DOI: 10.1556/2060.2022.00018



# The effectiveness of high-intensity interval training on body composition of rodent models of obesity: A systematic review and meta-analysis

ANA FLÁVIA SORDI<sup>1</sup>, BRUNO FERRARI SILVA<sup>3,4</sup>,
JULIA PEDROSA FURLAN<sup>1</sup>, SOLANGE MARTA FRANZÓI DE MORAES<sup>1</sup>,
DÉBORA ALVES GUARIGLIA<sup>2</sup> and SIDNEY BARNABÉ PERES<sup>1\*</sup>

Received: January 30, 2022 • Revised manuscript received: April 30, 2022 • Accepted: May 9, 2022 Published online: September 5, 2022

© 2022 Akadémiai Kiadó, Budapest



#### ABSTRACT

The present systematic review was compiled to analyze the effectiveness of High-intensity interval training (HIIT) protocols on the body composition of rodents with obesity. Databases were searched until February 2021 for experimental trials in rodents with a minimum duration of four weeks of HIIT and endpoints associated with obesity. The data were analyzed by meta-analysis performed for comparisons of body composition. Sensitivity analysis was performed to investigate the consistency of individual researches. Of all of the 524 studies found, only 14 were included. The analysis showed a significant reduction in body weight ([CI 95%: -8.35; -1.98]  $P \le 0.01$ ), adiposity index ([IC 95%: -1.04; -0.80]  $P \le 0.01$ ), and fat pads ([IC 95%: -0.59; -0.06]  $P \le 0.01$ ). HIIT performed on treadmill or water was effective to reduce body weight (P < 0.05). In conclusion, HIIT attenuated both body weight and adiposity induced either by HFD (high-fat diet) or by GOM (genetic obese model), thereby inducing positive changes in body composition.

#### **KEYWORDS**

exercise, obesity, adipose tissue, rodents

<sup>\*</sup> Corresponding author. Department of Physiological Sciences, State University of Maringá, Av. Colombo, 5790, Zone 7, H-79, Maringá, Brazil. Tel.: +55 44 3011 3895; fax: +55 44 55 44 99145 9565. E-mail: sbperes@uem.br, sbperes@icloud.com



<sup>&</sup>lt;sup>1</sup> Department of Physiological Sciences, State University of Maringá, Maringá, Brazil

<sup>&</sup>lt;sup>2</sup> Health Sciences Center, State University of North of Paraná, Jacarézinho, Brazil

<sup>&</sup>lt;sup>3</sup> UniCesumar University, Maringá, Brazil

<sup>&</sup>lt;sup>4</sup> Department of Physical Education, State University of Maringá, Maringá, Brazil

## INTRODUCTION

Obesity, a result of positive energy balance, is one of the most common epidemiological problems in public health worldwide [1]. Recently, the incidence of obesity has increased, and obesity prevalence has risen to almost pandemic proportions [2]. Lack of exercise decreases aerobic capacity, and unhealthy eating habits are closely associated with metabolic syndromes such as diabetes, hypertension, and obesity [3]. The benefits of regular exercise in addition to an active lifestyle are well documented, especially for the prevention and treatment of obesity [4, 5].

To improve adherence to exercise, public health agencies have recommended short exercise sessions to improve the acceptability of this form of exercise for the obese population [6].

High-intensity interval training (HIIT) is a model of training that involves repeated short-tolong bouts of high-intensity exercise interspersed with passive or active recovery periods [3, 7]. The major benefits of HIIT are improvement of cardiorespiratory function, anaerobic metabolism, and neuromuscular response in short exercise sessions [8]. Physical exercise has long been used as a non-pharmacological treatment for weight loss [9], and HIIT has been shown to improve fat oxidation [10]. However, there is no direct evidence linking the fat oxidation caused by HIIT with the improvement in body composition, mainly related to weight and fat loss, in rodent models. Furthermore, it is essential to analyze differences in HIIT protocols and their efficiency in experimental models involving animals.

Thus, the objective of this systematic review was to analyze the effect of HIIT on body composition in obese rodents and to compare the responses of different species, diets, and methods of training in terms of body weight.

## METHODOLOGY

# Search strategy

Data search was performed from September 2019 to February 2021 by two independent researchers on the following databases: MEDLINE, EMBASE, Web of Science, Scielo, PUBMED, and Science Direct, as well as manual search in specific journals and reviews already published. The search strategy was: ((HIIT) OR (HIIT) OR (HIIE) OR (high-intensity interval) OR (interval training) OR (sprint-interval training) OR (sprint repeated) OR (sprint training) OR ("very-heavy exhaustive exercise) OR (heavy intensity exercise)) AND ((fat) OR (adipose) OR (body composition) OR (adiposity)) AND ((animals) OR (mice) OR (rats)). The search strategy was adapted for each database as necessary, the search period was not limited, and articles in English and Spanish were included. The review protocol was registered in the *Systematic Review Center for Laboratory Animal Experimentation* (SYRCLE) for animal experimentation studies (www.radboudumc.nl/getmedia/efa3a409-bf71-428e-868a-7abf2dc10f38/SYRCLE-protocol-Effect-of-High-Intensity-Interval-Training.aspx).

## Inclusion and exclusion criteria

The selection of articles was carried out in pairs, and in the case of disagreements, a third examiner was consulted for a final consensus. The selected titles and abstracts were analyzed based on the following inclusion criteria: experimental trials with only obese rodents that



presented at least two intervention groups, at least one of them being characterized as HIIT. Four weeks was considered the minimum intervention period. Investigations were excluded when the animals were submitted to an acute exercise session and presented any dysfunction such as: metabolic syndrome, hypertension, or diabetes. Aged rodents, transgenic animals, case reports, and observational studies were also excluded. A manual search of the reference lists of the accepted articles was performed to cover all the potential articles for inclusion.

In addition, we considered the *American College of Sports Medicine* (ACSM) recommendations for vigorous-intensity exercise [11]. Only fully reported studies were eligible (e.g., short communications and abstracts were excluded). Subsequently, the articles were obtained in their full version for a complete analysis of the text. All articles that presented outcomes directly related to inclusion criteria were included.

## Risk of bias

To verify and ensure the quality of the selected studies, the SYRCLE, for systematic reviews on animal interventions, was individually applied to all the selected studies. The risk of bias consists of eleven items evaluated in pairs from simple and direct questions considering the following risk scales: "yes", "no" and "not reported" [12]. One point was assigned when the answer was marked as "yes". The global score ranged from zero to 11, where 11 was the best possible score. The closer an article got to score 11, the greater its strength and quality. However, in the current systematic review, it was not used as an exclusion criterion (Table 1).

# Meta-analysis

Statistical analysis was performed using Review R Language software (R-Project, version 3.5.1) using meta and metafor packages. A meta-analysis was performed to quantify the effects of HIIT on body weight, adiposity index, and fat pads. Body weight was analyzed in subgroups from the variables: species (rats and mice), diet (high-fat and obese model), methods of training (treadmill and swimming), and fat pads were analyzed in subgroups according to epididymal, retroperitoneal, and subcutaneous adipose tissue. To reduce bias, only randomized trials meeting the search criteria were considered for the analysis. Additional sensitivity analyses examined the individual effects of all the studies. The value of  $P \le 0.05$  was adopted as a statistically significant difference for the fixed and random effect model.

# **RESULTS**

#### Literature search

The flow chart of the studies' selection is shown in Fig. 1. Searches on electronic databases retrieved 524 potential references. After the removal of the duplicates, reading of the titles, abstracts, and examination of the complete texts, only 14 studies were selected for composing the current systematic review and included in the meta-analysis (Table 2).

## Risk of bias

Table 1 shows the bias risk assessment of included studies according to SYRCLE's tool [12]. The global ratings of the studies' quality assessment scores range from 3 to 8. All the studies





Table 1. Quality assessment of the included studies

		10000	Q 444111	, 40000		the me								
	Study ID													
Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Was it stated that the experiment was randomized at any level?	Y	Y	Y	Y	NR	NR	Y	Y	NR	NR	NR	Y	Y	Y
2. Was it stated that the experiment was blinded at any level?	Y	Y	Y	N	Y	Y	N	Y	N	N	N	Y	Y	Y
3. Was the allocation sequence adequately generated and applied?	Y	Y	Y	Y	Y	NR	N	Y	NR	NR	NR	Y	Y	Y
4. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was the allocation adequately concealed?	N	N	N	N	N	N	N	Y	N	N	N	Y	N	N
6. Were the animals randomly housed during the experiment?	N	N	Y	Y	Y	NR	NR	NR	Y	Y	NR	Y	Y	Y
7. Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
8. Were animals selected at random for outcome assessment?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
9. Was the outcome assessor-blinded?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
10. Were incomplete outcome data adequately addressed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. Was the study apparently free of other problems that could result in a high risk of bias?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total score	6	5	7	6	6	4	4	7	4	4	3	8	7	7

Abbreviations: Y: yes; N: no; NR: not reported.

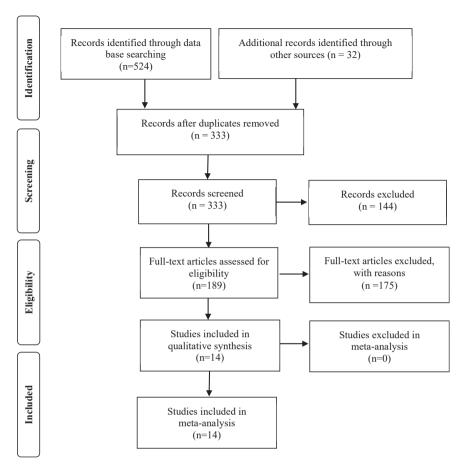


Fig. 1. Flow diagram of the systematic review

presented clear objectives and specific samples, nonetheless analysis showed potential confounding variables because of a considerable amount of unreported information and lack of randomization and blinding during the experimental animal studies.

# Characteristics of the sample and intervention

The characteristics of the studies are summarized in Table 2. As for the samples, 277 rodents (Wistar rats n = 49; Zucker rats n = 64; Sprague-Dawley rats n = 16; C57Bl/6 mice n = 128; ICR mice n = 20) were used in the included trials. Most of the studies used rodents with obesity induced by a high-fat diet (HFD: [3, 13–20]), high fat and carbohydrate content (HFDC: [21]), or high fructose (HF: [22]). Only the remaining three studies used a genetic obese model (GOM: [23–25]).

# **Training protocols**

The training protocols included in the analysis (Table 2) lasted for 4–16 weeks with the rodents submitted to 18 - 60 sessions of HIIT training. Trials used different variables to





Table 2. Characteristics of studies and HIIT protocols in rodents with obesity

Autor, Year	Groups	Animals	Diet	Time	Sessions	Intensity	Volume	Type
Batacan et al. 2016	HIIT $(n = 10)$ CLT $(n = 12)$	Wistar	High-fat-diet- carbohydrate	12 weeks	60	Inclination: 0–10% Active: maximal aerobic capacity Rest: passive	22 min of 4 bouts (2.5 min active/3 min rest)	Treadmill
Coll Risco L. et al. 2017	AIF al $(n = 8)$ SED al $(n = 8)$	Zucker	Genetic obese model	8 weeks	40	Inclination: 0% Active: $65-80\%$ VO <sub>2max</sub> Rest: $50-65\%$ VO <sub>2max</sub>	30 min of bouts (3 min active/3 min active rest)	Treadmill
Groussard et al. 2019	HIIT $(n = 12)$ CONT $(n = 12)$	Zucker	Genetic obese model	10 weeks	50	Inclination: 0% Active: $65-80\%$ VO <sub>2max</sub> Rest: $50-65\%$ VO <sub>2max</sub>	42 min of 6 bouts (4 min active/3 min active rest)	Treadmill
Khalafi et al. 2020	Ob-HIIT $(n = 8)$ Ob-22w $(n = 8)$	Wistar	High-fat diet	12 weeks	60	Inclination: 0% Active: 85–90% maximal running speed Rest: 50% maximal running speed	60 min of 10 bouts (4 min active/2 min active rest)	Treadmill
Maillard et al. 2019	HIIT $(n = 12)$ CONT $(n = 12)$	Zucker	Genetic obese model	10 weeks	50	Inclination: $0\%$ Active: $65-80\%$ VO <sub>2max</sub> Rest: $50-65\%$ VO <sub>2max</sub>	42 min of 6 bouts (4 min active/3 min active rest)	Treadmill
Marcinko et al. 2015	HFD+Exercise- WT $(n = 8)$ HFD-WT $(n = 6)$	C57Bl/6	High-fat diet	6 weeks	18	Inclination: 0% Active: maximal running speed Rest: passive	60 min of bouts (2 min active/2 min rest)	Treadmill
								(continued)

Table 2. Continued

Autor, Year	Groups	Animals	Diet	Time	Sessions	Intensity	Volume	Type
Marques-Neto et al. 2020	HFD+HIIT $(n = 5)$ $HFD (n = 6)$	Wistar	High-fat diet	4 weeks	20	Inclination: 0% Active: 85% VO <sub>2max</sub> Rest: 60% VO <sub>2máx</sub>	47 min of 7 bouts (3 min active/3 min active rest)	Treadmill
Martinez- Huenchullan et al. 2018	HFD+HIIT $(n = 12)$ $HFD untrained$ $(n = 12)$	C57Bl/6	High-fat diet	10 weeks	30	Inclination: 0% Active: 90% maximal running capacity Rest: 50% maximal running capacity	40 min of bouts (2.5 min active/2.5 active rest)	Treadmill
Motta et al. 2016 (a) [17]	OB-T $(n = 10)$ OB-NT $(n = 10)$	C57Bl/6	High-fat diet	12 weeks	36	Active: 10–15% of the body weight Rest: passive	50% maximal work bouts (20 s active/10 s rest)	Swimming
Motta et al. 2016 (b)	OB-T $(n = 10)$ OB-NT $(n = 10)$	C57Bl/6	High-fat diet	12 weeks	36	Active: 10–15% of the body weight Rest: passive	50% maximum work bouts (20 s active/10 s rest)	Swimming
Motta et al. 2019	F-HIIT $(n = 15)$ F-NT $(n = 15)$	C57Bl/6	High-fructose diet	8 weeks	24	Inclination: 0% Active: 80–90% VO <sub>2max</sub> Rest: 30% VO <sub>2max</sub>	Maximum repetition bouts (2 min active/1 min active rest)	Treadmill
Pimenta et al. 2015 [18]	SHAM-HF-T $(n = 10)$ SHAM-HF-NT $(n = 10)$	C57Bl/6	High-fat diet	8 weeks	24	Active: 10–14% of the body weight Rest: passive	50% maximum work bouts (20 s active/10 s rest)	Swimming
Rocha et al. 2016	ITH $(n = 8)$ CH $(n = 8)$	Sprague- Dawley	High-fat diet	8 weeks	40	Active: 5–16% of the body weight Rest: passive	10 min of 5 bouts (60 s active/60 s rest); 7 min of 14 bouts (20 s active/10 s rest)	Swimming
								(continued)



324



Table 2. Continued

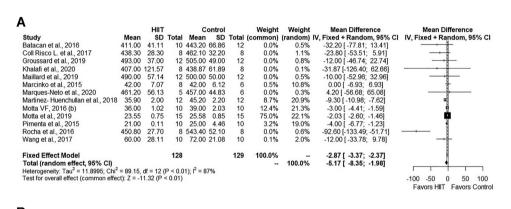
Autor, Year	Groups	Animals	Diet	Time	Sessions	Intensity	Volume	Type
Wang et al. 2017	HIIT $(n = 10)$ CON $(n = 10)$	ICR mice	High-fat diet	8 weeks	40	Inclination: 25% Active: 85–90% VO <sub>2max</sub> Rest: 30% VO <sub>2máx</sub>	60 min of 10 bouts (4 min active/2 min active rest)	Treadmill

Abbreviations: n = number of samples; HIIT: High-intensity interval training; CTL: Control/AIF al: Aerobic interval exercise combined with resistance training ad libitum; SED al: Sedentary ad libitum/HIIT: High-intensity interval training; CONT: Control/Ob-HIIT: Obesity + high-intensity interval training; Ob-22w: Obesity + sedentary/HFD+Exercise-WT: High-fat-diet + exercise - wild-type; HFD-WT: High-fat diet - wild-type/HFD+HIIT: High-fat diet + high-intensity interval training; HFD: High-fat diet/HFD+HIIT: High-fat diet + high-intensity interval training; HFD untrained: High-fat diet untrained/OB-T: Trained obese animals; OB-NT: Non-trained obese animals/F-HIIT: Fructose diet high-intensity interval training; F-NT: Fructose diet nontrained/SHAM HF-T: Sham-high-fat diet-trained; SHAM HF-NT: Sham-high-fat diet-non-trained/ITH: Interval training high-fat diet; CH: Control high-fat diet/HIIT: High-intensity interval training; CON: Control; VO<sub>2max</sub>.: Maximum oxygen uptake; Min: Minute; Sec: Second.

measure training intensity like inclination, maximal running speed, maximal aerobic capacity  $(VO_{2max})$ , and the body mass percentage. As to the rest intervals, eight studies used active rest [3, 14, 15, 20, 22–25] whereas the other six studies, passive rest [14, 16–19, 21]. Ten studies employed HIIT in the treadmill [3, 13–15, 20–25] and four used the water tank for swimming [16–19].

# Meta-analyses

Finally, 14 trials were included in the meta-analysis. Firstly, we analyzed the effects of HIIT on body weight (Fig. 2A). The data showed a general heterogeneity (I<sup>2</sup>) of 87% and a mean



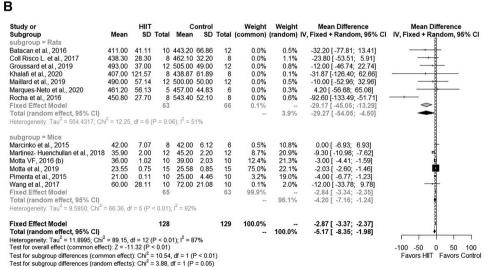


Fig. 2. Forest plot of (A) The changes in body weight in the trained and control groups; (B) The changes in body weight in the trained and control groups in rats vs. mice. Squares represent the mean difference (MD) for each trial, and diamonds represent the pooled MD across trials. SD: standard deviation; IV: inverse variance: 95% CI: 95% confidence intervals



difference of -5.17 [CI 95%: -8.35; -1.98] (Diamond). A significant effect was observed in the fixed model ( $P \le 0.01$ ), suggesting a reduction of body weight as an effect of HIIT intervention. In addition, to understand the responsiveness of the rodent species to training, we analyzed the body weight of animals submitted to HIIT vs. controls by subgroups (Fig. 2B). We observed that rats showed an  $I^2$  of 51% and a mean difference of -29.27 [CI 95%: -54.05; -4.50] exhibiting a higher magnitude of response compared with mice that presented an  $I^2$  of 92% and a mean difference of -4.20 [CI 95%: -7.16; -1.24], with significant random effect (P = 0.05).

In Fig. 3 we observed a significant effect in the fixed model ( $P \le 0.01$ ) for adiposity of rodents in favor of HIIT over to the control, with I<sup>2</sup> of 78% and mean difference of -0.92 [CI 95%: -1.04; -0.80]. Also, Fig. 4 shows that HIIT induced a significant decrease in fat pad weight ( $P \le 0.01$ ), with a high I<sup>2</sup> of 84% and mean difference of -0.32 [CI 95%: -0.59; -0.06]. Nonetheless, no statistical difference was observed between the subgroups in trained animals (Fig. 4). The epididymal tissue had a mean difference of -0.23 [CI 95%: -0.53; 0.07] and an I<sup>2</sup> of 56%, retroperitoneal tissue had a mean difference of -2.44 [CI 95%: -8.62; 3.74] and an I<sup>2</sup> of 74%, and subcutaneous tissue presented a mean difference of -0.39 [CI 95%: -0.93; 0.15] and an I<sup>2</sup> of 97% when compared to the control group.

Figure 5 shows the effect of HIIT on body weight according to different strategies to induce obesity in the animals. The analysis showed an  $I^2$  of 90% and a mean difference of -4.85 [CI 95%: -8.03; -1.68] for HFD and an  $I^2$  of 0% and a mean difference of -16.91 [CI 95%: -36.89; 3.08] for GOM, with overall significant effect in favor of HIIT ( $P \le 0.01$ ). No statistical difference was observed between groups.

Finally, the effects of HIIT performed in water (swimming) were compared to those of HIIT performed on the treadmill (Fig. 6). Both swimming and treadmill were efficient to decrease body weight ( $Z=-11.32,\ P\leq0.01$ ), and no statistical difference between the subgroups was identified. The mean difference of the body weight to the animals trained on the treadmill was -5.72 [CI 95%: -10.73; -0.71] with an I<sup>2</sup> of 87% and the mean difference to the animals trained in the water was -29.74 [CI 95%: -84.26; 24.78] with an I<sup>2</sup> of 89%.

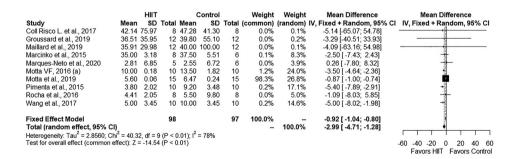


Fig. 3. Forest plot of the changes in adiposity index (%) in the trained and control groups. Squares represent the mean difference (MD) for each trial, and diamonds represent the pooled MD across trials.

SD: standard deviation: IV: inverse variance: 95% CI: 95% confidence intervals



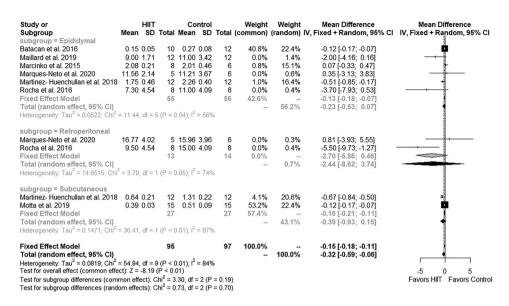


Fig. 4. Forest plot of the changes in fat pads in the trained and control groups. Squares represent the mean difference (MD) for each trial, and diamonds represent the pooled MD across trials. SD: standard deviation; IV: inverse variance; 95% CI: 95% confidence intervals

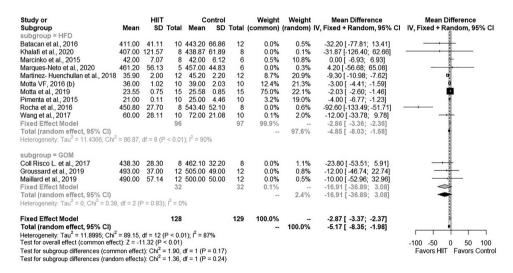


Fig. 5. Forest plot of the changes body weight in the trained and control groups subjected to a high-fat diet or genetically obese. Squares represent the mean difference (MD) for each trial, and diamonds represent the pooled MD across trials. SD: standard deviation; IV: inverse variance; 95% CI: 95% confidence intervals; HFD: high-fat diet; GOM: genetic obese model



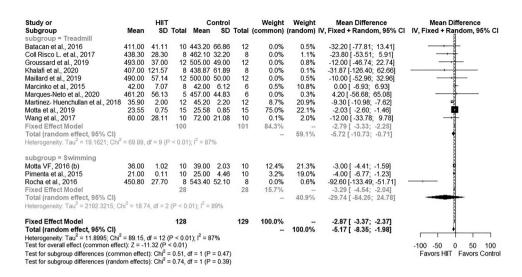


Fig. 6. Forest plot of the changes body weight in the trained and control groups submitted to treadmill vs. swimming. Squares represent the mean difference (MD) for each trial, and diamonds represent the pooled MD across trials. SD: standard deviation; IV: inverse variance; 95% CI: 95% confidence intervals

# DISCUSSION

The present systematic review and meta-analysis evaluated the effect of HIIT on the body composition of obese rodents. The primary outcomes indicated that HIIT induces a significant decrease in body weight, adiposity index, and fat pad weight and improves body mass composition. Also, HIIT effectively reduced the body weight of animals subjected to HFD and induced GOM. Finally, HIIT performed both on the treadmill and in water was effective in reducing body weight.

Since obesity is characterized by excessive adipose tissue accumulation [26], we could expect a concomitant reduction in the size and the number of adipocytes with physical exercise that accompanies weight loss [3]. However, previous studies have revealed histological changes in adipocytes that demonstrated a catabolic state without weight loss [3]. A study by Marques Neto et al. [14] suggested that HIIT can improve fitness without leading to fat loss. In contrast, we demonstrate the effectiveness of HIIT in inducing weight loss and reducing adiposity in this study. The decrease in fat deposits can be explained by specific changes in the lipolysis pathway, including the sensitivity of adrenergic or insulin receptors, lipase activity, and mitochondrial adaptations [24].

We also investigated whether HIIT reduced fat pad weights in specific subgroups of adipose tissue (epididymal, retroperitoneal, and subcutaneous). Although the results were in favor of the HIIT group compared to the control group, no statistical difference was observed between epididymal, retroperitoneal, and subcutaneous adipose tissue.

The visceral (epididymal and retroperitoneal) and subcutaneous adipose tissues present morphological similarities and are characterized mainly by white adipocytes that store lipids in the triglyceride form [27], yet they reveal different metabolic responses. It is known that the



lipolytic response induced by catecholamines in visceral adipose tissue is greater than that in subcutaneous adipocytes, suggesting greater sensitivity of visceral deposits to changes induced by exercise [24]. However, despite HIIT's reducing adipose tissue, in particular visceral adipose tissue [20, 25], which is responsible for numerous metabolic complications, we found no significant differences between the analyzed subgroups, i.e. visceral and subcutaneous. The present study provides evidence that HIIT performed chronically reduces body weight and adiposity (visceral and subcutaneous), improving body composition.

Based on the results, considering the bias of the response that may have generated high heterogeneity when using the two species in the same analysis, and the specificity of the magnitude of response that both species may contain, this study determined distinct responses between rodent species used in HIIT studies. We observed that rats were more responsive to HIIT and showed a greater reduction in body weight than mice. It is important to note that rats have greater body mass than mice. Thus, the mean difference between the final weight of the trained animals and the initial weight of the controls after the intervention was –31.9 and –5.05 g for rats and mice, respectively. The percentage of total weight reduction was observed to be –7.77% of the initial body mass in rats and –14.08% in mice.

Based on these data, we observed that although the absolute reduction in body weight measured in grams was greater in rats than in mice, the proportion of body weight lost in mice was higher than that in rats. These findings can be explained by the superior metabolic activity of mice and the reluctance of obese rats to undergo training [23]. So, we suggest here that obese mice are a good model to test the beneficial effects of physical exercise programs, especially HIIT training.

The effectiveness of HIIT in reducing the body weight of animals subjected to HFD and GOM was evaluated. HFD, a 60% fat diet, is commonly used to induce obesity as it promotes metabolic changes similar to those observed in human obesity [19] and increases fat stores in the form of triglycerides [19, 28]. On the other hand, in one type of genetic model of obesity, a leptin protein mutation predisposes rodents to hyperphagia [23, 29]. In this model, the animals also exhibit the entire pathological, biochemical, and metabolic profile of obesity, such as hyperinsulinemia, hyperlipidemia, insulin resistance, and adipocyte hypertrophy [24, 29]. Both models are efficient in stimulating adipocyte lipogenesis and hyperplasia that indicate obesity [30].

According to Muller et al. [31], HIIT demands the anaerobic glycolytic system to complement muscle energy production. Energy production through anaerobic glycolysis is oxygen-independent, thus representing the rapid but limited pathway of ATP delivery through glucose hydrolysis [32]. The depletion of glucose hydrolysis promotes the mobilization of lipids excess stored in white adipose tissue as triacylglycerol (TAG). The mobilization of lipids in WAT plays a key role in the metabolic alterations present in obesity. The sympathetic nervous system (SNS) is the main responsible factor for WAT lipolysis [33]. Lipolysis occurs in response to adrenergic stimulation by catecholamines, especially adrenaline, via adrenergic receptors in the adipocytes, increasing lipolytic activity through HSL phosphorylation that binds to the fatty acid binding proteins hydrolyzing the TAG in glycerol and free fatty acids to supply the energy demands of other tissues and organs [5] reducing body weight [34]. In addition to increasing lipolytic activity, HIIT can also inhibit appetite [34], which is another important point relevant to the constant exposure to HFD and hyperphagia in GOM animals.

Most human HIIT studies are performed on cycle ergometers, thus limiting the comparison with alternative protocols [10]. On the other hand, HIIT studies in rodents are commonly



performed on treadmills or in water tanks, allowing the analysis of different training protocols. In the present study, both training protocols were shown to efficiently reduce body weight.

Studies indicate that HIIT performed at  $90{\text -}100\%$  of  $VO_{2\text{max}}$  can generate metabolic and physiological adaptations for weight loss [13]. On the treadmill, the intensity used in the various studies ranged from 65 - 90%  $VO_{2\text{max}}$  or maximal running speed ( $16{\text -}24\,\text{m min}^{-1}$ ) [35], above the speed of the lactate threshold ( $12.5\,\text{m min}^{-1}$ ) [36]. In water (swimming), the use of individualized external overload, ranging from 5% to 16%, is seen in most studies [ $16{\text -}19$ ]. A previous study indicated that the lactate threshold was reached with loads between 5 and 6% of body weight [35]. Thus, when applied at intensities higher than those indicated to reach  $VO_{2\text{max}}$  and lactate threshold, both methods effectively reduce body weight. HIIT protocols vary widely among interventions [37], and critical variables such as intensity and volume directly influence training results by either decreasing or not altering body weight and adiposity. Studies comparing different volumes and methods of HIIT would help to evaluate differences between the two training types as per the different manipulations found in the variables used to control the training intensity, such as  $VO_{2\text{max}}$ , lactate threshold, maximum running speed, and load (referring to % body weight).

Traditionally, moderate-intensity continuous training (MICT) has been the common type of exercise recommended to improve body composition [20]. However, much is discussed about the efficiency of MICT versus HIIT in adiposity and obesity. Despite the limited data available for analyzing MICT versus HIIT it is important to note that previous studies have observed that HIIT suppresses the increase in fat mass, decreases the visceral adipose tissue, the fat mass and the body weight, when compared to MICT [10, 20, 38].

Our findings demonstrate that in a short time (4 weeks), HIIT provides a potent stimulus to reduce body weight and fat pads thus improving the body composition of obese rodents. Moreover, the reduction of visceral fat is extremely relevant since it implies improvements in the metabolic profile independent of weight loss. Another strength of this study is the assessment of different species and HIIT methods (treadmill vs. water tank), considering that studies commonly compare HIIT with moderate-intensity continuous exercise. Thus, this work may shed light on the importance of comparing different HIIT methods based on volume, intensity, and duration and the possibility of manipulating these variables as well as the importance of choosing the rodent species for studying physical exercise.

Furthermore, we believe that the findings of this study cannot be translated into humans, because rodents are not exposed to environmental factors that can influence the results obtained with HIIT. Thus, this study was developed to guide researchers from the experimental line of animals with obesity providing answers about the HIIT as a non-pharmacological treatment.

This review has some limitations, such as none of the studies reported how obesity is evaluated, for example by the Lee index or adiposity index [39], and we suggest to insert this information in the next clinical trials. Other limitations are the inability to compare the effect of HIIT before and after the intervention, and the limited data available for analyzing the fat pad weights. However, it is worth emphasizing that the high heterogeneity found in the data is common in laboratory animal studies.

In conclusion, the current study emphasizes that HIIT attenuates body weight and adiposity induced by HFD and GOM. Moreover, HIIT causes positive changes in body mass composition, with the advantage of short exercise bouts, thus suggesting HIIT as a form of obesity treatment.



Furthermore, mice were more responsive than rats, and both treadmill and swimming effectively reduced body weight.

Author contributions: A.F.S and D.A.G provided the conception and design of the research; A.F.S and J.P.F. performed searches, selected the articles and assessed the quality of the studies; A.F.S and B.F.S analyzed the data, interpreted the results, prepared the figures and drafted the manuscript; A.F.S, B.F.S, S.M.F and S.B.P edited, revised and approved the final version of the manuscript.

Conflict of interest statement: The authors declare no conflict of interest.

# **ACKNOWLEDGMENTS**

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES).

## REFERENCES

- 1. Pereira Junior M, Andrade RD, Silveira FV, Baldissera UM, Korbes AS, Navarro F. Exercício físico resistido e síndrome metabólica: uma revisão sistemática [Exercise resistance and metabolic syndrome: a systematic review]. Rev Bras Prescr Fisiol Exerc 2013; 7(42): 529–39.
- Verheggen RJ, Maessen MF, Green DJ, Hermus AR, Hopman MT, Thijssen DH. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. Obes Rev 2016; 17(8): 664–90. https://doi.org/10.1111/obr.12406.
- 3. Khalafi M, Mohebbi H, Symonds ME, Karimi P, Akbari A, Tabari E, et al. The impact of moderate-intensity continuous or high-intensity interval training on adipogenesis and browning of subcutaneous adipose tissue in obese male rats. Nutrients 2020; 12(4): 925. https://doi.org/10.3390/nu12040925.
- 4. Aldiss P, Lewis JE, Lupini I, Bloor I, Chavoshinejad R, Boocock DJ, et al. Exercise training in obese rats does not induce browning at thermoneutrality and induces a muscle-like signature in brown adipose tissue. Front Endocrinol (Lausanne) 2020; 11: 97. https://doi.org/10.3389/fendo.2020.00097.
- 5. Wedell-Neergaard AS, Lang Lehrskov L, Christensen RH, Legaard GE, Dorph E, Larsen MK, et al. Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling: A randomized controlled trial. Cell Metab 2019; 29(4): 844–55. e3. https://doi.org/10.1016/j.cmet.2018.12.007.
- Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004; 351(26): 2694–703. https://doi.org/10.1056/ NEJMoa042135.
- Davis RAH, Halbrooks JE, Watkins EE, Fisher G, Hunter GR, Nagy TR, et al. High-intensity interval training and calorie restriction promote remodeling of glucose and lipid metabolism in diet-induced obesity. Am J Physiol Endocrinol Metab 2017; 313(2): E243–56. https://doi.org/10.1152/ajpendo.00445.2016.
- 8. Hoshino D, Yoshida Y, Kitaoka Y, Hatta H, Bonen A. High-intensity interval training increases intrinsic rates of mitochondrial fatty acid oxidation in rat red and white skeletal muscle. Appl Physiol Nutr Metab 2013; 38(3): 326–33. https://doi.org/10.1139/apnm-2012-0257.



- 9. Higuera-Hernandez MF, Reyes-Cuapio E, Gutierrez-Mendoza M, Rocha NB, Veras AB, Budde H, et al. Fighting obesity: Non-pharmacological interventions. Clin Nutr ESPEN 2018; 25: 50–5. https://doi.org/10.1016/j.clnesp.2018.04.005.
- Shen Y, Xu X, Yue K, Xu G. Effect of different exercise protocols on metabolic profiles and fatty acid metabolism in skeletal muscle in high-fat diet-fed rats. Obesity (Silver Spring) 2015; 23(5): 1000–6. https://doi.org/10.1002/oby.21056.
- 11. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011; 43(7): 1334–59. https://doi.org/10.1249/MSS.0b013e318213fefb.
- 12. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014; 14: 43. https://doi.org/10.1186/1471-2288-14-43.
- 13. Marcinko K, Sikkema SR, Samaan MC, Kemp BE, Fullerton MD, Steinberg GR. High intensity interval training improves liver and adipose tissue insulin sensitivity. Mol Metab 2015; 4(12): 903–15. https://doi.org/10.1016/j.molmet.2015.09.006.
- 14. Marques Neto SR, Castiglione RC, da Silva TCB, Paes LDS, Pontes A, Oliveira DF, et al. Effects of high intensity interval training on neuro-cardiovascular dynamic changes and mitochondrial dysfunction induced by high-fat diet in rats. PLoS One 2020; 15(10): e0240060. https://doi.org/10.1371/journal.pone.0240060.
- 15. Martinez-Huenchullan SF, Maharjan BR, Williams PF, Tam CS, McLennan SV, Twigg SM. Differential metabolic effects of constant moderate versus high intensity interval training in high-fat fed mice: possible role of muscle adiponectin. Physiol Rep 2018; 6(4): e13599. https://doi.org/10.14814/phy2.13599.
- Motta VF, Aguila MB, Mandarim-de-Lacerda CA. High-intensity interval training beneficial effects in diet-induced obesity in mice: adipose tissue, liver structure, and pancreatic islets. Int J Morphol 2016; 34(2): 684–91. https://doi.org/10.4067/S0717-95022016000200042.
- 17. Motta VF, Aguila MB, Mandarim-de-Lacerda CA. High-intensity interval training (swimming) significantly improves the adverse metabolism and comorbidities in diet-induced obese mice. J Sports Med Phys Fitness 2016; 56(5): 655–63.
- Pimenta M, Bringhenti I, Souza-Mello V, Dos Santos Mendes IK, Aguila MB, Mandarim-de-Lacerda CA. High-intensity interval training beneficial effects on body mass, blood pressure, and oxidative stress in diet-induced obesity in ovariectomized mice. Life Sci 2015; 139: 75–82. https://doi.org/10.1016/j.lfs.2015.08.004.
- 19. da Rocha GL, Crisp AH, de Oliveira MR, da Silva CA, Silva JO, Duarte AC, et al. Effect of high intensity interval and continuous swimming training on body mass adiposity level and serum parameters in high-fat diet fed rats. ScientificWorldJournal 2016; 2016: 2194120. https://doi.org/10.1155/2016/2194120.
- 20. Wang N, Liu Y, Ma Y, Wen D. High-intensity interval versus moderate-intensity continuous training: Superior metabolic benefits in diet-induced obesity mice. Life Sci 2017; 191: 122–31. https://doi.org/10.1016/j.lfs.2017.08.023.
- 21. Batacan RB, Jr., Duncan MJ, Dalbo VJ, Buitrago GL, Fenning AS. Effect of different intensities of physical activity on cardiometabolic markers and vascular and cardiac function in adult rats fed with a high-fat high-carbohydrate diet. J Sport Health Sci 2018; 7(1): 109–19. https://doi.org/10.1016/j.jshs.2016.08.001.
- 22. Motta VF, Bargut TL, Souza-Mello V, Aguila MB, Mandarim-de-Lacerda CA. Browning is activated in the subcutaneous white adipose tissue of mice metabolically challenged with a high-fructose diet submitted to high-intensity interval training. J Nutr Biochem 2019; 70: 164–73. https://doi.org/10.1016/j.jnutbio.2019.05.008.
- 23. Coll-Risco I, Camiletti-Moirón D, Tirado DJ, Nebot E, Andrade A, Martínez R, et al. Efectos del ejercicio aeróbico interválico, combinado con entrenamiento de fuerza y de la restricción calórica, sobre la composición corporal de ratas obesas [Effects of aerobic interval exercise combined with resistance training and



- caloric restriction, on body composition in obese rats]. Rev Andal Med Deport 2017; 10(1): 3–8. https://doi.org/10.1016/j.ramd.2015.04.006.
- 24. Groussard C, Maillard F, Vazeille E, Barnich N, Sirvent P, Otero YF, et al. Tissue-specific oxidative stress modulation by exercise: A comparison between MICT and HIIT in an obese rat model. Oxid Med Cell Longev 2019; 2019: 1965364. https://doi.org/10.1155/2019/1965364.
- 25. Maillard F, Vazeille E, Sauvanet P, Sirvent P, Combaret L, Sourdrille A, et al. High intensity interval training promotes total and visceral fat mass loss in obese Zucker rats without modulating gut microbiota. PLoS One 2019; 14(4): e0214660. https://doi.org/10.1371/journal.pone.0214660.
- 26. Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: A systematic review and meta-analysis. Obes Rev 2017; 18(6): 635–46. https://doi.org/10.1111/obr.12532.
- 27. Ueta CB, Fernandes GW, Capelo LP, Fonseca TL, Maculan FD, Gouveia CH, et al. β(1) Adrenergic receptor is key to cold- and diet-induced thermogenesis in mice. J Endocrinol 2012; 214(3): 359–65. https://doi.org/10.1530/JOE-12-0155.
- 28. Speakman J, Hambly C, Mitchell S, Krol E. The contribution of animal models to the study of obesity. Lab Anim 2008; 42(4): 413–32. https://doi.org/10.1258/la.2007.006067.
- 29. Chorilli M, Michelin DC, Salgado HRN. Animais de laboratório: O camundongo [Laboratory animals: The mouse]. Rev Cienc Farm Basica Apl 2007; 28(1): 11–23.
- 30. Queiroz JC, Alonso-Vale MI, Curi R, Lima FB. Controle da adipogênese por ácidos graxos [Control of adipogenesis by fatty acids]. Arq Bras Endocrinol Metabol 2009; 53(5): 582–94. https://doi.org/10.1590/s0004-27302009000500011.
- 31. Muller GY, de Amo AHE, Vedovelli KS, Mariano IR, Bueno GC, Furlan JP, et al. Resistance high-intensity interval training (HIIT) improves acute gluconeogenesis from lactate in mice. Am J Sports Sci 2019; 7(2): 53–9. https://doi.org/10.11648/j.ajss.20190702.12.
- 32. Hardie DG. Organismal carbohydrate and lipid homeostasis. Cold Spring Harb Perspect Biol 2012; 4(5): a006031. https://doi.org/10.1101/cshperspect.a006031.
- 33. Rodrigues AC, Prímola-Gomes TN, Peluzio MCG, Hermsdorff HHM, Natali AJ. Aerobic exercise and lipolysis: A review of the  $\beta$ -adrenergic signaling pathways in adipose tissue. Sci Sports 2021; 36(1): 16–26. https://doi.org/10.1016/j.scispo.2020.04.006.
- Boutcher SH. High-intensity intermittent exercise and fat loss. J Obes 2011; 2011: 868305. https://doi.org/ 10.1155/2011/868305.
- 35. Gobatto CA, de Mello MA, Sibuya CY, de Azevedo JR, dos Santos LA, Kokubun E. Maximal lactate steady state in rats submitted to swimming exercise. Comp Biochem Physiol A Mol Integr Physiol 2001; 130(1): 21–7. https://doi.org/10.1016/s1095-6433(01)00362-2.
- 36. Rosa TS, Simoes HG, Rogero MM, Moraes MR, Denadai BS, Arida RM, et al. Severe obesity shifts metabolic thresholds but does not attenuate aerobic training adaptations in Zucker rats. Front Physiol 2016; 7: 122. https://doi.org/10.3389/fphys.2016.00122.
- 37. Jelleyman C, Yates T, O'Donovan G, Gray LJ, King JA, Khunti K, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: A meta-analysis. Obes Rev 2015; 16(11): 942–61. https://doi.org/10.1111/obr.12317.
- 38. Sun L, Li FH, Li T, Min Z, Yang LD, Gao HE, et al. Effects of high-intensity interval training on adipose tissue lipolysis, inflammation, and metabolomics in aged rats. Pflugers Arch 2020; 472(2): 245–58. https://doi.org/10.1007/s00424-020-02351-y.
- 39. Bastias-Perez M, Serra D, Herrero L. Dietary options for rodents in the study of obesity. Nutrients 2020; 12(11): 3234. https://doi.org/10.3390/nu12113234.

