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# The effect of weight loss therapies on sirtuin 1 regulation: a systematic review and meta-analysis of randomized controlled trials

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#### **Abstract**

**Background** Recent evidence shows the role of sirtuin 1(SIRT1), a family of evolutionarily conserved proteins, as a potential therapeutic target in the prevention and treatment of obesity and metabolic diseases. Some evidence shows the moderating effects of weight loss interventions on this factor. However, the findings are contradictory. In order to obtain a better viewpoint from them, this study aimed to comprehensively investigate the effects of weight loss interventions on SIRT 1 modulation.

**Methods** For this study, we searched four electronic databases using predefined keywords from inception until March 2024. We included and controlled trials that evaluated the effect of weight reduction strategies on SIRT1 levels. The random-effects model analysis was used to obtain the pooled weighted mean difference (WMD) and 95% confidence intervals (95% CI). The meta-analysis was conducted using RevMan version 5.3 software and Stata version 12.0.

**Results** Twelve studies with 627 volunteers were included. The pooled findings showed that weight loss interventions have no significant effect on the modulation of SIRT1 compared to the control group (pooled WMD of 0.58 ng/mL; 95% confidence interval [CI] -0.17 to 1.33; p = 0.130). However, subgroup analysis showed that weight loss interventions significantly modulate SIRT1 at metabolic disease (WMD: 1.2 ng/mL, 95% CI: 0.11 to 2.62,  $I^2$  = 82.9%). In addition, subgroup findings indicated health status and body mass index (BMI) as sources of high and potential heterogeneity.

**Conclusions** Based on the findings, weight loss therapies in individuals having a metabolic disorder appear to generate a considerable increase in SIRT1 levels.

**Keywords** SIRT-1, Weight loss, Nutrition, Meta analysis

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#### Introduction

The global epidemic of overweight and obesity has reached unprecedented levels, posing significant challenges to public health systems worldwide. Obesity, defined by the World Health Organization (WHO) as a body mass index (BMI) of 30 kg/m² or greater, is a complicated chronic condition characterized by an excessive deposit of fat or adipose tissue in the body. Since 1975, the number of obese people has more than tripled, with approximately 1.9 billion adults being overweight and over 650 million classed as obese [1, 2]. This growing trend not only contributes to a slew of chronic conditions like cardiovascular disease, diabetes, and certain cancers but it also pplaces a significant financial strain on health-care systems [3, 4].

Efforts to tackle the obesity epidemic have resulted in a wide range of weight loss interventions including dietary changes, medication and surgical procedures [5, 6]. These interventions aim to mitigate the adverse health effects associated with excess weight, thereby improving overall well-being and reducing the risk of obesity-related complications [6]. However, the efficacy and mechanisms of these therapies are still being studied and debated [7, 8].

Sirtuins (SIRTs) are nicotine adenine dinucleotide(+)dependent histone deacetylases regulating critical signaling pathways in prokaryotes and eukaryotes, and are involved in numerous biological processes [9]. Currently, seven mammalian homologs of yeast Sir2 named SIRT1 to SIRT7 have been identified. Increasing evidence has suggested the vital roles of seven members of the SIRT family in health and disease conditions [10]. Nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases and monoadenosine diphosphate (mono-ADP) ribosyl transferase enzymes play a crucial role in regulating various biological processes. These processes include mitochondrial biogenesis, cellular metabolism, stress response, and DNA transcription. As a result, these enzymes are effective at reducing inflammation, increasing insulin sensitivity, preventing atherosclerosis, protecting the nervous system, and inhibiting tumor growth [11–15]. Sirtuin 1 (SIRT1) has sparked great interest due to its regulatory role in a variety of physiological processes, including energy metabolism, insulin sensitivity, and inflammation [11, 12]. Modulating SIRT1 activity through drugs or lifestyle interventions holds the potential to ameliorate metabolic dysfunction and promote weight loss [16]. Recent research has focused on understanding the complex interplay between weight reduction therapies and SIRT1 regulation, offering insight on new therapeutic approaches [17-19]. For example, Chen et al. (2023) found that caloric restriction had a positive effect on SIRT1 expression in obese persons, indicating the potential of dietary interventions in SIRT1-mediated weight management [12]. Additionally, the work of Shen et al. (2024) unveiled the role of exercise-induced SIRT1 activation in promoting adipose tissue browning and metabolic health, underscoring the significance of physical activity in combating obesity-related complications [20]. Lu et al. (2023) investigated the impact of pharmacological SIRT1 activation on weight loss and metabolic parameters, providing insights into the therapeutic utility of SIRT1 modulators in clinical settings [18].

In this systematic review and meta-regression analysis, we aim to generate a robust evidence basis from current randomized controlled trials to better understand the effect of weight loss therapies on SIRT1 regulation which is one of the elements determing putative weight loss pathways. By extensively analyzing the association between various intervention modalities and SIRT1 activity, we want to uncover the underlying mechanisms and inform the development of focused methods for fighting obesity and its associated comorbidities.

#### Methods

The present study was documented in accordance with the PRISMA [Preferred Reporting Items for Systematic Review and Meta-analysis] guidelines [21]. We carried out a comprehensive systematic search in PubMed (MEDLINE), Web of Science, SCOPUS, and Embase from inception until March 2024 without using time or language restrictions. Randomized controlled trials (RCTs) that reported the effects of weight loss interventions on SIRT1 level were included. Medical Subject Headings (MeSH) and EMBASE Subject Headings (Emtree) were selected to search the online databases. The search strategy central is: ("Sirtuin 1 " OR " Silent Mating Type Information Regulator 2 " OR "Sirtuins " OR " SIRT " OR "SIRTs " OR Sirtuin OR "Sir2 like Proteins") AND ("Weight Loss " OR "Weight Reduction Programs" OR "Obesity Management" OR "diet therapy" OR "Weight intervention" OR "weight reduce" OR "caloric restriction" OR " Anti-Obesity Agents" OR " Antiobesity Drugs" OR "Weight Loss Drug" OR "Weight Loss Agents" OR "energy restriction" OR "Gastric Bypass" OR " gastroplasty " OR "Bariatric Surgery" OR "gastric banding " OR "Anastomosis, Surgical" OR "Anastomosis, Roux-en-Y" OR "biliopancreatic diversion" OR "jejunoileal bypass") AND ("Clinical Trials as Topic" OR "Cross-Over Studies" OR "Double-Blind Method" OR "Single-Blind Method" OR "Random Allocation" OR "Clinical Trial").(The specific search strategy is described in the Supplementary Appendix S1). Furthermore, the list of the retrieved papers, grey literatures, and related review studies were manually searched to identify qualifying trials that may have been overlooked. We also conducted a "snowball search" to included other RCTs (which were not included in this analysis).

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# Study selection

After excluding duplicate articles two authors independently reviewed titles, abstracts and full text of studies. Finally, original studies were included in the present meta-analysis if they had following criteria: (1) to be randomized clinical trials studies; (2) included therapies such as behavioral weight loss programs, medication, supplements and bariatric surgery, either individually or in combination. Exercise, supplements, and diet therapies that did not attempt to lose weight loss were omitted and (3) reported SIRT1. The duplicated data, studies with unclear information and which did not receive any feedback from the corresponding author(s) after email, non-randomised study designs, animal and observational studies, studies without a control group and reviews were excluded. Also, the studies that reported the duration of the intervention in hours were excluded from this study. The criteria used to determine which studies were included and excluded were the PICOS criteria. Population: All healthy or unhealthy individuals with an age greater than or equal to 18 years; Intervention: behavioral weight loss programs, pharmacotherapy, supplements, bariatric surgery, alone or in combination; Comparator: other intervention or placebo; Outcomes: SIRT1; Study design: randomized clinical trials.

# Data extraction

The data was examined by two independent researchers, and any discrepancies were settled by a third independent researcher. The abstracted information includes the reference, publication year, country, number of people at intervention and control groups, gender proportion, mean age, mean BMI in kg/m², BMI reduction, follow-up of intervention, type of intervention or control group, and the means and standard deviations of SIRT1 at baseline, post treatment, and/or changes between baseline and post treatment.

#### **Quality assessment**

Using the Cochrane risk-of-bias test for randomized trials (RoB 2), version 2, the quality of the included RCTs was methodologically evaluated [22]. The quality assessment technique includes the evaluation of several factors, such as the appropriateness of random sequence generation, allocation concealment, blinding, identification of missing outcome data, detection of selective outcome reporting, and identification of other potential sources of bias. According to the guidelines provided by the Cochrane Handbook, the assessment of each category was categorized as "Low", "High", or "Unclear" risk of bias. The resolution of any discrepancies in the data extraction and the assessment of bias was achieved with the involvement of a third reviewer. The overall analysis was evaluated utilizing the GRADE (Grading of Recommendations

Assessment, Development, and Evaluation) [23]. The GRADE checklist is a valid 10-point scoring system that measures factors influencing study quality. This scale includes 7 items 1) risk of bias, study quality, and study limitations, 2) precision, 3) heterogeneity, 4) directness, 5) publication bias, 6) funding bias, 7) study design.

#### Data synthesis and statistical analysis

The meta-analysis was conducted using the softwares RevMan version 5.3 and STATA version 12.0 (Stata Corp, College Station, TX, USA). Furthermore, the Endnote was utilized to detected duplicates. When the data was presented in a different format, standard procedures were performed to determine the mean and standard deviations [24, 25]. In cases where the standard deviations of the change were not provided in the trials, we calculated them using the following formula: The formula for calculating the change in standard deviation (SD) is the square root of [(SD baseline squared plus SD final squared) minus (2 times R times SD baseline times SD final)]. In cases when trials only provided the standard error of the mean (SEM), we calculated the standard deviations (SDs) using the formula SD=SEM  $\times \sqrt{n}$ , where "n" represents the number of participants in each group. The meta-analysis of study outcomes employed the random-effects model. The studies were weighted using the general inverse variance approach. For studies with several evaluations within a single group, the values corresponding to the longest time point were utilized for the analysis. The I-squared (I<sup>2</sup>) statistic was used to analyze heterogeneity. If the I<sup>2</sup> value was greater than 50%, or if there was inconsistency among the data from RCTs, the source of heterogeneity was found [26]. To explore possible sources of variation, a predetermined subgroup analysis was conducted. This analysis was based on the duration of the intervention, health status, mean age, and BMI at the baseline level. A sensitivity analysis was conducted to evaluate the impact of each study on the overall mean difference. We conducted an evaluation of publication bias by employing the formal Egger's test [27].

# **Results**

Figure 1 depicts the process of selecting research and the precise reasons for removing papers. Subsequently, 1588 publications were collected from the electronic databases. After removing duplicate studies, 963 papers remained. Next, we analyzed the title and abstract of the research and rejected those that did not meet the inclusion criteria. A total of 29 articles were obtained through the secondary screening with full-text. Of those, 17 studies were excluded for various reasons. Finally, 12 studies (with age range between 27 and 38) fulfilled the requirements and were incorporated into the quantitative meta-analysis.

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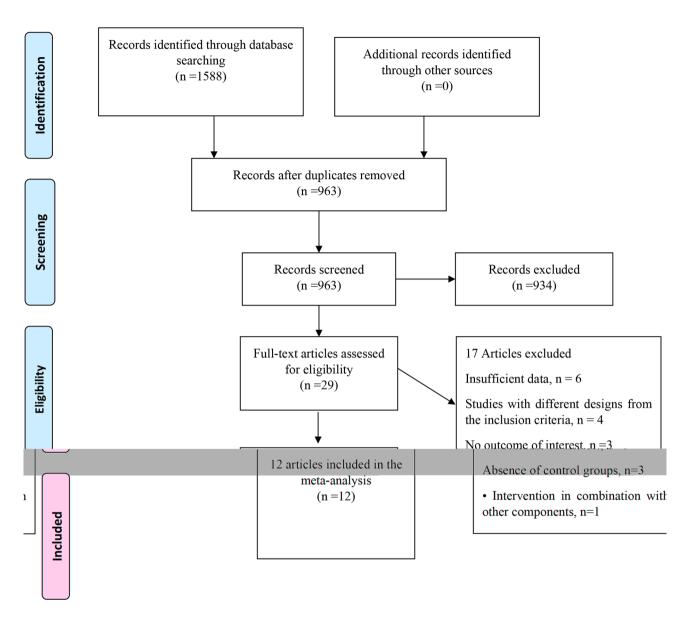


Fig. 1 Flow chart of the included studies, including identification, screening, eligibility and the final sample included

## **Study characteristics**

Table 1 presents the characteristics of the pooled studies. Six studies were undertaken in Iran, three articles in Brazil, and three studies in Italy, Mexico, and Egypt (each country had one study). All publications were published between the years 2013-2023 in a parallel design. All of the included studies were RCTs with study durations ranging from 4 to 24 weeks. The participants ages ranged from 34.88 to 63 years with male gender varied from 35 to 70.8% of the total. The level of reduction in BMI reported in the studies based on the intervention group ranged from -0.29 to -6.5. Depending on the type of intervention, one study used bariatric surgery, eight studies with caloric restriction alone or with exercise, two studies used a combination of pomegranate juice or

probiotics with caloric restriction, and one study used combination of omega-3 with 3 mg Glimepiride. Based on the information in the table, 3 studies have been conducted on healthy people and the rest on patients with metabolic diseases, including type 2 diabetes, non-alcoholic fatty liver disease, and obese and overweight people.

Table 2 shows the results of the quality evaluation. Furthermore, when assessing the quality of the current meta-analysis using the GRADE score method, a score of 8.9 (indicating very good quality) was computed. The Kappa result for the authors of our study for data screening and selection was approximately 0.92, iindicating almost complete agreement.

(kg/m<sup>2)</sup> duction BMI relevels -0.34 -1.48 -1.39 -0.48 -0.29 -0.98 -0.34 -6.5 -2.4 -0.4 0.2 -0.4 Restriction diet 500 kcal/day Performed Faradic exercise Resveratrol administration Resveratrol administration Resveratrol administration 500 mg/day resveratrol Resveratrol (100 mg/d) Glimepiride 3 mg with Control beverages Type of control (500 mg/day) (500 mg/day) (500 mg/day) placebo Placebo Placebo Placebo Glimepiride 3 mg with either omega-3 capsules Pomegranate juice 250 mL + restriction diet \_ Received 2 capsules containing 600 mg a-LA Low-calorie diet deficit of 500 to 1000 kcal/d along with a calorie-restricted diet and perweight reduction diet supplemented with Dose and type of supplementation Caloric restriction (1000 cal/day) Caloric restriction (1000 cal/day) Caloric restriction (1000 cal/day Probiotic + Caloric restriction contained fish oil 1000 mg 50,000 IU vitamin D3 pearl Intragastric Balloon (BIB®) formed Faradic exercise Caloric restriction Green cardamom physical activity Duration (Weeks) of intervention 12 12 24 12 24 4  $\infty$ 4  $\infty$ 4 sample Study Size 84 20 88 94 48 32 4 9 9 48 70 (Male 22/5 70.8 Sex 51.2 NR N/R 54.3 % 50 4 20 45 35 20 Mean 35.18 58.63 34.88 40.08 58.63 43.95 50.51 Age year 40.81 53.9 58.5 55 53 Healthy and Slight-Obese people undergoing a weight Healthy human Obese subjects Obese Patients ly Overweight Healthy adults Population population. loss diet NAFLD T2DM T2DM T2DM T2DM T2DM Parallel Study Design Parallel 
 Table 1
 Characteristics of eligible studies
Pub- Country Mexico Egypt. Brazil Brazil Brazil Italy Iran Iran Iran Iran Iran Iran 2016 2018 2018 2017 2018 2015 2019 2018 2023 lica-tion 2020 2023 2023 year Mohammadshahi Gonçalinho et al. García-Martínez Author (year) P. Mansur et al. Roggerio et al. Aliashrafi et al. Mariani et al. Asghari et al. Werida et al. Aghasi et al. Sohrab et al. Khalili et al.

Cbl Cobalamin; T2DM: Type 2 Diabetes Mellitus; NAFLD: Non-alcoholic fatty liver disease; BMI: body mass index; N/R: not reported

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Table 2 Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool

| Study, Year (reference) | Random<br>sequence<br>generation | Allocation<br>concealment | Blinding of<br>participants<br>and personnel | Blinding of out-<br>come assessment | Incomplete<br>outcome<br>data | Selective<br>reporting | Overall as-<br>sessment<br>of risk of<br>bias |
|-------------------------|----------------------------------|---------------------------|----------------------------------------------|-------------------------------------|-------------------------------|------------------------|-----------------------------------------------|
| P. Mansur et al.        | Unclear                          | Unclear                   | Unclear                                      | Unclear                             | Low                           | Low                    | Unclear                                       |
| Mohammadshahi et al.    | Low                              | Unclear                   | Unclear                                      | Low                                 | Low                           | Low                    | Unclear                                       |
| Aghasi et al.           | Unclear                          | Unclear                   | Unclear                                      | Unclear                             | Unclear                       | Unclear                | Unclear                                       |
| Asghari et al.          | Low                              | Unclear                   | Unclear                                      | Unclear                             | Low                           | Low                    | Unclear                                       |
| Sohrab et al.           | Low                              | Unclear                   | Low                                          | Low                                 | Low                           | Unclear                | Unclear                                       |
| Roggerio et al.         | Low                              | Low                       | Unclear                                      | Low                                 | Low                           | Low                    | Unclear                                       |
| Mariani et al.          | Unclear                          | Unclear                   | Unclear                                      | Unclear                             | Low                           | Low                    | Unclear                                       |
| Aliashrafi et al.       | Unclear                          | Unclear                   | Unclear                                      | Unclear                             | Unclear                       | Unclear                | Unclear                                       |
| Khalili et al.          | Low                              | Low                       | Unclear                                      | Low                                 | Unclear                       | Low                    | Unclear                                       |
| García-Martínez et al.  | Low                              | Unclear                   | Unclear                                      | Unclear                             | Unclear                       | Unclear                | Unclear                                       |
| Gonçalinho et al.       | Unclear                          | Unclear                   | Unclear                                      | Unclear                             | Unclear                       | Unclear                | Unclear                                       |
| Werida et al.           | Unclear                          | Unclear                   | Unclear                                      | Unclear                             | Unclear                       | Unclear                | Unclear                                       |

# Meta-analysis results

Weight reduction therapies had no significant effect on SIRT1 modulation in the overall population when compared to the control group (pooled WMD of 0.58 ng/mL; 95% CI -0.17 to 1.33; P=0.130). The Cochran Q test revealed high heterogeneity among trials for this outcome (P<0.001, I<sup>2</sup>=80.4%). Subgroup analysis was carried out to determine the likely reason of heterogeneity (Fig. 2).

# Subgroup analysis

We subsequently stratified the articles based on the health status, duration of the intervention period (weeks), mean age, and BMI at the baseline level (Figs. 3 and 4). Subgroup results showed that weight loss interventions significantly modulate SIRT1 in people with metabolic disease (WMD: 1.2 ng/mL, 95% CI: 0.11–2.628, I²=82.9%) compared to healthy people (WMD: -0.42 ng/mL, 95% CI: -0.91-0.07, I²=0.0%). However, the results were not significant for other subgroup analyses. In addition, subgroup findings indicated health status and average BMI as sources of high and potential heterogeneity.

# Meta-regression

Meta-regression between weight loss interventions and absolute mean differences in SIRT1 based on weight loss level (BMI reduction) and baseline values of mean age of participants were performed, but no significance was found (Coef=0.0470513, p=0.891 for weight loss level; Coef = -0.0493652, p=0.503 for mean age of participants; see Fig. 5).

# Sensitivity analysis

To determine the impact of each article on the combined effect size for SIRT1 levels, we systematically excluded each study from the analysis. The leave-one-out

sensitivity analysis demonstrated the durability of the findings (Supplementary Fig. 1).

## **Publication bias**

Upon visually inspecting the funnel plot, no evidence of publication bias was found based on the results of the Egger's tests (p=0.064) (Supplementary Fig. 2).

#### **Discussion**

The results of this meta-analysis indicated that, while therapies weight loss interventions had no significant overall effect on SIRT1 regulation across populations, subgroup analyses reveal subtle interactions based on participants'health state. Specifically, individuals with metabolic disease demonstrate a significant increase in SIRT1 levels following weight loss interventions, contrasting with non-significant changes observed in healthy individuals. These results corroborate with previous and recent animal studies highlighting the differential impact of weight loss on metabolic biomarkers in diseased versus healthy studies [18, 28, 29]. Obesity plays a key influence in the development of metabolic inflammation and increases the presence of inflammatory markers in the blood. While it is commonly accepted that weight loss helps to reduce inflammation, SIRT1 may play a role in this process.

SIRTs control metabolic balance in various cell types by stimulating metabolic enzymes, including PGC-1 $\alpha$ , PPAR- $\gamma$ , AMPK, FOXO1, and LXR, while decreasing the activity of proinflammatory cytokines, such as TNF $\alpha$  and IL-6 [30–32]. Furthermore, increased weight causes inflammatory reactions, disrupts cellular metabolism balance [33], is a key cause of the obese/metabolic syndrome, and lowers SIRT1 levels. As a result, the observed reduction in inflammation with weight loss be due to SIRT1 overexpression. It has attracted researchers' interest because it may generate multiple health benefits,

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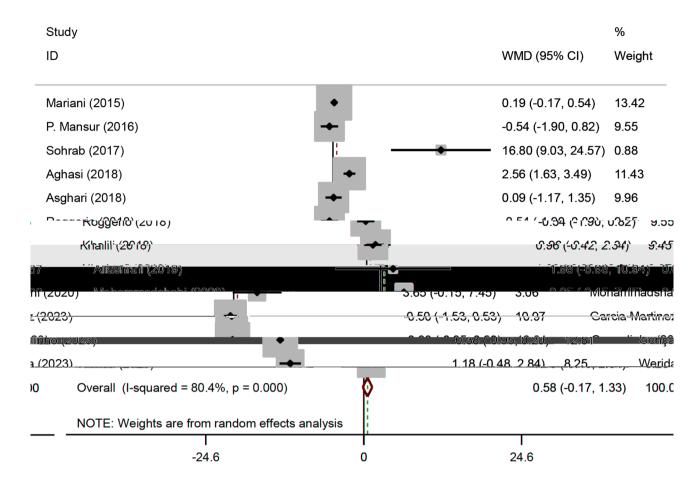


Fig. 2 Forest plot of randomized controlled trials investigating the effects of weight loss interventions on sirtuin 1 modulation (ng/mL)

mainly preventing and treating obesity and age-related diseases. The observed heterogeneity among studies underscores the importance of considering baseline characteristics and health statuses when interpreting the effects of weight loss interventions on SIRT1 modulation.

Meta-regression analyses aimed at clarifying putative moderators such as baseline age and intervention length produced non-significant results, indicating that these variables may not have a major influence the observed outcomes. However, it is critical to recognize the limits of meta-regression analyses [34], which include potential unmeasured confounders and differences in study methodology. Sensitivity analyses done to examine the robustness of the findings yielded consistent results, confirming the stability of the observed effect sizes [35]. This reinforces the validity of the meta-analysis findings.

However, it is important to recognize the limitations of our study. The short follow-up period of studies is one limitation. The length of time spent following up the studies seems to be an important factor [36]. Opstad et al. (2021) observed effects on Sirtuin1 concentrations only after 1 year of follow-up. Despite these limitations, our study contributes valuable insights for future

interventions targeting the improvement of the metabolic profile in patients with metabolic diseases. This is achieved through a valuable insight into the complex interplay between weight loss interventions and SIRT1 modulation. Significant variations were observed both clinically and statistically. These variations can be attributed to variances in intervention-specific parameters, such as the exact type of treatment, the dosage of supplements, and the duration of protocols. These differences may also be influenced by patient-specific characteristics such as genetic makeup, age, gender, ethnicity, medical history, and carbohydrates and fats intake. Furthermore, due to time contractarians, the current inquiry was not registred in PROSPERO, which was another limitation of this study.

# Conclusion

In conclusion, while no significant overall effect was detected across populations, subgroup analyses revealed variable responses based on health status, with patients with metabolic disorders exhibiting large increases in SIRT1 levels after weight loss programs. These findings highlight the importance of individualized weight

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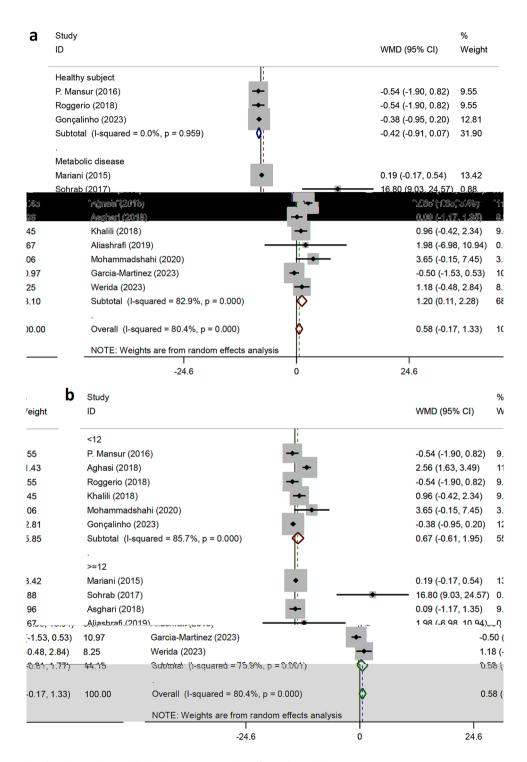


Fig. 3 (A) Forest plot of randomized controlled trials investigating the effects of weight loss interventions on sirtuin 1 modulation (ng/mL) based on health status. (B) Forest plot of randomized controlled trials investigating the effects of weight loss interventions on sirtuin 1 modulation (ng/mL) based on duration of intervention (Weeks)

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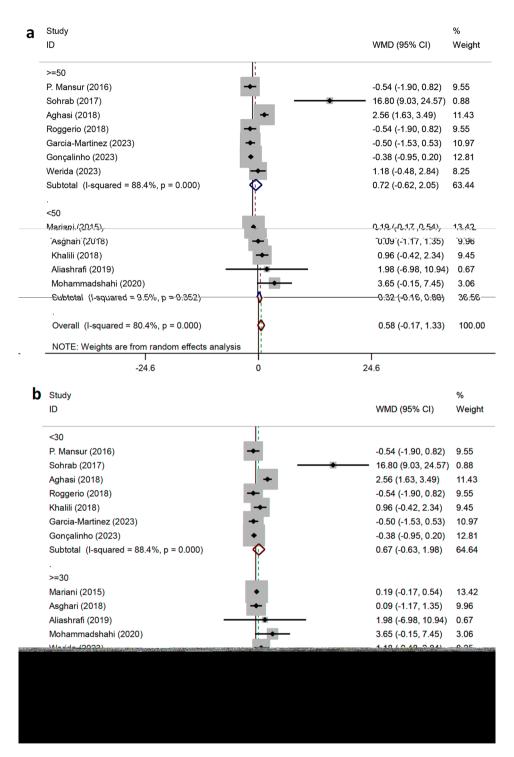


Fig. 4 (A) Forest plot of randomized controlled trials investigating the effects of weight loss interventions on sirtuin 1 modulation (ng/mL) based on mean age of participants (year). (B) Forest plot of randomized controlled trials investigating the effects of weight loss interventions on sirtuin 1 modulation (ng/mL) based on mean BMI of participants (year)

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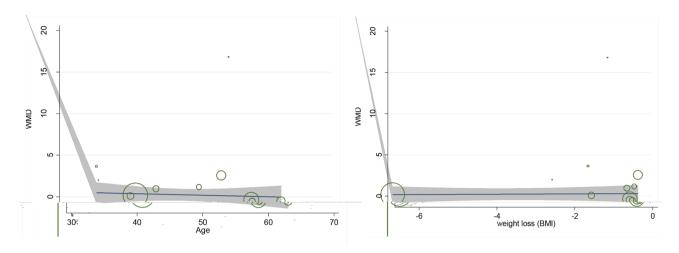


Fig. 5 Meta-regression analysis encompassing sirtuin 1 (ng/mL) changes according to the mean age of participants and levels of weight loss (BMI reduction of participants (kg/m²))

loss strategies that take into account individual health statuses and metabolic profiles. Future research should focus on clarifiying the molecular underpinnings of these divergent responses, as well as refining therapeutic techniques to capitalize on the potential benefits of SIRT1 regulation in metabolic health.

# **Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s40795-024-00921-2.

Supplementary Material 1

Supplementary Material 2

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# Author contributions

Mh.S and H.Z contributed in conception, design, and statistical analysis. Mh.S, N.SG, Gh.E, and P.R contributed in data collection and manuscript drafting. Mh.S and H.Z supervised the study. All authors approved the final version of the manuscript.

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#### Data availability

Data will not be made available in a public repository as we have not obtained ethical clearance to share data publicly. However, on request from corresponding author data could be provided while maintaining anonymity.

#### **Declarations**

#### Ethics approval and consent to participate

This study was approved by the research council and ethics committee Shahid Beheshti University of Medical Sciences, Tehran, Iran. The ethical declaration in this manuscript is made "based on the Declaration of Helsinki".

#### **Consent for publication**

Not applicable.

#### Consent to participate

Not applicable.

#### Competing interests

The authors declare no competing interests.

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