

LIMITATIONS OF PROLONGED WEIGHT REDUCTION THERAPIES IN OVERWEIGHT AND OBESE PEOPLE: A META-REGRESSION ANALYSIS

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ABSTRACT

Introduction. Presently, obesity is endemic in many countries. Many obese patients also suffer from diseases of high social impact, such as type 2 diabetes and cardiovascular disease. Generally, therapies combining energy-deficient diets and physical activity protocols are used for treating obesity. Nonetheless, presently, no universal intervention with exact parameters exists. The complexity of the problem is further exacerbated by difficulties associated with long-term weight maintenance following weight reduction therapies.

Purpose and objectives of the study. This analysis attempts to assess the impact of duration of combined diet-and-exercise weight reduction protocols on changes in body mass in overweight and obese people. *Applied methodology.* 3142 publications in total were retrieved by filtering the database of the National Library of Medicine, National Institutes of Health USA by keywords (“weight loss”, “diet” and “exercise”) for the period between 01.01.2008 and 01.01.2018. After a selection procedure was applied, 56 of them were included in this meta-regression analysis and were grouped into three strata according to duration.

Achieved major results. The results showed that therapies of short to moderate duration are the most efficient for weight reduction, with regard to both overall effects and the amount of weight reduced per week. These findings were visualized by graphical representations of the studied data.

Conclusions. On our opinion, short or moderately long weight reduction therapies with scheduled interruptions should be used for treating obesity. This strategy would successfully maintain patients’ psychological wellbeing, as well as prevent relapses and “yo-yo” effects. *Originality/Value.* Obesity is a problem of complex origins and simple approaches such as calorie counting are rarely effective. This study proposes a “spiral” methodology – short to moderately-long hypo-caloric regimens with scheduled interruptions.

Key words: diet, exercise, obesity, weight reduction, duration

INTRODUCTION

In recent years obesity has reached endemic dimensions, especially in wealthy countries. According to the data from 2015, approximately 39% of the world’s adult population is overweight and obese (Chooi et al., 2019). Among other health hazards, obesity is the main risk factor for diseases of high social impact, such as type 2 diabetes and cardiovascular disease

(Cuchiery & Mamo, 2016; Hu et al., 2001; Pisuiner, 1993). Presently, a lot of research is concentrated on elaborating universally effective methodological principles for manipulating the energy balance of the human body (generally, based on hypocaloric diets and/or physical exercise) for treating obesity. Nevertheless, experts are far from being unanimous about what the exact parameters of a successful therapy for

obesity treatment should be. The complexity of the problem is further exacerbated by difficulties associated with long-term weight maintenance following weight reduction interventions. Frequently, relapses ensue with adverse consequences such as yo-yo effects or recurring progressive unhealthy changes in body composition. In this article, we have attempted to bring clarity on some time-dependent variations in the efficiency of different weight reduction therapies. In our original research, we studied not only changes in body weight but also transformations in body composition, as most health effects of weight reduction are generally mediated by reductions in the absolute and relative amounts of adipose tissue. Accordingly, weight reduction should be achieved (predominantly) at the expense of adipose tissue utilization, with lean body mass being preserved (or, in the best-case scenario, increased). In this article, we published only the results of our research concerning changes in body mass.

The vast majority of existing weight reduction therapies control the energy intake and expenditure. All of them are similar in their attempt (with different rates of efficiency) to negativize energy balance by manipulating habitual energy intakes and/or expenditures via different types of diets and physical activity programs. Irrespective of the immense variety of different existing diets, they can be classified into several large groups, depending on their macronutrient composition. The diversity of physical activity protocols in use is not so great. Generally, low to medium-intensity aerobic exercise of relatively high duration is commonly applied (van Aggel-Leijssen et al., 2001; Brill et al., 2002; Racette et al., 1995; Wilmore et al., 1999). Activities of anaerobic/strength or interval types are rarely used.

Purpose and objectives of the study

In this study, we treated the analyzed com-

bined diet-and-exercise weight reduction interventions as a sample of protocols with similar effects on energy balance, irrespective of their diversity. Particularly, we focused on revealing relationships between therapy duration and amount (and rate) of weight reduction in overweight and obese people.

Main thesis and hypothesis of the research

In our opinion, short or moderately long weight reduction therapies with scheduled interruptions should be used for treating obesity. This strategy would successfully maintain patients' psychological wellbeing, as well as prevent relapses and "yo-yo" effects.

METHODOLOGY

Sources of information

This study was based on the data retrieved from the National Library of Medicine; National Institutes of Health USA accessible in <https://www.ncbi.nlm.nih.gov/pubmed/>. The studies published (randomized clinical trials, crossover trials and cohort studies) between January 15, 2008 and January 15, 2018 were reviewed and filtered by keywords. We used "weight loss", "diet" and "exercise" as keywords and monitored 3142 publications in total. In addition, search results were filtered by subjects (people) and publication language (English). Fifty-six publications were selected as being eligible for inclusion in the meta-analysis. As some of the trials used more than one experimental group, the total number of data points we analyzed was 85.

Types of weight reduction interventions

We studied combined diet-and-exercise weight reduction therapies irrespective of their particular parameters. Diets studied can be grouped into the *following categories*:

1. Conventional (hypocaloric) diet (only energy values of foods consumed are manip-

ulated without changing habitual nutrition compositions).

2. High Carbohydrate Diet (only carbohydrate content is controlled for).
3. Low Carbohydrate Diet (only carbohydrate content is controlled for; classic ketogenic diets are included in this category).
4. High Protein Diet (only protein content is controlled for).
5. Low Fat Diet (only the fat content is controlled for; vegetarian and vegan diets are in this category).
6. Intermittent fasting.
7. Diet of very-low-calorie content (very-low-calorie diets or VLCD).
8. Low-glycemic-index diet (only the glycemic index of foods is controlled for; the Mediterranean diet is included in this category).

Physical activity protocols of studied interventions could be classified into the following categories:

1. Aerobic exercise – cyclical activities of different intensities. Some studies used relatively high intensities, which most probably shifted energy supplies partially onto anaerobic pathways.
2. Anaerobic exercise – resistance training (including callisthenic exercise).
3. Interval exercise – interval type of training, of both cyclic and resistance types. Some interventions used cyclical exercise with parameters that may be categorized as both interval and high-intensity aerobic. In such cases, we applied the classifications used by the authors.
4. Mixed exercise protocols, which combined aerobic and resistance activities.

Inclusion criteria

We applied the following criteria for inclusion:

1. Original research published between January 15, 2008 and January 15, 2018.
2. Published in English or translation of arti-

cle available.

3. Randomized clinical trials, crossover trials or cohort studies.
4. Number of participants/sample size – minimum 15.
5. Experiment duration – between 4 and 104 weeks.
6. Participants – humans, healthy (excluding type 2 diabetes or metabolic syndrome) overweight or obese people (body mass index, BMI>25) over 18 years of age.
7. Results reported in absolute values for both mean differences and standard deviations (or variances).
8. Intervention parameters were accurately and precisely defined. For example, a particular type of diet had to be applied instead of mixtures of different diets; exercise parameters should be precisely defined – aerobic, resistance, interval or combinations of these. Protocols, which only generally described the physical activities they used (without disclosing their parameters in detail), were not included.

Exclusion criteria

We applied the following exclusion criteria:

1. Only means and variances (or standard deviations) of baseline and final values of studied parameters were reported. The data of mean differences and their volatilities were not disclosed.
2. Interventions that had studied specific predetermined effects – for example, a 5% reduction in body mass. This type of reporting does not allow for therapy effects to be regressed on their durations. Only experiments that had specified precisely their durations were included.
3. Studies of subjects with different comorbidities (e.g., women with advanced osteoporosis) or having undergone certain medical interventions (such as surgeries

- for vertebral disc injury or cancer).
4. Population age could be classified as adolescent, or juvenile (average age < 18 years).
 5. Meta-analyses and reviews.
 6. Animal studies.
 7. Studies not published in English.

Retrieving data

We retrieved mean differences and standard

deviations (or variances) for the variables we studied (at levels of significance of at least 95%).

Search in the database

We used the keywords “weight loss”, “diet”, “exercise” separated by the search operator “AND” (standard for www.pubmed.gov). The process of data selection is presented graphically in Figure 1.

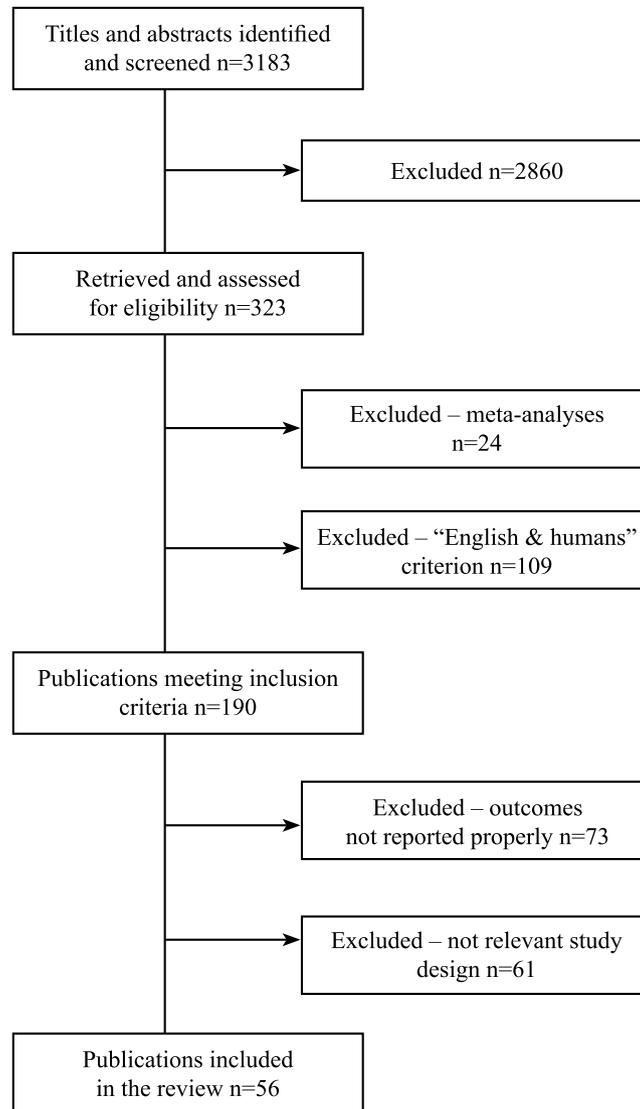


Figure 1. Diagram of the meta-analysis study selection process

Assessing the risk of bias in individual studies

During the selection process, we scrutinized for biases in protocols and reported results in our sample. This type of experiments inevita-

bly carries high potential risk for bias, mainly due to erroneous selection procedures, mistakes in implementation of interventions, and deviations from prescribed protocols (due to an inherent impossibility for controlling exhaus-

tively participants' behavior into their habitual environments). Notwithstanding that some experiments, in our opinion, lacked power due to small sample sizes or minute mean differences, generally, all included studies were of standard quality regarding the potential risk of inherent biases (whether deliberate or unintentional).

Summary effect estimation

We used the “*metaphor*” package of *R* for processing our results (Viechtbauer, 2010). For meta-regression, we used the mixed-effects model, which combines both commonly applied linear models. They have different initial assumptions regarding studied data. The fixed-effects model requires studied results to be sufficiently homogeneously distributed. They are treated as a representative sample of the general population of all the studies on the topic. On the other hand, the random-effects model relieves these assumptions by treating data as a random (replaceable) sample of the general population, thereby allowing effects to be assessed, irrespective of heterogeneity. Each model assigns different weights on trials. The mixed-effects model uses a fixed effect as an intercept (or a base) and random effects as moderator variables (Schwarzer et al., 2015; Basu, 2017). Generally, representative studies (these of large effect sizes, low variances, large sample volumes) receive bigger weights.

Assessing publication bias

This procedure assesses the representativeness of a meta-analysis. The main idea is that if some study uses a large sample size and reports expected positive results, it has a much bigger chance of being published than if the outcomes were controversial or statistically in-

significant. Publication bias analysis measures the magnitude of this phenomenon. The test is graphical and uses the so-called “Funnel plots” (Schwarzer et al., 2015; Del Re, 2015). Mean effects of studies are presented on the abscissa, and volatilities - on the ordinate (in terms of variances or standard deviations). If no publication bias is found in the data pool, the resultant graph would resemble a funnel with a few points clustered around the summary effect line for large and influential trials that report results of low volatility. Smaller studies of different effect sizes and/or high volatilities would be scattered evenly on both sides of the neutral line. Conversely, if there is publication bias in the sample, it is expected at least one quadrant to be deprived of any points. Conclusions are derived entirely by visual assessment of the data.

Performing a meta-regression procedure

We stratified the studied interventions into three subgroups by their duration: short term – between 4 and 14 weeks long; medium term – between 15 and 26 weeks long, and long term – more than 26 weeks long. In the mixed-effects model for meta-regression a fixed-effect is included as base (or intercept), and random effects are represented by additional moderator variables (variables, which are added to the equation for maximizing explained variance). This procedure estimates the influence of each moderator on the summary effect. The coefficients are calculated in two stages. Initially, the software evaluates the amount of residual heterogeneity. Consequently, the model assigns weights on each study and estimates moderator variables (and their confidence intervals assuming a Gaussian distribution). The general form of the mixed-effects model equation is as follows:

$$y_i = \beta_0 + b_1x_{i1} + b_2x_{i2} + \dots + b_nx_{in} + e_i ;$$

where x_{ij} is the j -th moderator of the i -th trial. The terms e_i represent a process of random

noise - $e_i \sim N(0, \tau^2)$. Similarly, to the simple linear regression model, the term β_0 is the in-

tercept. In addition to the conventional model, we fitted our data using the moderator variable with no intercepts. This procedure allows estimating average weekly rate of change of body mass by cohort. For each stratum, this type of modeling assumes that weight change was 0 during the first week and measures its progress for every consecutive week. For example, for long term therapies, the model assumes that during week 27 weight loss was 0 kg and estimates the amount of body mass change for every consecutive week up to week 104. Comparing and analyzing differences in outcomes of the two models for each cohort of publications is an important part of this study.

The procedure also tests for relationships between dependent and independent variables (excluding the base) by calculating the so-called Qm statistic. Generally, if its value is high, the null hypothesis (lack of relationship) should be rejected. Additionally, a coefficient for residual heterogeneity, Qe , is calculated. If its value is statistically significant, additional moderators should be included in the model to increase the explained between-study variance.

Additionally, two standard procedures were executed for assessing heterogeneity:

1. The so-called I^2 parameter was calculated. It measures heterogeneity-induced and randomness-induced fractions of data variance

– the fraction of volatility that is explained by the model. High I^2 values indicate a highly heterogeneous sample. Although generally, investigators are free to set thresholds of I^2 , samples of values higher than 30% are interpreted as heterogeneous.

2. The level of (residual) heterogeneity is assessed by the so-called τ^2 statistic. Consequently, it is used for assigning weights to analyzed publications for estimating model coefficients. The higher the value of τ^2 , the higher the data heterogeneity. If $\tau^2 = 0$ the points are absolutely homogeneous, and the fixed-effects model should be used.

RESULTS

The diagram in Figure 1 presents the process of publication selection of the meta-analysis. Figure 2 is the funnel plot of the complete data set. The distribution of data points is somewhat skewed towards values below the neutral line and there are also several outliers placed outside the funnel. However, around the mean effect size line, the points are more symmetrically distributed, and for that reason, we did not find strong evidence for publication bias in the data pool. For illustration purposes, we also present scatter plots of (un-weighted) effect sizes of studied interventions of different durations for the total sample and by strata (Figure 3).

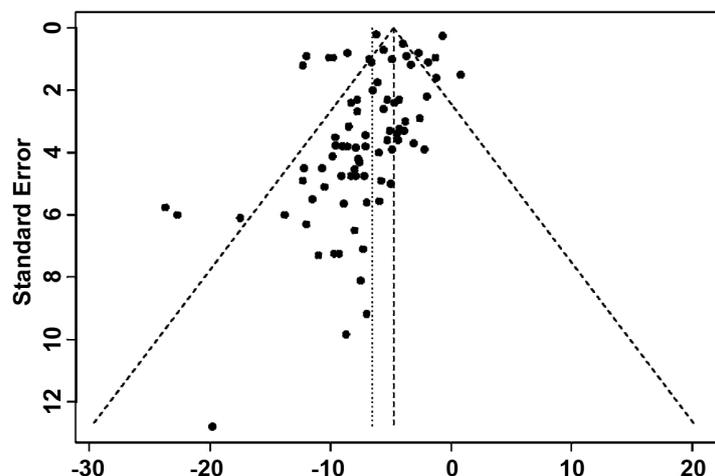


Figure 2. Funnel plot of the complete analyzed data set

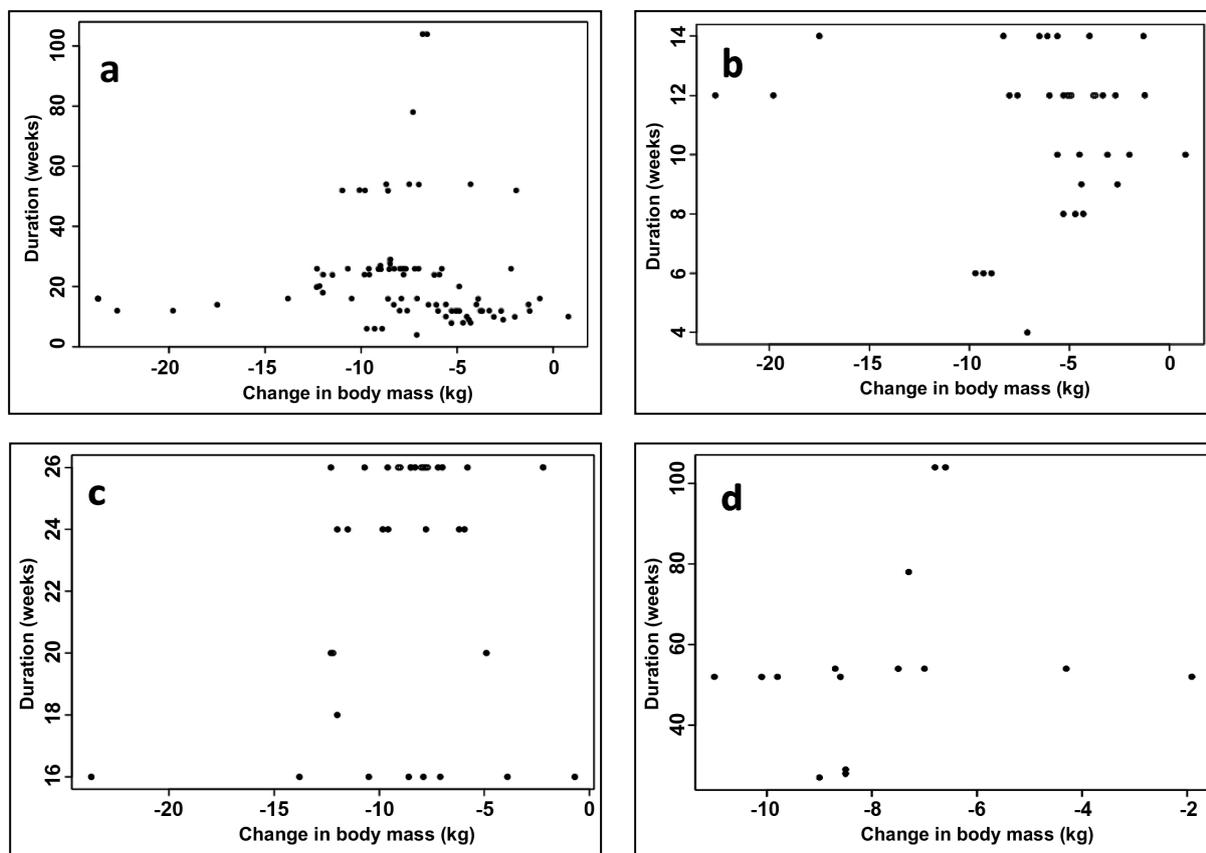


Figure 3. Scatterplots of changes in body mass vs. therapy duration.

a – overall sample; **b** – short term therapies; **c** – medium term therapies; **d** – long term therapies

The complete list of publications that are analyzed in the study is shown in Table 1.

Table 1. Data source of the meta-analysis

Data source	
1. Aicher B, Haser E, Freeman L, Carnie A, Stonik J, Wang X, Remaley A, Kato G and Cannon R. (2012). Diet-Induced Weight Loss in Overweight or Obese Women and Changes in High-Density Lipoprotein Levels and Function. <i>Obesity</i> , 20, 2057–2062.	Older Individuals with Metabolic Impairments. <i>J Nutr Health Aging</i> , 21(1), 67-74.
2. Alizadeh Z, Kordi R, Rostami M, Mansournia M, Hossein-Zadeh-Attar S, Fallah J. (2013). Comparison between the effects of continuous aerobic exercise on weight loss and body fat percentage in overweight and obese women: a randomized control trial. <i>Int J Prev Med.</i> , 4(8), 881-888	4. Amati F, Dube J, Shay C, Goodpaster B. (1985). Separate and combined effects of exercise training and weight loss on exercise efficiency and substrate oxidation. <i>J Appl Physiol</i> , 105(3), 825-831
3. Amamou T, Normandin E, Pouliot J, Dionne IJ, Brochu M, Riesco E. (2017). Effect of a High-Protein Energy-Restricted Diet Combined with Resistance Training on Metabolic Profile in	5. Avila JJ, Gutierrez JA, Sheehy ME, Lofgren IE, Delmonico MJ. (2010). Effect of moderate intensity resistance training during weight loss on body composition and physical performance in overweight older adults. <i>Eur J Appl Physiol.</i> , 109(3), 517-25.
	6. Beavers K, Beavers D, Nesbit B, Ambrosius W, Marsh A, Nicklas B, and Rejeski W. (2014). Effect of an 18 month physical activity and weight loss intervention on body composition in over-

- weight and obese older adults. *Obesity (Silver Spring)*, 22(2), 325–331.
7. Bhutani S, Klempel M, Kroeger C, Trepanowski J and Varady K. (2013). Alternate Day Fasting and Endurance Exercise Combine to Reduce Body Weight and Favorably Alter Plasma Lipids in Obese Humans. *Obesity*, 21(7), 1370-79
 8. Bo S, Ciccone G, Guidi S, Gambino R, Durazzo M, Gentile L, Cassader M, Cavallo-Perin P, and Pagano G. (2008). Diet or exercise: what is more effective in preventing or reducing metabolic alterations? *European Journal of Endocrinology*, 159, 685–691
 9. Borkowska A, Bronisz A, Budzyński J. (2015). The influence of a ten-week Nordic walking training-rehabilitation program on the level of lipids in blood in overweight and obese postmenopausal women. *J. Phys. Ther. Sci.*, 27, 3039–3044.
 10. Bouchonville M, Armamento-Villareal R, Shah K, Napoli N, Sinacore D, Qualls C, and Villareal D. (2014). Weight Loss, Exercise, or Both and Cardiometabolic Risk Factors in Obese Older Adults: Results of a Randomized Controlled Trial. *Int J Obes (Lond)*, 38(3), 423–431.
 11. Bray G, Smith S, DeJonge L, de Souza R, Rood J, Champagne C, Laranjo N, Carey V, Obarzanek E, Loria C, Anton S, Ryan D, Greenway F, Williamson D, and Sacks F. (2012). Effect of Diet Composition on Energy Expenditure during Weight Loss: The POUNDS LOST Study. *Int J Obes (Lond)*, 36(3), 448–455.
 12. Brekke H, Bertz F, Rasmussen K, Bosaeus I, Ellega L, Winkvist A. (20). Diet and Exercise Interventions among Overweight and Obese Lactating Women: Randomized Trial of Effects on Cardiovascular Risk Factors. *PlosOne*, 9(2), e88250.
 13. Brochu M, Malita M, Messier V, Doucet E, Strychar I, Lavoie J, Prud'homme D, and Rabasa-Lhoret R. (2009). Resistance Training Does Not Contribute to Improving the Metabolic Profile after a 6-Month Weight Loss Program in Overweight and Obese Postmenopausal Women. *Clin Endocrinol Metab*. September, 94(9), 3226–3233
 14. Christiansen T, Paulsen SK, Bruun JM, Overgaard K, Ringgaard S, Pedersen SB, Positano V, Richelsen B. (2009). Comparable reduction of the visceral adipose tissue depot after a diet-induced weight loss with or without aerobic exercise in obese subjects: a 12-week randomized intervention study. *Eur J Endocrinol.*, 160(5), 759-67.
 15. Coker R, Williams R, Yeo S, Kortebein P, Bodenner D, Kern P, Evans W. (2009). The impact of exercise training compared to caloric restriction on hepatic and peripheral resistance in obesity. *J Clin Endocrinol Metab.*, 94(11), 4258-4266
 16. Creasy S, Rogers R, Davis K, Gibbs B, Kershaw E and Jakicic J. (2017). Effects of supervised and unsupervised physical activity programmes for weight loss. *Obesity Science & Practice.*, 3(2), 143-152
 17. Danielsen K, Svendsen M, Mæhlum S, and Sundgot-Borgen J. (2013). Changes in Body Composition, Cardiovascular Disease Risk Factors, and Eating Behavior after an Intensive Lifestyle Intervention with High Volume of Physical Activity in Severely Obese Subjects: A Prospective Clinical Controlled Trial. *Journal of Obesity Volume 2013*, 325-46
 18. DeLany JP, Kelley DE, Hames KC, Jakicic JM, Goodpaster BH. (2014). Effect of physical activity on weight loss, energy expenditure, and energy intake during diet-induced weight loss. *Obesity (Silver Spring)*, 22(2), 363-70.
 19. Embree GG, Samuel-Hodge CD, Johnston LF, Garcia BA, Gizlice Z, Evenson KR, DeWalt DA, Ammerman AS, Keyserling TC. (2017). Successful long-term weight loss among participants with diabetes receiving an intervention promoting an adapted Mediterranean-style dietary pattern: the Heart Healthy Lenoir Project. *BMJ Open Diabetes Res Care.*, 5(1), e000339.
 20. Figueroa A, Vicil F, Marcos Sanchez-Gonzalez A, Wong A, Ormsbee M, Hooshmand S and Daggy B. (2013). Effects of Diet and/or Low-Intensity Resistance Exercise Training on Arterial Stiffness, Adiposity, and Lean Mass

- in Obese Postmenopausal Women. *American Journal of Hypertension*, 26(3), 416-423
21. Frimel T, sinacore D, and villareal D. (2008). Exercise Attenuates the Weight-Loss Induced Reduction in Muscle Mass in Frail Obese Older Adults. *Med Sci Sports Exerc.*, 40(7), 1213–1219.
 22. Gallaher D, Heska S, Kelley D, Thompton J, Boxt L, Pi-Sunier X, Patrico J, Mancino J, Clark J. (2014). Changes in Adipose Tissue Depots and Metabolic Markers Following a 1-Year Diet and Exercise Intervention in Overweight and Obese Patients with Type 2 Diabetes. *Diabetes Care*, 37, 3325–3332
 23. García-Unciti M, Izquierdo M, Idoate F, Gorostiaga E, Grijalba A, Ortega-Delgado F, Martínez-Labari C, Moreno-Navarrete J, Forga L, Fernández-Real J, Ibáñez J. (2012). Weight-Loss Diet Alone or Combined with Progressive Resistance Training Induces Changes in Association between the Cardiometabolic Risk Profile and Abdominal Fat Depots. *Ann Nutr Metab*, 61, 296–304,
 24. Hagner –Derengowska M, Kałużny K, Hagner W, Kochański B, Plaskiewicz A. (2015). The influence of a ten-week Nordic walking training-rehabilitation program on the level of lipids in blood in overweight and obese postmenopausal women. *J. Phys. Ther. Sci.*, 27, 3039–3044.
 25. Hudson JL, Kim JE, Paddon-Jones D, Campbell WW. (2017). Within-day protein distribution does not influence body composition responses during weightloss in resistance-training adults who are overweight. *Am J Clin Nutr.*, 106(5), 1190-1196.
 26. Jabekk P, Moe I, Meen H, Tomten S, Høstmark A. (2010). Resistance training in overweight women on a ketogenic diet conserved lean body mass while reducing body fat. *Nutrition & Metabolism*, 7:17
 27. Jakicic J, King W, Marcus M, Davis K, Helsel D, Rickman A, Gibbs B, Rogers R, Wahed A, and Belle S. (2015). Short-Term Weight Loss with Diet and Physical Activity in Young Adults: the IDEA Study. *Obesity (Silver Spring)*, 23(12), 2385–2397.
 28. Jakicic J, Rickman A, Lang W, Davis K, Gibbs B, Neiberg R, and Marcus M. (2015). Time-Based Physical Activity Interventions for Weight Loss: A Randomized Trial. *Med Sci Sports Exerc.*, 47(5), 1061–1069.
 29. Kahleova H, Matoulek* M, Malinska H, Oliyarnik O, Kazdova L, Neskudla T, Skoch A, Hajek M, Hill M, Kahle M and Pelikanova T. (2011). Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. *Diabet. Med.*, 28, 549–559
 30. Kerksick C, Thomas A, Campbell B, Taylor L, Wilborn C, Marcello B, Roberts M, Pfau E, Grimstvedt M, Opusunju J, Magrans-Courtney T, Rasmussen C, Wilson R and Kreider R. (2009). Effects of a popular exercise and weight loss program on weightloss, body composition, energy expenditure and health in obese women. *Nutrition & Metabolism*, 6, 23
 31. Kleist B, Wahrburg U, Stehle P, Schomaker R, Greiwing A, Stoffel-Wagner B, Egert S. (2017). Moderate Walking Enhances the Effects of an Energy-Restricted Diet on Fat Mass Loss and Serum Insulin in Overweight and Obese Adults in a 12-Week Randomized Controlled Trial. *J Nutr.*, 147(10), 1875-1884
 32. Koehler K, De Souza MJ, Williams NI. (2017). Less-than expected weight loss in normal-weight women undergoing caloric restriction and exercise is accompanied by preservation of fat-free mass and metabolic adaptations. *Eur J Clin Nutr.*, 71(3), 365-371.
 33. Kreider RB, Rasmussen C, Kerksick CM, Wilborn C, Taylor L 4th, Campbell B, Magrans-Courtney T, Fogt D, Ferreira M, Li R, Galbreath M, Iosia M, Cooke M, Serra M, Gutierrez J, Byrd M, Kresta JY, Simbo S, Oliver J, Greenwood M. (2011). A carbohydrate-restricted diet during resistance training promotes more favorable changes in body composition and markers of health in obese women with and without insulin resistance. *Phys Sportsmed.*, 39(2), 27-40.
 34. Kreider RB, Serra M, Beavers KM, Moreillon

- J, Kresta JY, Byrd M, Oliver JM, Gutierrez J, Hudson G, Deike E, Shelmadine B, Leeke P, Rasmussen C, Greenwood M, Cooke MB, Kerksick C, Campbell JK, Beiseigel J, Jonnalagadda SS. (2011A). structured diet and exercise program promotes favorable changes in weight loss, body composition, and weight maintenance. *J Am Diet Assoc.*, 111(6), 828-43.
35. Madjd A, Taylor MA, Shafiei Neek L, Delavari A, Malekzadeh R, Macdonald IA, Farshchi HR. (2016). Effect of weekly physical activity frequency on weight loss in healthy overweight and obese women attending a weight loss program: a randomized controlled trial. *Am J Clin Nutr.*, 104(5), 1202-1208.
36. Matsuo T, Y Kato¹, Murotake Y, Kim M, Unno H and Tanaka K. (2010). An increase in high-density lipoprotein cholesterol after weight loss intervention is associated with longterm maintenance of reduced visceral abdominal fat. *International Journal of Obesity.*, 34, 1742–1751
37. Nicklas B, Wang X, You T, Lyles M, Demons J, Easter L, Berry M, Lenchik L, and Carr J. (2009). Effect of exercise intensity on abdominal fat loss during calorie restriction in overweight and obese postmenopausal women: a randomized, controlled trial. *Am J Clin Nutr.*, 89, 1043–52.
38. Normandin E, Chmelo E, Lyles M, Marsh A, and Nicklas B. (2017). Effect of Resistance Training and Caloric Restriction on the Metabolic Syndrome. *Med Sci Sports Exerc.*, 49(3), 413–419.
39. Parr EB, Coffey VG, Cato LE, Phillips SM, Burke LM, Hawley JA. (2016). A randomized trial of high-dairy-protein, variable-carbohydrate diets and exercise on body composition in adults with obesity. *Obesity (Silver Spring).*, 24(5), 1035-45.
40. Philippou Ch, Andreou E, Menelaou N, Hajigeorgiou Ph, Papandreou D. (2012). Effects of diet and exercise in 337 overweight/obese adults. *HIPPOKRATIA*, 16(1):, 46-50
41. Rock C, Flatta S, Pakiz B, Quintana E, Heath D, Rana B, and Natarajana L. (2016). Effects of diet composition on weight loss, metabolic factors and biomarkers in a 1-year weight loss intervention in obese women examined by baseline insulin resistance status. *Metabolism.*, 65(11), 1605–1613.
42. Serra M, Treith M, and Ryan A. (2014). Dietary prescription adherence and non-structured physical activity following weight loss with and without aerobic exercise. *J Nutr Health Aging.*, 18(10), 888–893.
43. Snel M, Gastaldelli A, Ouwens D, Hesselink M, Schaart G, Buzzigoli E, Frolich M, Romijn J, Pijl H, Meinders A, and Jazet I. (2012). Effects of Adding Exercise to a 16-Week Very Low-Calorie Diet in Obese, Insulin-Dependent Type 2 Diabetes Mellitus Patients. *J Clin Endocrinol Metab.*, 97(7), 2512–2520
44. Straight CR, Berg AC, Reed RA, Johnson MA, Evans EM. (2018). Reduced body weight or increased muscle quality: Which is more important for improving physical function following exercise and weight loss in overweight and obese older women? *Exp Gerontol.*, 108, 159-165
45. Tay J, luscombe-Marsh N, Thompson C, noakes M, Buckley J, Wittert G, Yancy W and Brinkworth G. (2014). A Very Low-Carbohydrate, Low-Saturated Fat Diet for Type 2 Diabetes Management: A Randomized Trial. *Diabetes Care*, 37, 2909–2918
46. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, Yancy WS Jr, Brinkworth GD. (2015). Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. *Am J Clin Nutr.*, 102(4), 780-90.
47. Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD, Wittert GA, Yancy WS Jr, Brinkworth GD. (2017). Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes Obes Metab.*, 20(4), 858-871

48. Verreijen A, Engberink M, Memelink R, van der Plas S, Visser M and Weijts P. (2017). Effect of a high protein diet and/or resistance exercise on the preservation of fat free mass during weight loss in overweight and obese older adults: a randomized controlled trial. *Nutrition Journal*, 16(1), 10
49. Villareal D, Aguirre L, Gurney A, Waters D, Sinacore D, Colombo E, Armamento-Villareal R, and Qualls C. (2018). Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults. *N Engl J Med*, 376(20), 1943-1955.
50. Villareal D, Aguirre L, Gurney A, Waters D, Sinacore D, Colombo E, Armamento-Villareal R, and Qualls C. (2017). Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults. *N Engl J Med*, 376, 1943-55.
51. Villareal G, Chode S, Parimi N, Sinacore D, Hilton T, Armamento-Villareal R, Napoli N, Qualls C, and Shah K. (2011). Weight Loss, Exercise, or Both and Physical Function in Obese Older Adults. *N Engl J Med.*, 364(13), 1218–1229.
52. Vissersa D, Verrijken A, Mertens I, Van Gils C, Van de Sompel A, Truijen S, Van Gaalb L. (2010). Effect of Long-Term Whole Body Vibration Training on Visceral Adipose Tissue: A Preliminary Report. *Obes Facts*, 3, 93–100
53. Watson N, Dyer K, Buckley J, Brinkworth G, Coates A, Parfitt G, Howe P, Noakes M and Murphy K. (2016). Effects of Low-Fat Diets Differing in Protein and Carbohydrate Content on Cardiometabolic Risk Factors during Weight Loss and Weight Maintenance in Obese Adults with Type 2 Diabetes. *Nutrients*, 8(5), 289
54. Weinreich T, Filz H, Gresser U, Richartz B. (2017). Effectiveness of A Four-Week Diet Regimen, Exercise and Psychological Intervention for Weight Loss. *Journal of Clinical and Diagnostic Research.*, 11(3), 20-24
55. Weiss E, Albert S, Reeds D, Kress K, McDaniel J, Klein S, and Villareal D. (2016). Effects of matched weight loss from calorie restriction, exercise, or both on cardiovascular disease risk factors: a randomized intervention trial. *Am J Clin Nutr*; 104, 576–86.
56. Wood RJ, Gregory SM, Sawyer J, Milch CM, Matthews TD, Headley SA. (2012). Preservation of fat-free mass after two distinct weight loss diets with and without progressive resistance exercise. *Metab Syndr Relat Disord.*, 10(3), 167-74.
57. Wycherley TP, Noakes M, Clifton PM, Cleanthous X, Keogh JB, Brinkworth GD. (2010). A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. *Diabetes Care.*, 33(5), 969-76.

Therapies of short duration

The results about the data fitted by the two models are shown below. Thirty-five data points were included in this stratum in total. For the model without an intercept, the *Qe* coefficient is statistically significant – a sign that only a small fraction of between-study heterogeneity is explained (Table 2). Expectedly, more moderators

are necessary for this data pool. The calculated moderator variable (“duration”) is highly statistically significant and lies in a tight confidence interval. On the other hand, the heterogeneity of the data is quite high $I^2 = 94.39\%$ (the unexplained heterogeneity) and $\tau^2 = 17.0535$ (the residual heterogeneity), although the standard error of τ^2 is relatively high – 4.865.

$$\tau^2 = 17.0535 \text{ (SE} = 4.8650\text{); } I^2 = 94.39\%; Qe \text{ (df} = 34\text{)} = 194.6406, p < .0001$$

Table 2. Results of the model without an intercept (therapies of short duration)

Parameter	Estimate	SE	z	p	CI l.b.	CI u.b.
Duration	-0.5124	0.0675	-7.5955	< .0001	-0.6447	-0.3802

On the other hand, when an intercept is included, heterogeneity expectedly decreases at the cost statistical significance being lost by the estimates (Table 3). The intercept value should be equal to body mass change during week 0, which is obviously meaningless. As the lowest duration in the sample was 4 weeks, the sum-

mary effect can be calculated as $intercept + 4 * (duration)$ and equals -5.5839. Irrespective of the fact that the p-value of the base is close to 0.05, this result is not statistically significant by the standards and should be considered as only indicative.

$$\tau^2 = 15.8377 \text{ (SE} = 4.6304\text{); } I^2 = 88.64\%; Q_e \text{ (df} = 33\text{)} = 178.6734, p < .0001;$$

$$Q_m \text{ (df} = 1\text{)} = .0216, p = .8832$$

Table 3. Results of the model with an intercept ((therapies of short duration)

Parameter	Estimate	SE	z	p	CI l.b.	CI u.b.
Intercept	-5.4163	3.2049	-1.6900	.0910	-11.6978	0.8651
Duration	-0.0419	0.2849	-.1469	.8832	-0.6002	0.5164

Therapies of medium duration

Thirty-five trials were included in this stratum. Below are shown the results of modelling without and with an intercept (Table 4 and 5).

The first model reached high statistical significance for the moderator variable, which was lost in the second model. The intercept variable was statistically significant for this cohort.

Model 1:

$$\tau^2 = 14.3015 \text{ (SE} = 4.3579\text{); } I^2 = 87.77\%; Q_e \text{ (df} = 34\text{)} = 279.4173, p < .0001$$

Table 4. Results of the model without an intercept (therapies of medium duration)

Parameter	Estimate	SE	z	p	CI l.b.	CI u.b.
Duration	-0.3722	0.0314	-11.8556	< .0001	-0.4338	-0.3107

Model 2:

$$\tau^2 = 11.1012 \text{ (SE} = 3.7093\text{); } I^2 = 83.70\%; Q_e \text{ (df} = 33\text{)} = 279.3636, p < 0.0001;$$

$$Q_m \text{ (df} = 1\text{)} = 0.4426, p = .5059$$

Table 5. Results of the model with an intercept (therapies of medium duration)

Parameter	Estimate	SE	z	p	CI l.b.	CI u.b.
Intercept	-5.4163	3.2049	-1.6900	.0910	-11.6978	0.8651
Duration	-0.0419	0.2849	-.1469	.8832	-0.6002	0.5164

Therapies of long duration

The number of experiments in this stratum is smaller – 15. The no-intercept model measured high heterogeneity in this stratum $I^2 = 87.09\%$ and $\tau^2 = 15.3921$ – Table 6 (but the

standard error of τ^2 is also extremely high – 7.21 or almost 50%). The duration variable is of high statistical significance. Q_e statistic is statistically significant – $p < .0001$:

$$\tau^2 = 15.3921 \text{ (SE} = 7.2100\text{); } I^2 = 87.09\%; Q_e \text{ (df} = 14\text{)} = 123.7249, p < .0001$$

Table 6. Results of the model without an intercept (therapies of long duration)

Parameter	Estimate	SE	z	p	CI l.b.	CI u.b.
Duration	-0.1108	0.0183	-6.0511	< .0001	-0.1467	-0.0749

The second model reached statistical significance for the base but lost it for the duration (Table 7). Expectedly, heterogeneity decreases, in this case, dramatically:

$$\tau^2 = 4.7571 \text{ (SE} = 3.0982\text{); } I^2 = 66.62\%; Q_e \text{ (df} = 13\text{)} = 46.7756, p < .0001$$

$$Q_m \text{ (df} = 1\text{)} = .6216, p = .4305$$

Table 7. Results of the model with an intercept (therapies of long duration)

Parameter	Estimate	SE	z	p	CI l.b.	CI u.b.
Intercept	-8.9287	1.8885	-4.7280	< .0001	-12.6301	-5.2273
Duration	0.0235	0.0298	.7884	.4305	-0.0349	0.0819

The plots in Figure 3 show highly noisy pictures of visible heteroscedasticities and no distinguishable regression trends. In the first two diagrams, effect sizes are grouped in several layers by duration. If a clear positive relationship between weeks spent on therapy and the amount of weight loss existed, then a negatively sloped regression line should be noticeable, which in our graphs was not the case. Furthermore, no visible differences exist in ranges of effect sizes for all the duration layers. Roughly speaking, this finding indicates a lack of clearly noticeable relation between weight loss and therapy duration within strata (although the same is true for the overall sample – see the first plot). Technically, a simple linear regression model would find some negative regressions for both short and moderately long therapies. For short-term interventions, effect sizes increase to some extent in sync with duration. The trend is somewhat blurred, but still visible for moderately long therapies. On the other hand, the plot of long-term interventions even shows a slightly positively sloped (imaginary) regression line with effect size inversely proportional to duration. Interestingly, for long term interventions, the data points in

the middle of the graph (which correspond to 52-54-week long interventions) are almost uniformly distributed along the whole range of measured effect sizes. Nonetheless, if assessed in a strictly statistical sense, this sample would deliver a mean value (which would be smaller than that of the moderately long therapies) and a standard deviation. However, in light of all abovementioned considerations, these numbers would beget misleading conclusions. Additionally, only a few data points are included for durations different than this one, which complicates the statistical interpretation. Nevertheless, the longest interventions are clearly far from being the most effective within the sample. It should be noted, however, that if weighted effect sizes (which the mixed-effects model calculates) were plotted these graphs would be somewhat different. Nevertheless, the big picture would not change much.

The analysis of the results raises some interesting considerations. All the three strata of analyzed studies are highly heterogenic. An interesting trend emerges in the estimated summary effects between groups – the intercepts in the mixed-effects models (for short term interventions the “duration” variable should be

multiplied by 4 and added to the intercept as the shortest therapies included in the sample are 4 weeks long). Generally, common wisdom dictates that the amount of body weight lost to therapy should increase (although, not necessarily linearly) with its duration. This line of thinking implies that the longest interventions should deliver the biggest effects. Our results, however, draw a different picture – one of an inverted parabolic relationship with a maximum summary effect of -11.1 kg for moderately long interventions and -5.58 kg and -8.93 kg for short- and long-term therapies, respectively. Accordingly, this finding should classify these therapies as the most effective ones for weight reduction. On the other hand, this conclusion may be premature and over-simplistic as we have stratified our overall sample somewhat arbitrarily. If we delve into the calculations of the non-intercept mixed-effects model for the three groups of studies, a more detailed picture becomes visible. Estimates of moderator variables (the “duration” variable in no-intercept meta-regression results) clearly depict a decelerating pace of weight reduction by strata – from -0.5124 kg per week for short term interventions to -0.3722 kg per week for moderately long ones to -0.1108 kg per week for long term therapies (all estimates are highly statistically significant). The same trend emerges in the mixed-effects model with an intercept: while for short term therapies the moderator is negative (although, insignificant statistically), for the medium term and long term interventions it is positive, which means that summary effects decrease with time. (Short term interventions are somewhat expected to show the highest results as it is well established that at the initial stages of a diet plan, much water is lost with body mass). Theoretically, we could extrapolate these findings to the general population of trials of weight reduction (of which our group of studies is considered to be a ran-

dom sample by the model), but the inverted U-curve of summary effects by strata infers somewhat conflicting conclusions: weight regains should be present at some points in time in long term interventions, in order to explain these findings. In our opinion, most probably, they are due to relapses caused by the psychological discomfort of long-lasting dieting. On the other hand, the number of trials in the long-duration group is only 15, which necessitates a cautious interpretation. Additionally, the model calculated high values of heterogeneity statistics and statistically significant Q_e coefficients for all studied groups. This means that we are analyzing a highly scattered sample in which the “duration” moderator variable explains only a tiny bit of the sample variability. Generally, these results statistically proved that long-term interventions are less effective for weight reduction than those of short to moderate durations, which corroborates some previous findings (Ashtary-Larky et al., 2017, Nackers et al., 2010; Byrne et al., 2018). Interventions that are based on changing habitual nutrition behaviours for long periods of time are difficult to adhere to. These conclusions are in agreement with the results of the 2 experiments with the longest durations. Tay J et al. studied the effect of a combined 2-years long diet-and-exercise intervention on overweight and obese people with type 2 diabetes and reported moderate weight loss (Tay et al., 2017). Although the experiment was claimed to be successful, almost half of the participants did not manage to complete it. In our opinion, if their hypothetical results had been included, the outcomes would have been even more moderate. In the other trial, Beavers K et al. studied how an 18-month long diet-and-exercise intervention affected obese older adults (Beavers et al., 2014). They reported a relatively high adherence rate of 86.5% and moderate reductions in body mass. Their protocol, however, includ-

ed periods of maintenance, which, in our opinion, greatly facilitates adherence and alleviates potential diet-induced psychological discomforts. Frequently, long term therapies are associated with occasional relapses, during which patients regain some or all of the weight they have lost (Gibson & Sainsbury, 2017; Sacks et al., 2009). These interruptions diminish the efficiency of interventions in terms of both the net amount of lost weight (a pattern clearly visible in our sample of long-term therapies) and the rate of weight loss per unit of time. For that reason, in agreement with some experts, we recommend long term weight-reduction plans to contain scheduled regular interruptions (Brehm, 2014). Such an approach is also commonly used by many bodybuilders during their pre-contest preparation routines.

CONCLUSION

In conclusion, our meta-regression analysis proved that the highest rate of weight reduction is reached for moderately long therapies and slows down or vanishes for long-term interventions, mainly (in our opinion) due to declining with time adherence rate (Greenberg et al., 2009, Gillis-Januszewska et al., 2018). Additionally, short-term interventions induce the fastest weight loss per unit of time. Mathematically, these numbers prove that relapses should occur during long term interventions, which reduces or nullifies any achieved weight loss. Accordingly, most probably, body mass reduction therapies should be maintained short to moderately long and should be cycled several times in order to achieve expected results without provoking relapses, frustrations or burnouts. In our opinion, this approach is vital for the psychological comfort of overweight and obese patients. Their weight reduction goals require a lot of time to be achieved as they carry big amounts of excessive body weight. With increased food abstention time,

the risk of relapses, and consequently entering yo-yo effect spirals due to psychological reasons, increases. Bitter experiences from failed weight reduction attempts (which are quite common in this cohort) only further aggravate the problem. Applying short to moderately long interventions separated by occasional interruptions could be an efficient method for maintaining weight loss in the long term, while concomitantly sustaining patients' self-esteem and well-being high due to the sustainable and permanent "step-by-step" successful process of losing kilograms in such a fashion that they can achieve/witness it.

REFERENCES

- 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?. *Int J Endocrinol Metab.*, 15(3), e13249.
- Basu, A. (2017). How to conduct meta-analysis: A Basic Tutorial. *PeerJ Preprints*, 1-28
- Brill, JB., Perry, AC., Parker, L., Robinson, A., Burnett K. (2002). Dose-response effect of walking exercise on weight loss: how much is enough? *Int J Obes*, 26(11), 1484-93.
- Byrne, N., Sainsbury, A., King, N., Hills, A. & Wood, R. (2018). Intermittent energy restriction improves weight loss in obese men: the MATADOR study. *International Journal of Obesity*, 42, 129-138
- Chooi, Y., Ding, C., and Magkos, F. (2019). The epidemiology of obesity. *Metabolism*, 92, 6-10.
- Cuchieri, S., Mamo, J. (2016). Getting to grips with the obesity epidemic in Europe. *SAGE Open Med*, 4, 1-6.
- Del Re, A. (2015). A Practical Tutorial on Conducting Meta-Analysis in R. *The Quantitative Methods for Psychology*, 11(1), 37-50.

- Gibson, AA., Sainsbury, A. (2017). Strategies to Improve Adherence to Dietary Weight Loss Interventions in Research and Real-World Settings. *Behav Sci (Basel)*, 7(3), 44.
- Gilis-Januszewska, A., Barengo, NC., Lindström, J., Wójtowicz, E., Acosta, T., Tuomilehto, J., et al. (2018). Predictors of long term weight loss maintenance in patients at high risk of type 2 diabetes participating in a lifestyle intervention program in primary health care: The DE-PLAN study. *PLoS ONE*, 13(3), e0194589.
- Greenberg, I., Stampfer, MJ., Schwarzfuchs, D., Shai, I.; DIRECT Group. (2009). Adherence and success in long-term weight loss diets: the dietary intervention randomized controlled trial (DIRECT). *J Am Coll Nutr*, 28(2), 159-68.
- Hu, FB., Manson, JE., Stampfer, MJ., Cilditz, G., Liu, S., Solomon, CG., et al. (2001). Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*, 345(11), 790-7.
- 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?. *Int J Behav Med*, 17(3), 161-167
- Pisunyer, FX. (1993). Medical hazards of obesity. *Ann Intern Med*, 119(7), 655-60.
- Racette, SB., Schoeller, DA., Kushner, RF., Neil, KM., Herling-Iaffaldano, K. (1995). Effects of aerobic exercise and dietary carbohydrate on energy-expenditure and body-composition during weight-reduction in obese rate. *Am J Clin Nutr*, 61(3), 48
- Sacks, F.M., Bray, G.A., Carey, V.J., Smith, S.R., Ryan, D.H., Anton, S.D., McManus, K., Champagne, C.M., Bishop, L.M., Laranjo, N., et al. (2009). Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates. *N. Engl. J. Med.*, 360, 859-873.
- Schwarzer, G., Carpenter, J., Rucker, G. (2015). *Meta-analysis with R*. Springer, 1-28
- van Aggel-Leijssen, DP., Saris, WH., Wagenmakers, AJ., Hull, GB., van Baak, MA. (2001). The effect of low-intensity exercise training on fat metabolism of obese women. *Obes Res*, 9(2), 86-96.
- Viechtbauer, W. (2010). Conducting meta-analyses in R with the metaphor package. *Journal of Statistical Software*, 36(3), 1-48
- Wilmore, JH., Despres, JP., Stanforth, PR., Mandel, S., Rice, T., Gagnon, J., et al. (1999). Alterations in body weight and composition consequent to 20 wk of endurance training: the HERITAGE Family Study. *Am J Clin Nutr*, 70(3), 346-50.

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