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Title

EFFECT OF DIET COMBINED WITH EXERCISE INTERVENTION ON TUMOR NECROSIS FACTOR A IN OVERWEIGHT OR OBESE GROUPS: BASED ON THE EXERCISE DOSE-RESPONSE RELATIONSHIP.

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Abstract

Background: Chronic low-grade systemic inflammation, often linked to obesity or being overweight, is associated with various complications and an increased risk of disease development. Tumor necrosis factor α (TNF-α) is a key inflammatory factor that significantly impacts various body functions.

Objective: 1) To assess whether combined interventions are more effective than single interventions in combining diet and exercise. 2) To assess the effectiveness of exercise dose in different interventions on tumor necrosis factor (TNF-α) levels in obese or overweight patients.

Methods: A thorough search was conducted across four electronic databases of randomized controlled trials that focus on exercise or dietary interventions for patients with obesity or overweight. This comprehensive review encompasses data collected up to August 2024. Two independent researchers conducted a thorough evaluation of the literature's quality. Network and dose-response analyses were performed using random effects models to examine the impact of diverse interventions on TNF-α.

Results: A total of 19 randomized controlled trials with 1479 patients with obesity or overweight were included. The meta-analysis showed that the hypocaloric diet combined with aerobic training (HDAT) possessed the highest ranking (SMD= -1.00,95%CI -1.51 to -0.49), followed by the hypocaloric diet (HD) (SMD= -0.40,95%CI -0.89 to 0.09), hypocaloric diet combined with resistance training (HDRT) (SMD= -0.48,95%CI- 1.43 to 0.48), and aerobic training combined with resistance training (ART) (SMD= -0.18,95%CI -0.92 to 0.57). Additionally, a notable improvement in TNF-α levels was observed in individuals adhering to a hypocaloric diet in conjunction with exercise when the cumulative exercise volume reached 150 metabolic equivalent of task minutes per week.

Conclusion: Based on the GRADE rating guidelines, moderate-quality research evidence indicates that a hypocaloric diet combined with aerobic training (HDAT) is the most effective intervention for enhancing tumor TNF-α levels in individuals with obesity or overweight. Additionally, the dose-response relationship was observed between the total exercise dose and TNF-α levels. Future research should investigate the specific effects of various aerobic exercise modalities on TNF-α levels in obese or overweight patients to develop a more personalized approach to exercise prescription.

Keywords: Combination therapy, Exercise, Dose-response relationship, Obese population, Inflammatory factors

1 Introduction

The issue of global obesity is currently a matter of significant international concern. In China, a census encompassing nearly 600 million individuals revealed that over 300 million are overweight or obese, with the prevalence of obesity continuing to increase[1]. Concurrently, the prevalence and incidence of chronic diseases or illnesses associated with obesity are on the rise. These include cardiovascular disease, type 2 diabetes, asthma, cancer, arthritis or joint pain, and Alzheimer's disease[2]. This has the additional detrimental effect of impeding the physical health of patients, while also placing an unavoidable burden on society and the healthcare system [3]. Chronic low-grade systemic inflammation is recognized as a contributing factor to the etiology of numerous diseases associated with obesity. The primary mechanism involves the disruption of the body's inflammatory equilibrium, which is influenced by the secretion of adipocytokines that occurs in the context of obesity[4]. Therefore the search for simple and efficient methods of weight loss and de-inflammation has become inevitable in the clinic.

Tumor necrosis factor α (TNF-α) is a pro-inflammatory cytokine that is synthesized in response to an increase in adipocyte numbers and the onset of hyperplasia associated with obesity. This enables the infiltration of inflammatory cells and activates the immune system, leading to the release of pro-inflammatory adipocytokines.[5–7]. TNF-**α** is commonly present in the body at levels that can be regarded as a "threshold" concentration. When activated locally in tissues, this concentration can yield beneficial effects. However, in individuals with excess body fat, TNF-**α** is released in greater quantities throughout the body, which is associated with significant health risks. Sustained cytokine dysregulation resulting from obesity has been shown to have

detrimental effects on overall health[8]. TNF-α levels have been previously employed as a means of predicting disease, disability, and mortality in the elderly[9]. Early research identified tumor necrosis factor as a significant contributor to cardiovascular disease. This factor is fundamental to understanding the relationship among obesity, atherosclerosis, and insulin resistance[10]. The substantial release of obesity-related adipokines presents a significant challenge to the effective management of obesity and diabetes. There is a growing need to investigate pharmacological or physiological treatments that specifically target these adipokines, as this approach holds potential as a novel therapeutic strategy for diabetes management[11]. The studies on asthma prevalence in obese individuals found significantly higher levels of TNF-α in obese subjects compared to non-obese individuals, indicating a strong correlation between TNF-α and asthma[12,13]. Furthermore, TNF-α has been identified as a risk factor for neurodegenerative diseases, as well as for sarcopenia and weakness[14]. For instance, TNF-α has been associated with the onset of nerve root pain resulting from disc degeneration, a condition frequently linked to a sedentary lifestyle[15]. A comprehensive study with a large sample size demonstrated that the levels of TNF-α were significantly elevated in community-dwelling older individuals who exhibited frailty and sarcopenia compared to their counterparts who were robust and non-sarcopenic[16]. In conclusion, if obesity-induced diseases are considered a class of inflammatory diseases, then anti-inflammatory treatments for inflammation should have an important place.

Numerous studies have previously explored the effects of dietary control and exercise on TNF-α levels in obese populations. For example, a non-invasive study highlighted the acute inhibitory impact of exercise on TNF-α. Additionally, a follow-up study confirmed the long-term inhibitory effects of exercise on TNF-α in obese patients with coronary artery disease[17,18]. The most commonly prescribed forms of exercise are aerobic, resistance, high-intensity interval training, and some traditional sports[19]. Calorie restriction is also a common component of dietary regimens employed in the treatment of obesity [20,21]. Dietary regimens including the hypocaloric diet, the time-restricted eating diet, and the special Mediterranean diet plan (PREDIMED) have shown good efficacy in reducing body weight and inflammatory factor levels[22–24]. The integration of dietary management and physical exercise as a comprehensive therapeutic approach for the treatment of obese patients has emerged as a valid and effective strategy[25,26]. Additionally, a partial meta-analysis investigated the effects of combining exercise with dietary interventions on inflammatory factors in obese populations. The findings indicate that, among these individuals, a combined approach of exercise and dietary therapy may be more effective than dietary therapy alone in reducing inflammatory cytokines[27,28]. However, this part of the study did not analyze the amount and duration of exercise, in addition to the mode of exercise, which has previously been demonstrated to have a potential dose-response relationship with the level of body markers[29]. It can be reasonably deduced that it is of significant importance to evaluate the impact of exercise modality and dosage in conjunction with dietary control on TNF-α levels in the obese population. Therefore, we performed a Bayesian model-based (NMA) network with dose-response meta-analysis to assess the effects of different exercise modalities and doses in dietary and exercise interventions on TNF-α in an obese population. Furthermore, the objective is to investigate how different variables may influence the effectiveness of intervention outcomes.

2 Method

This trial has been pre-registered with PROSPERO (CRD42024590494), and the procedures described in this article adhere to the latest PRISMA statement, PERSiST guidelines, and the Cochrane Handbook[30,31]. The quality of the included articles was assessed using the GRADE grading system to evaluate the quality of the meta-analysis results[32].

2.1 eligibility criteria and information sources

PubMed, Web of Science, and SPORTDiscus databases were utilized. The search terms included ‘exercise intervention’, ‘dietary control’, ‘nutritional intervention’, ‘combination therapy’, and ‘inflammation’. Studies published through August 2024 were searched. See Supplementary Material for details.

Inclusion criteria: 1) Participants had to engage in a specific type of exercise modality (aerobic exercise, resistance exercise, combined exercise games, or traditional Chinese exercise) and complete a standard training cycle and program; 2) The intervention had to include a complete dietary control program or nutritional intervention. Both were required; 3) Included studies were randomized controlled trials, excluding low-quality crossover controlled trials. Qualitative studies of potential relevance were included as part of the systematic review; 4) Studies were required to include a blank control group, a placebo group, an exercise-only control group,

or a diet-only control group; 5) Inflammatory marker indicators had to include TNF-α as an outcome indicator in the research literature.

Exclusion criteria: 1) Studies that included only exercise interventions or only diet control interventions; 2) Studies in which there were significant differences in subjects baseline or outcome data that were not effectively controlled for by the experimenter; 3) The presence of a third interventions (pharmacological interventions, physical therapy interventions, nicotine interventions) in addition to exercise and diet interventions.

2.2 selection process

The selection of studies went through a two-stage process in which two evaluators independently evaluated each other to determine the inclusion of citations. The first stage consisted of an initial evaluation of the titles and abstracts of the literature base that had been searched by the system described above. Articles were included in the first version of this study if the title and abstract identified that the content of the article was relevant to exercise or dietary control in obese individuals. Subsequent inclusion in the study was read and assessed through the full text by two evaluators. The title and abstract screening, as well as the full-text screening processes, were conducted independently by two evaluators, C. W. and L. S. Any disagreements were resolved by a third evaluator, J. L. The decision to include an article in this study was based on an assessment of the title, abstract, and full text. Notably, no automated tools were utilized for identification or screening at any stage of the process.

2.3 data collection process and data items

Two assessors (C.W. and L.S.) conducted independent data extraction from studies that fulfilled the established inclusion criteria. Means (M) and standard deviations (SD) were extracted directly from the text where data were available from research articles. Data extraction tools used included PlotDigitizer and the Cochrane Collaboration's tool for converting medians and interquartile ranges and finding standard deviations[33,34]. Data information extracted included author, publication year, demographic characteristics (gender, age, participants number ,weight or BMI), mode of intervention (mode of intervention, duration, frequency, intensity), and other relevant outcome indicators. In the case of the unavailability of data from a research article, a formal email request was sent to the relevant author.

To specifically measure the dose effect of exercise interventions, we utilized the metabolic equivalents task (MET) as a measure of the amount of exercise intervention. Metabolic Equivalent Task (MET) = single exercise session time * weekly exercise frequency [35]. The single exercise time was expressed as the actual exercise time of each exercise intervention, excluding the warm-up time and the rest time of the intervals to express the total single exercise time. Due to the ambiguity surrounding the actual duration of exercise and the variations in exercise time, the average total exercise duration was used to represent individual exercise sessions. Weekly exercise frequency was defined as the total number of exercise interventions conducted each week, while the overall exercise intervention was expressed in METs-min/week[36,37]. Final classification of weekly METs-min/week into 6 categories: 150, 240, 360, 540, 1440, and 0 (placebo) to facilitate network connectivity analysis and dose network analysis[38].

2.4 study risk of bias assessment

Risk of bias analysis was performed by two reviewers (C. W. and L. S.) using the Cochrane Risk Assessment Tool to assess the included studies[39]. We assessed risk in six areas: 1) selection bias, 2) performance bias, 3) detection bias, 4) attrition bias, 5) reporting bias, 6) other bias. The GRADE methodology was employed to assess the quality of evidence pertaining to the outcomes of various interventions. Any discrepancies that arose were resolved by a third reviewer (J.L.)[40].

2.5 effect measures and synthesis methods

The change in standardized mean difference (SMD) and standard deviation (SD) from baseline was utilized to calculate the effect size within a single study, enabling the combination and comparison of various outcomes assessed. Statistical analyses were conducted using R software and STATA 18.0. We initially conducted a paired

control meta-analysis comparing various intervention models using a random effects model. The combined effect sizes were reported along with 95% confidence intervals, calculated based on the standardized mean difference (SMD) of the intervention effects. To assess heterogeneity among the studies, we utilized the Cochrane Q p-value and the I^2 statistic, designating studies as highly heterogeneous if $p < 0.05$ and $I^2 > 50\%$. Furthermore, potential publication bias was evaluated through funnel plots, along with Egger's test and Begg's test, using STATA 18.0 software. A sensitivity analysis was also performed with STATA to investigate the impact of small sample sizes associated with a high risk of bias on the overall intervention effect.

Changes in standard deviation were estimated using the formula outlined in the Cochrane Handbook. For the calculation of standard deviation (SD) differences, a correlation coefficient of $r = 0.5$ was employed, reflecting a moderate level of measurement reproducibility that is widely accepted in the literature. When data were presented as standard errors (SE), SD values were computed using the Finding Standard Deviations Tool, developed by Amy Drahota and Elaine Bellor, which is based on the calculations provided in the Cochrane Handbook. If the data are provided as means and interquartile ranges, the mean difference (MD) and SD values can be calculated using the interquartile range conversion tool.

2.5.1 Network Meta-analysis

Network meta-analysis using the Metainsight tools(version 5.0.1) for Bayesian NMA[41]. First, we transformed the raw data from the included studies into a format compatible with the MBNMAdose program package in the R statistical environment, utilizing STATA. Next, we assessed the intervention characteristics of these studies along with the baseline participant information to evaluate the transferability assumptions, looking for evidence of connectivity within the network. We then created network plots to visualize the specific effects of the various exercise modalities included in the review. Additionally, we employed the Metainsight tools to generate cumulative sorted area under the curve (SUCRA) values for the different interventions and to construct the corresponding Mori plots. We produced Mori plots with both the control group and the hypocaloric diet to analyze the effects of the exercise group, the diet group, and the combined diet and exercise group, respectively. The SUCRA values were 0-100, with higher SUCRA values indicating that the treatments were approximately effective[42].

2.5.2 Dose-response analysis

The dose-response analysis was performed using the MBNMAdose package in the R software, and the ggplot2 package was used to plot and organize the dose-response curves. A Bayesian random effects model was used to analyze the relationship between exercise and TNF-α at different doses. First, the included intervention modalities and data were examined for dose-response relationships and whether the data response curves were linear. After testing, there was evidence that this study met the MBNMA assumptions of network transmissibility, data consistency, and network connectivity[43,44]. Second, the provided data were modeled as dose-response based on the dose-response function and output using the “mbnma.run” command. In this study, parametric dose-response modeling (Emax) and nonparametric response modeling (Nonparam) were used for analysis and comparison, respectively[45]. The dose-response model was then reestimated, and the fit of the model to the data was assessed using a deviation plot and a plot of fitted values to determine whether the model was a good fit for the included data. The treats function was then used to estimate relative effects and perform rank ranking analysis, and the corresponding histograms of ranking results and SUCRA ranking curves were plotted. Comparisons were also made with the SUCRA ranking plot generated by the Metainsight tool above to assess accuracy. Finally, a prediction curve was plotted with an exercise dose of 0 METs-min/week as the placebo response and a 95% confidence interval excluding 0 as statistically significant. Extrapolate potential effects of interventions using 95% prediction intervals as a range of possible response changes to future outcomes[46].

2.5.3 Network Regression Analysis

We hypothesized that all interventions would have a treatment effect. Mean age, year of publication, sample size, intervention duration, male/female ratio, number of calories restricted by diet (kcal/d), and intervention dose were included as possible potential effect variables. Missing data were imputed with means. Effect sizes were estimated using the B coefficient of the model, with 95% confidence intervals not including 0 representing statistical significance.

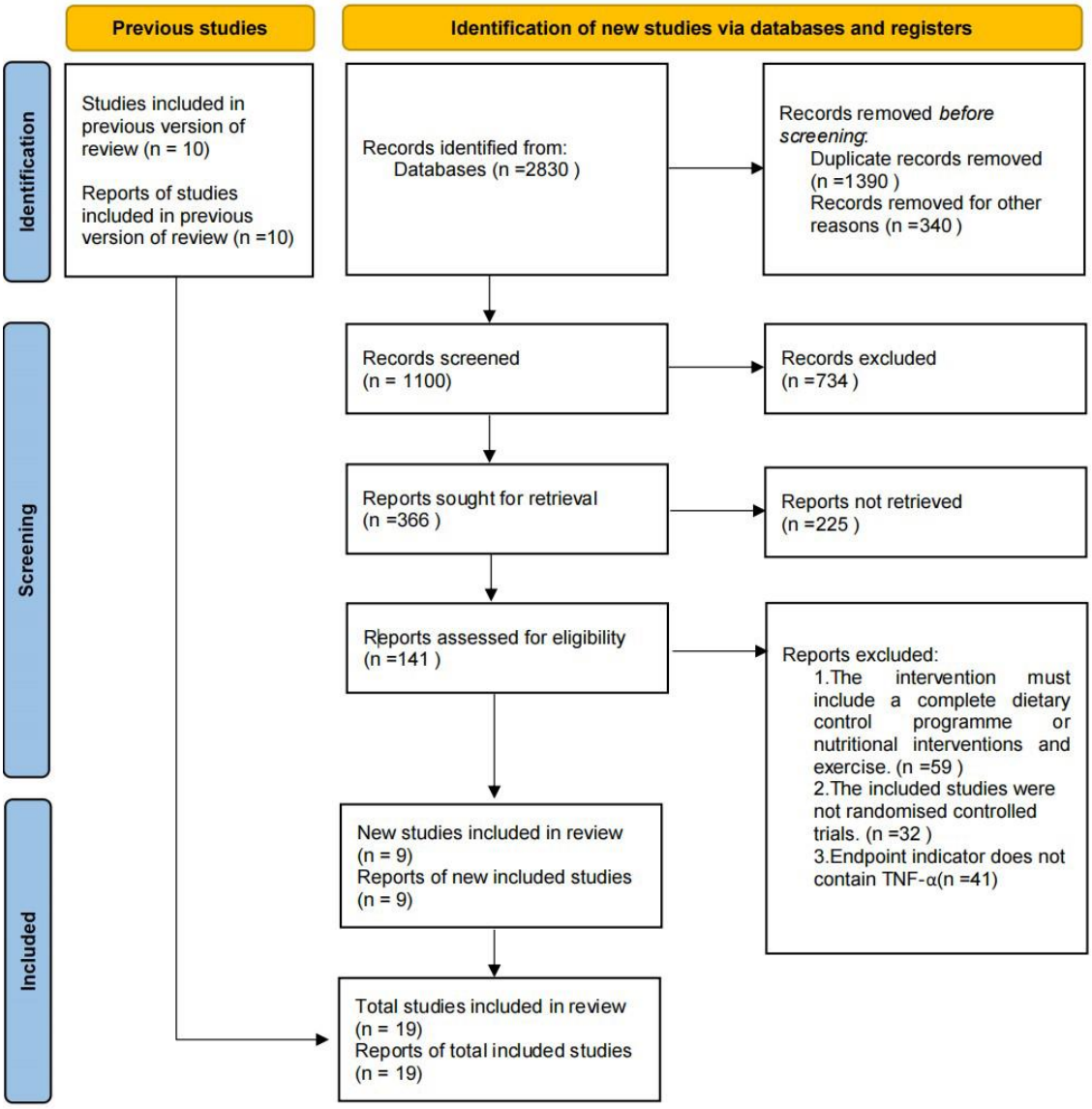
3. Results

3.1 study selection and characteristics

A total of 2,830 articles were retrieved from electronic databases. Following the screening of titles and abstracts, 141 articles were subjected to full-text evaluation. After a collaborative assessment conducted by three reviewers, 132 articles were excluded from consideration. Consequently, 19 randomized controlled trials (RCTs) were incorporated into the network meta-analysis[21–23,25,26,47–60]. A total of 1,479 subjects participated in this study, comprising 724 females, which accounts for 48.95% of the overall sample. (Fig.1)

The characteristics of the included studies are shown in Supplementary Materials. All subjects were overweight or obese. Exercise interventions included aerobic exercise (e.g., walking, cycling, swimming) followed by resistance training. The dietary interventions were the hypocaloric diet (HD), the very low-calorie diet (VLCD), or time-restricted eating (TRE). Fourteen studies totaling 341 subjects received the hypocaloric diet (HD). 13 studies totaling 457 subjects received the hypocaloric diet with aerobic training (HDAT). 3 studies totaling 81 subjects received the hypocaloric diet with resistance training (HDRT). Three studies with a total of 102 subjects received the hypocaloric diet with aerobic training and resistance training (HDART). One study with 12 subjects received the increased diet with aerobic training (IDAT). 6 studies with 115 subjects received aerobic training (AT). Three studies with a total of 46 subjects received resistance training (RT). A total of 80 subjects participated in two studies that focused on aerobic training and resistance training (ART). Additionally, six studies involving 245 subjects served as a control group (CG). The publication years of the included studies varied from 2004 to 2021, with a median publication year of 2012. Exercise interventions occurred between 1 to 6 times per week, with each session lasting from 30 to 240 minutes, resulting in an average duration of 83.1 minutes.

Fig.1: PRISMA 2020 flow diagram.



3.2 results of individual studies and syntheses

3.2.1 Network meta-analysis results

Figure 2 illustrates the results of the paired comparisons among the various interventions. Compared to the control group (CG), four out of eight interventions (50%) demonstrated a potential effect in reducing tumor necrosis factor in the obese population. Notably, one intervention, HDAT (SMD: -1.00, 95% CI -1.51 to -0.49), exhibited a significant impact on lowering tumor necrosis factor levels. When analyzing the combined interventions in relation to the single dietary control, only HDAT (SMD: -0.6, 95% CI -0.99 to -0.2) and HDRT (SMD: -0.08, 95% CI -0.96 to 0.8) were likely to show a significant effect on TNF-α reduction.

Figure 3 shows the main evidence for specific interventions. The SUCRA curves were used to visualize the treatment effects of the different interventions. The SUCRA value of 97.45% for HDAT was clearly superior to

the other interventions. This was followed by HD with a SUCRA of 70.32%, HDRT with a SUCRA of 66.79%, ART with a SUCRA of 63.08%, CG with a SUCRA of 57.72%, AT with a SUCRA of 35.39%, RT with a SUCRA of 27.76%, HDART with a SUCRA of 27.24%, and IDAT with a SUCRA of 4.25%. As shown in Table II, compared with the control group, HDAT(SMD:-1.00, 95%CI -1.51 to -0.49), HD(SMD:-0.40,95%CI -0.89 to 0.09), HDRT(SMD:-0.48, 95%CI -1.43 to 0.39), ART(SMD:-0.18, 95%CI -0.92 to 0.57), HDART(SMD:-0.13, 95%CI -0.84 to 0.58), AT(SMD:-0.33, 95%CI -1.43 to 0.76), IDAT(SMD:-0.66, 95%CI -2.29 to 0.98).

Figure 2: Forest plot comparing the effects of different interventions on TNF-α. (based on HD and CG, respectively)

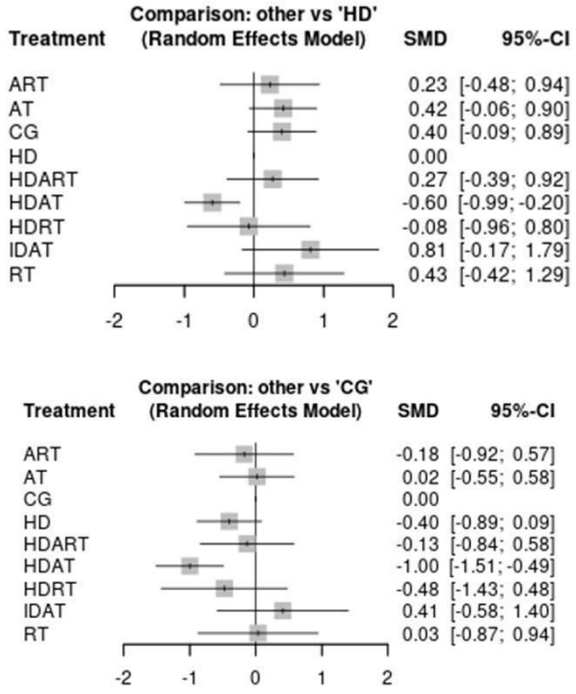
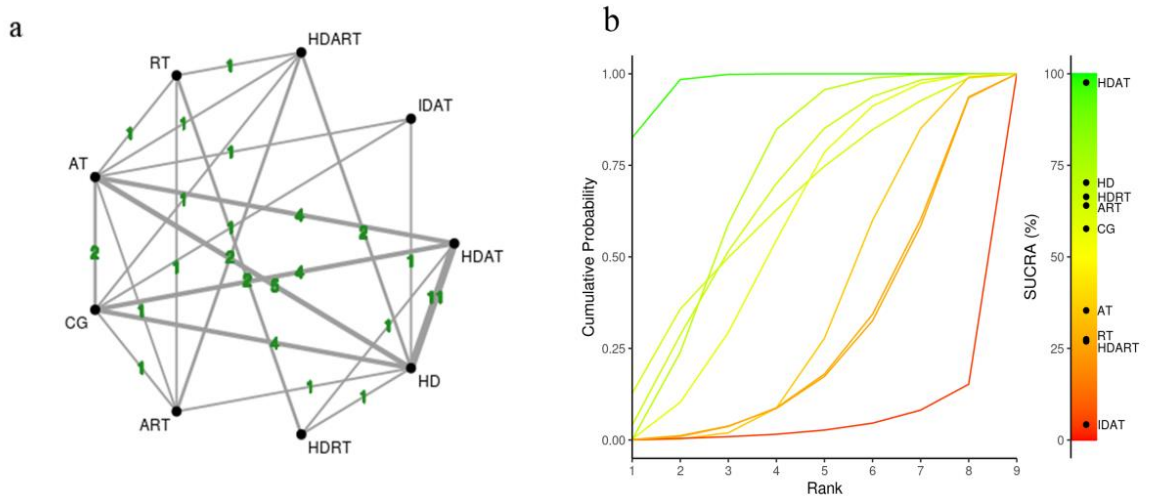


Table 2: Pooled table comparing direct and indirect effects of various interventions on TNF-α. (Data in the table are presented as standard mean difference (SMD) along with 95% confidence intervals. For post-intervention effects, a mean difference of less than 0 indicates a preference for TNF-α treatment. The interventions are organized based on SUCRA surface scores.)

HDAT	-0.35 [-0.83; 0.12]	-0.56 [-2.03; 0.91]	.	.	-1.63 [-2.40; -0.86]	.	-1.02 [-1.89; -0.16]	.
-0.60 [-0.99; -0.20]	HD	-0.30 [-1.79; 1.18]	0.11 [-1.35; 1.57]	0.38 [-0.67; 1.44]	-0.09 [-0.87; 0.70]	.	-0.48 [-1.23; 0.26]	-0.50 [-2.13; 1.13]
-0.52 [-1.41; 0.37]	0.08 [-0.80; 0.96]	HDRT	.	.	.	-0.76 [-1.91; 0.39]	.	.
-0.83 [-1.58; -0.07]	-0.23 [-0.94; 0.48]	-0.30 [-1.34; 0.73]	ART	-0.10 [-1.16; 0.96]	0.01 [-1.45; 1.47]	-0.08 [-1.62; 1.46]	-0.03 [-1.55; 1.50]	.
-0.87 [-1.58; -0.15]	-0.27 [-0.92; 0.39]	-0.35 [-1.35; 0.66]	-0.04 [-0.77; 0.69]	HDART	0.08 [-1.38; 1.53]	0.31 [-1.24; 1.87]	0.42 [-1.12; 1.96]	.
-1.00 [-1.51; -0.49]	-0.40 [-0.89; 0.09]	-0.48 [-1.43; 0.48]	-0.18 [-0.92; 0.57]	-0.13 [-0.84; 0.58]	CG	.	-0.33 [-1.43; 0.76]	-0.66 [-2.29; 0.98]
-1.03 [-1.91; -0.15]	-0.43 [-1.29; 0.42]	-0.51 [-1.41; 0.39]	-0.21 [-1.11; 0.70]	-0.17 [-1.06; 0.72]	-0.03 [-0.94; 0.87]	RT	0.16 [-1.37; 1.70]	.
-1.02 [-1.53; -0.50]	-0.42 [-0.90; 0.06]	-0.49 [-1.43; 0.44]	-0.19 [-0.93; 0.55]	-0.15 [-0.85; 0.55]	-0.02 [-0.58; 0.55]	0.02 [-0.84; 0.88]	AT	-0.46 [-2.08; 1.17]
-1.41 [-2.42; -0.39]	-0.81 [-1.79; 0.17]	-0.89 [-2.17; 0.40]	-0.58 [-1.74; 0.57]	-0.54 [-1.67; 0.59]	-0.41 [-1.40; 0.58]	-0.37 [-1.63; 0.88]	-0.39 [-1.38; 0.60]	IDAT

Figure 3:A: The network plot illustrates the direct and indirect effects of each intervention type for the reticulated meta-analysis. Connections between nodes represent direct comparisons among different interventions. The numbers on the lines denote the quantity of comparative trials, while the line thickness reflects the strength of direct evidence. B: The Bayesian sorted panel plot assesses relative effects between interventions using cumulative sorted curve under area (SCURA) values.



HD: hypocaloric diet, HDAT: hypocaloric diet with aerobic training, HDRT: hypocaloric diet with resistance training, HDART: hypocaloric diet with aerobic training and resistance training, IDAT: increase diet with aerobic training, AT: aerobic training, RT: resistance training, ART: aerobic training with resistance training, CG: control group.

3.2.2 Dose-response analysis results

We examined the dose-response relationship between exercise levels and tumor necrosis factor in total exercise. Our findings suggest that the predicted maximum significant response occurs at 150 minutes of METs-min/week (SMD: -0.287; 95% CI: -0.494 to -0.089). Additionally, we identified that the optimal range of exercise dosage for reducing tumor necrosis factor in obese or overweight individuals lies between 76 and 450 METs-min/week.

Figure 5 illustrates the dose-response relationships for the five intervention modalities. Our findings indicate that HDAT exhibited a significant nonlinear dose-response relationship with TNF-α levels, demonstrating statistical significance. Conversely, ART, AT, HDART, and HDAT showed a negative nonlinear dose-response relationship with TNF-α levels. In contrast, HDRT was linked to a positive nonlinear dose-response relationship with TNF-α levels. Specifically, HDAT, ART, AT, and HDART demonstrated a nonlinear increase in the reduction of TNF-α levels among obese or overweight individuals as exercise doses increased. Meanwhile, HDRT led to an increase in TNF-α levels in this population with escalating exercise doses. The minimum activity levels required to achieve the lowest effective dose were calculated at 120 METs-min/week for HDAT, and 112 METs-min/week for both ART and HDART. The remaining two interventions in the predictive curves did not appear to influence the reduction of TNF-α levels. Due to the limited number of included literature, ART, HDART, and HDRT were unable to generate smooth predictive response curves due to the small sample size. In addition, the 95% confidence intervals of the predictions for the amount of exercise and intervention modality suggest that in future studies of inflammatory factor interventions in obese or overweight patients, calorie-restricted diets in combination with exercise interventions may have a lesser effect on improving inflammatory factors compared with exercise interventions alone. Meanwhile, the results of the sequential analyses also showed that HDAT produced "better" results.

Figure 4: The dose-response relationship between total exercise and TNF-α changes in obese or overweight individuals is illustrated. The green shaded area indicates significant effects, while the dotted line represents the 95% confidence interval. ED: Experimental group.

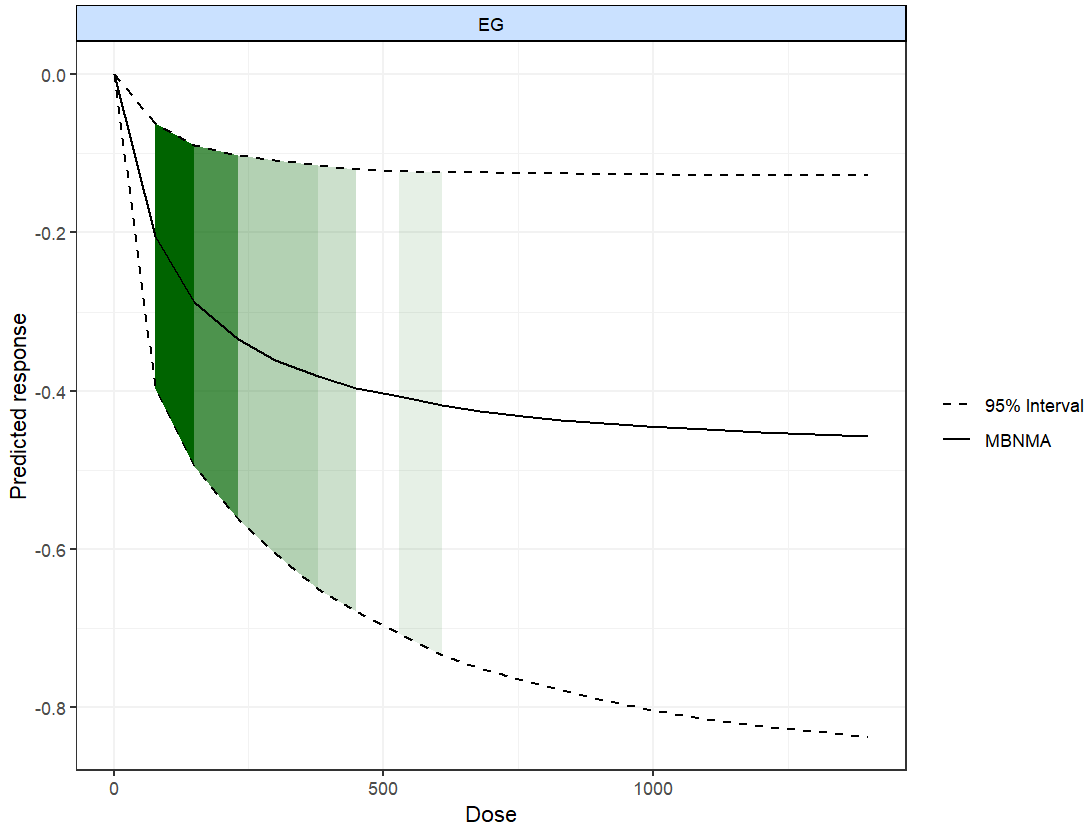


Figure 4: Network plot showing the connectivity effects of different intervention modalities across doses. Connectivity is a key assumption in network meta-analysis, and our study assessed network connectivity between intervention modality and intervention dose, with no evidence of network discontinuity.

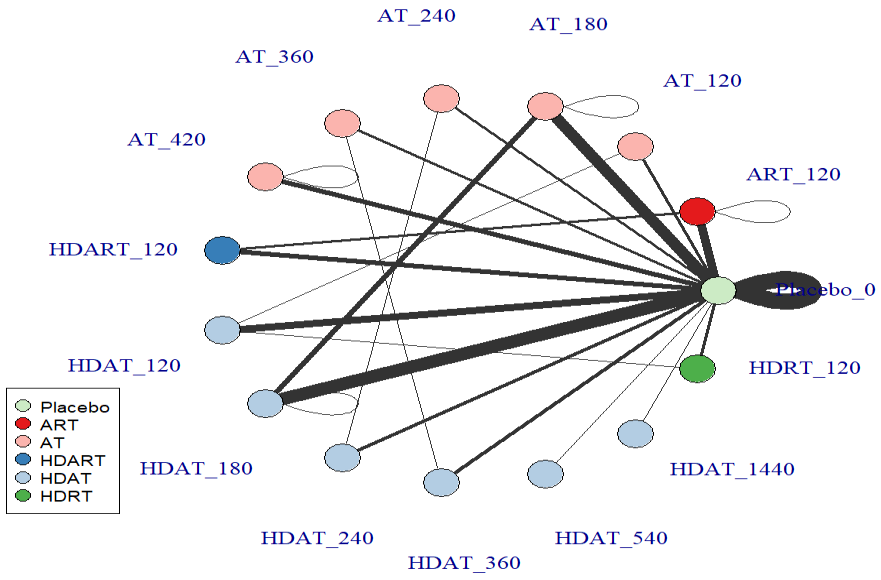
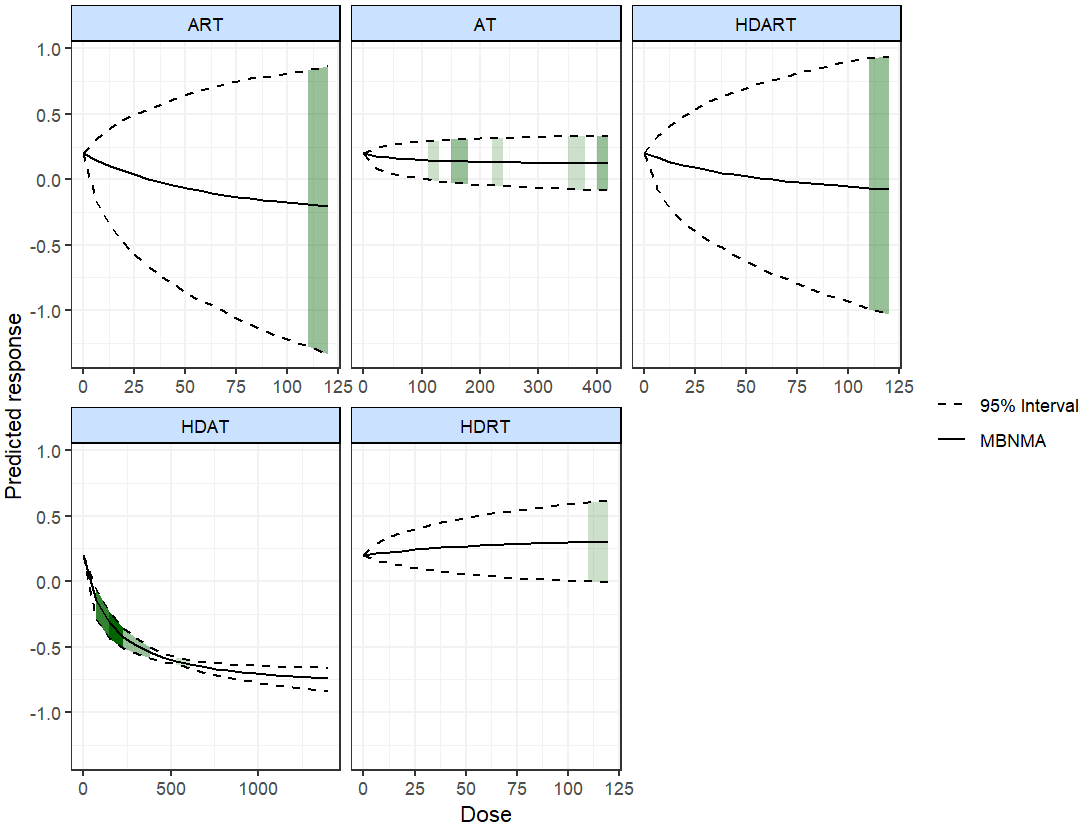


Figure 5: Dose-response relationship between intervention modalities and TNF-α levels in obese or overweight patients, nodes represent the original data set. The dashed area represents the beginning and end of the significant 95% confidence intervals, and the green shaded area represents the significant 95% confidence intervals.



3.3 reporting biases and certainty of evidence

The majority of the 19 studies included in this meta-analysis exhibited high heterogeneity ($I^2 > 50$). Of these studies, four (21%) presented a high risk of bias, and all 19 studies raised some concerns regarding bias. A detailed assessment of the risk of bias can be found in the supplementary material. Additionally, publication bias was evaluated using the Egger test and the Begg test, with both tests (Egger test: $P > 0.05$; Begg test: $P > 0.05$) indicating no evidence of publication bias, as explained in the supplementary material. The overall level of evidence concerning tumor necrosis factor is considered moderate. Further details of the study's findings are available in the Supplementary Materials.

3.4 sensitivity analyses and network meta-regression

The results of the network regression meta-analysis are shown in Table III. We found that publication date (beta:-0.95,95% -1.57 to -0.36) and intervention duration (beta:0.75,95% 0.10 to 1.43) appeared to significantly influence the effect of the intervention regimen in attenuating TNF-α in obese or overweight individuals. However, mean age, sample size, male/female ratio, and intervention dose did not significantly modulate the relative effect size of the intervention compared to the control group.

Table 3: Network regression meta-analysis. The following table describes the results of changes in heterogeneity in each of the network meta-regression models

Covariate	Shared beta(median and 95%CI)	Heterogeneity standard deviation(median and 95%CI)
None	-	0.44 (0.30 to 0.63)
Mean Age	0.25 (-5.57 to 1.27)	0.48 (0.28 to 1.65)
Published Year	-0.95 (-1.57 to -0.36)[a]	0.40 (0.27 to 0.58)
Sample Size	1.03 (0.11 to 1.99)	0.42 (0.29 to 0.61)
Intervention Period	0.75 (0.10 to 1.43)[b]	0.40 (0.27 to 0.59)
Percentage Female	-0.85 (-2.05 to 0.34)	0.43 (0.29 to 0.62)
Calorie Restriction dose	-0.03 (-0.47 to 0.39)	0.45 (0.30 to 0.65)
Intervention dose	-0.34 (-0.68 to 0.02)	0.41 (0.28 to 0.59)

[a] Significance Influence Factor, CI: Confidence Interval

4 Discussion

4.1 major finding

This study represents the dose-response meta-analysis examining the relationship between exercise dosage and TNF-α levels in combined diet and exercise interventions among obese populations. A network meta-analysis of randomized controlled trials was conducted to explore the effects of various categories of diet and exercise interventions on TNF-α levels in individuals who are obese or overweight. The effectiveness of these interventions was ranked and analyzed using the MBNMAdose package. Nineteen randomized controlled trials with 1479 participants were included. We found that only HDAT significantly reduced TNF-α levels in paired network comparisons. There were significant differences in efficacy between the individual interventions, with the HDAT having a high level of effect size (SMD = -0.6) and a significant beneficial effect (Table II). In addition, our study suggests that AT , RT, and IDAT have no significant effect on changes in TNF-α compared with control groups, and may have the opposite effect. This dose-response meta-analysis reveals a nonlinear relationship between exercise, diet, and TNF-α levels. Our findings indicate that different intervention modalities result in varying TNF-α levels, as demonstrated by the MBNMAdose model. We estimate that the effective exercise dose range lies between 76 and 540 METs-min/week, with a minimum effective dose of 76 METs-min/week. Notably, once the total exercise dose exceeds 600 METs-min/week, its effect on tumor necrosis factor becomes negligible, and the slope of the curve begins to decline. Upon analyzing each intervention individually for predictive outcomes, we discovered that the dose-response patterns exhibited nonlinear correlation curves. Notably, only HDRT displayed a nonlinear positive correlation, while the other interventions demonstrated nonlinear negative correlations. Specifically, ART, when administered at a minimum of 120 METs-min/week without accompanying calorie-restricted dietary interventions, may yield beneficial effects on TNF-α. Moreover, in conjunction with calorie-restricted dietary control, an additional 120 METs-min/week of aerobic exercise or 112 METs-min/week of aerobic

exercise combined with resistance training may also positively impact TNF-α levels[61]. The most significant of these was HDAT, which was able to achieve significant efficacy with minimal dose. Finally, in a network meta-regression analysis, we found that publication date (B: -0.95, 95% CI -1.57 to -0.36) and intervention duration (B: 0.75, 95% CI 0.10 to 1.43) appeared to influence the intervention effect of the intervention. Age, sample size, male/female ratio, and intervention dose did not influence the intervention effect. Overall, our study contributes to future research on the use of combined diet and exercise interventions to address inflammatory factors in obese populations, with the goal of enhancing the health and quality of life for individuals who are overweight or obese.

A previous meta-analysis explored the impact of various diet and exercise regimens on inflammatory factors in overweight or obese patients[28]. These trials aimed to evaluate whether a hypocaloric diet combined with an exercise intervention, rather than a calorie-restricted diet alone, would impact inflammatory factors (such as C-reactive protein, TNF-α, and interleukin-6) in obese or overweight individuals. Our study specifically examined the effects of various types of exercise—namely, aerobic exercise, resistance training, and a combination of both—when paired with a calorie-restricted diet, on chronic low-grade systemic inflammation in the body. Based on the results of the web ranking comparison, we found that the hypocaloric diet with aerobic training (SMD: -0.60, 95CI -0.99 to -0.20) significantly reduced TNF-α and had a high SUCRA ranking. In the dietary regimens included in this paper, the amount of caloric restriction ranged from -250 kcal/d to -1460 kcal/d. However, in the network regression analysis, the dose of caloric restriction did not appear to have a significant effect on the outcome of the study (B: -0.03, 95%CI -0.47 to 0.39). Some of the previous studies have also emphasized the ameliorative effect of the combination of dietary regimen and aerobic exercise on the levels of inflammatory factors[48,49]. It is mainly attributed to the fact that the combination of the two reduces fat mass and induces the body to produce an anti-inflammatory environment associated[50,62]. The study concluded that there is a direct relationship between TNF-α levels and the amount of white abdominal fat in obese people[63]. The reduction in fat mass achieved through a combination of caloric restriction and exercise is substantial. However, there seems to be some disagreement among studies regarding the optimal type of exercise to pair with this approach. In a study examining inflammatory factors in an obese population, findings suggest that combining aerobic exercise with resistance training may have a significant impact on abdominal subcutaneous adipose tissue[64,65]. However, some studies have found even better effects with aerobic exercise[66]. As far as the results of the present study are concerned, we seem to be more in favor of an effect of aerobic exercise, since for TNF-α a significant effect was found in this study in the context of dietary control combined with aerobic exercise. Another reason is that the exercise-induced contraction of skeletal muscle appears to direct the production of "muscle factors" by the exercising skeletal muscle, a related endocrine effect involving several muscle factors that have a direct anti-inflammatory effect on visceral fat in a hormone-like manner[67,68]. The most important of these may be interleukin-6 (IL-6), which is rapidly released in large quantities during exercise and induces the expression of the anti-inflammatory factors interleukin-1α and interleukin-10 while inhibiting the expression of TNF-α[69]. This represents the anti-inflammatory environment that may be created by the body as a result of exercise. In fact, previous studies have implicated tumor necrosis factor as a driver of insulin resistance and dyslipidemia[70]. In non-alcoholic steatohepatitis conditions associated with metabolic syndrome, chronic exercise was found to alter levels of liver-associated TNF-α and TNF-α mRNA in obese mice[71]. A significant reduction in immune cell infiltration into adipose tissue was also observed, suggesting positive changes in the immune system during exercise[72]. All of these factors can be considered potential mechanisms for the beneficial effects of diet and exercise on TNF-α.

As previously stated, a significant factor influencing the outcomes of the current study is the duration of the intervention. Furthermore, numerous prior studies have demonstrated the inhibitory effects of extended exercise on TNF-α[17]. However, this was not confirmed in this network regression meta-analysis. On the contrary, too long an intervention time (B: 0.75, 95% CI 0.10 to 1.43) seems to have a negative effect on tumor necrosis factor levels in obese or overweight patients. This result was also confirmed in our prediction model, with almost no effect for intervention durations longer than 500 METs-min/week. Furthermore, previous studies have indicated that the connection between exercise intensity and improvements in inflammatory markers may be stronger than previously thought. Specifically, low-intensity aerobic exercise seems to have little effect on circulating inflammatory markers or those in abdominal adipose tissue when compared to the combination of resistance exercise and dietary changes[53,73,74]. This point was not explored in this study due to methodological limitations and needs to be further explored in future studies. Due to the limitations of this paper, the nonlinear relationship should be explored in subsequent studies by considering the intervention date and exercise intensity as important factors affecting obese or overweight patients.

4.2 Strengths and Limitations

Firstly, it comprised three components: a paired meta-analysis, a network analysis, and a dose-response network modeling analysis. These were employed to explore the impact of an intervention that combines dietary intervention and exercise on TNF-α levels in obese or overweight individuals. The robust methodology enabled us to identify the most effective forms of exercise to pair with dietary interventions, along with the appropriate dosage. Second, this study included a large level of sample size, including 19 publications with a total of 1479 obese or overweight individuals. Separate means of exercise combined with non-dietary control interventions were also included for comparison. This allowed for better statistical power and selection of comparisons for this article. Third, we excluded high-risk articles and studies with small sample sizes to improve the stability of our findings through GRADE ratings and balanced risk and sensitivity analyses. Fourth, the population of this study included adolescents, adults, and older adults, with a relatively even distribution of males and females, making the results of this study advantageous for generalization to different populations. Finally, we performed a network regression analysis on a subset of the potential confounding variables to explore the influence of potential variables on the effect of dietary control combined with exercise intervention.

Nevertheless, this study still has some limitations in several aspects. First, in the predicted dose analysis in this paper, the HD and CG groups were used together as placebo groups to make the analysis smooth, which potentially biased the predicted dose analysis. Second, some of the dose-response analyses for certain intervention types failed to show significance or failed to generate smooth curves. In addition to the limitations of the intervention modality itself, another important reason for this is that the sample size of the specific intervention types included was small, resulting in insufficient dosage ranges, which need to be considered in future studies or additional studies. Consequently, it is crucial to approach the predictive outcomes of dose-response with caution and to focus more on the impact of total exercise dosage on patients' tumor necrosis factor levels. Additionally, while this study explored the dose-response relationship, it did not clarify the underlying physiological mechanisms contributing to the observed effects, indicating a need for further in-depth research. Lastly, it would be beneficial to specify different types of aerobic exercise (such as walking, swimming, cycling, etc.) along with their corresponding dose-response analyses as potential future directions for this study.

In conclusion, the present study determined the effective dose range and minimum threshold dose in different types of interventions, providing a guideline that can be used for the future development of exercise prescriptions. Importantly, this study accounted for the changes in tumor necrosis factor associated with the duration of exercise intervention, and although sample size limitations within a group did not allow for the observation of an ideal U-shaped response curve, it is still possible to determine that the duration of exercise intervention is not as long as possible, but rather that there is a certain threshold for rapid decline. Further investigation is needed in subsequent studies.

5. Conclusion

The current review included 19 randomized controlled trials involving 1479 obese or overweight people. It provides some reference value for the control of exercise dose in combined exercise and diet interventions. Compared with the traditional control group, only the hypocaloric diet combined with aerobic exercise can effectively reduce the content of TNF-α in obese people. At the same time, we compared diet combined with exercise intervention with diet intervention and determined the threshold dose of effective exercise intervention based on diet intervention. On the basis of dietary control, we seem to find that only aerobic exercise is effective and the rest of the two combined interventions have no effect. Also, exercise is beneficial for a certain period of time, but the efficacy of exercise on TNF-α is almost nonexistent beyond 500 METs-min/week. These findings provide a valuable reference for the development of diet-exercise combination type prescriptions.

Declaration

Author contributions

All authors contributed to the study idea and design. Conceptualization, C.W.; methodology, C.W.; software C.W.; check, C.W., L.S., and J.L.; formal analysis, C.W.; investigation, C.W.; resources, C.W.; data curation, C.W.; writing - rough preparation, C.W.; writing - review and editing, C.W.; visualization, C.W.; supervision, S.L., K.W. and J.L.; project administration, J.L., All authors have read and agreed with the published version of the manuscript.

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Conflict of Interest Statement

All authors declare that they have no potential competing interests.

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