggest that tailoring fasting protocols to individual characteristics may enhance their efficacy.

Future research should prioritize long-term studies to elucidate the sustained hormonal effects of FRs, with a particular focus on sex-specific and geographic differences. Larger trials are essential to clarify the impact on resistin and to further explore the mechanisms underpinning these hormonal adaptations. These efforts will be critical in optimizing fasting protocols as viable dietary strategies for metabolic health. Moreover, integrating molecular and genetic analyses could provide deeper

insights into individual variations in response to fasting, paving the way for precision nutrition approaches.

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AT, BPG designed the study; and AT, BPG did the literature search and screening data; AT and MVB conducted data analysis; and AT, MVB, PZ performed data extraction; and FT did quality assessment; independently; and all authors participated in writing the article; and all authors read and approved the final manuscript.

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