Metabolism Clinical and Experimental xxx (xxxx) xxx-xxx



Contents lists available at ScienceDirect

Metabolism Clinical and Experimental



journal homepage: www.metabolismjournal.com

Exercise in the management of obesity

Anatoli Petridou¹, Aikaterina Siopi¹, Vassilis Mougios *

Laboratory of Evaluation of Human Biological Performance, School of Physical Education and Sport Science at Thessaloniki, Aristotle University of Thessaloniki, Greece

ARTICLE INFO

Article history: Received 29 August 2018 Received in revised form 10 October 2018 Accepted 22 October 2018 Available online xxxx

Keywords: Energy balance Exercise Obesity Weight maintenance Weight management

ABSTRACT

Obesity is a multifactorial disease with increasing incidence and burden on societies worldwide. Obesity can be managed through everyday behavioral changes involving energy intake and energy expenditure. Concerning the latter, there is strong evidence that regular exercise contributes to body weight and fat loss, maintenance of body weight and fat reduction, and metabolic fitness in obesity. Appropriate exercise programs should ideally combine large negative energy balance, long-term adherence, and beneficial effects on health and well-being. Endurance training appears to be the most effective in this respect, although resistance training and high-intensity interval training play distinct roles in the effectiveness of exercise interventions. With weight regain being so common, weight loss maintenance is probably the greatest challenge in the successful treatment of obesity. There is an established association between higher levels of physical activity and greater weight loss maintenance, based on the abundance of evidence from prospective observational studies and retrospective analyses. However, proving a causative relationship between exercise and weight loss maintenance is difficult at present. Exercise has the potential to alleviate the health consequences of obesity, even in the absence of weight loss. All in all, exercise constitutes an indispensable, yet often underestimated, tool in the management of obesity.

© 2018 Elsevier Inc. All rights reserved.

Contents

4	
	Introduction
2.	Exercise to Reduce Body Weight and Fat
	2.1. Exercise Volume
	2.2. Exercise Type
3.	Exercise to Maintain the Reduction of Body Weight and Fat
4.	Exercise for Metabolic Fitness in Obesity
	4.1. Observational Studies
	4.2. Interventional Studies
	Avoiding Adverse Effects and Mistakes when Training Obese Individuals
6.	Concluding Remarks
Auth	or Contribution
Fund	ing
	arations of Interest
Refer	rences

Abbreviations: ACSM, American College of Sports Medicine; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; HIIT, high-intensity interval training; MET, metabolic equivalent of task; MICT, moderate-intensity continuous training; NAFLD, non-alcoholic fatty liver disease; RCT, randomized controlled trial.

E-mail address: mougios@auth.gr (V. Mougios).

¹ These authors have contributed equally to this work.

https://doi.org/10.1016/j.metabol.2018.10.009 0026-0495/© 2018 Elsevier Inc. All rights reserved.

1. Introduction

Adipose tissue represents the largest energy depot in the human body. More and more people exhibit excessive fat deposition in adipose tissue, which leads to obesity, a multifactorial disease with both adverse health effects and economic implications. Although obesity has troubled humanity since ancient times, it has reached epidemic proportions only in recent years [1]. Since its primary cause is a chronic imbalance

Please cite this article as: Petridou A, et al, Exercise in the management of obesity, Metabolism Clinical and Experimental (2018), https://doi.org/ 10.1016/j.metabol.2018.10.009

^{*} Corresponding author at: TEFAA, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece.

2

ARTICLE IN PRESS

between energy intake and energy expenditure in favor of the former, the road to fighting obesity (excluding pharmaceutical interventions) necessarily passes through creating a negative energy balance.

A plethora of studies have shown that the most effective approach to achieving a negative energy balance is a combination of diet, exercise and behavioral modification [2–4]. Although restriction of energy intake through dietary interventions is more efficient than exercise in accomplishing significant weight loss, drastic decreases in energy intake could result in nutritional deficiencies and decreased resting metabolic rate due to loss of lean body mass [5], whereas weight regain occurs if a dietary intervention is stopped [1,6]. Therefore, implementing a long-term diet characterized by moderate restriction of energy intake, in combination with regular exercise, is important [6]. In addition, adhering to an exercise program plays a key role in maintaining a healthy body weight and fat over time [2], as adding exercise to diet leads to sustained weight loss for up to 36 months [7].

Although body weight loss is the main concern in the treatment of obesity, reduction in visceral adipose tissue may occur irrespective of changes in body weight and is considered more important than weight reduction [8]. Interestingly, exercise training and lifestyle-modification programs characterized by increased physical activity elicit appreciable reductions in abdominal obesity [9]; they even tend to show a larger decrease in visceral fat compared to dietary restriction [8], thus highlighting the unique role of exercise in the management of obesity. Moreover, exercise is credited with a beneficial role in the health of obese individuals, even in the absence of weight loss [10], which means that exercise is more than just a calorie-burning agent [11].

The aim of this narrative review is to highlight the evidence for the effectiveness of exercise and physical activity in the management of obesity. In its four main sections, we will explore the contribution of exercise to body weight and fat loss, maintenance of body weight and fat reduction, and metabolic fitness in obesity, followed by recommendations on how to avoid adverse effects and mistakes when training obese individuals. The review is focused on studies performed in obese people and is not exhaustive due to space limitations.

2. Exercise to Reduce Body Weight and Fat

Increasing daily energy expenditure to tip the energy balance is an effective strategy in the treatment of obesity, and the larger the negative energy balance, the greater the weight loss. Increased energy expenditure can be obtained by increasing physical activity in forms of supervised or non-supervised exercise, occupational activity, work around the home, personal care, commuting, and leisure-time activities [12]. Energy expenditure rises through physiological processes and cellular mechanisms that accelerate the breakdown of the body's major energy stores, that is, glycogen and triacylglycerols, leading to weight loss. Specifically, exercise speeds up glycogenolysis in muscle and liver; glycolysis, the citric acid cycle and oxidative phosphorylation in muscle; lipolysis in adipose tissue and muscle; and fatty acid oxidation in muscle. All these effects are primarily achieved through the stimulated secretion of hormones and changes in substrate concentrations that lead to activation of enzymes catalyzing key steps in the aforementioned catabolic pathways.

Although increased energy expenditure is the primary way in which exercise fights obesity, research has also been directed at investigating whether exercise affects energy intake by modulating appetite. Although variable, the results of the studies on this topic suggest that people do not alter food intake after exercise [13]. This finding obtains even though exercise usually elicits favorable changes in the plasma concentrations of orexigenic and anorexigenic hormones.

Since many obese people have reduced cardiorespiratory fitness (CRF), are not familiar with exercise, and are at increased risk for musculoskeletal injuries due to excess body weight, it is important to prescribe exercise that is safe and makes them feel comfortable, thus ensuring adherence to the exercise training program. Such a program should be defined by the appropriate parameters of frequency, duration, intensity, type, and progressivity, which, in turn, should be determined according to individual abilities, preferences, and responses. It is also recommended that exercise be supervised by a specialized trainer, at least during an initial period. The recommendations apply to both women and men, as there seem to be no differences between sexes in the weight loss caused by equivalent exercise [14].

2.1. Exercise Volume

Exercise volume determines energy expenditure and depends on duration and intensity. According to the American College of Sports Medicine (ACSM) position stands [2,12], European College of Sport Science position statement [15], and American College of Cardiology and American Heart Association task force [16], exercise consistent with the minimum levels of physical activity recommendations (approximately 150 min of moderate-intensity exercise per week) without dietary restriction may induce modest weight loss (about 2 to 3 kg) but is inadequate for clinically significant weight loss (\geq 5%). To achieve that, individuals should complete approximately 225 to 420 min of exercise per week [12,17]. Thus, although 150 min of moderately intense physical activity per week may provide important health benefits and assist in weight control, a greater amount of physical activity is necessary for weight loss and successful long-term weight management [18]. It is estimated that every 50 min of exercise per week result in a loss of about 1 kg over a 6-month period. So, if one exercises for 250 min each week, one can expect a loss of 5 kg in 6 months (that is, from exercise alone).

Moderate-intensity exercise is characterized by 3 to 6 metabolic equivalents of task (METs, i.e., multiples of the energy expenditure at rest), or 64% to 76% of maximal heart rate [19]. An empirical (though less accurate) way of knowing when one is exercising at moderate intensity is when one cannot pronounce more than three medium-size words in a row without taking a breath. Moderate-intensity activities include moderate to fast walking, cycling, or swimming at moderate speed, aerobics, dancing, vigorous household and gardening activities, etc. [20].

Splitting the daily exercise schedule into multiple short periods appears to be as effective in weight management as performing exercise of the same total volume en bloc [15], thus supporting the notion that "every minute counts" [21]. In a review by Dunn [22], the concept that lifestyle activities have similar effectiveness in weight control with structured exercise programs is analyzed. It is concluded that lifestyle interventions possess the ability to improve cardiovascular disease (CVD) outcomes, although the short-term nature of many of the studies supporting this conclusion and the importance of future research focusing on the maintenance of these lifestyle behaviors is noted. According to Kushner [23], weight-loss counseling should encourage both structured exercise and lifestyle physical activity as part of the treatment of obesity.

2.2. Exercise Type

Apart from exercise volume, exercise type is a parameter that should be taken into account in the treatment of obesity. Endurance exercise is probably the most popular and effective exercise type for body weight loss, as it is easily applicable to obese people and ensures high energy expenditure. Nevertheless, resistance exercise and intermittent exercise can also be included in a weight management program, offering variety and additional beneficial effects on health and fitness determinant.

Resistance exercise stimulates adipose tissue lipolysis in both lean and obese men [24], similar to endurance exercise [25], suggesting that it can aid in fat mobilization, although lipolysis is only the first step in this process, the oxidation of the resulting fatty acids constituting the determining step in body fat loss. However, because resistance exercise contains long rest intervals, its energy expenditure is low compared to continuous endurance exercise. Thus, a large part of the fatty acids

produced from lipolysis are not oxidized; rather, they are re-esterified to triacylglycerols, making resistance training an intervention that, alone, does not induce clinically significant weight loss [17]. Nevertheless, resistance exercise may influence body weight by increasing fatfree mass, which may result in increased resting metabolic rate. Resistance exercise also improves muscular strength, which may result in more free-living physical activity and, hence, increased total daily energy expenditure [1], although caution is warranted because of the increased risk of musculoskeletal injury associated with this type of exercise. Thus, although the inclusion of resistance training in a weight management program may not enhance short-term weight loss, it does result in healthy changes in body composition and may play an important role in successful long-term weight management [18]. For these reasons, resistance training is recommended to obese individuals not to a higher degree, but similarly to the general population, i.e., exercising the major muscle groups two or three times a week [19].

High-intensity interval training (HIIT) is characterized by short bouts of high-intensity exercise alternating with periods of rest or low-intensity exercise. HIIT has recently become a popular strategy of weight loss in the general population [26]. It has also been shown to be feasible and well tolerated by people with obesity [27]. According to a meta-analysis by Jelleyman and coworkers [28], HIIT caused a significant reduction of 1.3 kg in body weight compared with nonexercising control groups, but not compared to moderate-intensity continuous training (MICT) in mainly overweight and obese individuals. HIIT and MICT appear to be similarly effective in body fat reduction, even in the absence of changes in body weight, in obese people, despite the fact that HIIT requires approximately 40% less time commitment [29]. A meta-analysis by Türk and collaborators [27] showed a significant reduction in percentage body fat by HIIT compared to "traditional" exercise (that is, MICT), but no difference in the amount of weight, BMI or waist circumference reduction between the two. Therefore, HIIT seems to be a promising alternative to MICT in the promotion of fat and weight loss thanks to its effectiveness with short-time commitment, although it may not be feasible in obese individuals with physical limitations [26]. According to De Feo [30], the most efficient exercise program in obese people is to begin at a moderate intensity and increase by 5% of exercise intensity every six training sessions, up to 65% of maximal capacity. After sufficient adaptations have been achieved, it is better to insert short repeats of interval training at sub-maximal intensity. Future studies are needed to determine the optimal type of HITT for obese individuals, ensuring long-term adherence and avoidance of injuries.

3. Exercise to Maintain the Reduction of Body Weight and Fat

Achieving significant weight loss in obesity is, unfortunately, only half the job. Weight regain is extremely common and, even a mild degree of weight increase (i.e., 2% to 6%), seems to reverse the metabolic benefits of weight loss [31]. The high incidence of weight regain can be explained by the fact that weight loss results in physiological and psychological changes (like changes in appetite and levels of orexigenic or anorexigenic hormones, decrease in resting metabolic rate, and lower compliance with lifestyle changes) that promote weight regain [32–34]. Only about 20% of overweight people seem to succeed in maintaining a 10% weight loss for over one year [35]. Being a lifelong challenge for obese or formerly obese individuals, weight loss maintenance is probably the greatest problem in the successful treatment of obesity. That is why it is of critical importance to better understand the processes of weight regain and develop effective strategies against it.

Exercise is universally perceived as an integral part of a weight maintenance strategy. Besides it being an intuitive choice, most evidence supporting its effectiveness for weight loss maintenance comes from observational studies. The National Weight Control Registry is the largest prospective observational study tracking the characteristics of individuals who have successfully maintained a significant weight loss (\geq 10%) for a substantial period of time (at least a year) [35]. Selfreported data [36] and objective measures (use of accelerometers) [37] provide evidence that high levels of physical activity are strongly associated with successful long-term weight loss maintenance. People who maintained weight loss reported spending an average of 2621 kcal on physical activity per week. This translates to >60 min of moderate-intensity exercise (e.g., brisk walking) or >35 min of vigorous exercise (e.g., jogging) per day [36].

In a meta-analysis of randomized controlled trials (RCTs), Dombrowski and associates reported that interventions combining diet and exercise result in a significantly smaller weight regain (-1.56 kg on average), compared to controls, at 12 months [38]. However, evidence proving a causative relationship between exercise alone and weight loss maintenance is less conclusive. In another metaanalysis of RCTs on weight maintenance after an initial weight loss with very-low-calorie or low-calorie diets, addition of exercise did not significantly improve weight loss maintenance compared to nonexercising controls [39]. In fact, many of the RCTs that targeted weight regain as a primary outcome have not shown a significant effect of exercise [40-43] despite showing a significant association of physical activity level and weight maintenance after retrospective analyses [40,42,43]. On the other hand, Jeffery and colleagues [44] showed significant differences in weight loss maintenance between an exercise group spending 2500 kcal per week (roughly equivalent to 75 min of walking per day) and a standard behavioral therapy group spending 1000 kcal per week (roughly equivalent to 30 min of walking per day) at 12 months (-8.5 kg vs. -6.1 kg, respectively) and at 18 months (-6.7 kg vs - 4.1 kg, respectively).

It is worth noting that most of the aforementioned studies suffer from limitations, such as low adherence rates, weaknesses in design, and self-reported data due to lack of objective measures of physical activity or performing unsupervised exercise [12]. A recent retrospective analysis [45] was the first to use objective measures of energy intake and energy expenditure through the gold-standard method of doubly labeled water. The authors confirmed previous findings that large increases in physical activity (corresponding to about 80 min of moderate-intensity activity, or 35 min of vigorous activity, per day above pre-weight loss levels) are associated with long-term (6 years) weight loss maintenance. Summarizing existing evidence, the standing recommendations from ACSM for weight maintenance after weight loss are 200 to 300 min of moderate-intensity physical activity per week, where more seems to be better than less [12]. It is fair to say that reaching these levels of exercise on a regular basis seems a rather ambitious goal in the context of modern lifestyles. This is why it is worth investing in the research on new, time-efficient, and more feasible exercise regimens (like the aforementioned HIIT).

In a recent review, Foright and coworkers [46] presented, in a comprehensive manner, the arguments questioning and supporting the effectiveness of exercise for weight loss maintenance. In favor of questioning, the authors cited the lack of clear evidence from RCTs, compensatory behaviors after exercise (such as increase in food consumption or decrease in free-living physical activity), high interindividual variability in the responses to exercise, and extremely low compliance to exercise recommendations, coupled to very low adherence to exercise regimes. Conversely, the abundance of evidence from prospective observational studies and retrospective correlations, practical issues (mainly lack of adherence and lack of exercise supervision) that make it extremely difficult to establish causative relationships through RCTs, and evidence supporting that the physiological effects of exercise counter adaptive responses to weight loss that favor weight regain, make it impossible to rule exercise out of any strategy promoting weight maintenance [46].

The most recent report by the National Institutes of Health working group on weight loss maintenance suggests that, regarding exercise, further research should focus on two main areas: (i) deepening our understanding of the mechanisms by which exercise can counter the

biological factors that cause weight regain, and (ii) understanding factors that influence and promote long-term adherence to exercise prescription [33]. Future studies also need to focus on matters such as interindividual variability in the responses to exercise (for example, why there are "responders" and "non-responders", or "high responders" and "low responders"), sex differences, factors influencing compensatory behavior after exercise, and the molecular mechanisms behind the effects of exercise on energy flux and weight regulation [33,46].

On a final note, an interesting study by Thomas and collaborators [47] showed that, when programmed weight regain (50% of weight loss) was accompanied by supervised endurance training for 4 to 6 months, the exercise group maintained many of the beneficial effects of weight loss on cardiometabolic risk factors, in contrast to non-exercising controls, who did not. That goes to show that exercise affects multiple parameters in the obesity-and-health equation, as also shown in the next section.

4. Exercise for Metabolic Fitness in Obesity

In addition to its role in achieving body weight reduction and maintaining a reduced body weight, regular exercise may improve the health of obese individuals independent of weight loss. Indeed, research over the past two decades has shown that regular exercise can alleviate part of the metabolic complications of obesity in the absence of weight loss.

4.1. Observational Studies

A multitude of observational studies, originating primarily from the research group of Steven Blair, demonstrate the importance of exercise in the prevention of chronic disease and premature death associated with obesity. A selection of these studies is briefly presented below. See the review by Ortega and collaborators [48] for a more detailed discussion.

In one of the first studies on the subject, Lee and coworkers [49] examined the risk of all-cause and CVD mortality in a cohort of 21,925 men in relation to percentage body fat and CRF (assessed through a maximal exercise test on treadmill). Although CRF depends on many factors, a major determinant of it is regular exercise [50]. Unfit (low CRF) men were found to have a higher risk of all-cause and CVD mortality compared to fit men regardless of body fat content. What is more, unfit lean men had a higher risk of all-cause and CVD mortality than did fit obese men. Farrell and colleagues [51] obtained similar results by studying 11,335 women: Unfit women had a higher risk of allcause mortality than fit women, regardless of adiposity level.

Nevertheless, Stevens and associates [52], who examined 2506 women and 2860 men, concluded that both high BMI and low CRF are risk factors for all-cause and CVD mortality and that being fit does not completely reverse the increased risk associated with excess adiposity. Hu and colleagues [53] reached a similar conclusion by examining 116,564 women, although they based their stratification on the subjective parameter of self-reported weekly time spent on moderate and vigorous physical activity, rather than the objective measure of CRF.

Moving on to specific population groups, Church and collaborators [54] calculated the risk of all-cause mortality depending on CRF and BMI in 2196 diabetic men. The results showed a steep decrease in mortality with increasing fitness, independent of BMI. Similarly, Lyerly and coworkers [55] found an inverse association between CRF and allcause mortality, regardless of BMI, in 3044 women with impaired fasting glucose or undiagnosed diabetes mellitus. Sui and associates [56] measured all-cause mortality in a cohort of 2603 older men and women depending on BMI, waist circumference, percentage body fat, and CRF. Again, the results showed a decrease in mortality with increasing fitness, independent of overall or abdominal adiposity. Furthermore, McAuley and colleagues [57] confirmed the essential role of fitness in a cohort of 13,155 hypertensive men by showing that those with moderate or high CRF had a lower risk of all-cause and CVD mortality than those with low CRF and that fitness negates the all-cause and CVD mortality risk associated with obesity.

A meta-analysis of ten prospective studies that associated objectively measured CRF and BMI with all-cause mortality [58] has concluded that (i) compared to fit normal-weight individuals, unfit individuals run twice the mortality risk regardless of BMI and (ii) fit overweight and obese individuals have similar mortality risks as fit normal-weight individuals. These findings are epitomized in the "fatbut-fit paradox" [59], which is explained by the fact that regular exercise lowers most CVD risk factors, even in obese individuals. Thus, fitness can counteract the adverse effects of obesity on CVD risk factors, thus reducing CVD mortality [48].

Of note is a study that examined the independent and combined association of changes in CRF (expressed as the METs achieved in a maximal exercise test) and BMI with all-cause and CVD mortality in 14,345 men over 6.3 years [60]. The researchers found that those participants who retained or increased their CRF had a 27% to 42% lower risk of death compared to those who experienced a decrease in CRF, whereas the change in BMI was not independently associated with mortality. Every MET of improvement in CRF was associated with 15% and 19% lower risk of all-cause and CVD mortality, respectively.

All studies cited so far in this subsection have examined mortality as outcome measure, thus having an indirect, not direct, relationship with the metabolic complications of obesity. By contrast, the study of Wing and coworkers [61] examined the association of BMI and CRF with cardiovascular risk factors in 5145 overweight or obese individuals with type 2 diabetes. The authors found that glycated hemoglobin, the ankle/brachial pressure index (an index of peripheral artery disease), and the Framingham risk score (an index of cardiovascular risk) were more strongly associated with fitness than fatness, whereas systolic blood pressure was more strongly associated with fatness. The authors concluded that fitness and fatness seem to have different impacts on specific CVD risk factors.

4.2. Interventional Studies

Research employing exercise interventions in overweight and obese individuals demonstrates the ability of exercise to improve risk factors for health, independent of weight loss. Donnelly and associates [62] subjected 22 untrained obese women to two 18-month long training programs (one with continuous, the other with intermittent exercise), none of which elicited clinically significant weight loss (being 1% to 2%). Nevertheless, HDL cholesterol increased (on average, from 40 to 46 mg/dL) and the area under the serum insulin curve in an oral glucose tolerance test decreased by 30%. Along the same lines, Kraus and colleagues [63] subjected 58 sedentary overweight men and women to either of three training programs, none of which caused a weight reduction higher than 2% after eight months. However, all three exercise groups had a better lipidemic profile at the end of the intervention than a control group that did not exercise.

Research has compared the effects of exercise on metabolic complications of obesity with the effects of dieting and shown the former to be at least as beneficial as the latter. For example, Larson-Meyer and associates [64] divided 35 healthy overweight men and women into two weight-loss groups and a weight-maintenance (control) group. Weight loss was achieved in one group through a 25% reduction in energy intake, while, in the other, through a 12.5% reduction in energy intake plus a 12.5% increase in exercise energy expenditure. After 24 weeks, the two intervention groups had similar weight loss (by about 10%) and similar total as well as visceral fat loss (by about 25%). As expected, only the exercise group improved their CRF. In addition, only the exercise group displayed statistically significant changes in total serum cholesterol (decrease by 9%), LDL cholesterol (decrease by 13%), insulin sensitivity (increase by 66%) and diastolic blood pressure (decrease by

<u>ARTICLE IN PRESS</u>

A. Petridou et al. / Metabolism Clinical and Experimental xxx (xxxx) xxx-xxx

5%). Thus, including exercise in a weight loss program improved metabolic fitness.

A comparison of dieting and exercise was also performed in two other studies [65,66]. Ross and coworkers [65] assigned 52 obese men to one of four study groups (diet-induced weight loss, exerciseinduced weight loss, exercise without weight loss, and control) and monitored the participants for three months. Body weight decreased only in the weight loss groups, and CRF increased only in the exercise groups. Although total fat decreased in both weight loss groups, the reduction was greater in the exercise-induced weight loss group than in the diet-induced weight loss group. Visceral fat decreased in the weight loss groups, but also in the exercise without weight loss group. Improvement in glucose disposal was similar in the two weight loss groups and greater than those in the other two groups.

Similarly to the aforementioned study, Coker and collaborators [66] divided 34 obese older men and women into four groups: (A) weight maintenance without exercise, (B) energy restriction with weight loss, (C) training with weight maintenance (through compensatory energy intake), and (D) training with weight loss equal to that of group B. After 12 weeks of intervention (followed by two weeks of refeeding and four weeks of weight stabilization), only the exercise groups (C and D) exhibited an increase in CRF, whereas only the weight loss groups (B and D) had a decrease in body weight and body fat, as expected. However, specifically regarding visceral fat, exercise with weight maintenance (group C) caused a reduction similar to the one caused by dieting (group B), whereas exercise with weight loss (group D) caused a more-than-twofold reduction. The response of the insulin-stimulated suppression of glucose production (an index of hepatic insulin sensitivity) to the interventions was similar: while it increased similarly in groups B and C, the increase was more-thandouble in group D. Finally, the insulin-stimulated glucose disposal (an index of peripheral insulin sensitivity) increased in group C and, more than twice as much, in groups B and D. These findings show the ability of exercise to mitigate the metabolic complications of obesity, even in the absence of weight loss, although the benefit increases when exercise is accompanied by weight loss.

Apart from dyslipidemia and insulin resistance, an excessive accumulation of triacylglycerols in the liver constitutes a serious metabolic complication of obesity. This leads to non-alcoholic fatty liver disease (NAFLD), which, independent of obesity, increases the risk of insulin resistance, the metabolic syndrome, and CVD [67]. A meta-analysis of 20 randomized controlled trials on mostly overweight and obese NAFLD patients [68] concluded that regular exercise lowers the serum concentrations of alanine aminotransferase and aspartate aminotransferase (two known indices of liver damage) and the fat content of the liver, independent of body weight change.

5. Avoiding Adverse Effects and Mistakes when Training Obese Individuals

When applying exercise programs to obese individuals, special care should be taken to avoid misuse of exercise and mistakes that lead to injuries and cessation of participation. As mentioned above, obese people are at increased risk for musculoskeletal injuries, since their knee and hips joints experience increased pressure. Because obesity seems to induce several pathways that predispose to symptomatic osteoarthritis [69] and because joint overload becomes larger if the pace of exercise is increased, it may be necessary to perform low-impact exercises of short duration until some weight loss is achieved [70].

Additionally, when more exercise than needed is provided to obese people, especially at the onset of a training program, it is more likely to cause fatigue within a short period and, as a result, aversion to continuing the program. Thus, progressive increase of the exercise load is important to ensure adherence to a training program and avoid injuries. In addition, it is important to pay attention to what precedes and what follows an exercise session, that is, perform a thorough warm-up and devote sufficient time to cool-down and recovery. Finally, a clear goal definition and continuous monitoring of progress increases the chances for a successful exercise program. Supervision of training sessions by a knowledgeable trainer, at least at the beginning of a program, ensures application of all these key points.

While following the recommendations mentioned above, it is also important to ward off some more-or-less common misconceptions surrounding exercise for weight loss. One such misconception is that it is possible to cause local fat loss (also referred to as spot reduction) by exercising a specific part of the body (for example, to reduce abdominal fat by performing sit-ups). However, since adipose tissue itself does not exercise and since the signals to speed up lipolysis are primarily hormonal (that is, global rather than local), there is little theoretical ground for targeted fat reduction through local exercises. In addition, studies that tested this hypothesis, such as by Katch and coworkers [71], have refuted it. If one performs sufficient exercise to achieve fat loss, it will come from all over the body, regardless of which parts of it are involved in the exercise.

Passive exercise through equipment that moves parts of the body or electrical stimulation is sometimes advocated as an effortless means of reducing body weight and fat. Such equipment has been developed primarily for rehabilitation purposes, but part of it has found its way into the large and profitable weight reduction market. Since instruments of this kind cause no or little increase in energy expenditure (which can be deduced by the simple fact that they cause no panting), there is no way they can reduce body weight or fat.

Finally, exercise in intentionally hot environment, water deprivation during exercise, and exercising in sweat bands or other clothing that increases sweating are often touted as means of enhancing weight loss. These practices (i) erroneously target water, rather than fat, (ii) are ineffective, since the body will withhold more water and excrete less water after the next fluid intake thanks to its powerful homeostatic mechanisms, and (iii) are potentially harmful, since they increase the risk of dehydration, with consequences upon physical performance and health. No such practice should be endorsed.

6. Concluding Remarks

Evidence summarized in this review supports the view that exercise constitutes an indispensable tool in the management of obesity. Yet, in our experience, this tool is often underestimated, and preference is given to other means such as dieting, medication, and surgery. It is our firm belief that health practitioners should better understand that exercise is indeed medicine and exploit its unique features. These go beyond its contribution to body weight and fat loss, maintenance of body weight and fat reduction, and physical fitness in obesity. Exercise contributes to one's mental and social well-being, a better quality of life, and protection of the environment, if one chooses physically active means of transportation over motorized ones. Exercise also has the potential to fight the chronic, low-grade inflammation that is associated with obesity. Conversely, sedentary behavior is equally important (in an opposite way) as moderate-to-vigorous physical activity/exercise, and substituting or interrupting sedentary time with light-intensity physical activity is also beneficial to cardiometabolic health, independent of weight loss. Finally, physical fitness has a negative relationship with both all-cause and cardiovascular mortality.

Author Contribution

AP and AS performed a literature search, wrote parts of the manuscript and revised it in its entirety. VM wrote part of the manuscript and revised it in its entirety.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

A. Petridou et al. / Metabolism Clinical and Experimental xxx (xxxx) xxx-xxx

Declarations of Interest

None.

References

- Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, et al. The science of obesity management: an Endocrine Society scientific statement. Endocr Rev 2018: 79–132. https://doi.org/10.1210/er.2017-00253.
- [2] Jakicic JM, Clark K, Coleman E, Donnelly JE, Foreyt J, Melanson E, et al. American College of Sports Medicine position stand. Appropriate intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2001;33:2145–56.
- [3] Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. J Acad Nutr Diet 2014;114:1557–68. https:// doi.org/10.1016/j.jand.2014.07.005.
- [4] Jakicic JM, Rogers RJ, Davis KK, Collins KA. Role of physical activity and exercise in treating patients with overweight and obesity. Clin Chem 2018;64:99–107. https://doi.org/10.1373/clinchem.2017.272443.
- [5] DiPietro L, Stachenfeld NS. Exercise treatment of obesity. Endotext; 2000. p. 1–11.
- [6] Headland M, Clifton PM, Carter S, Keogh JB. Weight-loss outcomes: a systematic review and meta-analysis of intermittent energy restriction trials lasting a minimum of 6 months. Nutrients 2016;8:354. https://doi.org/10.3390/nu8060354.
- [7] Avenell A, Brown TJ, McGee MA, Campbell MK, Grant AM, Broom J, et al. What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. J Hum Nutr Diet 2004; 17:293–316. https://doi.org/10.1111/j.1365-277X.2004.00530.x.
- [8] Verheggen RJHM, Maessen MFH, Green DJ, Hermus ARMM, Hopman MTE, Thijssen DHT. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. Obes Rev 2016;17:664–90. https://doi.org/10.1111/obr.12406.
- [9] Ross R, Bradshaw AJ. The future of obesity reduction: beyond weight loss. Nat Rev Endocrinol 2009;5:319–25. https://doi.org/10.1038/nrendo.2009.78.
- [10] Laskowski ER. The role of exercise in the treatment of obesity. PM R 2012;4:840–4. https://doi.org/10.1016/j.pmrj.2012.09.576.
- [11] Chaput J-P, Klingenberg L, Rosenkilde M, Gilbert J-A, Tremblay A, Sjödin A. Physical activity plays an important role in body weight regulation. J Obes 2011; 2011:360257. https://doi.org/10.1155/2011/360257.
- [12] Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK, et al. American College of Sports Medicine position stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2009;41:459–71. https://doi.org/10.1249/MSS.0b013e3181949333.
- [13] Schubert MM, Desbrow B, Sabapathy S, Leveritt M. Acute exercise and subsequent energy intake. A meta-analysis. Appetite 2013;63:92–104. https://doi.org/10.1016/ j.appet.2012.12.010.
- [14] Hagobian TA, Evero N. Exercise and weight loss: what is the evidence of sex differences? Curr Obes Rep 2013;2:86–92. https://doi.org/10.1007/s13679-012-0035-6.
 [15] Fogelholm M, Stallknecht B, Van Baak M. ECSS position statement: exercise and obe-
- sity. Eur J Sport Sci 2006;6:15–24. https://doi.org/10.1080/17461390600563085.
- [16] Jensen Michael D, Ryan Donna H, Apovian Caroline M, Ard Jamy D, Comuzzie Anthony G, Donato Karen A, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the obesity society. J Am Coll Cardiol 2014;63:2985–3023. https://doi.org/10.1161/01. cir.0000437739.71477.ee.
- [17] Swift DL, McGee JE, Earnest CP, Carlisle E, Nygard M, Johannsen NM. The effects of exercise and physical activity on weight loss and maintenance. Prog Cardiovasc Dis 2018. https://doi.org/10.1016/j.pcad.2018.07.014 [#pagerange#].
- [18] Sword DO. Exercise as a management strategy for the overweight and obese. Strength Cond J 2012;34:47–55. https://doi.org/10.1519/SSC.0b013e31826d9403.
- [19] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59. https://doi.org/10. 1249/MSS.0b013e318213fefb.
- [20] Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol 1990;13: 555–65. https://doi.org/10.1002/clc.4960130809.
- [21] Fan JX, Brown BB, Hanson H, Kowaleski-Jones L, Smith KR, Zick CD. Moderate to vigorous physical activity and weight outcomes: does every minute count? Am J Health Promot 2013;28:41–9. https://doi.org/10.4278/ajhp.120606-QUAL-286.
- [22] Dunn AL. Effectiveness of lifestyle physical activity interventions to reduce cardiovascular disease. Am J Lifestyle Med 2009;3:11S–8S. https://doi.org/10.1177/ 1559827609336067.
- [23] Kushner RF. Weight loss strategies for treatment of obesity. Prog Cardiovasc Dis 2014;56:465–72. https://doi.org/10.1016/j.pcad.2013.09.005.
- [24] Chatzinikolaou A, Fatouros I, Petridou A. Adipose tissue lipolysis is upregulated in lean and obese men during acute resistance exercise. Diabetes Care 2008;31: 1397–9. https://doi.org/10.2337/dc08-0072.
- [25] Petridou A, Chatzinikolaou A, Avloniti A, Jamurtas A, Loules G, Papassotiriou I, et al. Increased triacylglycerol lipase activity in adipose tissue of lean and obese men

during endurance exercise. J Clin Endocrinol Metab 2017;102:3945–52. https://doi.org/10.1210/jc.2017-00168.

- [26] Obert J, Pearlman M, Obert L, Chapin S. Popular weight loss strategies: a review of four weight loss techniques. Curr Gastroenterol Rep 2017;19:17–20. https://doi. org/10.1007/s11894-017-0603-8.
- [27] Türk Y, Theel W, Kasteleyn MJ, Franssen FME, Hiemstra PS, Rudolphus A, et al. High intensity training in obesity: a meta-analysis. Obes Sci Pract 2017;3:258–71. https:// doi.org/10.1002/osp4.109.
- [28] Jelleyman C, Yates T, O'Donovan G, Gray LJ, King JA, Khunti K, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. Obes Rev 2015;16:942–61. https://doi.org/10.1111/obr.12317.
- [29] Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. Obes Rev 2017; 18:635–46. https://doi.org/10.1111/obr.12532.
- [30] De Feo P. Is high-intensity exercise better than moderate-intensity exercise for weight loss? Nutr Metab Cardiovasc Dis 2013;23:1037–42. https://doi.org/10. 1016/j.numecd.2013.06.002.
- [31] Kroeger CM, Hoddy KK, Varady KA. Impact of weight regain on metabolic disease risk: a review of human trials. J Obes 2014;2014:614519. https://doi.org/10.1155/2014/ 614519.
- [32] Anastasiou CA, Karfopoulou E, Yannakoulia M. Weight regaining: from statistics and behaviors to physiology and metabolism. Metabolism 2015;64:1395–407. https:// doi.org/10.1016/j.metabol.2015.08.006.
- [33] MacLean PS, Wing RR, Davidson T, Epstein L, Goodpaster B, Hall KD, et al. NIH working group report: innovative research to improve maintenance of weight loss. Obesity (Silver Spring) 2015;23:7–15. https://doi.org/10.1002/oby.20967.
- [34] Soleymani T, Daniel S, Garvey WT. Weight maintenance: challenges, tools and strategies for primary care physicians. Obes Rev 2016;17:81–93. https://doi.org/10.1111/obr. 12322.
- [35] Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr 2005;82: 222S–55. https://doi.org/10.1093/ajcn/82.1.222S.
- [36] Catenacci VA, Ogden LG, Stuht J, Phelan S, Wing RR, Hill JO, et al. Physical activity patterns in the national weight control registry. Obesity (Silver Spring) 2008;16: 153–61. https://doi.org/10.1038/oby.2007.6.
- [37] Catenacci VÄ, Grunwald GK, Ingebrigtsen JP, Jakicic JM, McDermott MD, Phelan S, et al. Physical activity patterns using accelerometry in the National Weight Control Registry. Obesity (Silver Spring) 2011;19:1163–70. https://doi.org/10.1038/oby.2010.264.
- [38] Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. BMJ 2014;348: g2646. https://doi.org/10.1136/bmj.g2646.
- [39] Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2014;99:14–23. https://doi.org/10.3945/ajcn.113.070052.
- [40] Borg P, Kukkonen-Harjula K, Fogelholm M, Pasanen M. Effects of walking or resistance training on weight loss maintenance in obese, middle-aged men: a randomized trial. Int J Obes Relat Metab Disord 2002;26:676–83. https://doi.org/10.1038/ sj.ijo.0801962.
- [41] Fogelholm M, Kukkonen-Harjula K, Nenonen A, Pasanen M. Effects of walking training on weight maintenance after a very-low-energy diet in premenopausal obese women: a randomized controlled trial. Arch Intern Med 2000;160:2177–84.
- [42] Jakicic JM, Marcus BH, Lang W, Janney C. Effect of exercise on 24-month weight loss maintenance in overweight women. Arch Intern Med 2008;168:1550–60. https:// doi.org/10.1001/archinte.168.14.1550.
- [43] Tate DF, Jeffery RW, Sherwood NE, Wing RR. Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain? Am J Clin Nutr 2007;85:954–9. https:// doi.org/10.1093/ajcn/85.4.954.
- [44] Jeffery RW, Wing RR, Sherwood NE, Tate DF. Physical activity and weight loss: does prescribing higher physical activity goals improve outcome? Am J Clin Nutr 2003; 78:684–9. https://doi.org/10.1093/ajcn/78.4.684.
- [45] Kerns JC, Guo J, Fothergill E, Howard L, Knuth ND, Brychta R, et al. Increased physical activity associated with less weight regain six years after "the biggest loser" competition. Obesity (Silver Spring) 2017;25:1838–43. https://doi.org/10.1002/oby.21986.
- [46] Foright RM, Presby DM, Sherk VD, Kahn D, Checkley LA, Giles ED, et al. Is regular exercise an effective strategy for weight loss maintenance? Physiol Behav 2018;188: 86–93. https://doi.org/10.1016/j.physbeh.2018.01.025.
- [47] Thomas TR, Warner SO, Dellsperger KC, Hinton PS, Whaley-Connell AT, Rector RS, et al. Exercise and the metabolic syndrome with weight regain. J Appl Physiol 2010;109:3–10. https://doi.org/10.1152/japplphysiol.01361.2009.
- [48] Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. Circ Res 2016;118: 1752-70. https://doi.org/10.1161/CIRCRESAHA.115.306883.
- [49] Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. Am J Clin Nutr 1999; 69:373–80.
- [50] Lundby C, Montero D, Joyner M. Biology of VO₂max: looking under the physiology lamp. Acta Physiol 2017;220:218–28. https://doi.org/10.1111/apha.12827.
- [51] Farrell SW, Fitzgerald SJ, McAuley PA, Barlow CE. Cardiorespiratory fitness, adiposity, and all-cause mortality in women. Med Sci Sports Exerc 2010;42:2006–12. https:// doi.org/10.1249/MSS.0b013e3181df12bf.
- [52] Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the Lipid Research Clinics Study. Am J Epidemiol 2002;156:832–41. https://doi.org/10.1093/aje/ kwf114.

Please cite this article as: Petridou A, et al, Exercise in the management of obesity, Metabolism Clinical and Experimental (2018), https://doi.org/ 10.1016/j.metabol.2018.10.009

A. Petridou et al. / Metabolism Clinical and Experimental xxx (xxxx) xxx-xxx

- [53] Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004; 351:2694–703. https://doi.org/10.1097/01.ogx.0000160575.50215.93.
- [54] Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. Diabetes Care 2004;27:83–8. https://doi.org/10.2337/diacare.27.1.83.
- [55] Lyerly G William, Sui Xuemei, Lavie Carl J, Church Timothy S, Hand Gregory A, Blair Steven N. The association between cardiorespiratory fitness and risk of all-cause mortality among women with impaired fasting glucose or undiagnosed diabetes mellitus. Mayo Clin Proc 2009;84:780–6. https://doi.org/10.4065/84.9.780 [pii:84/9/780].
- [56] Sui X, LaMonte MJ, Laditka JN, Hardin JW, Chase N, Hooker SP, et al. Cardiorespiratory fitness and adiposity as mortality predictors in older adults. JAMA 2007;298: 2507–16. https://doi.org/10.1001/jama.298.21.2507.
- [57] McAuley PA, Sui X, Church TS, Hardin JW, Myers JN, Blair SN. The joint effects of cardiorespiratory fitness and adiposity on mortality risk in men with hypertension. Am J Hypertens 2009;22:1062–9. https://doi.org/10.1038/ajh.2009.122.
- [58] Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. fatness on allcause mortality: a meta-analysis. Prog Cardiovasc Dis 2014;56:382–90. https://doi. org/10.1016/j.pcad.2013.09.002.
- [59] Ortega FB, Ruiz JR, Labayen I, Lavie CJ, Blair SN. The fat but fit paradox: what we know and don't know about it. Br J Sports Med 2018;52:151–3. https://doi.org/10. 1136/bjsports-2016-097400.
- [60] Lee D-C, Sui X, Artero EG, Lee I-M, Church TS, McAuley PA, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. Circulation 2011;124:2483–90. https://doi.org/10.1161/CIRCULATIONAHA.111.038422.
- [61] Wing RR, Jakicic J, Neiberg R, Lang W, Blair SN, Cooper L, et al. Fitness, fatness, and cardiovascular risk factors in type 2 diabetes: Look AHEAD study. Med Sci Sports Exerc 2007;39:2107–16. https://doi.org/10.1249/mss.0b013e31815614cb.
- [62] Donnelly JE, Jacobsen DJ, Heelan KS, Seip R, Smith S. The effects of 18 months of intermittent vs. continuous exercise on aerobic capacity, body weight and composition, and metabolic fitness in previously sedentary, moderately obese females. Int J Obes Relat Metab Disord 2000;24:566–72. https://doi.org/10.1038/sj.ijo.0801198.

- [63] Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med 2002;347:1483–92. https://doi.org/10.1056/NEJMoa020194.
- [64] Larson-Meyer DE, Redman L, Heilbronn LK, Martin CK, Ravussin E. Caloric restriction with or without exercise: the fitness versus fatness debate. Med Sci Sports Exerc 2010;42:152–9. https://doi.org/10.1249/MSS.0b013e3181ad7f17.
- [65] Ross R, Dagnone D, Jones PJH, Smith H, Paddags A, Hudson R, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exerciseinduced weight loss in men: a randomized, controlled trial. Ann Intern Med 2000; 133:92–103. https://doi.org/10.7326/0003-4819-133-2-200007180-00008.
- [66] Coker RH, Williams RH, Yeo SE, Kortebein PM, Bodenner DL, Kern PA, et al. The impact of exercise training compared to caloric restriction on hepatic and peripheral insulin resistance in obesity. J Clin Endocrinol Metab 2009;94:4258–66. https://doi. org/10.1210/jc.2008-2033.
- [67] Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology 2009;50:1105–12. https://doi.org/10.1002/hep. 23129.
- [68] Katsagoni CN, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with nonalcoholic fatty liver disease: a meta-analysis. Metabolism 2017;68:119–32. https:// doi.org/10.1016/j.metabol.2016.12.006.
- [69] Vincent HK, Heywood K, Connelley J, Hurley RW. Weight loss and obesity in the treatment and prevention of osteoarthritis. Am Acad Phys Med Rehabil 2012;4: S59–67. https://doi.org/10.1016/j.pmrj.2012.01.005.Weight.
- [70] Zdziarski LA, Wasser JG, Vincent HK. Chronic pain management in the obese patient: a focused review of key challenges and potential exercise solutions. J Pain Res 2015; 8:63–77. https://doi.org/10.2147/JPR.S55360.
- [71] Katch FI, Clarkson PM, Kroll W, McBride T, Wilcox A. Effects of sit-up exercise training on adipose cell size and adiposity. Res Q Exerc Sport 1984;55:242–7.