Accepted manuscript

Effects of gradual weight loss vs rapid weight loss on body composition and resting metabolic rate: A systematic review and meta-analysis

Damoon Ashtary Larky [1], Reza Bagheri [2], Amir Abbasnezhad [3], Grant M. Tinsley [4], Meysam Alipour [1], and Alexei Wong [5, *]

1- Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

2- Department of Exercise Physiology, University of Isfahan, Isfahan, Iran.

3- Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran.

4- Department of Kinesiology & Sport Management, Texas Tech University, Lubbock, TX 79424, USA.

5- Department of Health and Human Performance, Marymount University, Arlington, United States.

Running title: Gradual vs rapid weight loss

Corresponding author: Alexei Wong, Email: awong@marymount.edu

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI
10.1017/S000711452000224X
The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

Abstract

This systematic review and meta-analysis compared the effects of different rates of weight loss (WL), but equivalent total WL, on body composition and resting metabolic rate (RMR). Studies examining gradual vs. rapid WL on body composition and RMR in participants with overweight/obesity published up to October 2019 were identified through PubMed, the Cochrane Library, Web of Science, Embase, SCOPUS, and Ovid databases. Meta-analysis was carried out using a fixed or random-effects model as appropriate. Although the magnitude of WL was similar (mean difference: 0.03 kg, 95% CI [-0.65, 0.71]), gradual WL promoted greater reductions in fat mass (FM) (-1 kg, 95% CI [-1.70, -0.29]) and body fat percentage (BFP) (-0.83%, 95% CI [-1.49, -0.17]). Gradual WL significantly preserved RMR compared with rapid WL (97.39 kcal, 95% CI [76.76, 118.01]). However, there was no significant difference in waist and hip circumferences, waist-to-hip ratio (WHR), and fat-free mass (FFM) between gradual and rapid WL. The present systematic review and meta-analysis indicates beneficial effects of gradual WL, as compared to rapid WL, on FM, BFP, and RMR in individuals with overweight/obesity. However, FFM changes and anthropometric indices did not significantly differ following different rates of WL.

Keywords: weight loss; obesity; fat free mass; fat mass; diet, body composition; resting metabolic rate; meta-analysis.

Introduction

Obesity is a major public health concern across the world[1]. Based on the World Health Organization (WHO) reports, 39% of adults aged 18 years and older (38% of men and 40% of women) were overweight [2]. The worldwide prevalence of obesity nearly doubled between 1980 and 2014, with 11% of men and 15% of women - equivalent to more than half a billion adults - classified as obese[2].

The definition of obesity is dependent upon the assessment method used (i.e. body mass index [BMI], waist circumference [WC], or body fat percentage [BFP]). BMI is the most common metric used for population and clinical screening for obesity[3; 4]. However, it has been clearly demonstrated that obesity is characterized by an excess accumulation of body fat rather than excess body weight alone[5; 6]. WHO defines obesity as an excessive accumulation of fat to the extent that health may be impaired[7]. Therefore, in addition to weight loss (WL) in general, preferential reduction of fat mass (FM) may be the best way to manage obesity and its complications[8]. As such, the relationships between FM and fat-free mass (FFM) during WL are worthy of consideration. Mathematical modeling by Hall expanded upon early attempts to quantify the proportion of body weight changes attributable to FFM and indicated a small effect of the magnitude of body weight change when initial FM is taken into account and changes in body weight are not large, such as is often observed in lifestyle interventions. [9] However, the rate of body weight change was not considered in these models, and the importance of further longitudinal investigations was emphasized.

Dietary interventions for WL have always been considered the first step in obesity management[10]. Accordingly, a variety of dietary interventions for WL have been suggested[11]. Numerous strategies are based on the distribution of macronutrients such as low-carbohydrate/high-fat, high-carbohydrate/low-fat [12], or low-carbohydrate/high protein diet[13], as well as manipulation of energy balance to promote either gradual or rapid WL[8]. Although rapid WL strategies remain appealing to individuals with obesity, it has been hypothesized that gradual WL may produce superior changes in body composition and anthropometric indices[8]. In the scientific literature, some researchers and professional organizations [14; 15; 16] have recommended a gradual WL approach, contending that gradual WL may produce better long-term weight management as compared to rapid WL, which is unlikely to be sustained. However, other researchers [17; 18; 19; 20] have posited that larger calorie deficits and subsequent rapid WL are more likely to reinforce the weight-change process and produce superior long-term WL outcomes. As a result, uncertainty remains regarding the ideal energy intake and rate of WL needed for optimal obesity management. Additionally, other physiological variables could reasonably be influenced by the rate of WL and its potential effects on body composition. Resting metabolic rate (RMR), as the largest component of total energy expenditure, is a proxy indicator of FFM[21]. Some studies showed that obese subjects decreased their RMR following

WL, which is influenced by a decrease in FFM [22; 23]. Moreover, the existence of a low RMR is likely to contribute to reaching to a WL plateau and/ or the high rate of weight regain[24; 25]. Changes in RMR with WL could potentially be influenced by the rate of WL *per se* or through effects on FFM.

It is hypothesized that slower WL leads to greater FM loss, and therefore gradual WL diets may better preserve FFM and RMR[26]. Yet, the general impact of the WL rate on body composition changes is unsettled, demonstrating the need for comprehensive systematic reviews and meta-examinations of clinical trials on this topic. Therefore, the aim of this study was to conduct a systematic review and meta-analysis of the pooled data from controlled adult human trials to compare the efficacy of dietary WL with different rates in individuals with overweight and obesity for body composition variables including FM, FFM, BFP, WC, hip circumference (HC), and waist to hip ratio (WHR), as well as RMR.

Experimental methods

The present systematic review and meta-analysis adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [27].

Data sources and search strategies

A comprehensive literature search of six databases, including PubMed, the Cochrane Library, Web of Science, Embase, SCOPUS, and Ovid, was performed using the keywords "weight loss," "rapid", "quick," "slow," "gradual," "rate of weight loss," "weight reduction", "diet", and "caloric restriction" in combination with the keywords "body composition", "fat mass", "fat free mass" and "resting metabolic rate" to identify studies in English languages published up to October 10, 2019. The process of study selection is shown in the flow diagram (Figure 1).

Study Selection and Quality Assessment

Two authors independently assessed trial eligibility and quality. To be eligible for inclusion, dietary trials had to evaluate gradual vs. rapid WL in patients with overweight/obesity (BMI>25) and report at least one additional body composition parameter or RMR. Trials where both rapid and gradual WL groups lost similar weight (≤ 2 kg between-group differences [28; 29] and/or no significant between-group differences) were included. The Cochrane Collaboration's tool for assessing the risk of bias was used to assess the risk of bias as previously described[30]. Briefly, nine items were scored, and these items were divided into 6 domains of bias with 3 rating categories available for each item: (1) low risk of bias; (2) unclear risk of bias; and (3) high risk of bias. All selected articles were scored by 2 authors (DAL and RB). The disagreement between the assessors was resolved by discussion, and in case of remaining discussion, a third assessor (AA) was consulted in order to make a final decision (Table 1).

Inclusion and exclusion criteria

Articles were included if they satisfied the following criteria: (1) original research article; (2) designed as a parallel or crossover trial; (3) conducted on humans 18 years of age or older; (4) used dietary-induced WL for interventions; (5) conducted on participants with overweight and/or obesity (6) assessed body composition parameters, anthropometric indices, or RMR; (7) intervention groups did not receive any food or supplement; and (8) similar total WL in both gradual and rapid WL group (<2kg between-group differences). Articles were excluded for: (1) unclear data; (2) lack of clear inclusion and exclusion criteria; (3) different amounts of WL and/or ≥ 2 kg differences between gradual and rapid WL groups; (4) inclusion of normal weight and/or athletic participants; and (5) short study durations (<2 weeks). For articles that contained unclear data, e-mail communications were sent to the corresponding authors to obtain additional information.

Outcomes and Data Extraction

Data from eligible studies were extracted by two investigators (DAL and MA) using an Excel form. The following data were extracted from each eligible study: first author, publication year, study location, study population, study design, sample size, type of body composition analysis, method of RMR measurement, age, sex ratio, measures of association, and brief results together with the adjusted covariates.

Data synthesis and analysis

Meta-analysis was carried out using Stata version 12.0 (Stata Corp., College Station, TX, USA). The fixed-effects model was used for the assessment of the pooled effect size. When heterogeneity was present, the random-effects model was used. Heterogeneity was tested using the I2 statistic, and an I2 value ≥50% with a level of significance of P<0.05 by the Cochran Q-test was interpreted as evidence of substantial heterogeneity. Publication bias was assessed by a funnel plot analysis, the Begg adjusted rank correlation test, and the Egger regression asymmetry test.

Additionally, the meaning test was used to assess the effect of individual studies by estimating the r values obtained when each study was omitted.

Results

Study selection

The first step of searching yielded 462, 47, 83, and 69 citations in PubMed, Cochrane Library, Web of Science and SCOPUS, respectively. Of these, 287 articles were excluded due to the duplication. The titles and abstracts of 338 articles were reviewed. Of these 323 studies were excluded due to the following reasons: animal model, reviews, non-dietary WL, and unrelated studies. Therefore, the full text of 15 studies assessed for eligibility. Eventually, 7 articles were included in this meta-analysis [8; 26; 31; 32; 33; 34; 35] (Figure 1). It should be noted that not all outcomes were reported in the 7 studies included.

Power analysis

A fixed-effect meta-analysis necessarily results in an increase in power[36]. Therefore, we have performed a power analysis for random effect meta-analysis[37]. According to the results, we used a random effect model only for FFM. The power calculated for FFM was 0.95.

Characteristics of included studies

All studies except for one were randomized-controlled studies. The intervention duration ranged from 9 to 36 weeks and 5 to 12 weeks in gradual and rapid groups, respectively. Pooled data included 167 participants from gradual WL intervention arms and 194 participants from rapid WL arms. The age range of the participants was 18 to 70 years old. All the included studies were parallel in design. Five studies were conducted on both sexes, and two other studies were performed on only females. Of seven studies were included in the systematic review and meta-analysis, all seven studies reported weight, FM and FFM[8; 26; 31; 32; 33; 34; 35], five studies reported WC[8; 26; 32; 33; 35], four studies reported BMI and HC[8; 26; 32; 33], RMR[8; 26; 31; 34], BFP[8; 26; 33; 34], and three studies reported WHR[8; 26; 33]. The basis on the Cochrane Collaboration's tool, four studies had a low risk of bias (≥4) and a quality score of three studies were lower than 4 (Table 1). The calorie intake also varied between studies. The characteristics of the included studies are summarized in Table 2.

Gradual Weight Loss vs. Rapid Weight Loss

Based on the analysis of 7 RCTs, gradual WL produced greater reductions in FM (weighted mean difference (WMD) kg: -1.00, 95% CI [-1.70, -0.29]) and BFP (WMD: -0.83%, 95% CI [-1.49, -

0.17]). Moreover, gradual WL significantly attenuated the reduction of RMR (WMD: 97.39 kcal, 95% CI [78.78, 118.01]) compared with rapid WL. However, there was no significant difference in body weight (WMD: 0.03 kg, 95% CI [-0.65, 0.71]), BMI (WMD: 0.14 kg/m^2, 95% CI [-0.25, 0.52]), HC (WMD: 0.21 cm, 95% CI [-1.20, 1.63]), WC (WMD: -0.32 cm, 95% CI [-1.80, 1.16]), FFM (WMD: 0.74 kg, 95% CI [-0.15, 1.64]) and WHR (WMD: -0.00, 95% CI [-0.02, 0.01]) between gradual and rapid WL (Figure 2-10). Mean changes in body composition and RMR in rapid and gradual WL, respectively are as follow: weight: -7.7 ± 3.5 and -7.5 ± 3.5; BMI: -3 ± 1.6 and -3 ± 1.5; FM: -5.6 ± 3.6 and -6.7 ± 3.7; PBF: -2.5 ± 1.8 and -3.8 ± 1.2; WC: -7.8 ± 4.5 and -8.7 ± 4.2; HC: -6.3 ± 4.7 and -7.4 ± 5; WHR: -0.04 ± 0.05 and -0.05 ± 0.5; FFM: -1.6 ± 1.3 and -0.6 ± 0.6; RMR: -136.9 ± 58.6 and -87.5 ± 74.3.

Publication Bias and sensitivity analysis

Publication bias as assessed by Egger's regression asymmetry test were as follows: RMR (p = 0.005), FFM (p = 0.327), HC (p = 0.004), WC (p = 0.093), BFP (p = 0.012), FM (p = 0.405), BMI (p = 0.093), body weight (p = 0.920). Results of the sensitivity analysis indicated that the elimination of each individual study did not change the pooled effect size (Supplementary File 1).

Discussion

In this meta-analysis, we compared the effects of gradual versus rapid WL on body composition in individuals with overweight and obesity. The main result of our analysis was that, when a similar magnitude of WL occurred, gradual WL was associated with greater declines in FM and BFP, as well as superior preservation of RMR. However, the rate of WL was not associated with differential changes in FFM, WC, HC, and WHR.

Previous studies have shown that obesity is a risk factor for all-cause mortality and fatal cardiovascular events[38; 39]. Moreover, increases in body fat may result in distinct disease risk as compared to increases in BMI alone[40]. It has been posited that gradual WL may increase the proportion of weight lost as FM. Although our results supported this contention by demonstrating that compared to rapid WL, gradual WL induced larger FM decrements, we did not detect significant differences in metrics of central obesity (i.e., WC and WHR). Several factors could be responsible for the disparity in whole-body FM and anthropometric measures related to central obesity. First, while WC and HC are well-known predictors of central obesity and decrease following dietary WL, they are not the best indices in terms of correlation with FM (as a criterion in obesity evaluation) during dietary WL[8]. Secondly, while the magnitude of WL observed in the present analysis (6.94 kg in gradual WL and 6.98 kg in rapid WL) elicited decreases in WC and HC, differences in these anthropometric indicators of central obesity based on the rate of WL may not have been large enough to become distinguishable. Therefore, further studies with long-term interventions, greater magnitudes of WL, or more precise anthropometric measurement methods[41] may be needed to allow for additional evaluation of changes in surface anthropometric indices following gradual and rapid WL.

Preservation of muscle mass accompanied by FM loss is the ideal outcome following dietary WL. In practice, WL achieved through a calorie-reduced diet decreases both FM and FFM, the latter of which contains the majority of skeletal muscle[42]. In individuals with overweight or obesity, FFM contributes approximately 20–30% to total WL [43; 44; 45; 46; 47; 48]. It is well-established increasing dietary protein attenuates the weight-loss-induced reduction in muscle mass [49; 50; 51]. However, the potential health benefits of WL could be attenuated by the WL–associated reduction of FFM [52; 53; 54], which when present along with other co-factors such as smoking and lack of exercise could increase the risk of additional disease states such as sarcopenia [54; 55; 56]. Traditionally, a gradual WL has been suggested to be better preserve FFM. Some studies reported that rapid WL diets are suboptimal for FFM preservation [26; 33; 57]. However, the present meta-analysis demonstrated that although rapid WL appeared to result in ~1 kg greater mean FFM loss than gradual WL, the difference between WL rates was not statistically significant. Several factors could be responsible for these results. First, it is well-established increasing dietary protein may attenuate the WL-induced reduction in muscle mass[58; 59]. Some (two of seven) studies [31; 32] included in the meta-analysis did not report sufficient dietary information for these variables to be considered in the present analysis, meaning it is possible that the percentage of energy derived from different macronutrients, notably protein, could have differed between experimental arms or studies. Second, it has been suggested that the size of the calorie deficit determines the extent of FFM loss[60], and the calorie deficit varied widely in the included studies, even though all investigations implemented some form of a very low-calorie diet (VLCD). Third, although most of the included studies in our analysis directionally favored gradual WL for FFM preservation, the lack of a significant difference could be due to a relatively small magnitude of the effect and the limited duration of these studies. Fourth, studies measured body composition using different methods including bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), and air displacement plethysmography (ADP) using Bod Pod®. Previous reports have demonstrated that there are significant differences in FFM estimates obtained by these methods[61]. Thus, the difference in techniques might explain some variability in the analyzed data. Conversely, only one of seven studies included in our analysis showed apparently superior FFM changes after rapid WL as compared to gradual WL[32]. Since this study had a higher number of participants than any other investigation (n=127), the results had a large impact on the overall effect size. In contrast to our analysis, an earlier study that compared gradual and rapid WL, with body-weight reductions of 1.9 vs 1.1 kg/week over 8 weeks, demonstrated that the rapid WL group experienced a larger reduction in FFM[62]. However, after adjusting for the magnitude of WL, differences between groups no longer remained. In addition, Vink et al. (2016) showed during similar WL, rapid WL induced greater loss of FFM compared to gradual WL (1.8 vs 0.6 kg/week)[33]. These contradictory findings indicate the need for more high quality and long-term research to determine if gradual WL is better suited for the preservation of FFM during WL in individuals with overweight and/or obesity. Additionally, despite the lack of statistical significance, the practical significance of the ~1 kg mean difference in FFM between gradual and rapid WL in the present analysis should be considered.

Decreases in RMR are a well-known consequence of WL [62; 63; 64; 65; 66]. A prior investigation demonstrated reductions in RMR following WL occur as early as the first week, with a continued decline until the end of the 10 to 20-week intervention[31]. Similarly, other studies observed a decline in RMR from the early portion of caloric restriction interventions[65; 67]. It has been shown that both rapid and gradual WL may cause decreases in RMR[26]. Our results showed that the rapid WL group presented a larger decrease in RMR. Since FFM contributes to metabolic rate, RMR decreases as FFM is decreased [68]. However, given that changes in FFM do not fully explain the alteration in RMR after WL[69], it has been suggested that the metabolic, neuroendocrine, and autonomic systems regulating energy stores may be involved[70]. The adipocyte secreted hormone leptin is one such factor, along with Peptide YY and thyroid hormones[71], which may mediate these adaptive changes in energy expenditure[70; 72]. It has been shown that dietary WL may decrease the plasma levels of both, 3,5,3' triiodo-L-thyronine (T3) [70; 73]and leptin. Müller and Bosy-Westphal reported a trend for a decline in serum triiodothyronine concentrations (0.2 ± 0.4 ng/dL) that correlated ($r = -0.56$; $p< 0.05$) with the decrease in REE adjusted for FFM and FM following 3 weeks of calorie restriction[74]. However, there are limited data concerning the differences in hormonal and neurological responses following slow and rapid WL. Nonetheless, modulation of these physiological factors could be a possible reason for the attenuation in RMR reduction with gradual WL compared to rapid WL despite no statistically significant differences in FFM changes in our analysis. However, only four studies measured RMR while all seven studies measured FFM. Because of limited data on the metabolic effect of the rate of WL, more studies are needed to determine the effects of gradual and rapid WL on RMR.

Our present analysis is not without its limitations. The meta-analysis was based on only seven trials, and some studies did not report dietary contents in each intervention. Thus, it is not possible to evaluate the effects of macronutrient composition or meal frequency on the observed results. Furthermore, since all but one trial lasted less than 4 months, our analysis is unable to show the long-term differences of gradual and rapid WL on anthropometric indices and RMR in individuals with overweight and/or obesity. Another limitation is the devices used for body composition analysis in the included studies. From seven studies, three studies measured body composition by BIA, two studies used DXA, and two other studies used Bod Pod. Although all three methods are established valid methods of assessing body composition in certain contexts, they do not always reflect changes in body composition associated with WL similarly[61]. Moreover, included studies provided different measures of non-fat tissue, i.e. lean body mass and FFM. It has been mentioned that the differences between LBM and FFM are about 2-3% [75]. Therefore, the terms LBM and FFM are often used interchangeably[76]. Lastly, the lack of an energy deficit demarcation to define gradual and rapid WL is another limitation of our analysis. While future analyses could perform meta-regression to examine these effects, this is tenuous due to substantial concerns regarding self-reported dietary intake [77] and was beyond the scope of the present analysis.

In conclusion, gradual WL is associated with greater loss of FM and BFP, as well as enhanced maintenance of RMR, in participants with overweight and obesity. However, the rate of WL was not associated with different changes in FFM, WC, HC, and WHR. Additional longer-term and high-quality clinical trials are needed to evaluate the differences of gradual and rapid WL, when similar WL is achieved, on body composition and physiological variables in individuals with overweight and/or obesity to further evaluate and confirm these findings.

Declaration of interest

The authors declare no conflict of interest.

References

1. Bagheri R, Rashidlamir A, Ashtary-Larky D *et al.* (2019) Does Green Tea Extract Enhance the Anti-inflammatory Effects of Exercise on Fat Loss? *British journal of clinical pharmacology*.

2. Organization WH (2014) *Global status report on noncommunicable diseases 2014*. World Health Organization.

3. Cabler S, Agarwal A, Flint M *et al.* (2010) Obesity: modern man's fertility nemesis. *Asian journal of andrology* **12**, 480.

4. Adab P, Pallan M, Whincup PH (2018) Is BMI the best measure of obesity?: British Medical Journal Publishing Group.

5. Deurenberg P, Deurenberg-Yap M, Guricci S (2002) Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obesity reviews* **3**, 141-146.

6. Deurenberg-Yap M, Schmidt G, van Staveren WA *et al.* (2000) The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. *International journal of obesity* **24**, 1011.

7. Organization WH (2016) World Health Organization obesity and overweight fact sheet.

8. Ashtary-Larky D, Daneghian S, Alipour M *et al.* (2018) Waist Circumference to Height Ratio: Better Correlation with Fat Mass Than Other Anthropometric Indices During Dietary Weight Loss in Different Rates. *International journal of endocrinology and metabolism* **16**.

9. Hall KD (2007) Body fat and fat-free mass inter-relationships: Forbes's theory revisited. *British journal of nutrition* **97**, 1059-1063.

10. Jakicic JM, Clark K, Coleman E *et al.* (2001) Appropriate intervention strategies for weight loss and prevention of weight regain for adults. *Medicine & Science in Sports & Exercise* **33**, 2145-2156.

11. Freire R (2020) Scientific evidence of diets for weight loss: Different macronutrient composition, intermittent fasting, and popular diets. *Nutrition* **69**, 110549.

12. Yancy WS, Olsen MK, Guyton JR *et al.* (2004) A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Annals of internal medicine* **140**, 769-777.

13. Floegel A, Pischon T (2012) Low carbohydrate-high protein diets: British Medical Journal Publishing Group.

14. Hill JO (2008) Can a small-changes approach help address the obesity epidemic? A report of the Joint Task Force of the American Society for Nutrition, Institute of Food Technologists, and International Food Information Council. *The American journal of clinical nutrition* **89**, 477-484.

15. Lutes LD, Winett RA, Barger SD *et al.* (2008) Small changes in nutrition and physical activity promote weight loss and maintenance: 3-month evidence from the ASPIRE randomized trial. *Annals of Behavioral Medicine* **35**, 351-357.

16. Sbrocco T, Nedegaard RC, Stone JM *et al.* (1999) Behavioral choice treatment promotes continuing weight loss: Preliminary results of a cognitive–behavioral decision-based treatment for obesity. *Journal of Consulting and Clinical Psychology* **67**, 260.

17. Astrup A, Rössner S (2000) Lessons from obesity management programmes: greater initial weight loss improves long-term maintenance. *obesity reviews* **1**, 17-19.

18. Carels RA, Cacciapaglia HM, Douglass OM *et al.* (2003) The early identification of poor treatment outcome in a women's weight loss program. *Eating Behaviors* **4**, 265-282.

19. Elfhag K, Rössner S (2005) Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. *Obesity reviews* **6**, 67-85.

20. Nackers LM, Ross KM, Perri MG (2010) The association between rate of initial weight loss and long-term success in obesity treatment: does slow and steady win the race? *International journal of behavioral medicine* **17**, 161-167.

21. Carpenter WH, Poehlman ET, O'Connell M *et al.* (1995) Influence of body composition and resting metabolic rate on variation in total energy expenditure: a meta-analysis. *The American journal of clinical nutrition* **61**, 4-10.

22. Ballor DL, Poehlman ET (1995) A meta-analysis of the effects of exercise and/or dietary restriction on resting metabolic rate. *European journal of applied physiology and occupational physiology* **71**, 535-542.

23. Kiortsis D, Durack I, Turpin G (1999) Effects of a low-calorie diet on resting metabolic rate and serum tri-iodothyronine levels in obese children. *European journal of pediatrics* **158**, 446-450.

24. Astrup A, Gøtzsche PC, van de Werken K *et al.* (1999) Meta-analysis of resting metabolic rate in formerly obese subjects. *The American journal of clinical nutrition* **69**, 1117-1122.

25. Trexler ET, Smith-Ryan AE, Norton LE (2014) Metabolic adaptation to weight loss: implications for the athlete. *Journal of the International Society of Sports Nutrition* **11**, 7.

26. Ashtary-Larky D, Ghanavati M, Lamuchi-Deli N *et al.* (2017) Rapid weight loss vs. slow weight loss: which is more effective on body composition and metabolic risk factors? *International journal of endocrinology and metabolism* **15**.

27. Moher D, Liberati A, Tetzlaff J *et al.* (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.

28. Brochu M, Mathieu ME, Karelis AD *et al.* (2008) Contribution of the lean body mass to insulin resistance in postmenopausal women with visceral obesity: a Monet study. *Obesity* **16**, 1085-1093.

29. Brochu M, Tchernof A, Turner AN *et al.* (2003) Is there a threshold of visceral fat loss that improves the metabolic profile in obese postmenopausal women? *Metabolism* **52**, 599-604.

30. Higgins JP, Altman DG, Gøtzsche PC *et al.* (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* **343**, d5928.

31. Hintze LJ, Goldfield G, Seguin R *et al.* (2019) The rate of weight loss does not affect resting energy expenditure and appetite sensations differently in women living with overweight and obesity. *Physiology & behavior* **199**, 314-321.

32. Purcell K, Sumithran P, Prendergast LA *et al.* (2014) The effect of rate of weight loss on long-term weight management: a randomised controlled trial. *The Lancet Diabetes & Endocrinology* **2**, 954-962.

33. Vink RG, Roumans NJ, Arkenbosch LA *et al.* (2016) The effect of rate of weight loss on long-term weight regain in adults with overweight and obesity. *Obesity* **24**, 321-327.

34. Coutinho SR, With E, Rehfeld JF *et al.* (2018) The impact of rate of weight loss on body composition and compensatory mechanisms during weight reduction: A randomized control trial. *Clinical Nutrition* **37**, 1154-1162.

35. Sénéchal M, Arguin H, Bouchard DR *et al.* (2012) Effects of rapid or slow weight loss on body composition and metabolic risk factors in obese postmenopausal women. A pilot study. *Appetite* **58**, 831-834.

36. Jackson D, Turner R (2017) Power analysis for random-effects meta-analysis. *Research synthesis methods* **8**, 290-302.

37. Valentine JC, Pigott TD, Rothstein HR (2010) How many studies do you need? A primer on statistical power for meta-analysis. *Journal of Educational and Behavioral Statistics* **35**, 215-247.

38. Lissner L, Odell PM, D'Agostino RB *et al.* (1991) Variability of body weight and health outcomes in the Framingham population. *New England Journal of Medicine* **324**, 1839-1844.

39. Blair SN, Shaten J, Brownell K *et al.* (1993) Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial. *Annals of internal medicine* **119**, 749-757.

40. Saito Y, Takahashi O, Arioka H *et al.* (2017) Associations between body fat variability and later onset of cardiovascular disease risk factors. *PloS one* **12**, e0175057.

41. Tinsley GM, Moore ML, Dellinger JR *et al.* (2019) Digital anthropometry via three-dimensional optical scanning: evaluation of four commercially available systems. *European Journal of Clinical Nutrition*, 1-11.

42. Cava E, Yeat NC, Mittendorfer B (2017) Preserving healthy muscle during weight loss. *Advances in nutrition* **8**, 511-519.

43. Gormsen LC, Svart M, Thomsen HH *et al.* (2017) Ketone Body Infusion With 3-Hydroxybutyrate Reduces Myocardial Glucose Uptake and Increases Blood Flow in Humans: A Positron Emission Tomography Study. *Journal of the American Heart Association* **6**, e005066.

44. Leino RL, Gerhart DZ, Duelli R *et al.* (2001) Diet-induced ketosis increases monocarboxylate transporter (MCT1) levels in rat brain. *Neurochemistry international* **38**, 519-527.

45. Gardner CD, Trepanowski JF, Del Gobbo LC *et al.* (2018) Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *Jama* **319**, 667-679.

46. Sackner-Bernstein J, Kanter D, Kaul S (2015) Dietary intervention for overweight and obese adults: comparison of low-carbohydrate and low-fat diets. A meta-analysis. *PloS one* **10**, e0139817.

47. Hession M, Rolland C, Kulkarni U *et al.* (2009) Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obesity reviews* **10**, 36-50.

48. Tobias DK, Chen M, Manson JE *et al.* (2015) Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. *The lancet Diabetes & endocrinology* **3**, 968-979.

49. Verreijen AM, Verlaan S, Engberink MF *et al.* (2014) A high whey protein–, leucine-, and vitamin D–enriched supplement preserves muscle mass during intentional weight loss in obese older adults: a double-blind randomized controlled trial. *The American journal of clinical nutrition* **101**, 279-286.

50. Backx E, Tieland M, Borgonjen-van Den Berg K *et al.* (2016) Protein intake and lean body mass preservation during energy intake restriction in overweight older adults. *International Journal of Obesity* **40**, 299.

51. Layman DK, Evans E, Baum JI *et al.* (2005) Dietary protein and exercise have additive effects on body composition during weight loss in adult women. *The Journal of nutrition* **135**, 1903-1910.

52. Layman DK, Boileau RA, Erickson DJ *et al.* (2003) A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. *The Journal of nutrition* **133**, 411-417.

53. Gill LE, Bartels SJ, Batsis JA (2015) Weight management in older adults. *Current obesity reports* **4**, 379-388.

54. Miller S, Wolfe RR (2008) The danger of weight loss in the elderly. *The Journal of Nutrition Health and Aging* **12**, 487-491.

55. Cruz-Jentoft AJ, Baeyens JP, Bauer JM *et al.* (2010) Sarcopenia: European consensus on definition and diagnosisReport of the European Working Group on Sarcopenia in Older PeopleA. J. Cruz-Gentoft et al. *Age and ageing* **39**, 412-423.

56. Fielding RA, Vellas B, Evans WJ *et al.* (2011) Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *Journal of the American Medical Directors Association* **12**, 249-256.

57. Peos JJ, Norton LE, Helms ER *et al.* (2019) Intermittent Dieting: Theoretical Considerations for the Athlete. *Sports* **7**, 22.

58. Pasiakos SM, Cao JJ, Margolis LM *et al.* (2013) Effects of high-protein diets on fat-free mass and muscle protein synthesis following weight loss: a randomized controlled trial. *The FASEB Journal* **27**, 3837-3847.

59. Church DD, Gwin JA, Wolfe RR *et al.* (2019) Mitigation of Muscle Loss in Stressed Physiology: Military Relevance. *Nutrients* **11**, 1703.

60. Garthe I, Raastad T, Refsnes PE *et al.* (2011) Effect of two different weight-loss rates on body composition and strength and power-related performance in elite athletes. *International journal of sport nutrition and exercise metabolism* **21**, 97-104.

61. Ritz P, Salle A, Audran M *et al.* (2007) Comparison of different methods to assess body composition of weight loss in obese and diabetic patients. *Diabetes research and clinical practice* **77**, 405-411.

62. Coxon A, Kreitzman S, Brodie D *et al.* (1989) Rapid weight loss and lean tissue: evidence for comparable body composition and metabolic rate in differing rates of weight loss. *International journal of obesity* **13**, 179-181.

63. Martin CK, Heilbronn LK, De Jonge L *et al.* (2007) Effect of calorie restriction on resting metabolic rate and spontaneous physical activity. *Obesity* **15**, 2964-2973.

64. Heshka S, Yang M-U, Wang J *et al.* (1990) Weight loss and change in resting metabolic rate. *The American journal of clinical nutrition* **52**, 981-986.

65. Müller MJ, Enderle J, Bosy-Westphal A (2016) Changes in energy expenditure with weight gain and weight loss in humans. *Current obesity reports* **5**, 413-423.

66. Browning MG, Franco RL, Cyrus JC *et al.* (2016) Changes in resting energy expenditure in relation to body weight and composition following gastric restriction: a systematic review. *Obesity surgery* **26**, 1607-1615.

67. Bray G (1969) Effect of caloric restriction on energy expenditure in obese patients. *The Lancet* **294**, 397-398.

68. Byrne NM, Weinsier RL, Hunter GR *et al.* (2003) Influence of distribution of lean body mass on resting metabolic rate after weight loss and weight regain: comparison of responses in white and black women. *The American journal of clinical nutrition* **77**, 1368-1373.

69. Siervo M, Faber P, Lara J *et al.* (2015) Imposed rate and extent of weight loss in obese men and adaptive changes in resting and total energy expenditure. *Metabolism* **64**, 896-904.

70. Rosenbaum M, Hirsch J, Murphy E *et al.* (2000) Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *The American journal of clinical nutrition* **71**, 1421-1432.

71. McNeil J, Schwartz A, Rabasa-Lhoret R *et al.* (2015) Changes in leptin and peptide YY do not explain the greater-than-predicted decreases in resting energy expenditure after weight loss. *The Journal of Clinical Endocrinology & Metabolism* **100**, E443-E452.

72. Park H-K, Ahima RS (2015) Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. *Metabolism* **64**, 24-34.

73. Gardner DF, Kaplan MM, Stanley CA *et al.* (1979) Effect of tri-iodothyronine replacement on the metabolic and pituitary responses to starvation. *New England Journal of Medicine* **300**, 579-584.

74. Müller M, Bosy-Westphal A (2013) Adaptive thermogenesis with weight loss in humans. *Obesity* **21**, 218-228.

75. Withers R, Craig N, Ball C *et al.* (1991) The Drinkwater-Ross anthropometric fractionation of body mass: Comparison with measured body mass and densitometrically estimated fat and fat-free masses. *Journal of sports sciences* **9**, 299-311.

76. Prado CM, Heymsfield SB (2014) Lean tissue imaging: a new era for nutritional assessment and intervention. *Journal of Parenteral and Enteral Nutrition* **38**, 940-953.

77. Dhurandhar NV, Schoeller D, Brown AW *et al.* (2015) Energy balance measurement: when something is not better than nothing. *International journal of obesity* **39**, 1109-1113.

Figure legends:

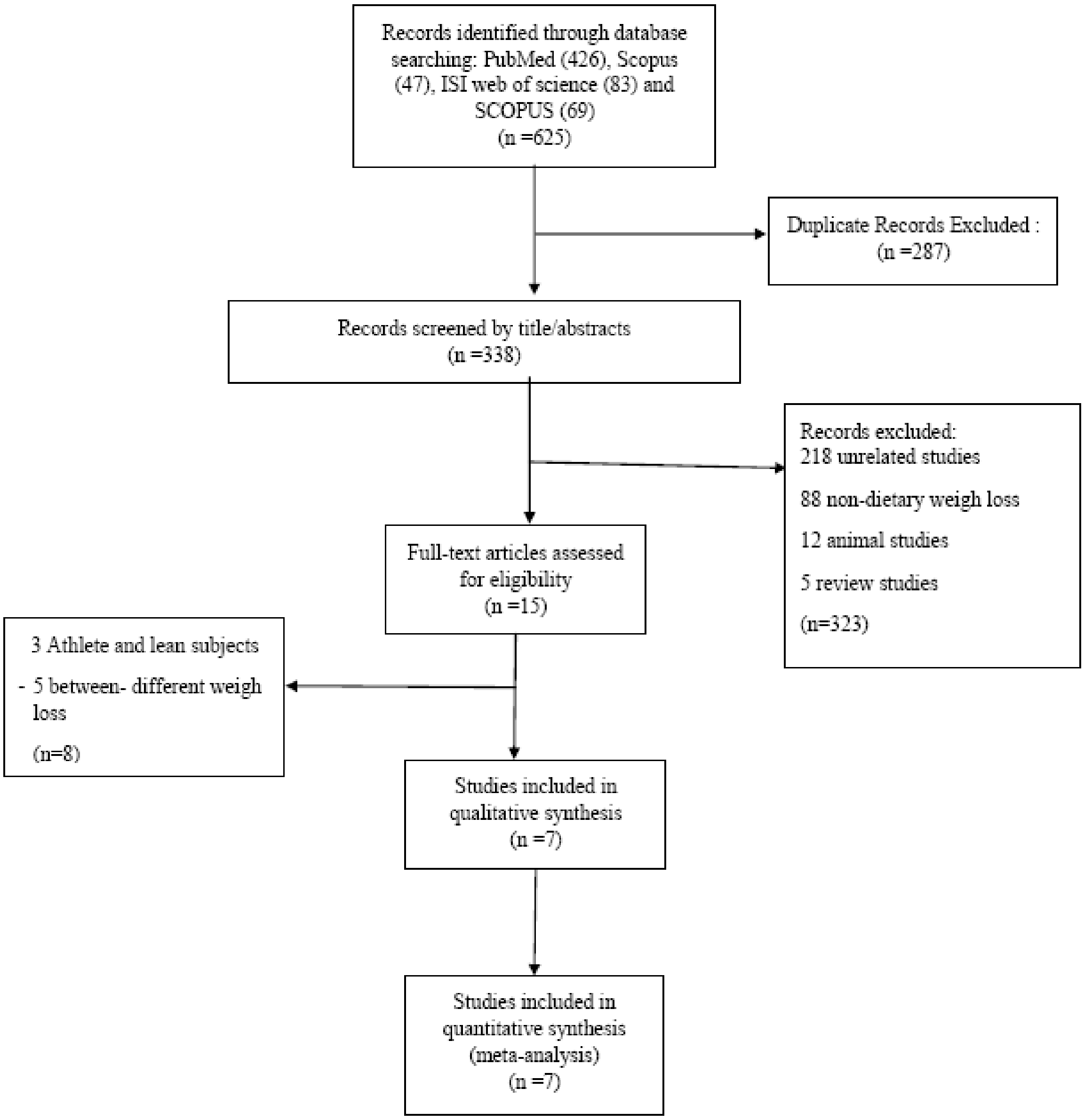

Figure 1. Flow diagram of the literature search.

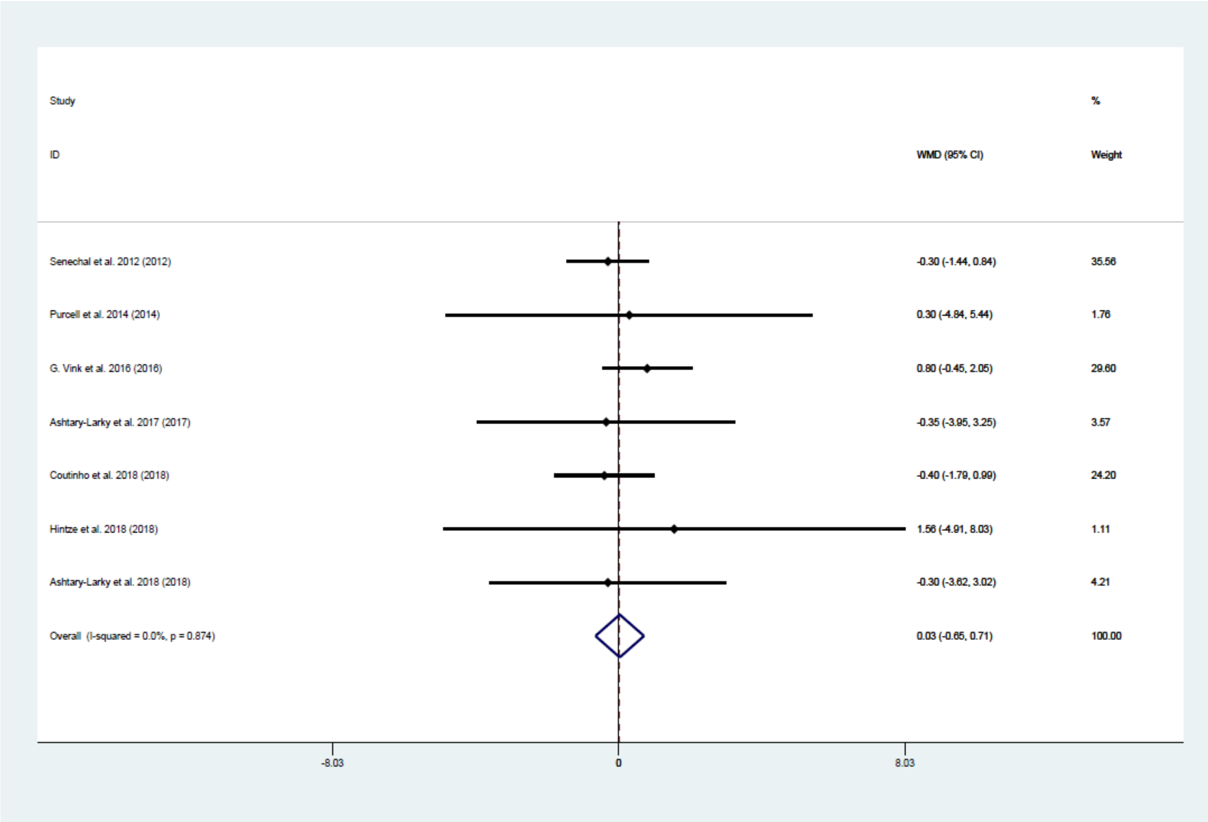

Figure 2. Forest plot of the fixed-effects meta-analysis of the effect of gradual vs. rapid weight loss on body weight.

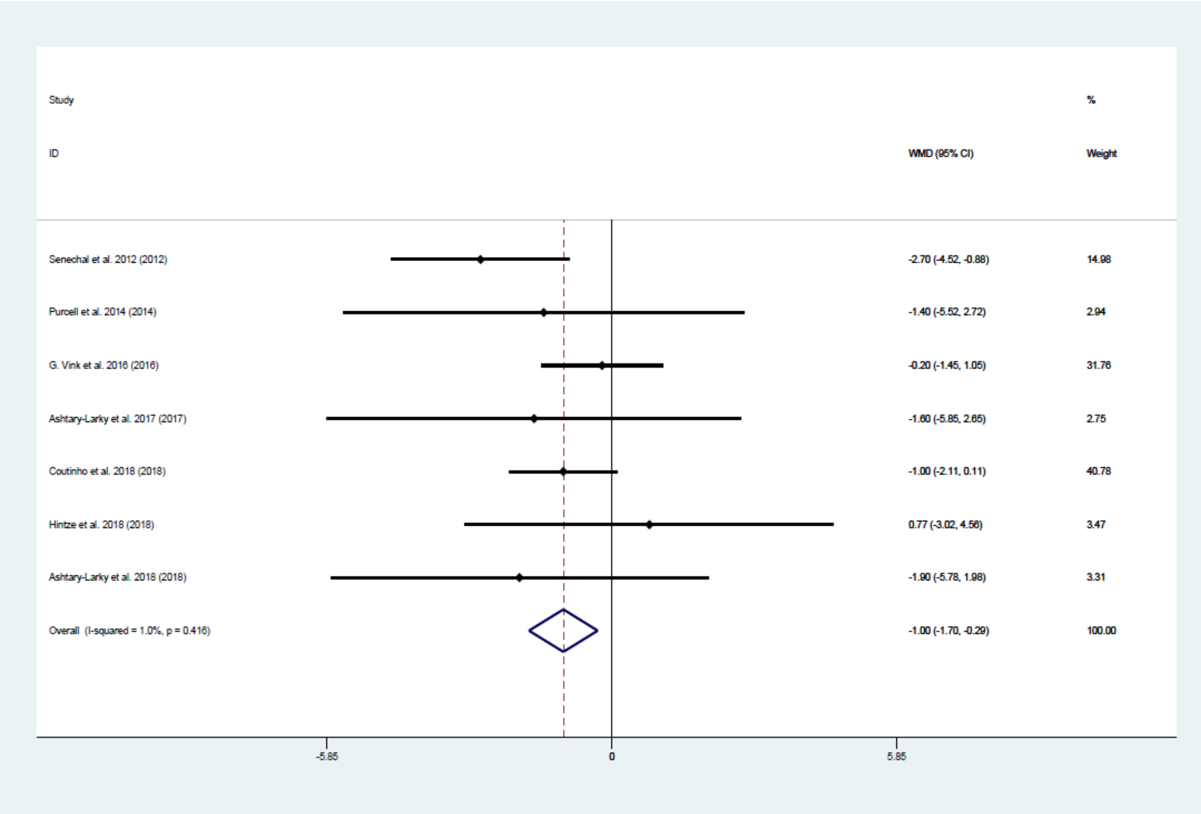

Figure 3. Forest plot of the fixed-effects meta-analysis of the effect of gradual vs. rapid weight loss on fat mass.

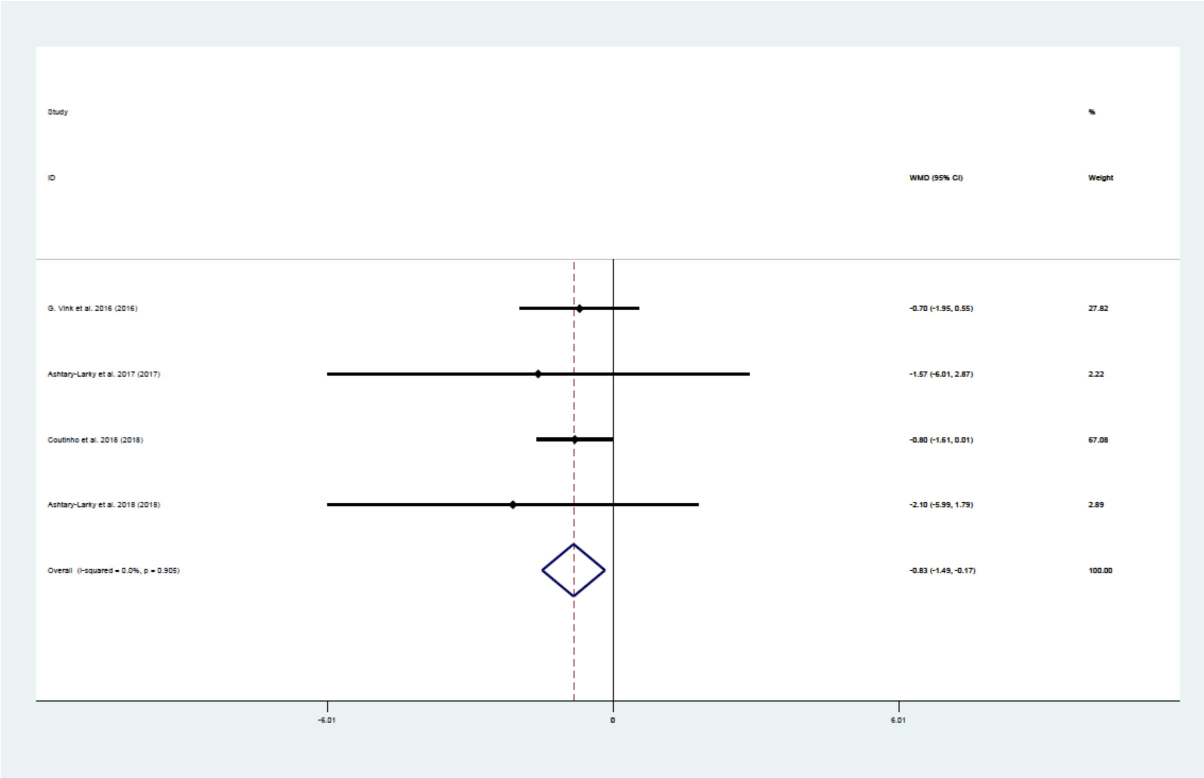

Figure 4. Forest plot of the fixed-effects meta-analysis of the effect of gradual vs. rapid weight loss on body fat percentage.

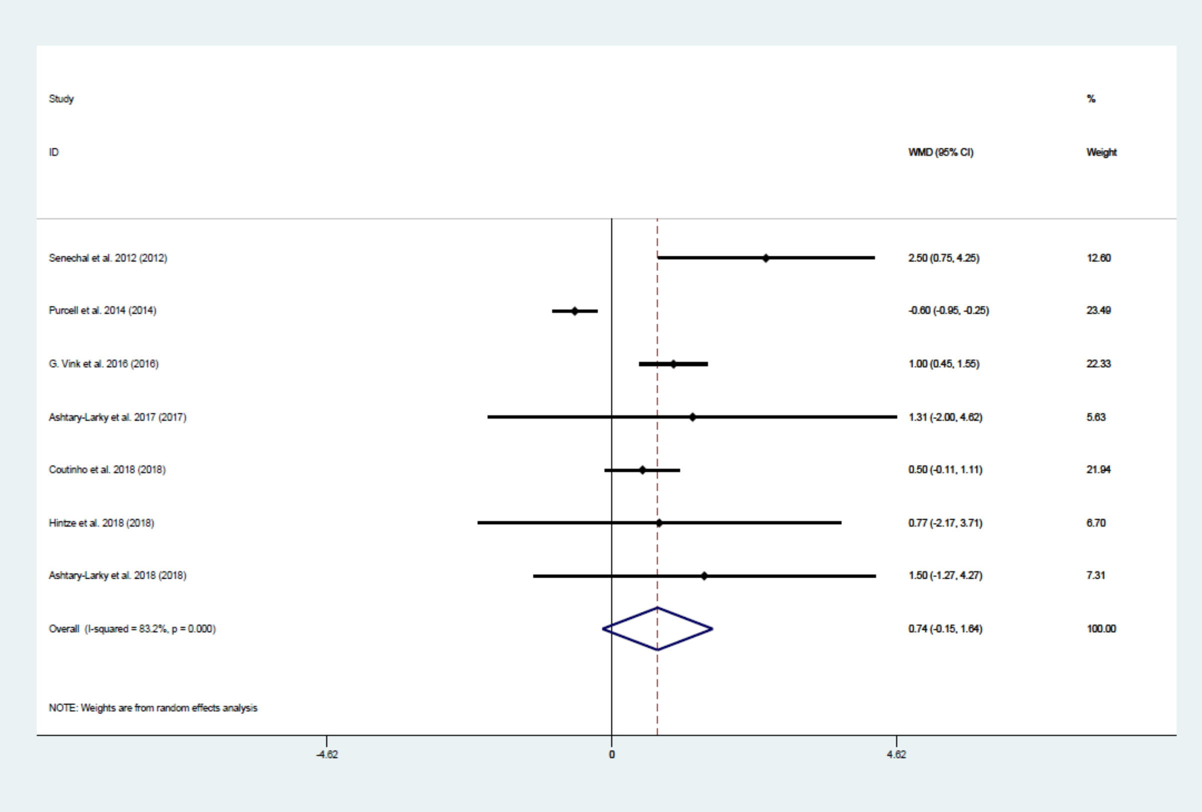

Figure 5. Forest plot of the random-effects meta-analysis of the effect of gradual vs. rapid weight loss on fat free mass.

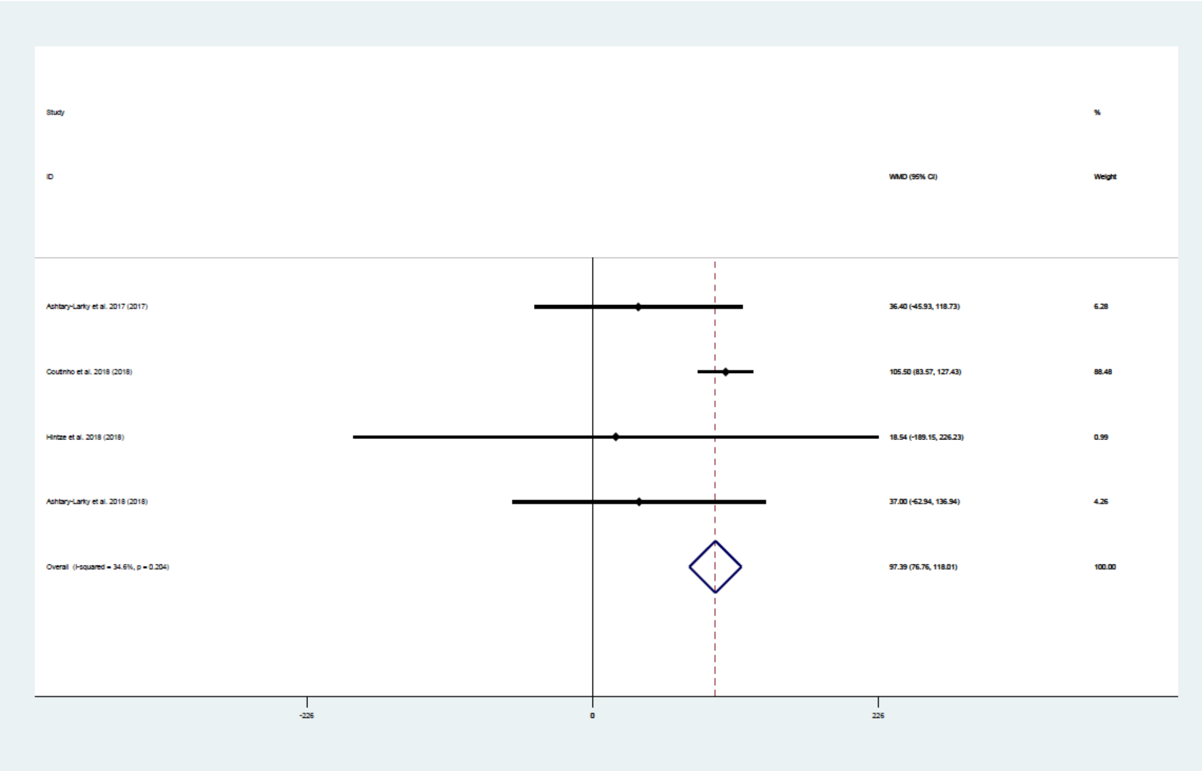

Figure 6. Forest plot of the fixed-effects meta-analysis of the effect of gradual vs. rapid weight loss on resting metabolic rate.

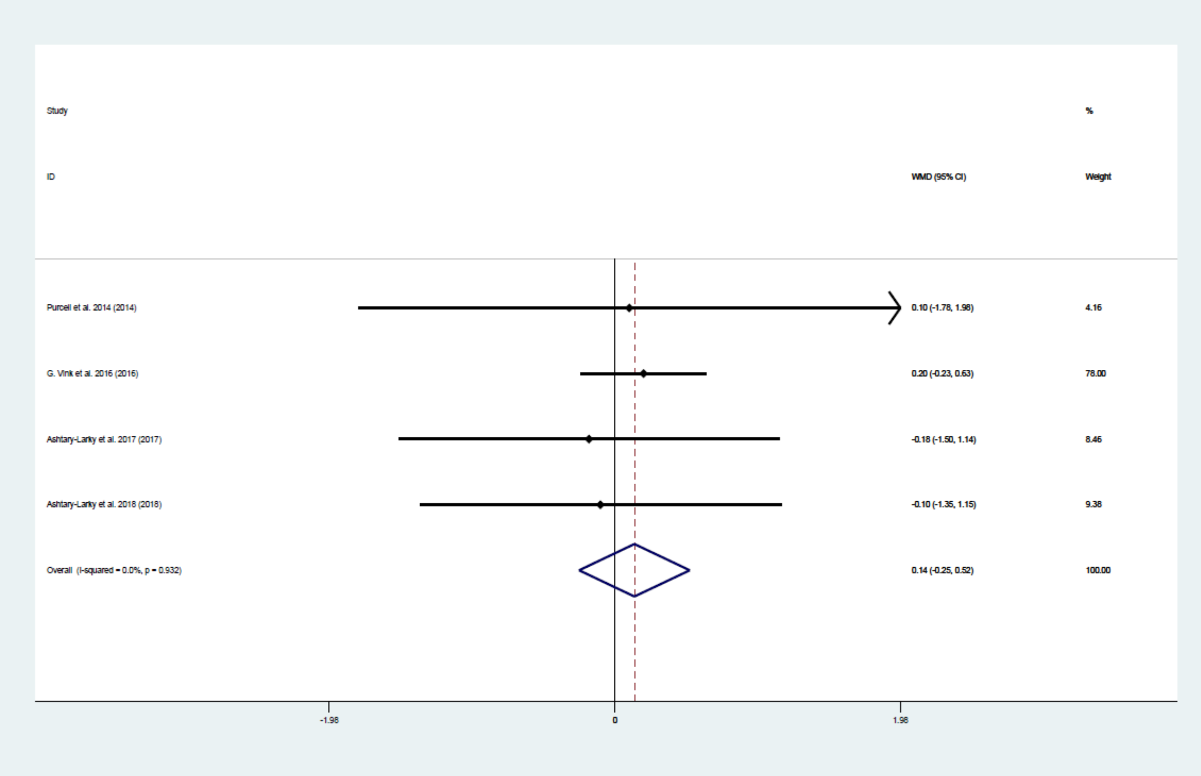

Figure 7. Forest plot of the fixed-effects meta-analysis of the effect of slow vs. rapid weight loss on body mass index.

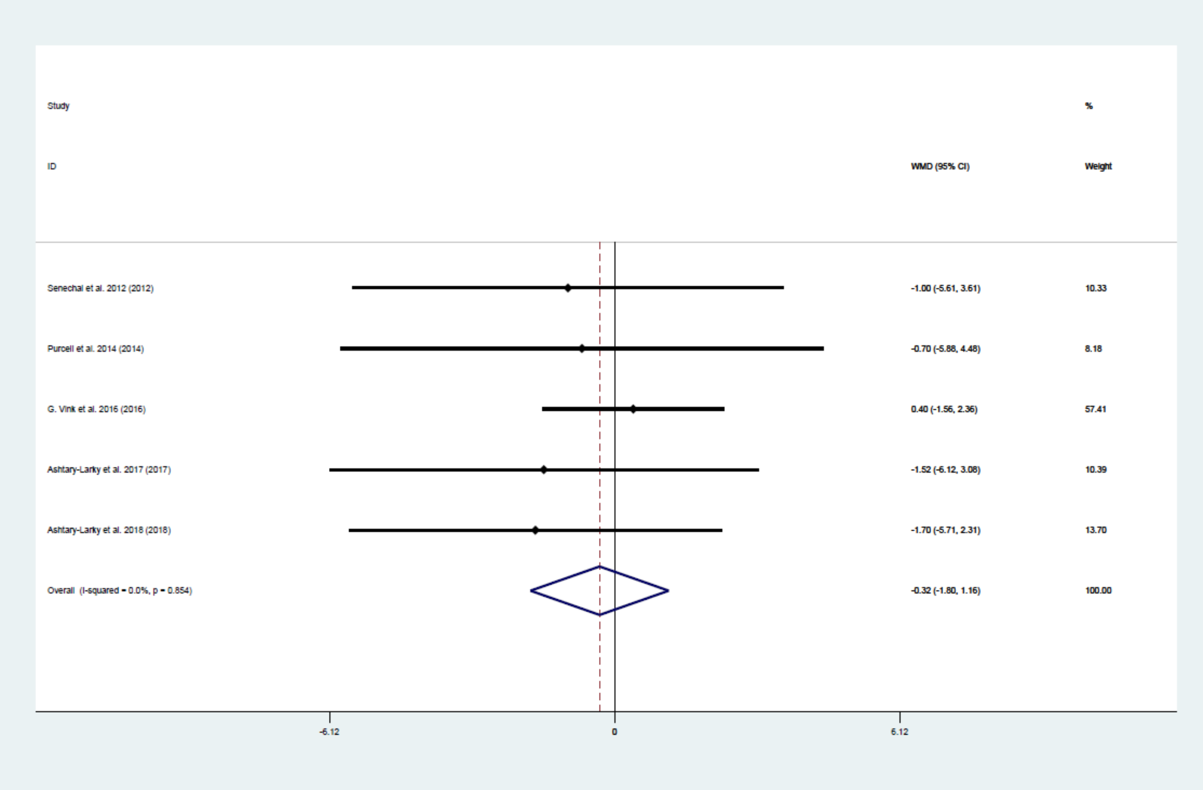

Figure 8. Forest plot of the fixed-effects meta-analysis of the effect of slow vs. rapid weight loss on waist circumference.

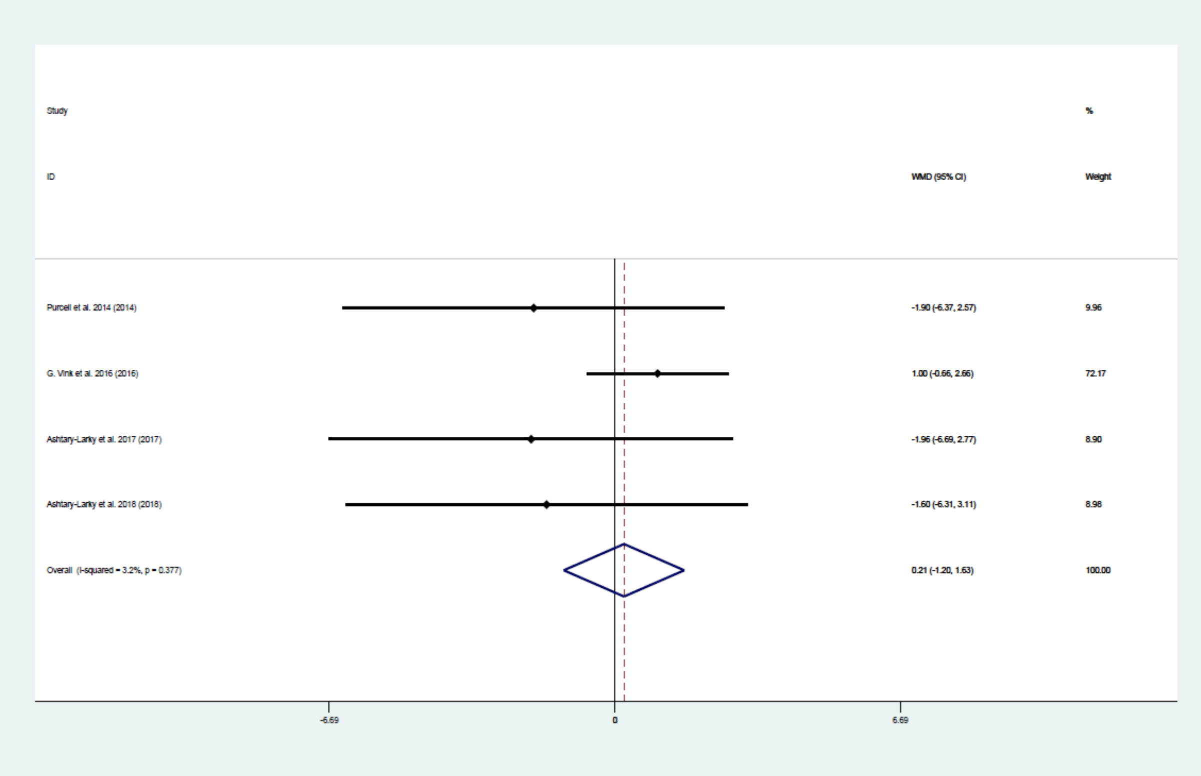

Figure 9. Forest plot of the fixed-effects meta-analysis of the effect of slow vs. rapid weight loss on hip circumference.

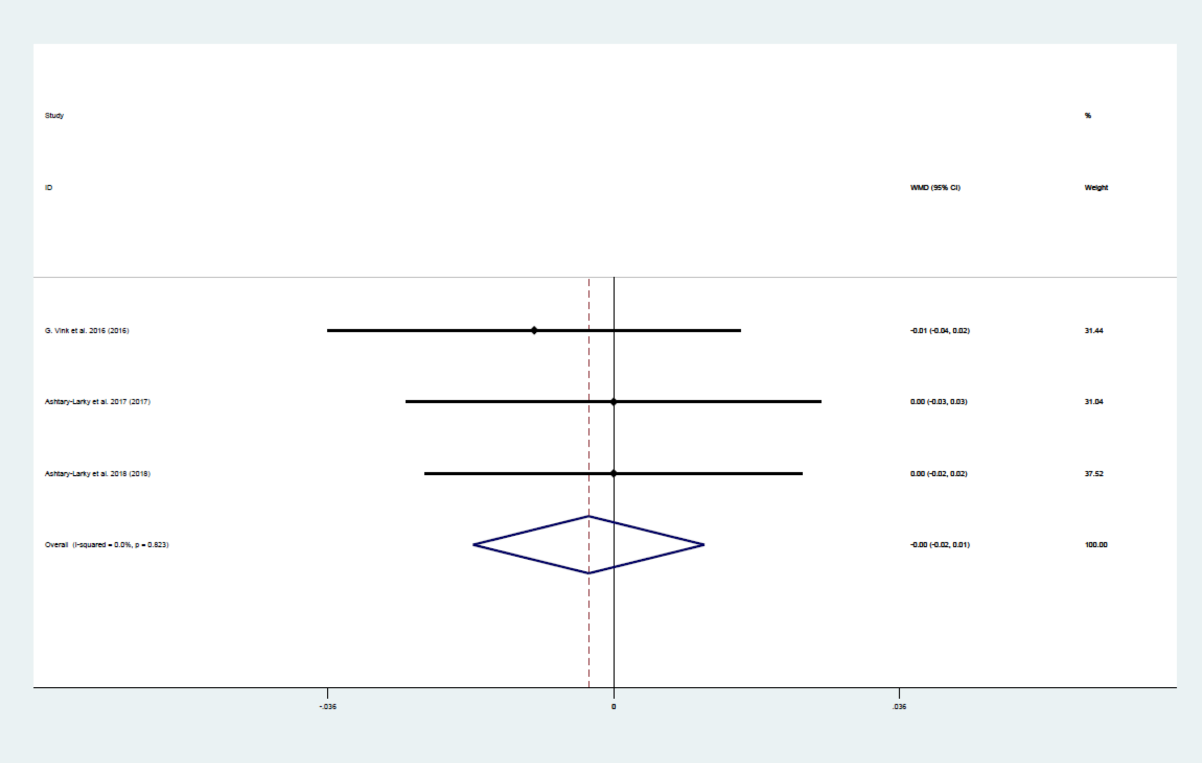

Figure 10. Forest plot of the fixed-effects meta-analysis of the effect of slow vs. rapid weight loss on waist-hip ratio.