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SYSTEMATIC REVIEW

Effects of physical activity and dietary supplement on fat free mass and bone mass density during weight loss – a systematic review and meta-analysis. [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: After a diet- or surgery induced weight loss almost 1/3 of lost weight consists of fat free mass (FFM) if carried out without additional therapy. Exercise training and a sufficient supply of protein, calcium and vitamin D is recommended to reduce the loss of FFM.

Objective: To investigate the effect of exercise training, protein, calcium, and vitamin D supplementation on the preservation of FFM during non-surgical and surgical weight loss and of the combination of all interventions together in adults with obesity.

Methods: A systematic review was performed with a pairwise meta-analysis and an exploratory network meta-analysis according to the PRISMA statement.

Results: Thirty studies were included in the quantitative analysis. The pairwise meta-analysis showed for Exercise Training + High Protein vs. High Protein a moderate and statistically significant effect size (SMD 0.45; 95% CI 0.04 to 0.86), for Exercise Training + High Protein vs. Exercise Training a high but statistically not significant effect size (SMD 0.91; 95% CI -0.59 to 2.41) and for Exercise Training alone vs. Control a moderate but statistically not significant effect size (SMD 0.67; 95% CI -0.25 to 1.60). In the exploratory network meta-analysis three interventions showed statistically significant effect sizes compared to Control and all of them included the treatment Exercise Training.

Open Peer Review

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Conclusions: Results underline the importance of exercise training and a sufficient protein intake to preserve FFM during weight loss in adults with obesity. The effect of calcium and vitamin D supplementation remains controversial and further research are needed.

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article can be found at the end of the article.

Keywords

weight loss, obesity, fat free mass, body composition, exercise training

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List of Abbreviations

BIA: Bioelectrical impedance analysis
 BMD: Bone mineral density
 BMI: Body mass index
 CI: confidence interval
 DXA: Dual Energy X-ray Absorptiometry
 FFM: Fat free mass
 SD: Standard deviations
 SMD: standardized mean difference

Introduction

In the past three decades, the prevalence of obesity and overweight has risen substantially. Worldwide, the proportion of adults with overweight or obesity increased between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women.¹ Accordingly, the rising prevalence of overweight and obesity has been described as a global pandemic.² Treatment options for obesity include conservative interventions (diet and/or exercising) and surgical interventions. A 5-10% reduction in baseline weight is frequently recommended by conservative treatment.³ It was reported in the literature that weight loss in this range has not only has a beneficial impact on several obesity-related health conditions and co-morbidities, but also could be cost-effective.⁴⁻⁶ The non-surgical approach is the initial treatment and consists of multiple components such as improved nutritional aspects, exercise training, cognitive behavioral therapy and a variety of pharmacotherapies.⁷ Bariatric surgery is considered when conservative approaches fail and is recommended for individuals with a body mass index (BMI) >35 kg/m² with serious co-morbidities related to obesity.⁸ A surgical procedure complements but does not replace behavioral, medical and lifestyle treatments.⁷ Besides the desired weight loss, management and treatment of obesity should have broader objectives than weight loss alone and should include risk reduction and health improvement.⁷

A repeatedly stated challenge during weight loss is the undesired decrease of fat-free mass (FFM) such as muscle mass and bone mineral density (BMD).⁹ This undesirable loss of FFM can have serious consequences for patients. Recent studies, for example, reveal that patients undergoing bariatric surgery typically develop an osteoporosis pattern characterized with bone loss and are therefore at higher risk for fractures than obese or non-obese controls.¹⁰ FFM is an important component for basal metabolic rate, regulation of body temperature, preservation of skeletal integrity, functional capacity and quality of life.¹¹ Due to this, preserving or minimizing the loss of FFM while losing fat mass is considered optimal and has been referred to as “high-quality weight loss”.¹²

Literature has shown that after an excessive diet induced weight loss ($\geq 20\%$ of body weight) 27.8% of lost weight consists of FFM, if carried out without additional therapy.¹¹ The same problem occurs with surgically induced weight loss. Subsequent to a gastric bypass surgery without any other intervention, FFM accounts for only 31.3% of the lost weight.¹¹

Current literature shows the importance of resistance training and/or high impact training and a sufficient supply of calcium and vitamin D intake in order to maintain or reduce the FFM and more specifically the loss of BMD.¹³ Both endurance- and resistance-type exercises seem to help preserve muscle mass during weight loss.⁹ Resistance-type exercise additionally improves muscle strength.⁹ Inadequate protein intake results in loss of FFM, a sufficient protein supply is further recommended.⁹

A recent survey from England revealed that healthcare professionals who take care of bariatric patients often do not follow recommendations on multivitamin, calcium and vitamin D supplementation.¹⁴ Furthermore, there is evidence that 67% of the bariatric surgery patients are not physically active enough to maintain their achieved weight loss (compared to 38% in the non-surgical group).¹⁵ Considering these findings, it seems evident that the role of exercise training and dietary supplementations such as protein, calcium and vitamin D during weight loss need to be further investigated and their beneficial effects summarized in order to underline their importance.

Even if there is a well-established body of literature on exercise training and dietary supplementation such as protein, calcium or vitamin D during weight loss, no systematic review and meta-analysis has been carried out to evaluate the effects of these interventions on preserving FFM. The purpose of this systematic review and meta-analysis was to summarize the current evidence on maintaining FFM through exercise training and/or dietary supplementation of protein, calcium, and vitamin D during weight loss in adults. We aimed to calculate the effects of each particular intervention, namely exercise, protein supplementation, calcium supplementation and vitamin D supplementation on the preservation of FFM during weight loss. In addition, we investigated whether the combination of all interventions (overall effect of

exercise training, protein, calcium, and vitamin D supplementation) has a more beneficial impact on the maintenance of FFM than each intervention individually. This leads to the following research question:

What effect does exercise training have, with or without dietary supplementation (protein or calcium or vitamin D), on the preservation of fat FFM (BMD and muscle mass) in obese adults who experienced weight loss (operative or conservative)?

We hypothesized that a) exercise training with or without dietary supplementation has a beneficial effect on maintaining FFM during weight loss and b) that the combination of exercise therapy and dietary supplementation has a stronger effect on maintaining FFM than each intervention alone. A systematic review with a pairwise meta-analysis and an exploratory network meta-analysis was performed to test our hypothesis.

Methods

Design

A systematic review with a meta-analysis and a network meta-analysis was conducted in accordance with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.¹⁶ The study protocol was registered on PROSPERO (registration number: CRD42019134651).

Eligibility criteria

Included were studies assessing adults (≥ 18 years of age) with overweight or obesity (BMI of 25-29.9 kg/m² or BMI ≥ 30 kg/m²¹⁷) undergoing a weight loss (diet- or surgery induced) and without secondary diagnosis limiting their exercise activity (e.g. fractures, cancer, neurological diseases). Considered were randomized controlled trials or clinical trials comparing any type of exercise (aerobic and/or resistance type exercise) alone or in combination with dietary supplementation (protein, calcium and/or vitamin D) with a placebo intervention, controlled comparison intervention or standard care. Studies assessing the FFM and/or BMD and/or muscle mass pre- and post-intervention were included. Only studies in English, German and French were included. Studies that used alternative treatment methods for weight loss (such as drugs) were excluded.

Information sources

A systematic literature search was performed in the following electronic databases:

- **Ovid Medline** (date of inception [1946] – 27.08.2020) (RRID:SCR_002185)
- **Ovid Embase** (date of inception [1974] – 27.08.2020) (RRID:SCR_001650)
- **Cochrane Central Register of Controlled Trials** (CENTRAL) (date of inception [1996] – 27.08.2020) (RRID:SCR_001650)
- **ISI Web of Science** (date of inception [1900] – 27.08.2020)

Search strategy

A search strategy was built using the following keywords: (“weight loss” OR overweight OR obesity OR adiposity OR “body weight changes”) AND (“physical training” OR “physical activity” OR exercise OR “exercise therapy”) AND (“dietary supplements” OR nutritional OR supplementation OR protein OR “amino acids” OR calcium OR “vitamin D”) AND (“body composition” OR “fat free mass” OR “lean mass” OR “bone density” OR “muscle mass”). Keywords and medical subject headings were identified with the assistance of a librarian of the Bern University of Applied Sciences (BFH). The Cochrane highly sensitive filter was used to identify randomized controlled trials. No language restrictions were applied. The search strategy was adapted for each database. A detailed search strategy for the database Ovid MEDLINE can be found in the additional files (see Appendix A).⁷⁰ Additionally, the bibliographies of relevant reviews and of included studies were examined for further potential studies. The search for all databases was conducted on the 10.10.2019 and again on the 27.08.2020.

Selection process

The title and abstract of publications found in the electronic databases were screened by two independent investigators (AR and CS). In case of disagreement between the two investigators on the selected articles, a discussion occurred, and a consensus was found. The included studies were imported into the reference management software EndNote X9.3.2.3 (Clarivate Analytics, Philadelphia, US) (RRID:SCR_014001) Imported duplicates were removed. An eligibility

assessment was performed based on title and abstract. To be included, the studies had to meet all the inclusion criteria. In cases of uncertainty regarding the content of the article based on title and abstract, the full text was accessed and evaluated. The online platform [Covidence](#) was used for simplifying the screening process. Full-text versions of studies meeting the inclusion criteria were retrieved for methodological quality assessment and data extraction.

Data extraction

The information of each study included in this review was extracted and entered in an excel file in duplicate by one investigator. Data were extracted on study characteristics (e.g. author, year, country, study design, inclusion and exclusion criteria, funding, intervention groups, follow-up time, limitations), participants traits (e.g. sample size in each group, mean age, sex, mean weight, BMI and FFM, muscle mass and BMD at baseline) and study results (outcome data, measurement methods, drop-outs). Missing data was obtained for four studies^{18–21} by contacting the study authors. If available, change score means and standard deviations (SD) were extracted. Otherwise, final values were used. SD's were derived from the 95% confidence intervals for two studies.^{22,23} The SD's for seven studies^{19,21,24–28} were imputed by using the p-value. To have equal scales, outcome data reported in percentages were proportionally converted into kilograms.^{29–33}

Statistical analysis

If only one study was available for a treatment comparison (i.e., statistical pooling was not possible), findings were reported as standardized mean differences (SMD) and corresponding 95% confidence intervals (CI). The minimum number of studies needed to perform a meta-analysis was set to 2 studies, if studies were sufficiently similar, as recommended by Valentine *et al.*³⁴ and by Higgins *et al.*³⁵ The analyses were performed using change scores if possible, otherwise final values were used.³⁶ Where enough studies per treatment comparison and outcome were available and the assumption of transitivity was fulfilled, a network meta-analysis was performed using a frequentist model. The assumption of transitivity was assessed for all studies included into the network meta-analysis.³⁷ The studies had to be similar regarding clinical and methodological aspects with exception of the compared interventions.

For all meta-analyses, a random effect model was chosen, because of clinical and methodological diversity among the included studies. Pairwise meta-analyses were performed using the Meta package³⁸ of the statistical analysis software R (R Core Team, Austria) (RRID:SCR_00195).³⁸ The Netmeta package³⁹ was used for the network meta-analysis. SMD's were calculated and expressed as Hedges' g. The DerSimonian-Laird estimator was used to analyze the between study variance (τ^2).⁴⁰ In addition, the Hartung-Knapp-Sidik-Jonkman adjustment for random effects models was applied.⁴¹ A meta-regression for the variables age at baseline and BMI at baseline was calculated using a mixed-effects model.⁴²

All outcomes of interest were reported as continuous data. The interpretation of the effect sizes was made according to the Cochrane Handbook.⁴³ A small effect size is indicated as 0.2 to 0.49, a moderate effect size as 0.5 to 0.79 and a large effect size as ≥ 0.8 . Statistical heterogeneity between studies was assessed using a Chi²-test and the I²-statistics. The interpretation of those calculations was also made according to the Cochrane handbook.⁴³ Results with a p-value <0.05 were considered as statistically significant. If studies assessed different groups, only data of groups meeting our eligibility criteria were analyzed.

Risk of bias assessment

To assess the quality of the studies the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0),⁴⁴ the updated version of the most used tool for assessing the risk of bias in randomized trials was used.⁴⁴ Each criterion was evaluated according to the key questions and finally classified as “low risk”, “some concerns” or “high risk”. The risk of bias assessment was performed after the data extraction by two independent reviewers (AR und CS). Disagreements between reviewers were resolved by consensus. A potential publication bias could not be assessed using funnel plots or statistical test's such as Egger's test as such methods possess too low power to distinguish chance from real asymmetry when there are less than 10 studies involved in a pairwise meta-analysis.⁴³

Results

Thirty-one studies were eligible,⁶⁹ but quantitative synthesis was only possible for 30 of those. One study only reported muscle mass and not FFM as the outcome, therefore could not be included in any comparison with another study.⁴⁵ The study selection process is summarized in [Figure 1](#). A list of all included studies and a table of the characteristics of each study is presented in the additional files (see Appendix B and C).^{71,72} The included articles that were published between 1999 and 2019 with sample sizes ranging from 5 to 169 subjects. Ages of the participants ranged from 21 to 74 years and BMIs ranged from 25.8 to 56.8 kg/m². The length of the follow-up period ranged from 4 weeks to 24 months. Most of the trials were from the USA (k = 11),^{19,20,22,24,30,32,33,46–49} followed by Canada (k = 5)^{25,50–53} and Brazil (k = 3).^{18,21,26} Six studies used resistance training for Exercise Training intervention,^{25,32,45,53–55} eight used aerobic training^{12,23,33,46,49,56–58} and 17 used combined training programs.^{18–22,24,26–31,47,48,50–52}

Figure 1. PRISMA flow chart describing the selection process of articles.

Risk of bias assessment

Figure 2 presents the detailed results of the risk of bias assessment. The randomization process was clearly described in 73.3% of the studies. Deviations from the intended interventions were not clearly described or not appropriately analyzed in 53.3% of the studies. Missing outcome data were reported properly in 56.7% of the studies. The measurement of the outcome data was reliable and valid in 96.7% of all studies. 20% of the included studies are at stake for a potential selective reporting bias. Fifty percent of the included studies in the network meta-analysis were conducted without mentioning sponsors or funding resources.

FFM

Effect of diet induced weight loss on FFM

There were 23 pairwise comparisons with a total of 1642 patients assessing the effect on the outcome FFM. All participants underwent a diet induced weight loss. The commonest comparison was Exercise Training versus Control ($k = 7$),^{20,25,31–33,46,55} followed by Exercise Training + High Protein versus Exercise Training ($k = 6$)^{12,22,50,52,54,57} and Exercise Training + High Protein versus High Protein ($k = 5$).^{24,30,53,56,58}

Figure 3 presents the forest plot of the pairwise meta-analysis. The analysis of the comparison Exercise Training + High Protein versus High Protein^{24,30,53,56,58} was the only statistically significant comparison including more than one study. It showed a small to moderate weighted effect size favoring Exercise Training + High Protein (SMD 0.45; 95% CI 0.04 to 0.86). It was also the only meta-analysis demonstrating no heterogeneity ($I^2 = 0\%$). The comparison Exercise Training versus Control^{20,25,31–33,46,55} showed a moderate but statistically not significant weighted effect size favoring the intervention group (SMD 0.76; 95% CI -0.37 to 1.89). The comparison Exercise Training + High Protein versus Exercise Training^{12,22,50,52,54,57} resulted in a large but again, not statistically significant weighted effect size favoring the intervention group (SMD 0.91; 95% CI -0.59 to 2.41). The between study heterogeneity for these two comparisons was considerable and statistically significant ($I^2 = 84\%$, and $I^2 = 94\%$ respectively). The subgroup Exercise Training + Calcium versus Exercise Training^{19,49} showed a small effect size with a wide 95% CI favoring

Figure 2. Risk of bias according to revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0).

Exercise Training + Calcium (SMD 0.15; 95% CI -4.62 to 4.93). The heterogeneity for this comparison was substantial ($I^2 = 70\%$). For the comparison Exercise Training + Calcium + Vitamin D versus Exercise Training²⁸ a small and statistically not significant weighted effect size favoring Exercise Training + Calcium + Vitamin D was detected (SMD 0.30, 95% CI -0.32 to 0.93). Heterogeneity was not applicable. Whereas for the comparison Exercise Training + Calcium + Vitamin D versus Calcium & Vitamin D⁵⁹ a large and statistically significant weighted effect size favoring Exercise Training + Calcium + Vitamin D was detected (SMD 0.81, 95% CI 0.25 to 1.36). Heterogeneity was not applicable.

Figure 3. Forest plot for head-to-head comparisons for the outcome fat free mass (kg) during diet induced weight loss. Data are presented as standardized mean differences with 95% CI. The outcome FFM is expressed as change scores and final values.

The comparison Exercise Training + Vitamin D versus Exercise Training⁴⁷ showed a large and statistically significant effect size (SMD 1.17; 95% CI 0.88 to 1.46) favoring Exercise Training + Vitamin D. Again, heterogeneity was not applicable.

In addition to the pairwise meta-analysis, a network meta-analysis was performed for the studies that assessed the outcome FFM after a diet induced weight loss. The treatment Exercise Training + Vitamin D resulted in the highest

weighted effect size (SMD 1.99; 95% CI 0.15 to 3.82) and therefore was ranked as the most effective treatment in this network meta-analysis. Followed by Exercise Training + High Protein (SMD 1.70; 95% CI 0.68 to 2.73) and High Protein (SMD 1.13; 95% CI -0.19 to 2.44). Three interventions showed statistically significant weighted effect sizes and all of them included the treatment Exercise Training: Exercise Training + Vitamin D, Exercise Training + High Protein and Exercise Training alone. The treatment Calcium + Vitamin D resulted in a relatively small weighted effect size with a wide confidence interval compared to the other interventions (SMD 0.31, 95% CI -2.30 to 2.91). **Figure 4** presents the effect sizes of each treatment compared to the control group and their ranking. The geometry of the network comprised $n=8$ nodes and $n=7$ edges. The network did not comprise of any closed loops (i.e. these are parts of the network where all comparisons are connected to each other⁶⁰). Therefore, it was not possible to explore the inconsistency within the network by comparing direct and indirect treatment estimates as suggested by Veroniki *et al.*⁶¹ The network graph with the number of trials is presented in **Figure 5**. The pooled effect estimations of all direct and network meta-analysis comparisons and the p-scores are presented as well in the additional files (see Appendix D and E).^{73,74}

A meta-regression was only applicable for the comparison Exercise Training versus Control for the variables age and BMI at baseline. For the variable age at baseline the overall model could explain 15.21% of the variability of the effect sizes and was statistically not significant (R^2 : 39.41%, p-value: 0.33). There was only a weak relationship between the explanatory variable and the effect estimate ($b1$: -0.04; 95%CI -0.15 to 0.07, t : -1.11, p : 0.33). For the variable BMI at baseline the overall model could explain 0.00% of the variability of the effect sizes and was statistically not significant (R^2 : 0.00%, p-value: 0.59). The explanatory variable could not be used as predictor of the effect estimate ($b1$: 0.1; 95%CI -0.37 to 0.57, t : 0.57, p : 0.59).

Figure 4. Network meta-analysis ranking and summary of the weighted effect size.

Figure 5. Geometry of the network and number of studies in each comparison. Every intervention is compared to Control. Weighted effect sizes are presented as SMD and corresponding 95%-CI.

Effect of surgery induced weight loss on FFM

Six studies^{18,21,23,26,27,29} that included 443 participants in total reported the change score for FFM during a surgery induced weight loss. Figure 6 represents a summarizing forest plot of the results.

Exercise training versus control

Three studies reported FFM as the outcome variable in this subgroup.^{18,21,26} The analysis for this outcome showed a small to moderate weighted effect size in favor of Exercise Training over Control (SMD 0.39; 95% CI -1.01 to 0.78) but the analysis was statistically not significant. There was no evidence of heterogeneity between these studies ($I^2 = 0\%$).

Exercise training + high protein versus high protein

Two studies reported FFM in this subgroup.^{23,27} The analysis for this outcome showed a small weighted effect size favoring Exercise Training + High Protein over High Protein (SMD 0.25; 95% CI -1.15 to 1.65) but the analysis was statistically not significant. There was no evidence of heterogeneity between these studies ($I^2 = 0\%$).

Exercise training + high protein + calcium + vitamin D versus control

One study reported FFM in this subgroup.²⁹ A very large and statistically significant weighted effect size favoring Exercise Training + High Protein + Calcium + Vitamin D and the control group was detected (SMD 5.16; 95% CI 4.60 to 5.71).

BMD

Effect of diet induced weight loss on BMD

One study investigated BMD during a diet induced weight loss.⁵¹ It described a lower amount of BMD-loss at the total-body level in the intervention group. The comparison Exercise Training + High Protein versus Exercise Training⁵¹ showed a large weighted effect size (SMD 4.17, 95% CI 3.24 to 5.09) favoring Exercise Training + High Protein.

Effect of surgery induced weight loss on FFM

Two studies investigated BMD after a surgery induced weight loss.^{18,29} They described a lower amount of BMD-loss at the total-body level in the intervention group. The comparison Exercise Training versus Control¹⁸ resulted in a moderate weighted effect size (SMD 0.51; 95% CI 0.01 to 1.01) favoring Exercise Training. And the comparison Exercise Training + High Protein + Calcium + Vitamin D versus Control²⁹ also resulted in a large, weighted effect size (SMD 3.88; 95% CI 3.43 to 4.34). A forest plot of the results for BMD is presented in Figure 7.

Muscle mass

One four-arm study including 25 participants assessed muscle mass loss during diet induced weight loss comparing Exercise Training + High Protein versus Control versus Exercise Training versus High Protein.⁴⁵ No statistically

Figure 6. Forest plot for meta-analysis for the outcome change score of fat free mass (kg) during surgery induced weight loss.

Figure 7. Weighted effects and corresponding 95% CI for the outcome change score in bone mass density at total-body level during diet and surgery induced weight loss.

significant difference in muscle mass loss was reported between all groups. Nevertheless, the Exercise Training + High Protein group was the one with the lowest muscle mass loss reported.

Discussion

The aim of this study was to determine the effect of exercise training, protein, calcium and vitamin D supplementation on the preservation of FFM during weight loss in overweight and obese adults as well as to investigate if the combination of all interventions (overall effect of exercise training, protein, calcium and vitamin D supplementation) has a more beneficial impact on the maintenance of FFM than each single intervention alone. This systematic review with pairwise and network meta-analyses included 2560 participants considered overweight or obese in 31 randomized controlled trials. All the included trials are presented in Appendix B.⁷¹ In accordance with our hypothesis, results underline the importance of exercise training and a sufficient protein intake to preserve FFM during weight loss in adults with obesity. The effect of calcium and vitamin D supplementation remains controversial and further research are needed.

Regarding the effect of diet induced weight loss on FFM, results of this study indicate that Exercise Training plus dietary supplementation is superior to only exercise training, to only dietary supplementation and to no additional therapy during weight loss. Results of the pairwise meta-analysis show that the intervention Exercise Training + High Protein was superior in all comparisons and independent of the outcome and type of induced weight loss. Similar findings were reported in earlier research.⁹

Nevertheless, a heterogeneity could be observed in the results of studies comparing Exercise Training + High Protein versus Exercise Training during diet induced weight loss. This heterogeneity could be partially due to quality differences in the studies. The two studies which favored the exercise training + high protein group to preserve FFM^{52,57} were rated as “low risk” for bias, whereas the three studies claiming the contrary were “high risk” for bias or at least showed “some concerns”.^{12,22,54}

Results were consistent in favoring exercise training over control during diet induced weight loss although not always statistically significant. These findings are in line with previous reviews.^{9,11,15} Only one included study²⁰ stands out for favoring control over exercise training. In this study the change score for FFM was reported in kg. However, when considering FFM loss in relation to the amount of weight lost, the exercise training group was superior to the control group.²⁰ That being said, reporting only change score of FFM in kg may lead to misinterpretation of study results. Future studies should therefore report both metrics.

Regarding the results of the network meta-analysis, the intervention Exercise Training + Exercise D had the largest weighted effect size on FFM during diet induced weight loss, followed by Exercise Training + High Protein. It has to be mentioned that the weighted effect size calculation for Exercise Training + Vitamin D is based on one single study. Researchers and clinicians should therefore be careful with the interpretation of this results.

Regarding the effect of surgery induced weight loss on FFM, studies showed a tendency to favor exercise training over control in the pairwise meta-analysis, but the effect was not statistically significant. Further studies are needed to investigate the effect of exercise training after bariatric surgery on bone and muscle mass and outcomes assessing the exercise function of the participants.

The combination of exercise training, high protein and calcium and vitamin D supplementation seems to be the most effective treatment for the maintenance of FFM during surgery induced weight loss. However, only one relevant study could be found which investigated the combination of all these interventions which limits the informative value.

After our analyses, a new controlled trial investigating the effect of exercise, protein, calcium and vitamin D supplementation during weight loss was published.⁶² The authors concluded that calcium and vitamin D appeared to have no additional benefit to dietary and exercise interventions in terms of body composition during weight loss. The same researchers discuss though a possible beneficial effect of calcium and vitamin D supplementation for persons who were deficient in these micronutrients prior to supplementation. This might limit the number of people who could benefit from the calcium and vitamin D supplementation. It might further explain why there was such a large effect during surgery induced weight loss in our review, since bariatric surgeries with a malabsorptive component result in a limited nutritional intake.^{9,11,13} As such a surgery induced weight loss is more likely to cause deficiencies in nutrients that are important for FFM (including calcium, vitamin D and protein¹⁰) than a dietary induced weight loss. In a meta-analysis by Krieger *et al.*⁶³ a higher daily protein intake of >1.05 to ≤ 1.20 g/kg body weight was associated with greater FFM maintenance than a lower protein intake of <0.7 g/kg body weight during weight loss. Therefore, the often recommended daily protein intake of 0.8 g/kg body weight may be inadequate for individuals during weight loss.⁶³ Stockton *et al.* reported in their meta-analysis⁶⁴ that vitamin D supplementation improves muscle function in adults with a vitamin D deficiency but not in non-deficient individuals. Another meta-analysis found a small overall beneficial effect of vitamin D supplementation on BMD at the femoral neck, with larger positive effects in individuals with 25-hydroxyvitamin D levels ≤ 20 nmol/L.⁶⁵ Goode *et al.*⁶⁶ observed a dramatically decreased intestinal calcium uptake and elevated bone resorption markers in patients who underwent gastric bypass even with recommended calcium (1.2 g/d) and vitamin D (8 µg/day) intake. The authors concluded that individuals undergoing bariatric surgery with a malabsorptive component may require even higher dosages to suppress bone loss. However, more research is needed to investigate the question, if individuals following a surgery induced weight loss benefit from calcium and vitamin D supplementation then why don't non-deficient individuals following a diet induced weight loss?

The methodologies chosen for the estimation of the FFM might influence the FFM values. One review reported that dual energy X-ray absorptiometry (DXA) is the most popular method used, but has also certain biases that may lead to an overestimation of the FFM.⁶⁷ As almost all included studies (23 out of 29) used DXA to measure FFM we might have an overestimation, but it is unlikely that the method used explains the major differences. Only one study used skinfold measurements for FFM estimation.²⁶ This method relies on the technique and skill of the tester and does not measure FFM *per se*, but rather provides data for calculations to predict FFM based upon body density and fat percentage.⁶⁷ Three studies assessed FFM using bioelectrical impedance analysis (BIA).^{19,27,28} As this method has inherently large predictive errors, it is insensitive to small improvements in response to treatment.⁶⁷ Therefore, studies assessing FFM with BIA might have missed small changes in FFM. There is no one-size-fits-all approach for the assessment of FFM in the obese, but future research should be aware of each modality with its benefits and drawbacks and choose the methods appropriate to their situation.⁶⁷

Major strengths of our study are the large number of included studies ($k = 31$) and a large sample size ($n = 2560$). The quality assessment was performed by two independent reviewers which is a further strength. Combining a wide variety of treatments and merging diet- and surgery-induced weight loss strategies leads to an extended overview which adds new knowledge to this research area. However, we are also aware of some limitations of our study. The included studies present heterogeneous samples (e.g., broad age, BMI and follow-up length ranges) and a certain diversity of the exercise training interventions and the supplemental dosages. This might also explain the high heterogeneity in the meta-analyses together with the sometimes very low number of participants in the individual studies. Additionally, the network meta-analysis did not comprise closed loops (i.e., a set of treatments which have been compared against each other). Therefore, it was not possible to analyze the consistency within our network by comparing direct and indirect treatment estimates.⁶¹ It should be noted that this network meta-analysis has an exploratory character and therefore should be interpreted with caution. A further statistical limitation represents the fact, that we did not plan a meta-regression from the beginning thus did not report it in the study protocol. It should be interpreted skeptically as there are fewer studies than 10 studies included.⁴³ However, it is of clinical importance that the variables age and BMI at baseline seem to have no influence on the treatment effect. For a more conclusive result, further investigations are needed. The sense of pooling data if only two studies are available can also be questioned but remains in line with current recommendations^{34,35}. The fact that a network

meta-analysis was carried out can also be criticized considering the small number of articles included. However, this method ensures that only comparable data are analyzed together.

Some studies only provided incomplete outcome data, which obligated us to calculate results as prescribed in the methods section. With respect to further empirical trials, research is needed to better identify the effect of the combination of exercise training, protein, calcium, and vitamin D supplementation in obese or overweight patients during dietary or surgically induced weight loss on BMD and muscle mass separately. Additionally, the long-term effect should be addressed and cost effectiveness of exercise interventions and dietary supplementation for obese patients undergoing weight loss examined.

We further have to mention that all types of exercise were classified under “exercise therapy” without distinction between strength training and endurance training even if strength training does not have the same effect than endurance training in the preservation of FFM.⁶⁸

Conclusion

The present systematic review with meta-analysis and exploratory network meta-analysis investigated the effect of exercise training, protein, calcium and vitamin D supplementation alone or in all possible combinations on the preservation of FFM during weight loss in adults considered overweight or obese. Results did show a consistent preference of Exercise Training over Control as well as Exercise Training + High Protein over Exercise training alone. These findings underline the importance of exercise training and a sufficient protein intake in order to preserve FFM during weight loss in overweight or obese adults regardless the weight loss approach. The effect of calcium and vitamin D supplementation remains controversial, and it has been hypothesized that only deficient individuals benefit from such intervention. Further research is needed to investigate this hypothesis. The gap in knowledge regarding the combination of all treatments to maintain FFM during weight loss in adults with overweight or obesity could not yet be closed and needs further studies.

Data availability

Underlying data

Figshare: DATA SET - EFFECTS OF PHYSICAL ACTIVITY AND DIETARY SUPPLEMENTATION ON FAT FREE MASS AND BONE MASS DENSITY DURING WEIGHT LOSS <https://doi.org/10.6084/m9.figshare.17086520>.⁶⁹

The project contains the following underlying data:

- [data_SR_Roth.xlsx] (Raw deidentified data).

Extended data

Figshare: Appendix A Search Strategy Medline Ovid <https://doi.org/10.6084/m9.figshare.17113475>⁷⁰

This project contains the following extended data:

- AppendixA_Search_Strategy_Ovid.pdf

Figshare: Appendix B: List of all included studies <https://doi.org/10.6084/m9.figshare.17113511>⁷¹

This project contains the following extended data:

- AppendixB_List_Included_Studies.pdf

Figshare: Appendix C: Characteristics of studies <https://doi.org/10.6084/m9.figshare.17113520>⁷²

This project contains the following extended data:

- AppendixC_Characteristics_of_Studies.pdf

Figshare: Appendix D: Netleague table <https://doi.org/10.6084/m9.figshare.17113547>⁷³

This project contains the following extended data:

- AppendixD_netleagueTable.csv

Figshare: Appendix E p-scores:

<https://doi.org/10.6084/m9.figshare.17113586>⁷⁴

This project contains the following extended data:

- AppendixE_PScore.xlsx

Reporting guidelines

The Prisma checklist for this systematic review is available at: <https://doi.org/10.6084/m9.figshare.17085932>⁷⁵

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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References

1. Ng M, Fleming T, Robinson M, *et al.*: **Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013.** *Lancet.* 2014; **384**: 766–781.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Swinburn BA, Sacks G, Hall KD, *et al.*: **The global obesity pandemic: shaped by global drivers and local environments.** *Lancet.* 2011; **378**: 804–814.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Jensen MD, Ryan DH, Apovian CM, *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.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Knowler WC, Barrett-Connor E, Fowler SE, *et al.*: **Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin.** *N Engl J Med.* 2002; **346**: 393–403.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Magkos F, Fraterrigo G, Yoshino J, *et al.*: **Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans with Obesity.** *Cell Metab.* 2016; **23**: 591–601.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Trueman P, Haynes SM, Felicity Lyons G, *et al.*: **Long-term cost-effectiveness of weight management in primary care.** *Int J Clin Pract.* 2010; **64**: 775–783.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Yumuk V, Tsigos C, Fried M, *et al.*: **European Guidelines for Obesity Management in Adults.** *Obes Facts.* 2015; **8**: 402–424.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Gloy VL, Briel M, Bhatt DL, *et al.*: **Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials.** *BMJ.* 2013; **347**: f5934.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Cava E, Yeat NC, Mittendorfer B: **Preserving Healthy Muscle during Weight Loss.** *Adv Nutr.* 2017; **8**: 511–519.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Rousseau C, Jean S, Gamache P, *et al.*: **Change in fracture risk and fracture pattern after bariatric surgery: nested case-control study.** *BMJ.* 2016; **354**: i3794.
[Publisher Full Text](#)
11. Chaston TB, Dixon JB, O'Brien PE: **Changes in fat-free mass during significant weight loss: a systematic review.** *Int J Obes (Lond).* 2007; **31**: 743–750.
[PubMed Abstract](#) | [Publisher Full Text](#)

12. Larsen AE, Bibby BM, Hansen M: **Effect of a Whey Protein Supplement on Preservation of Fat Free Mass in Overweight and Obese Individuals on an Energy Restricted Very Low Caloric Diet.** *Nutrients*. 2018; **10**.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Hunter GR, Plaisance EP, Fisher G: **Weight loss and bone mineral density.** *Curr Opin Endocrinol Diabetes Obes*. 2014; **21**: 358–362.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Dunstan MJ, Molena EJ, Ratnasingham K, et al.: **Variations in oral vitamin and mineral supplementation following bariatric gastric bypass surgery: a national survey.** *Obes Surg*. 2015; **25**: 648–655.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Coen PM, Goodpaster BH: **A role for exercise after bariatric surgery?** *Diabetes Obes Metab*. 2016; **18**: 16–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Hutton B, Salanti G, Caldwell DM, et al.: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations.** *Ann Intern Med*. 2015; **162**: 777–784.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Jensen MD, Ryan DH, Apovian CM, 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.** *Circulation*. 2014; **129**: S102–S138.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Murali JH, Roschel H, Dantas WS, et al.: **Exercise Mitigates Bone Loss in Women With Severe Obesity After Roux-en-Y Gastric Bypass: A Randomized Controlled Trial.** *J. Clin. Endocrinol. Metab*. 2019; **104**: 4639–4650.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Wagner G, Kindrick S, Hertzler S, et al.: **Effects of various forms of calcium on body weight and bone turnover markers in women participating in a weight loss program.** *J Am Coll Nutr*. 2007; **26**: 456–461.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. Messier SP, Mihalko SL, Legault C, et al.: **Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial.** *JAMA*. 2013; **310**: 1263–1273.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Campanha-Versiani L, Pereira DAG, Ribeiro-Samora GA, et al.: **The Effect of a Muscle Weight-Bearing and Aerobic Exercise Program on the Body Composition, Muscular Strength, Biochemical Markers, and Bone Mass of Obese Patients Who Have Undergone Gastric Bypass Surgery.** *Obes Surg*. 2017; **27**: 2129–2137.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Kersick C, Thomas A, Campbell B, et al.: **Effects of a popular exercise and weight loss program on weight loss, body composition, energy expenditure and health in obese women.** *Nutr Metab (Lond)*. 2009; **6**: 23.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Oppert JM, Bellicha A, Roda C, et al.: **Resistance Training and Protein Supplementation Increase Strength After Bariatric Surgery: A Randomized Controlled Trial.** *Obesity (Silver Spring)*. 2018; **26**: 1709–1720.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Layman DK, Evans E, Baum JL, et al.: **Dietary protein and exercise have additive effects on body composition during weight loss in adult women.** *J Nutr*. 2005; **135**: 1903–1910.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Bouchard DR, Soucy L, Senechal M, et al.: **Impact of resistance training with or without caloric restriction on physical capacity in obese older women.** *Menopause*. 2009; **16**: 66–72.
[Publisher Full Text](#)
26. Castello V, Simoes RP, Bassi D, et al.: **Impact of aerobic exercise training on heart rate variability and functional capacity in obese women after gastric bypass surgery.** *Obes Surg*. 2011; **21**: 1739–1749.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Hassannejad A, Khalaj A, Mansournia MA, et al.: **The Effect of Aerobic or Aerobic-Strength Exercise on Body Composition and Functional Capacity in Patients with BMI ≥ 35 after Bariatric Surgery: a Randomized Control Trial.** *Obes Surg*. 2017; **27**: 2792–2801.
[Publisher Full Text](#)
28. Holecki M, Zahorska-Markiewicz B, Wiecek A, et al.: **Influence of calcium and vitamin D supplementation on weight and fat loss in obese women.** *Obes Facts*. 2008; **1**: 274–279.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Muschitz C, Kocijan R, Haschka J, et al.: **The Impact of Vitamin D, Calcium, Protein Supplementation, and Physical Exercise on Bone Metabolism After Bariatric Surgery: The BABS Study.** *J Bone Miner Res*. 2016; **31**: 672–682.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Arciero PJ, Gentile CL, Pressman R, et al.: **Moderate protein intake improves total and regional body composition and insulin sensitivity in overweight adults.** *Metabolism*. 2008; **57**: 757–765.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Duthell F, Lac G, Lesourd B, et al.: **Different modalities of exercise to reduce visceral fat mass and cardiovascular risk in metabolic syndrome: the RESOLVE randomized trial.** *Int J Cardiol*. 2013; **168**: 3634–3642.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Jo E, Worts PR, Elam ML, et al.: **Resistance training during a 12-week protein supplemented VLCD treatment enhances weight-loss outcomes in obese patients.** *Clin Nutr*. 2019; **38**: 372–382.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Redman LM, Rood J, Anton SD, et al.: **Calorie restriction and bone health in young, overweight individuals.** *Arch Intern Med*. 2008; **168**: 1859–1866.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Valentine JC, Pigott TD, Rothstein HR: **How many studies do you need? A primer on statistical power for meta-analysis.** *J. Educ. Behav. Stat*. 2010; **35**: 215–247.
[Publisher Full Text](#)
35. Higgins JP, Thomas J, Chandler J, et al.: **Cochrane handbook for systematic reviews of interventions.** John Wiley & Sons; 2019.
[Publisher Full Text](#)
36. da Costa BR, Nuesch E, Rutjes AW, et al.: **Combining follow-up and change data is valid in meta-analyses of continuous outcomes: a meta-epidemiological study.** *J Clin Epidemiol*. 2013; **66**: 847–855.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Salanti G: **Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool.** *Res Synth Methods*. 2012; **3**: 80–97.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. R Core Team. **R: A language and environment for statistical computing.** Vienna, Austria: R Foundation for Statistical Computing; 2021.
[Reference Source](#)
39. Gerta Rücker GS: **Ulrike Krahn, Jochem König, Maintainer Guido Schwarzer. Package 'Netmeta'. Network Meta-Analysis Using Frequentist Methods 0.7-0 ed2015.**
40. DerSimonian R, Laird N: **Meta-analysis in clinical trials.** *Control Clin Trials*. 1986; **7**: 177–188.
[Publisher Full Text](#)
41. Int'Hout J, Ioannidis JP, Borm GF: **The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method.** *BMC Med Res Methodol*. 2014; **14**: 25.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Schwarzer G, Carpenter J, Rücker G: **Heterogeneity and Meta-Regression. Meta-analysis with R:** Springer; 2015.
[Publisher Full Text](#)
43. Higgins JP, Green S: **Cochrane handbook for systematic reviews of interventions.** Hoboken, NJ.: Wiley; 2011.
44. Sterne JAC, Savovic J, Page MJ, et al.: **RoB 2: a revised tool for assessing risk of bias in randomised trials.** *BMJ*. 2019; **366**: l4898.
[Publisher Full Text](#)
45. Garcia-Unciti M, Martinez JA, Izquierdo M, et al.: **Effect of resistance training and hypocaloric diets with different protein content on body composition and lipid profile in hypercholesterolemic obese women.** *Nutr Hosp*. 2012; **27**: 1511–1520.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Evans EM, Saunders MJ, Spano MA, et al.: **Effects of diet and exercise on the density and composition of the fat-free mass in obese women.** *Med Sci Sports Exerc*. 1999; **31**: 1778–1787.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Mason C, Tapsoba JD, Duggan C, et al.: **Effects of Vitamin D3 Supplementation on Lean Mass, Muscle Strength, and Bone Mineral Density During Weight Loss: A Double-Blind Randomized Controlled Trial.** *J Am Geriatr Soc*. 2016; **64**: 769–778.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Villareal DT, Aguirre L, Gurney AB, et al.: **Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults.** *N Engl J Med*. 2017; **376**: 1943–1955.
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Zemel MB, Donnelly JE, Smith BK, et al.: **Effects of dairy intake on weight maintenance.** *Nutr Metab (Lond)*. 2008; **5**: 28.
[PubMed Abstract](#) | [Publisher Full Text](#)

50. Longland TM, Oikawa SY, Mitchell CJ, *et al.*: **Higher compared with lower dietary protein during an energy deficit combined with intense exercise promotes greater lean mass gain and fat mass loss: a randomized trial.** *Am J Clin Nutr.* 2016; **103**: 738–746.
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Josse AR, Atkinson SA, Tarnopolsky MA, *et al.*: **Diets higher in dairy foods and dietary protein support bone health during diet- and exercise-induced weight loss in overweight and obese premenopausal women.** *J Clin Endocrinol Metab.* 2012; **97**: 251–260.
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Josse AR, Atkinson SA, Tarnopolsky MA, *et al.*: **Increased consumption of dairy foods and protein during diet- and exercise-induced weight loss promotes fat mass loss and lean mass gain in overweight and obese premenopausal women.** *J Nutr.* 2011; **141**: 1626–1634.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Amamou T, Normandin E, Pouliot J, *et al.*: **Effect of a High-Protein Energy-Restricted Diet Combined with Resistance Training on Metabolic Profile in Older Individuals with Metabolic Impairments.** *J Nutr Health Aging.* 2017; **21**: 67–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Wycherley TP, Noakes M, Clifton PM, *et al.*: **A High-Protein Diet With Resistance Exercise Training Improves Weight Loss and Body Composition in Overweight and Obese Patients With Type 2 Diabetes.** *Diabetes Care.* 2010; **33**: 969–976.
[PubMed Abstract](#) | [Publisher Full Text](#)
55. Fisher G, Hyatt TC, Hunter GR, *et al.*: **Effect of diet with and without exercise training on markers of inflammation and fat distribution in overweight women.** *Obesity (Silver Spring).* 2011; **19**: 1131–1136.
[PubMed Abstract](#) | [Publisher Full Text](#)
56. Deibert P, König D, Schmidt-Trucksass A, *et al.*: **Weight loss without losing muscle mass in pre-obese and obese subjects induced by a high-soy-protein diet.** *Int J Obes Relat Metab Disord.* 2004; **28**: 1349–1352.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Watson N, Dyer K, Buckley J, *et al.*: **Effects of Low-Fat Diets Differing in Protein and Carbohydrate Content on Cardiometabolic Risk Factors during Weight Loss and Weight Maintenance in Obese Adults with Type 2 Diabetes.** *Nutrients.* 2016; **8**.
[PubMed Abstract](#) | [Publisher Full Text](#)
58. Berg A, Frey I, Deibert P, *et al.*: **Gewichtsreduktion durch Lebensstilintervention.** *Ernährungs-Umschau.* 2005; **52**: 310–314.
59. Villareal DT, Chode S, Parimi N, *et al.*: **Weight loss, exercise, or both and physical function in obese older adults.** *N Engl J Med.* 2011; **364**: 1218–1229.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Mills EJ, Thorlund K, Ioannidis JP: **Demystifying trial networks and network meta-analysis.** *BMJ.* 2013; **346**: f2914.
[PubMed Abstract](#) | [Publisher Full Text](#)
61. Veroniki AA, Vasilidis HS, Higgins JP, *et al.*: **Evaluation of inconsistency in networks of interventions.** *Int J Epidemiol.* 2013; **42**: 332–345.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. Kerksick CM, Roberts MD, Campbell BI, *et al.*: **Differential Impact of Calcium and Vitamin D on Body Composition Changes in Post-Menopausal Women Following a Restricted Energy Diet and Exercise Program.** *Nutrients.* 2020; **12**.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Krieger JW, Sitren HS, Daniels MJ, *et al.*: **Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression 1.** *Am J Clin Nutr.* 2006; **83**: 260–274.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Stockton KA, Mengersen K, Paratz JD, *et al.*: **Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis.** *Osteoporos Int.* 2011; **22**: 859–871.
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Reid IR, Bolland MJ, Grey A: **Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis.** *Lancet.* 2014; **383**: 146–155.
[Publisher Full Text](#)
66. Goode LR, Brolin RE, Chowdhury HA, *et al.*: **Bone and gastric bypass surgery: effects of dietary calcium and vitamin D.** *Obes Res.* 2004; **12**: 40–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
67. Duren DL, Sherwood RJ, Czerwinski SA, *et al.*: **Body composition methods: comparisons and interpretation.** *J Diabetes Sci Technol.* 2008; **2**: 1139–1146.
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Willis LH, Slentz CA, Bateman LA, *et al.*: **Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults.** *J Appl Physiol.* 1985; **113**(113): 1831–1837.
[Publisher Full Text](#)
69. Roth A, Sattelmayer M, Schorderet C, *et al.*: **Data set - Effects of physical activity and dietary supplementation on fat free mass and bone mass density during weight loss.** figshare. Dataset. 2021.
[Publisher Full Text](#)
70. Sattelmayer M: **Appendix A Search Strategy Medline Ovid.** figshare. Journal contribution. 2021.
[Publisher Full Text](#)
71. Sattelmayer M: **Appendix B List of included studies.** figshare. Journal contribution. 2021.
[Publisher Full Text](#)
72. Sattelmayer M: **Appendix C: Characteristics of studies.** figshare. Journal contribution. 2021.
[Publisher Full Text](#)
73. Sattelmayer M: **Appendix D Netleague table.** figshare. Journal contribution. 2021.
[Publisher Full Text](#)
74. Sattelmayer M: **Appendix E p-scores.** figshare. Journal contribution. 2021.
[Publisher Full Text](#)
75. Roth A, Sattelmayer M, Schorderet C, *et al.*: **PRISMA checklist - Effects of physical activity and dietary supplement on fat free mass and bone mass density during weight loss - A systematic review and meta-analysis.** figshare. Journal contribution. 2021.
[Publisher Full Text](#)

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In this systematic review and meta-analysis, Roth *et al.* examined the effect of exercise training, protein, calcium, and vitamin D supplementation on the preservation of fat-free mass during non-surgical and surgical weight loss and of the combination of all interventions together in adults with obesity. This manuscript deals with an interesting topic. However, there are several points to be addressed. The language needs editing. Furthermore, the process should be thoroughly described. Generally, the paper is well written and the topic is highly relevant. Nevertheless, there are some limitations in this piece of work that could be improved.

- The method of the search strategy is faced with limitations. First, the search query is not designed properly, so it could not find all relevant papers, especially the papers that have reported "fat free mass" and "bone mass density" as secondary outcomes. Second, some important databases such as PubMed, Scopus, and Embase have been not searched.
- Statistical analysis: The authors stated, "To have equal scales, outcome data reported in percentages were proportionally converted into Kilograms". So, why did the authors use the SMD? SMD is usually used when studies have reported the outcome variables using different scales and scales cannot be converted to each other.
- Eligibility criteria: Did you include also non-randomized studies? Regarding the inclusion of non-RCTs, I highly suggest that the authors include only RCTs or perform subgroup analysis based on randomization.
- The section of eligibility criteria lacks any description/definition of high protein. Please describe high protein thoroughly.
- From Figure 1, I do not understand what is meant by "inadequate patient population" and "inadequate setting". Please rephrase this to improve clarity.
- Certainty of evidence assessment needs to be performed with the GRADE approach and

findings to be included in the results section and conclusion section of the abstract.

- Please provide information regarding the gender of participants in the table of characteristics of studies.
- The manuscript must be also revised with regard to the English language.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nutritionist & Diet therapist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Aug 2022

Chloé Schorderet, HES-SO Valais Wallis, Sion, Switzerland

Point-to-point response

○ **Comment 1:**

The method of the search strategy is faced with limitations. First, the search query is not designed properly, so it could not find all relevant papers, especially the papers that have reported "fat free mass" and "bone mass density" as secondary outcomes. Second, some important databases such as PubMed, Scopus, and Embase have been not searched.

Authors' response:

Thank you for this comment. We agree that the search terms for the secondary outcomes were not exhaustive. However, within the manuscript, only an overview of the search terms is presented. We searched the databases with more details as presented in Appendix A. For example, the terms muscle and bone were combined with adjacency of 3 words with the following terms:

#40 ((muscle* or bone*) adj3 {health* or mass* or volume* or strength* or density or lass or augment* or metabolism* or turn?over* or preservation*}).ti,ab,kw.

However, we added this point in the limitations of the manuscript.

Discussion, page 13:

A first limitation concerns the search strategy. Indeed, few synonyms were used for the secondary outcomes.

Regarding the second part of the comment, we followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (<https://training.cochrane.org/handbook/current/chapter-04>). To clarify, we searched for eligible studies in Medline (using Ovid's search engine). Records were also searched in EMBASE (using Ovid's search engine). In addition, we searched also in Cochrane Central and Web of Science. We believe that the chosen databases fulfilled the requirements of the Cochrane Handbook for Systematic Reviews.

◦ **Comment 2:**

Statistical analysis: The authors stated, "To have equal scales, outcome data reported in percentages were proportionally converted into Kilograms". So, why did the authors use the SMD? SMD is usually used when studies have reported the outcome variables using different scales and scales cannot be converted to each other.

Authors' response:

The selection of the appropriate effect size is controversé discussed in the literature. Several guidelines present opposing recommendations. For example, the Cochrane Collaboration suggests using the MD if all studies used the same outcome measure [1]. In contrast, Borenstein [2] recommends the use of the SMD when the clinical interpretation of outcome measures is not familiar to all readers. The advantage of SMD as an effect size is that there are easily understood rules of thumb that allow for quick interpretation of the effect size. In our case, the interpretation of the reduction of fat-free mass or change in bone mass density is not straightforward and we believe that results are clinically more interpretable when SMDs are used. In addition, Takeshima *et al.* [3] demonstrated that the SMD is more generalizable than the MD. We adapted the manuscript to clarify this point.

Methods, statistical analysis, page 6:

The SMD was selected as effect size for the meta-analyses because they allow a quick interpretation of the size of the effect. The interpretation of the reduction of fat free mass or a change in bone mass density is not straightforward and we believe that results are clinically more interpretable when SMDs are used. In addition, Takeshima et al. [3] demonstrated that the SMD is more generalizable than the MD.

◦ **Comment 3:**

Eligibility criteria: Did you include also non-randomized studies? Regarding the inclusion of non-RCTs, I highly suggest that the authors include only RCTs or perform subgroup analysis based on randomization.

Authors' response:

Thank you for your comment. Yes, only RCTs were included in this systematic review. We specified this point in the results section.

Results, page 7:

All included studies were randomized controlled studies.

◦ **Comment 4:**

The section of eligibility criteria lacks any description/definition of high protein. Please describe high protein thoroughly.

Authors' response:

Thank you for your comment. The term high protein has now been defined in the manuscript.

Results, FFM, effect of diet induced weight loss on FFM, page 8

"High Protein" meant that the participants exceeded the regular recommendation of 0.8g/kg body weight per day or hit 20% or more of caloric intake from protein [4].

◦ **Comment 5:**

From Figure 1, I do not understand what is meant by "inadequate patient population" and "inadequate setting". Please rephrase this to improve clarity.

Authors' response:

Thank you for your comment. This term is indeed imprecise. We have now removed it from the flow chart. The term "inadequate" meant that studies were not included because the comparator/intervention/outcome/patient population/setting/study design did not meet the inclusion criteria.

◦ **Comment 6:**

Certainty of evidence assessment needs to be performed with the GRADE approach and findings to be included in the results section and conclusion section of the abstract.

Authors' response:

We agree with you that the certainty of evidence should be presented. We added the following sections to the manuscript:

Methods, risk of bias assessment, page 7:

Recommendations from the GRADE working group were used to rate the quality of the available evidence.

Results, grade level of evidence, page 12:

The level of evidence for each analysis is presented in Appendix F. For diet induced weight loss on FFM the quality of evidence ranged from very low to moderate. The subgroup-analyses with a moderate level were: i) Exercise + High Protein vs. Exercise and ii) Exercise + Calcium + Vitamin D vs. Calcium + Vitamin D. For surgery induced weight loss on FFM the level of evidence ranged between very low and moderate (Exercise + High Protein + Calcium + Vitamin D vs. Vitamin D).

Discussion, page 14:

Another issue is that the quality of evidence measured using the "grade" approach ranged from very low to moderate quality. No analysis was rated as high-quality evidence. Therefore, the true effects might substantially differ from the presented estimated effects.

◦ **Comment 7:**

Please provide information regarding the gender of participants in the table of

characteristics of studies.

Authors' response:

Thank you for your comment. We added the gender of participants in the table of characteristics of studies (Appendix C).

◦ **Comment 8:**

The manuscript must be also revised with regard to the English language.

Authors' response:

Thank you for your comment. We used the services of a copy editor to improve the language.

References

[1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022), www.training.cochrane.org/handbook; 2022.

[2] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; 2021.

[3] Takeshima N, Sozu T, Tajika A, Ogawa Y, Hayasaka Y, Furukawa TA. Which is more generalizable, powerful and interpretable in meta-analyses, mean difference or standardized mean difference? BMC medical research methodology 2014;14:1-7

[4] World Health Organization. Protein and amino acid requirements in human nutrition, Report of a Joint WHO/FAO/UNU Expert Consultation. WHO Technical Report Series. World Health Organization ed. World Health Organization; 2007.

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 March 2022

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The study of Roth et al. summarizes the effect of exercise training and dietary supplement on fat free mass and bone mass density during weight loss in adults with overweight or obesity.

The study is well designed and reported according to PRISMA guidelines. The study is well written;

however, some English corrections need to be done (e.g. was not statistically significant).

Title:

- Change physical activity to exercise training because the study is not about physical activity.

Abstract:

- Omit "The effect of calcium and vitamin D supplementation remains controversial and further research are needed." Or add these results in the abstract.
- Add that overweight patients were also included.

Introduction:

- Line 7: correct: "... but also could be cost-effective."

Methods:

- Eligibility criteria: line 4: two times exercise.
- Exercise training is a broad term, define it more clearly.

Results:

- Figure 1: please comment on the excluded studies more clearly, what is meant with "inadequate".
- Figure 2: An explanation of the yellow "!" is missing.

Discussion:

- Last paragraph of the discussion: Please present more details about the effect of different types of exercise training on the preservation of the FFM. Probably your study showed no clear favor of exercise training alone because not the right type of exercise training and intensity was chosen.
- You included around 12 studies which were only performed in women. However, there is no statement about this fact. Are there any differences between men and women?

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: exercise, physical activity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 03 Aug 2022

Chloé Schorderet, HES-SO Valais Wallis, Sion, Switzerland

Point-to-point response

◦ **Comment 1:**

Change physical activity to exercise training because the study is not about physical activity.

Authors' response:

Thank you for your comment. We replaced the term "physical activity" with the term "exercise training" throughout in the title of the manuscript.

◦ **Comment 2:**

Omit "The effect of calcium and vitamin D supplementation remains controversial and further research are needed." Or add these results in the abstract.

Authors' response:

Thank you for your comment. We omitted the sentence "The effect of calcium and vitamin D supplementation remains controversial and further research are needed".

◦ **Comment 3:**

Add that overweight patients were also included.

Authors' response:

Thank you for your comment. We included this information in the abstract.

Abstract, page 2:

Methods: *A systematic review was performed with a pairwise meta-analysis and an exploratory network meta-analysis according to the PRISMA statement. Studies assessing adults with overweight or obesity undergoing a weight loss and without secondary diagnosis limiting their exercise activity were included.*

◦ **Comment 4:**

Line 7: correct: "... but also could be cost-effective."

Authors' response:

Thank you for your comment. We modified the sentence.

Introduction, page 4:

The literature reports that weight loss within this range not only has a beneficial impact on several obesity-related health conditions and co-morbidities but can also be cost-effective.

◦ **Comment 5:**

Eligibility criteria: line 4: two times exercise.

Authors' response:

Thank you very much. We corrected this error of inattention.

○ **Comment 6:**

Exercise training is a broad term, define it more clearly

Authors' response:

Thank you for your comment. The exercise regimen has been defined according to the physical activity guidelines by the WHO [1]. The term exercise training, therefore, meant the performance of "at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week" (p. 2) [1], or the performance of "muscle strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week" (p. 2) [1]. We adapted the manuscript in order to clarify this point.

Method, eligibility criteria, pages 4 and 5:

Considered were randomized controlled trials or clinical trials comparing exercise training (defined as "at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week" (p. 2), or as "muscle strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week" (p. 2) according to the WHO [1]) alone or in combination with dietary supplementation (protein, calcium and/or vitamin D) with a placebo intervention, controlled comparison intervention or standard care.

○ **Comment 7:**

Figure 1: please comment on the excluded studies more clearly, what is meant with "inadequate". -> can you expand on inclusion criteria for each "inadequate statement"

Authors' response:

Thank you for your comment. This term is indeed imprecise. We have now removed it from the flow chart. The term "inadequate" meant that studies were not included because the comparator/intervention/outcome/patient population/setting/study design did not meet the inclusion criteria.

○ **Comment 8:**

Figure 2: An explanation of the yellow "!" is missing.

Authors' response:

Thank you for your comment. We added the meaning of the yellow "!" in the legend of Figure 2.

Page 9

Figure 2. Risk of bias according to the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0). NB. "!" in the "overall" category corresponds to "Some concerns".

◦ **Comment 9:**

Last paragraph of the discussion: Please present more details about the effect of different types of exercise training on the preservation of the FFM. Probably your study showed no clear favor of exercise training alone because not the right type of exercise training and intensity was chosen.

Authors' response:

Thank you for your comment. We added information in the results and in the discussion to clarify this point.

Results, page 8

All exercises interventions are described in Appendix C. Among the group of exercise training alone, different training modalities were used. Some had strength and other endurance training and among those who had the strength training different training parameters were chosen (i.e. different training volumes and intensities).

Discussion, page 16:

We should also mention that all the types of exercise reported in our review were classified as "exercise therapy", with no distinctions made between strength training and endurance training, even though these do not have the same effects on the preservation of FFM [2]. Some of the chosen training modalities do not target an increase in muscle mass or a decrease in fat mass which might underestimate the effectiveness on the outcome FFM.

◦ **Comment 10:**

You included around 12 studies which were only performed in women. However, there is no statement about this fact. Are there any differences between men and women?

Authors' response:

You are right this is important to consider. We added two sentences about this point in the discussion. In addition, we also added this variable in Appendix C.

Discussion, page 13:

Another limitation is that 12 of the 31 included studies evaluated only women. Therefore, it could be difficult to generalize the findings of this review to a mixed or to a male population.

References

- [1] WHO guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization; 2020.
- [2] Willis LH, Slentz CA, Bateman LA, Shields AT, Piner LW, Bales CW, et al. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J Appl Physiol* (1985) 2012;113:1831-7. doi: 10.1152/jappphysiol.01370.2011

Competing Interests: No competing interests were disclosed.

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