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Title: Associations between the rate, amount and composition of weight loss as predictors of spontaneous weight regain in adults achieving clinically significant weight loss: a systematic review and meta-regression.

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Abstract

Background: Weight regain following weight loss is common although little is known regarding the associations between amount, rate and composition of weight loss and weight regain.

Methods: 43 studies (52 groups; n=2,379) with longitudinal body composition measurements were identified in which weight loss (≥5%) and subsequent weight regain (≥2%) occurred. Data was synthesized for changes in weight and body composition. Meta-regression models were used to investigate associations between amount, rate and composition of weight loss and weight regain.

Results: Individuals lost 10.9% of their body weight over 13 weeks comprised of 19.6% fat-free mass, followed by a regain of 5.4% body weight over 44 weeks comprised of 21.6% fat-free mass. Associations between the amount ($p<0.001$) and rate ($p=0.049$) of weight loss, and their interaction ($p=0.042$) with weight regain were observed. Fat-free mass ($p=0.017$) and fat mass ($p<0.001$) loss both predicted weight regain although the effect of fat-free mass was attenuated following adjustment. The amount ($p<0.001$), but not the rate of weight loss ($p=0.150$) was associated with fat-free mass loss.

Conclusion: The amount and rate of weight loss were significant and interacting factors associated with weight regain. Loss of fat-free mass and fat mass explained some variance in weight regain.

Introduction

Over half of the UK population are currently considered overweight or obese and it is estimated that around 55% of individuals worldwide will be affected by obesity by 2050 [1]. At any one time, approximately 40% of adults report they are engaged in attempts to control their weight [2]. While these attempts show initial success, relapse is common [3] and less than 20% of those losing 10% of their weight maintain the loss for a year or more [4]. It is likely several factors during weight loss influence subsequent weight regain, however, although commonly measured in clinical weight loss studies, the extent to which the rate, amount and composition (e.g. fat-mass (FM) and fat-free mass (FFM)) of weight loss are associated with weight regain remains unclear.

Studies of weight loss with follow-up periods in which weight regain occurs may be used as a model to identify predictive factors associated with weight regain. Factors such as a rapid rates and large amounts of weight loss have previously been associated with weight regain [5]. For this reason, some public health guidelines suggest that individuals reduce their weight slowly in small increments [6]. However, it remains unclear whether those losing greater amounts of weight are more prone to weight regain than those losing smaller amounts [7, 8]. Similarly, evidence documenting the effect of the rate of weight loss on subsequent regain remains inconsistent and although rapid weight loss (such as that achieved by very low-calorie diet; VLCD) is traditionally considered to predispose weight regain [9], several recent studies have not observed this effect [10–13].

The rate and amount of weight loss may also potentially influence body composition changes. Indeed, previous trials have reported detrimental effects on body composition (characterised by a greater proportionate loss of FFM) at greater rates of weight loss [13–17]. Further, as the amount of weight loss increases, the ratio of FFM:FM being lost is known to increase [18]. As such, rapidly losing large amounts of weight might cause excessive loss of protein in the body. Changes in the composition of weight loss and gain are potentially influenced by several other factors including: initial body composition [18, 19], exercise training [20], dietary composition (specifically protein content; [21]) and age [22].

Recently, there has been considerable interest in the functional role of body composition in relation to energy intake behaviours and weight control [23–27]. Initial work by Dulloo and colleagues (1997) suggested that both

FM and FFM compartments play a crucial role in the autoregulation of weight and exert an integrated effect, driving post-weight loss hyperphagia in lean men who have experienced semi-starvation [28]. These analyses were conducted in initially lean males, and whether these effects are observed in individuals with overweight and obesity individuals is unclear. This is further complicated by the knowledge that the p-ratio of weight loss (ΔFFM/ΔBW) is more substantial in leaner compared to heavier individuals [18]. These proposed functional roles of FM and FFM have varying effects in different states of energy balance. Cross-sectional evidence suggests that at, or close to energy balance, FFM is positively associated with hunger and energy intake (potentially mediated by metabolic requirements; [29]) whereas FM shows weak or no association with these measures [23, 30].

During weight loss, appetite is known to increase [31, 32], although the extent to which changes in FM and FFM are responsible for this response is unclear. The data on FFM loss (FFML) during weight loss and subsequent energy intake or weight regain have typically been derived from small, select samples under extreme conditions [33], although, a recent study reported that FFML during therapeutic weight loss predicted subsequent weight regain, and that this reduction in FFM was positively associated with the rate of weight loss [13]. Taken together, these lines of evidence suggest that changes in the size and functional integrity of FFM influence energy intake and may be related to the rate of weight loss (although this effect was not directly observed). It is important to further examine whether functional changes in body composition may be significant for subsequent weight control under conditions of therapeutic weight loss in individuals with overweight/obesity using longitudinal studies.

The aim of this systematic review and meta-regression was to investigate the effect of (a) the rate and amount of weight loss as predictors of weight regain following $\geq$5% weight loss and (b) the rate and amount of weight loss as predictors of FFML during weight loss; and (c) FML and FFML as predictive factors of weight regain.

Methods

This review was prospectively registered on PROSPERO (ID: CRD42018106638).

Inclusion and exclusion criteria

Studies included were primary research in the English language published up until the 27th July 2018 in humans. Study participants were limited to adults (≥18 years) but included all age and ethnic groups as well as those with pre-existing health conditions (e.g. cardiovascular disease or type 2 diabetes). The minimum weight loss duration was set at 4 weeks to limit the confounding effect of initial water and glycogen losses which may be recorded as loss in FFM. Studies included were weight loss intervention studies in which clinically significant weight loss (≥5%) was achieved and subsequent weight regain (≥2% of baseline weight) occurred during the follow-up period. We chose to include only studies which reported weight regain to allow us to examine predictive factors associated with the amount of weight regained. Inclusion of studies with successful weight loss maintenance would have allowed for no variability in the dependent variable with which to generate predictive models of weight regain. A minimum of 2% weight regain (vs. baseline) was required as short-term weight fluctuations of 1-2kg are common [34], therefore this allowed us to be more certain individuals had regained weight. Studies included measured body composition before and after weight loss, and, if reported, following weight regain. Studies were excluded if weight loss was achieved by pharmacological, surgical or moderate to vigorous exercise interventions as these methods may alter the relationship between weight loss and physiological changes [20, 35]. Studies in healthy weight individuals (BMI <25 kg/m^2) were excluded due to a lack of studies necessary for sub-analysis. Studies in athletes were excluded as the dynamic of weight loss in this group varies from the target population (i.e. rapid weight loss is used to target water and glycogen depletion [36]).

Literature search

A literature search was carried out on the 27th of July 2018. MEDLINE, EMBASE and PubMed databases were searched, and the search strategy employed can be found in supplementary table 1. Grey literature was searched for thesis articles and a reference search of relevant articles and reviews was conducted to make sure no relevant material was omitted.

Study selection

References were extracted into Microsoft Excel (2016; version 1805) and duplicates were removed. A title and abstract screen was conducted initially to remove studies unrelated to the topic by two authors (J.T. and R.O.D.). All remaining studies were subject to a full paper screen conducted by the lead author (JT) and one secondary author (R.O.D., K.B. or G.F.). Discrepancies were resolved by discussion between authors.

Data extraction

Data relevant to the population (sample size, gender, age and BMI), intervention type, intervention and follow-up duration, weight lost, weight regained (absolute and relative values) and body composition at a minimum of two points (baseline and following weight loss) were extracted. Body composition following weight regain was extracted if provided. Body composition data relating to a 2-compartment model (e.g. FM and FFM) was extracted. We did not extract data relating to 4-compartment models reported in some studies [37, 38] as these studies were limited in number and not enough data was available to generate statistical models. Where a single study had more than one discrete group [13, 39–43], these were treated as separate groups in the analysis.

Risk of bias

A modified Downs and Black scale was used to assess risk of bias independently by two authors (J.T. and R.O.D.). The Downs and Black instrument is an established tool for determination of the quality of a study within a systematic review and meta-analysis [44]. Two questions related to randomisation were removed as randomisation to groups was not relevant to our outcomes and two questions specific to case-control and cohort studies were removed. Three aspects of bias were assessed: reporting (10 questions), external validity (3 questions) and internal validity (8 questions). The maximum possible score was 21. High, medium and low risk of bias were assessed as follows: high (>7 reporting; >1 external validity; >5 internal validity); medium (>3 reporting; >1 external validity; >3 internal validity) and low (<3 reporting; <1 external validity; <3 internal validity).

Data Analysis

Study characteristics are described as median (range), and outcomes as mean (standard deviation; SD). Where missing, SDs were calculated from standard errors. If SDs were not provided at all time points, they were imputed from previous time points. A random effects meta-regression model was selected prior to analysis due to anticipated high levels of unexplained variance between studies. All meta-regressions were performed using the restricted maximum likelihood (REML) method with Hartung-Knapp adjustment. Both of these approaches are recommended as conservative methods and therefore the risk of type 1 errors was reduced [45]. Two unstandardized outcome variables were used: (1) weight regain (the absolute difference between weight following loss and at follow-up) and (2) fat-free mass loss (the absolute difference between FFM at baseline and following weight loss). Absolute amount (kg) and rate of weight loss (kg/week; calculated as the weight lost divided by weight loss duration) were used to predict both outcomes (1) and (2). Absolute FFML and FML were used to predict outcome (1). As a post-hoc analysis, we tested whether FM content (kg) previous to weight loss and gain predicted the p-ratio (ΔFFM/ΔBW) of the weight change. Pre-post correlations were calculated if SD of change was provided as per Cochrane guidelines [46] or where raw data was provided by authors [37]. A pre-post correlation value of 0.9 was used in the analysis as it was most common from calculated correlations. A sensitivity analysis was conducted between the lowest and highest calculated correlation (0.7 - 1.0) and this did not change the significance of any results. Results are presented as unstandardized regression coefficients and 95% confidence intervals, p-values, R^2 values, measure of heterogeneity (Tau^2) and all models are presented both with and without adjustment for baseline BMI. BMI was chosen as a covariate due to its known interaction with body composition changes [18]. The meta-regression was conducted using Comprehensive Meta-Analysis Software (v3.0; Biostat, Englewood, NJ).

Results

The database search returned a total of 3,441 results of which 2,569 were not duplicates. Of these, 203 were retrieved for full text screening, resulting in the inclusion of 43 studies which comprised of 52 eligible groups (supplementary figure 1). The main reasons for exclusion included inadequate weight regain and lack of body composition measurement.

Study characteristics

Study characteristics are presented in supplementary table 2. Three studies included two independent groups [13, 39, 43] and three studies included three independent groups [40–42]. Each group used one or more of the following methods to achieve weight loss: calorie restriction (CR; n=20), very-low calorie diet (n=19), low calorie diet (LCD; n=15), behaviour change intervention (n=2), high protein diet (n=2), high-fibre diet (n=2), alternate day fasting (ADF; n=1), high fat diet (n=1), low carbohydrate diet (n=1) and Medifast diet (n=1). Body composition was measured using dual energy X-ray absorptiometry (DXA; n=21); water displacement (n=6); deuterium dilution (n=7); bioelectrical impedance (BIA; n=5) and air displacement plethysmography (ADP; n=4). In 27 studies there was a passive follow-up period where no contact with participants occurred [13, 22, 52–61, 37, 62–69, 38, 39, 47–51] whereas 16 studies conducted an active weight loss maintenance (WLM) intervention [40, 41, 75–79, 42, 43, 49, 70–74]. The median weight loss period was 13 (4 – 52) weeks and the median follow-up period was 44 (18 – 249) weeks. The median sample size was 27 (5-506), yielding a total of 2,379 participants, of which 66% were female.

Participant characteristics

At baseline, individuals had a median age of 44.8 (34.5-70.6) years and a median BMI of 32.9 (27.3-38.5) kg/m^2. Baseline outcome values are reported in supplementary table 3. The initial body weight was 92.9 (9.9) kg, FM was 38.4 (5.6) kg and FFM was 53.4 (7.6) kg.

Weight and body composition changes

Changes in body weight and composition during loss and regain are reported in supplementary table 3. The mean weight loss was 10.1 (3.0) kg which accounted for 10.9% of initial body weight. During weight loss, FFM and FM were reduced by 1.9 (1.0) kg and 7.8 (2.7) kg respectively, resulting in a 19.6% proportion of the weight lost as FFM. The mean rate of weight loss was 0.79 (0.39) kg/week equaling 0.86%/week. A total of 5.0 (3.0) kg, or 5.4% was regained in the follow-up period, comprised of 1.1kg (3.1) FFM and 4.0 (2.7) kg FM, providing a proportionate weight gain of 21.6% FFM.

Effect of baseline FM on the p-ratio of loss and gain

Results for the effect of prior FM content on the p-ratio (e.g. ΔFFM/ΔBW) of loss and gain are presented in table S4, with meta-regression plots provided in figure S3. We observed no relationship between prior FM content and the p-ratio of weight loss (β =0.002 (-0.004, 0.009), R^2 = 0.04, p= 0.48), or gain (β =-0.014 (-0.048, 0.021), R^2 = 0, p= 0.42).

[insert table 1, 2, 3 around here]

Effect of extent and rate of weight loss on weight regain

Results for the effect of amount and rate of weight loss on weight regain are reported in table 1 and meta-regression plots can be found in figure S4 (A-B). Both the amount of weight loss (β=0.50 (0.25, 0.74), R^2 = 0.29, p<0.001) and the rate of weight loss (β=2.06 (0.01, 4.11), R^2 = 0.06, p=0.049) were positively associated with weight regain in univariate and BMI-adjusted analyses. After adjustment for the amount of weight lost, the rate of weight loss was no longer a significant predictor of weight regain (p=0.42). However, the amount of weight loss remained significantly associated with weight regain when controlling for the rate of weight loss (p=0.001). In model 2, the interaction term (rate *x* amount) was positively associated with weight regain (p=0.042) (figure 1), although this reduced to a trend after adjustment for BMI (p=0.09).

[insert figure 1 around here]

Effect of FFM and FM loss on weight regain

Results for the effect of FFML and FML on weight regain are reported in table 2 and meta-regression plots can be found in figure S4 (C-D). In a univariate analysis, both FFML (β=1.04 (0.20, 1.87), R^2 =0.12, p=0.017) and FML (β=0.61 (0.35, 0.87), R^2=0.37, p<0.001) predicted weight regain and these results remained similar after adjustment for BMI. After adjustment for FFML, FML remained significantly associated with weight regain (p<0.001) but FFML was no longer associated with weight regain after adjustment for FML (p=0.15). These results were similar when adjusted for baseline BMI.

Effect of extent and rate of weight loss on FFML

Results for the effect of amount and rate of weight loss on FFML are reported in table 3. The amount of weight lost was positively associated with the degree of FFML (β=0.20 (0.11, 0.30), R^2 = 0.37, p<0.001) whereas the rate of weight loss was not associated with FFML (β=0.56 (-0.22, 1.34), R^2 = 0.04, p=0.15). These results remained similar after adjustment for BMI. When both amount and rate of weight loss were entered, amount (p=0.003) but not rate (p=0.92) of weight loss was associated with FFML in both unadjusted and BMI-adjusted models. In model 2, rate of weight loss, as well as the interaction between rate and amount showed a trend after adjustment for BMI (p=0.072 for both).

Risk of bias

Results for risk of bias can be found in supplementary figure 2. One study had high risk of bias [53], four studies had low risk of bias [22, 55, 61, 67] and all other studies had medium risk of bias. No studies were deemed to worthy of exclusion due to bias.

Discussion

This is the first systematic review and meta-regression to investigate the relationship between the rate, amount and composition of weight loss as predictors of weight regain following clinically significant weight loss (≥5%) in participants with overweight and obesity engaged in weight management interventions. We examined 43 studies which included 52 groups comprised of 2,379 individuals. Both the amount and rate of weight loss were positively associated with the amount of weight regain, and the interaction between both factors was also significant (i.e. the rate of weight loss became a stronger predictor of weight regain at larger amounts of weight loss (as shown in figure 1)). Both FFML and FML were predictors of weight regain, although the effect of FFML was attenuated after adjustment for FML. Amount, but not rate, of weight loss was positively associated with FFML, and there was a tendency for their interaction to predict FFML. Lastly, FM content prior to weight change did not predict the p-ratio of subsequent weight change during weight loss or weight gain.

Amount and rate of weight loss as predictors of weight regain

There was a positive association between both the amount and rate of weight loss and subsequent weight regain. While weight regain following weight loss, regardless of the method used, is very well documented [3] whether there is an association between the amount of weight lost and subsequently regained is less clear [8].

While some studies have reported that greater weight loss during intervention was associated with more successful weight loss maintenance [7, 80, 81], others have reported that greater weight loss has been associated with greater weight regain [82–84] or found no effect of prior weight loss [8, 85]. The reason for the discrepancy between these findings may be due to the manner in which authors define 'successful' weight loss maintenance. Some studies may choose to define success as, for example, maintenance of ≥5% weight loss [82], or another binary definition. In this case, 'successful' weight loss maintenance in these studies is likely to be simply a function of losing more weight, yet individuals with greater weight loss may actually regain more weight than some unsuccessful individuals. To overcome this, Barte and colleagues (2010) considered the fraction of weight lost subsequent regained and found no difference in this fraction during follow up between those losing 5-10% (55% regained) and those losing >10% (49% regained) body weight. The greater weight loss group did, however, have greater overall reductions in weight after 1 year of follow-up.

We observed a positive association between the rate of weight loss and subsequent weight regain. Similar to the amount of weight loss, the effect of rate of weight loss on subsequent regain is unclear. Indeed it has long been suggested that gradual weight loss brought on by small changes in lifestyle produce more manageable weight loss for long-term maintenance [9, 86, 87] and as such this advice has been adapted into public health guidelines [6]. Despite this, existing evidence has challenged this contention by suggesting that rapid weight loss is not associated with weight regain [10, 12, 13] and, in some cases may actually provide more beneficial long-term weight outcomes [11]. In each of these studies, authors compared two discrete rates (e.g. rapid vs gradual [12] or LCD vs VLCD [13]) with weight regain. In the present analysis, we included studies utilizing a wide range of caloric deficits ranging from 500 kcal VLCDs [40, 49, 53, 61, 63, 88] to less stringent caloric restrictions of around 25% over periods of up to one year [39, 64, 70, 73, 77–79]. Consequently, we observed high variability in the rate of weight loss, ranging from 0.1 to 1.8kg/week. Further study is required using individual level data to confirm the effect of the rate of weight loss on weight regain.

Next, we found a significant interaction between amount and rate of weight loss in predicting weight regain. To our knowledge, this is the first study to investigate the interaction between amount and rate of weight loss in relation to weight regain. As figure 1 suggests, for individuals losing small amounts of weight, the rate of weight loss is of minimal importance. As weight loss increases, so does the influence of the rate on subsequent weight regain. This interaction may have important clinical implications for those making a weight control attempt as it suggests that if an individual intends to make a substantial weight loss attempt they may wish to consider a more conservative method, whereas if only a small amount of weight loss is planned, the rate at which it is lost may not affect subsequent regain. In particular, this could be have implications in areas where large amounts of weight lost by VLCD are recommended, such as in diabetes treatment [89].

Fat-free mass and fat mass loss as predictors of weight regain

To further examine the relationship between changes in body composition during weight loss and subsequent weight regain, we examined associations with reductions in FM and FFM compartments. When entered separately, FML and FFML predicted weight regain in unadjusted and BMI-adjusted models. However, the association between FFML and weight regain became non-significant after accounting for changes in FML. These data are suggestive of a mechanistic role of FML, and provide evidence of a potential role of FFML, to influence weight regain, and loss of body composition compartments explained greater variance in weight regain than weight loss alone (40% vs 29%). However, further longitudinal research is required under conditions where more substantial changes body composition changes occur. The functional role of FM reduction during weight loss in promoting weight regain has been well studied and mechanisms have been reviewed previously [90].

We found that FFML was associated with weight regain (although this explained proportionately less of the variance than FML), and that this effect was attenuated following correction for FML. Limited evidence exists examining the effect of FFML on weight regain, although it has been suggested that FFML during weight loss may be part of an integrated response driving post-weight loss increases in energy intake in order to restore structural integrity of FFM compartments [91, 92]. In their re-analysis of the Minnesota Starvation study data, Dulloo and colleagues reported that prior depletion of FM and FFM each explained significant variance in the subsequent hyperphagic response, although weight regain continued until FFM was fully restored suggesting a fundamental role for FFM in energy balance regulation following weight loss. In a recent study Vink et al.

(2016) added support to this model, reporting that FFML during 9% weight loss predicted subsequent weight regain 9 months later [13].

In the present analysis, it is possible we were limited in observing a more pronounced role of FFML due to the minor amounts of FFML observed, as well as heterogeneity in measurement, uncertainty of composition of FFML and the dynamic changes that occur in (i) the proportion of weight lost as FM and FFM and (ii) the dynamic changes in the composition of FFM lost in the first few weeks of weight loss [93]. Indeed, the relative contribution of body composition compartments to weight loss varies greatly as weight loss proceeds, which is reflected by initial rapidity of weight loss, followed by gradual slowing. These different dynamic rates of weight loss were initially identified by Forbes (1987) and later termed phase 1 and phase 2 [18, 93]. The first phase is characterised by rapid depletion of FFM, the loss of which which stabilises to a slower rate of loss after phase 1 (4-6 weeks, maximally 12 depending on factors such as initial body composition , extent of energy deficit [18, 19], degree of exercise, gender [20], diet composition [21], hormones and drugs[94]). This initial rapid depletion of FFM is associated with rapid glycogen losses (in the region of 250-300g), relatively large losses of nitrogen (i.e., protein). electrolytes and associated body water. Thus, large dynamic changes in FFM appear to be associated with large dynamic changes its composition (glycogen, protein and associated water), and the rate of weight loss tends to stabilise typically around 4-6 weeks (and up to 12 weeks), such that glycogen is depleted, protein and water losses decelerate, and fat loss increases as weight loss progresses. Furthermore, the source of protein loss may change from phase 1 to phase 2, largely coming from peripheral organs in phase 1 and shifting to skeletal muscle in phase 2. These changes are associated with the reductions in energy requirements and increases in the energy density of tissues lost that collectively tend to reduce the overall rate of weight loss beyond 12 weeks [95]. A key issue in the present analysis is that the weight loss durations investigated cross phase 1 and 2 of the dynamic changes in fuel metabolism and associated changes in both the composition of FFM and the ratio of FFM to FM lost. While we have attempted to limit some of this effect with a 4-week cut-off for weight loss studies, it is likely that there were still dynamic changes in the ratio of FFM:FM in operation during and potentially after the periods of initial weight loss in the studies reviewed. These factors may have made it difficult to observe a functional role of protein loss in energy balance regulation, as previously suggested [96].

The kinetics of FML during weight loss follow an opposite trajectory from FFML, whereby the proportionate rate of FML gradually increases over time as individuals enter the later phases of weight loss. Temporal differences in the rate of compartment changes, similar to patterns observed in FFM, have been identified previously in adipose tissue. In their systematic review, Chaston and Dixon reported initial preferential loss of visceral adipose tissue (VAT) versus subcutaneous adipose tissue (SAT) in 61 studies of modest weight loss, although this effect was lost in 12-14 weeks [97], with similar results being provided by Hall's predictive allometric models [98]. The extent to which whether fat distribution may affect energy balance regulation still remains unclear.

The use of the 2-compartment does not allow us to differentiate between components of FFM nor FM, and limits our analysis to an understanding of the role of FFM and FM. Indeed, each of the methods used in the present study (including DXA (n=21), deuterium dilution (n=7), water displacement (n=6), BIA (n=5) and ADP (n=4)) relies on one or more assumptions that may not hold during the process of early weight loss. For example, water displacement, and air displacement plethysmography assume a steady state fat free mass density of 1.100kg/L and water displacement, deuterium dilution, bioelectrical impedance, air displacement plethysmography all assume that FFM has a constant hydration factor of 73% [99], however, it is likely that neither of these assumptions are likely to hold during phase 1 of weight loss. To fully understand the way that dynamic changes in body composition predict subsequent weight gain beyond 2-compartment models it will be necessary to combine multi-compartment models with 3D imaging techniques and biomarkers of water (e.g. deuterium), nitrogen (urinary nitrogen and skeletal muscle loss (e.g. urinary creatinine) in longitudinal studies.

Measurement heterogeneity may have affected the present results, particularly in shorter duration studies. Some methods have been shown to be more prone to overestimation of water loss in the presence of rapid weight loss than others. In one study, measurement of body composition by BIA overestimated total body water reduction by a mean of 1.8kg compared to deuterium dilution following 10.9kg weight reduction [100]. As such, FFML in studies with shorter duration and in those using BIA may be more likely to be reflective of water loss, whereas in longer duration studies using other methods, FFML may be more likely to be protein from skeletal muscle. Further confounding is added by the fact that the direction of the error associated with the comparison of different methods may not be consistent. For example, due to variation in equipment and formulas used, both overestimation and underestimation of body fat (%) by BIA in comparison to DXA has been observed, ranging between -3.2% and 6.6% [101]. One study in the present analysis chose to use magnetic resonance imaging (MRI) [37] which is a considered gold standard method of measuring body composition, and allows for greater structure of body compartments to be analysed, although we were not able to include models beyond 2-compartments in the present analysis.

Multi-compartment models of body composition such as four-compartment models (including fat, water, protein and mineral [38]) and even eight-compartment models (including brain, heart, liver, kidneys, skeletal muscle mass, bone mass, adipose tissue and residual mass [37]) are important for gaining further information on body structure. Although we were not able to analyse these models due to the sparsity of data, such information would allow us to (1) further sub-divide changes in FM (e.g VAT and SAT) and FFM (e.g. water, glycogen, organ weights, skeletal muscle and bone mass) during weight loss and regain and (2) begin to understand the functional importance of each of these compartments in relation to energy balance homeostasis and cardiometabolic health. Indeed, early attempts to compartmentalize FFM changes during weight loss and regain showed that after correction for other compartments, the energy mobilized as protein during weight loss was strongly correlated with subsequent weight regain [96]. Similarly, dividing adipose tissue into VAT and SAT compartments and distribution may give further information on disease risk [102] and potentially energy balance regulation. For these reasons, defining functional body composition-derived phenotypes using multi-compartment models is becoming of increasing scientific interest [27] and longitudinal studies of weight change using advanced methods are required.

We chose to explore characteristics of weight loss (amount, rate and composition) as predictors of weight regain. However, these factors are only part of a complex network of physiological, psychological and behavioral mechanisms which each influence weight regain [103]. Indeed, reductions in energy expenditure due to changes in body composition, alongside potentially greater-than-predicted reductions caused by a series of adaptive responses such as reductions in leptin, thyroid and adrenal hormones are also likely to contribute to weight regain [95], as are increases in energy intake through appetitive and behavioral changes which may be sustained for over 1-6 years following weight loss [104, 105].

Amount and rate of weight loss as predictors of FFML

We observed a strong relationship between the amount of weight loss achieved and FFML. This is not surprising given that weight loss can only be a function of FML and FFML and thus FFML must occur continuously with weight loss. The rate of weight loss was not associated with FFML but there was a tendency towards an interaction effect between both factors (rate *x* amount) which demonstrated stronger associations between the rate of weight loss and FFML when absolute amounts of weight loss were smaller.

Research examining the effect of rate of weight loss on FFML is limited. In a systematic review by Chaston et al., (2007) authors concluded that weight loss through VLCDs resulted in greater FFML than calorie restricted diets which produced more gradual weight loss, although this was based on descriptive data and no statistical tests were conducted to confirm this [20]. Similarly, in two more recent studies, it was found that when comparing weight-matched rapid weight loss by VLCD over 5 weeks to more gradual weight loss over 12-15 weeks, rapid weight loss resulted in greater FFML [13, 17] with consistent results being reported in similar analyses [15, 16]. The present study aimed to investigate the continuous relationship between rate of weight loss and FFML. We examined a wide range of rates and found no linear relationship with FFML. However, we observed a tendency towards an association between rate *x* amount to predict FFML after adjustment for FML and BMI, suggesting that at higher amounts of weight loss, the rate becomes less important in predicting FFML. We hypothesized that the rate of weight loss would affect both FFML and weight regain, and that FFML may have provided a physiological signal driving weight regain, but our results were not able to support this model, perhaps due to the limited changes in FFM during weight loss.

It is important to note that i) FFM loss/gain is a function of FM, (ii) larger weight losses result in greater predicted proportional loss of FFM and (iii) higher initial FM leads to a lower proportion of FFM gained and, as weight gain proceeds, a lower proportion of weight gain is due to increases in FFM [18, 19]. In the present analysis, we were not able observe the curvilinear relationship between prior FM and subsequent p-ratio of weight change reported by Forbes [18], likely due to the methodological limitations associated with 2-compartment models of body composition, measurement heterogeneity and group-level modelling. Given these considerations and bearing in mind the above mentioned limitations, we hypothesize that the potential effects of body composition changes during weight loss on subsequent weight regain would be amplified under conditions where the proportion of FFM/FM loss were greater, such as in subjects with a wider range of body weight (including lean individuals) at the beginning of weight loss and under conditions where there is a greater extent of weight loss. Furthermore, compartmentalising FFM in future studies using 3D imaging techniques and biomarkers may allow for the effects of rate of weight loss on FFM compartments to be more accurately investigated.

Limitations

Some notable limitations in this study must be considered. First, the results were limited by use of group level data, rather than individual data. While this approach may allow for greater sample size, we were unable to incorporate variability within studies in some covariates (e.g. age, gender) into our models. Second, it was not possible to adjust for factors such as exercise or dietary composition (both during weight loss and follow-up) which may affect the composition of weight loss and subsequent regain. However, care was taken to exclude all exercise interventions in order to avoid capturing exercise-induced changes in body composition. Third, we were unable to account for the effect of behaviour change interventions and dose in some studies. Indeed, participation in an active weight loss maintenance intervention, including guidance or behavior change techniques (e.g. prescription of commercially available physical activity trackers which are increasingly available in research environments [106]), is likely to produce better weight outcomes [107]. We were not able to investigate this effect as the studies included did not have the resolution with which to discriminate and code these aspects of the intervention. By using a random-effects statistical model we accounted for some of the between-study heterogeneity encountered.

Fourth, FFML across the sample was minor which meant that (i) it was likely to be more prone to measurement error and (ii) there was limited variability to fully explore its effect on weight regain. Fifth, a variety of body composition methods were used, and this may limit comparability between studies. Next, we were forced to treat the rate of weight loss as linear (by calculating the rate as amount divided by duration of weight loss), however, this was likely not the case and indeed it is challenging to define a “true” weight trajectory without very frequent longitudinal weight measurements. We cannot be certain that weight loss did not continue following the ‘end’ of the weight loss period, although the inability to define a true weight trajectory is an issue faced by similar studies [11–13]. Next, heterogeneity in body composition measures may reduce the clarity when making comparisons, however, all measures provided in estimates of FM and FFM and we did not use other indices of body composition (e.g. lean soft tissue or skeletal muscle tissue). In the context of the current analysis it is worth noting that 2C models of BC assume constancy in the composition of FFM loss, which is unlikely to be the case during the early phase of weight loss. Last, we limited the analysis to individuals with overweight and obesity due to the sparsity of weight loss studies in lean individuals. The inability to investigate the effects of weight loss and regain on body composition in lean individuals has been discussed previously and is a known limitation in this area [108]. It is hypothesised that the observed effect of FFML on energy intake and weight gain following weight loss is more pronounced in lean individuals [109], although we were unable to test this.

Conclusion

This systematic review examined changes in body composition during clinically significant weight loss and regain in individuals with overweight and obesity, and meta-regression methods were employed to examine their association with the amount and rate of weight loss and subsequent weight regain. The amount of weight lost was found to be positively associated with weight regain and the rate of weight loss appeared to be of increasing significance at higher amounts of weight loss. Amount, but not rate of weight loss was associated with FFML. Loss of both FM and FFM compartments explained some variance in subsequent weight regain, although FML played a significantly greater role. Further research on the role of functional body composition measured using advanced methods and multi-compartment models across a range of initial body compositions (including lean individuals) and weight losses would provide additional mechanistic insight.

Author contributions

J.T was the lead author and was involved in conceptualization, searching, screening, data extraction, statistical analysis, drafting and editing processes. R.O.D, G.F and K.B were involved in screening and editing. K.D. was involved in statistical analysis and editing. R.J.S. was involved in conceptualization of research questions and editing.

Supporting information

Figure S1. PRISMA study flow diagram illustrating identification, screening, eligibility and inclusion processes including reasons for exclusion.

Figure S2. Risk of bias results by modified Downs and Black tool.

Figure S3. Meta-regression plots showing prior FM as a predictor of p-ratio of weight change during loss and regain

Figure S4. Meta-regression plots showing predictors of weight regain (adjusted for baseline BMI).

Table S1. Systematic search strategy.

Table S2. Study characteristics.

Table S3. Descriptive results: relative and absolute changes in FM, FFM and weight for all included groups.

Table S4. Results for the effect of prior FM on subsequent p-ratio of weight change

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Figure 1. Interaction between rate and amount of weight loss and subsequent regain illustrated using a 3D bar chart with two groups with two levels. Simple slopes analysis was used: one standard deviation was added (high) and removed (low) from the mean value for each moderating variable. This was then entered into the interaction regression equation to generate weight regain values under 4 possible conditions. Abbreviations: LR, low rate; HR, high rate, LWL, low weight loss; HWL, high weight loss

Table 1. Effect sizes are unstandardized β coefficients representing unit change per 1kg weight regain. Model 1 included amount and rate of weight loss. Model 2 included amount and rate of weight loss and their interaction. Abbreviations: WL, weight loss

Table 2. Effect sizes are unstandardized β coefficients representing unit change per 1kg weight regain. Model 1 included both FFM and FM loss. Abbreviations: FFM; fat-free mass; FM, fat mass

Table 3. Effect sizes are unstandardized β coefficients representing unit change per 1kg FFM lost. Model 1 included amount and rate of weight loss. Model 2 included amount and rate of weight loss and their interaction. Abbreviations: WL, weight loss, FFM; fat-free mass; FM, fat mass