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REVIEW

The effects of weight loss approaches on bone mineral density in adults: a systematic review and meta-analysis of randomized controlled trials

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Abstract
Summary We assessed the impact of weight loss strategies including calorie restriction and exercise training on BMD in adults using a systematic review of randomized controlled trials. Weight reduction results in reduced BMD at the hip, but has less effect on the spine. Both calorie restriction and a combination of calorie restriction and exercise result in a decrease in hip bone density, whereas weight loss response to exercise training without dietary restriction leads to increased hip BMD.
Introduction Findings are not consistent on the effect of weight loss on bone mineral density (BMD). We conducted a systematic review on the randomized controlled trials to assess the effect of weight loss strategies, including calorie restriction and exercise programs on BMD in adults.
Methods A structured and comprehensive search of MEDLINE and EMBASE databases was undertaken up to March 2016. Study-specific mean differences (MD) were pooled using a random-effects model. Subgroup analysis and meta-regression were used to find possible sources of between-study heterogeneity.
Results Thirty-two randomized controlled trials met predetermined inclusion criteria. The meta-analysis revealed no significant difference on total BMD (MD 0.007, 95 % CI −0.020–0.034, $p = 0.608$). In contrast, the pooled data of studies showed a significant effect of weight loss on hip BMD (MD −0.008, 95 % CI −0.09 to −0.006 g/cm^2, $p < 0.001$) and also lumbar spine BMD (MD −0.018 g/cm^2, 95 % CI −0.019 to −0.017, $p < 0.001$). BMD in the hip site decreased after more than 4 months, especially in those who were obese. Moreover, calorie restriction interventions longer than 13 months showed a significant decreased in lumbar spine BMD.
Conclusion Weight loss led to significant decreases at the hip and lumbar spine BMD but not at the total. Weight loss response following calorie restriction resulted in a decrease in hip and lumbar spine bone density especially more than 1 year; whereas an exercise-induced weight loss did not.

Keywords Bone mineral density · Calorie restriction · Meta-analysis · Obesity · Systematic review · Weight reduction

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Introduction

Obesity contributes to risk for many chronic diseases such as hypertension, type 2 diabetes mellitus, and hyperlipidemia [1–3]. Obesity is a global public health concern, while diet and exercise are the main treatments [4]. Weight loss programs improve metabolic fitness and reduce morbidity and mortality associated with overweight and obesity. However, accumulating evidence suggests that obesity protects against bone loss due to weight-bearing effect of excess weight on the skeleton and the mechanical stress on bone, which stimulates osteoblast differentiation [5, 6]. On the other hand, obesity has been associated with low bone quality [7]. Moreover, a

Japanese prospective cohort study with a 6.7-year follow-up found incidence rate of vertebral fracture in overweight and obese women was significantly higher than normal weight women [8].

Weight loss leads to systematic endocrine changes that probably influence bone mineral density (BMD) [9]. Reducing estrogen, leptin, and insulin during weight loss can decrease their anabolic effects on bone [9] while on the other hand a concomitant increase in cortisol and parathyroid hormone [10] concentration may cause detrimental impact on bone mass [9]. Increased adiponectin level during weight loss predicted greater risk of bone loss at the lumbar spine [11]. It has been suggested that adiponectin stimulates osteoblastogenesis and inhibits osteoclastogenesis [12]. However, findings of the effect of weight loss on bone are confusing because of the heterogeneous nature of the methods and subject populations. For example, studies with mixed populations including pre-, peri-, and post-menopausal women, and/or men showed a loss of total BMD, ranged 0–2.5 % [13–15]. A previous meta-analysis [16] reported weight loss interventions on overweight/obese subjects led to a significant reduction in BMD of 0.010 to 0.015 g/cm^2 in the hip and 0.011 g/cm^2 in total body BMD after 6 months. Moreover, clinical trials with no control groups were also included in that review [16]. Therefore we conducted an updated systematic review of randomized controlled trials to assess the impact of weight loss strategies including calorie restriction and exercise training on BMD in adults.

Methods

A comprehensive search and systematic assessment of studies and data extraction were conducted in a stepwise process in accordance with our specific question: What is the effect of weight loss strategies including calorie restriction and exercise training on BMD in adults?

The PICOS model [17], where the acronym PICOS stands for population (>18 years old), intervention (diet and exercise programs), comparison (no or other balance enhancing exercise or diet programs), outcome (weight loss and bone loss), and study design (randomized controlled trials), was applied to formulate our question.

Box 1 PICOS criteria (Patient/Population, Intervention, Comparison, Outcome, Setting)

Patient/Population: Population (>18 years old)
Intervention: Weight loss program (exercise or energy restriction diet)
Comparison: No or other balance enhancing exercise or diet programs
Outcome: BMD of the total hip, lumbar spine (L1–L4 or L2–L4) or of the total body which was measured by dual X-ray absorptiometry and body weight
Setting: Randomized control trial

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used for writing this systematic review [18]. The protocol was previously published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO), under registration no CRD42015016005.

Search strategy

We searched the English-language medical literature published up to October 2014 using the MEDLINE and EMBASE databases for studies investigating the impact of weight loss on bone mass. The electronic literature search was last updated on March 2016. Search terms, keywords, and study design in the searches are presented in Appendix 1. Review articles were also assessed to find additional eligible articles. The bibliographies of relevant articles were checked to ensure that all relevant studies were found.

Eligibility and study selection

Three reviewers (S.S, A.K, and S.S-b) independently screened the eligibility of studies according to the following pre-established criteria. Studies were included in this meta-analysis if they fulfilled the following criteria: the study design was randomized controlled trial; the intervention arm of the study had to include a weight loss program (exercise or energy restriction diet). The outcome of interest was BMD of the total hip, lumbar spine (L1–L4 or L2–L4), or of the total body which was measured by dual X-ray absorptiometry (DXA). BMD of the hip and spine was chosen based on the recommendation of the National Osteoporosis Foundation because low BMD in hip and spine sites are candidate for treatment risk fracture in post-menopausal women and men 50 years and older [19]. The exclusion criteria were reviews, conference papers, editorials, non-human studies, and non-randomized trials; investigations that participants were pregnant and lactating women or child and adolescent, studies on patients with renal, digestive tract, endocrine disorders and cancers; as well as studies employing bariatric surgery or medications for weight reduction. Studies were also excluded if the subjects had treatment with hormone replacement therapy or treatment with bisphosphonates, other medication analogues, and multi-mineral supplements. The reference lists of all included studies and previous meta-analysis were hand searched to identify studies not found by the search of electronic databases. In case of multiple publications from the same population, we considered those with the largest sample size.

Data extraction

S.S extracted quantitative data from each study included in the review using a pre-formatted spreadsheet. The extracted data was checked by two independent investigators (A.K, S.S-b) to

reduce reviewer errors. If there were discrepancies, group consensus and a third reviewer was consulted to ensure accuracy of data. The data extracted included the following: year of publication, country in which conducted; study design, the participants' age; number of allocated participants; sex and menopausal status; details of weight loss approaches (exercise; energy restriction diet) for intervention and control group; length of intervention (months); baseline BMI of participants; weight change, and BMD outcome measurement sites (BMD values with standard deviation of whole body, hip, and spine). BMD in all studies was reported as grams per square centimeter (g/cm^2). We attempted to contact the authors to obtain information not furnished but needed.

Quality assessment

Jadad scale was used to assess the quality of included trials [20]. The factors contributing to study quality were randomization (described as randomized, 1 point; randomized process, additional 1 point), double-blind (described as double-blind, 1 point; use of masking such as identical placebo, additional 1 point), and follow-up (the numbers and reasons for drop out in each group; 1 point) in the report of RCTs. Studies with a score of 2 or less indicated low quality and studies with a scores of 3 or more as high quality study. As blinding is almost impossible for dietary and exercise programs, we considered the blinding as staff personnel of studies who performed scans and subsequent analysis for BMD were unaware of intervention allocation.

Statistical analysis

We calculated the mean difference between the intervention and control group for each individual study, which is equal to change in intervention group minus change in control group, where changes are the absolute differences in BMD between each follow-up and the baseline measure for the intervention and control groups. Imputing of standard deviations from other studies was used to estimate variance of calculated mean difference. If only the range was given as the measure of variation, then the SD was calculated as the range divided by 5.88 (6 SDs). If the SE was reported as variance, the SD was computed as SE × √n. For 95 % confidence intervals, the SD for each group was obtained by dividing the length of the confidence interval by 3.92, and then multiplying by the square root of the sample size.

For meta-analysis, a random-effects model was used to report heterogeneous results. Data was pooled by the generic inverse variance method by the user written "metan" command [21]. We computed the between-study variance for the random-effects model using the DerSimonian and Laird formula [22]. Statistical heterogeneity was assessed using the χ^2 test and I^2 statistic (I^2 represents the percentage of variability due to between-study variability). To investigate sources of heterogeneity, a list of predefined variables for subgroup analysis were used including the following: participants' age (<65 vs. >65 years old), gender, initial BMI (<25 vs. >25 kg/m^2 or both), follow-up period (<3 months; 4–6 months; 7–9 months, 10–12 months, and >1 year), weight loss approaches (exercise, energy restriction diet, or both) for intervention, and multi vitamin-minerals supplementation. Subgroup analyses were carried out by disaggregating results with the user written "metan" command ("by option") [21]. We conducted an influence analysis to assess the influence of each individual trial on the overall summary estimate with the user written "metaninf" command. We also carried out formal statistical tests for funnel plot asymmetry with the user written "metabias" command [21]. All statistical analyses were conducted using STATA software version 14.0 (Stata Corp, College Station, TX, USA). A p value less than 0.05 was considered to be statistically significant.

Results

Study selection

Figure 1 shows the process for the inclusion of studies in this systematic review. The systematic search identified 8319 references, of which 1244 were duplicated and 6904 were excluded at initial screening of the title and abstract. Of these, 139 studies were excluded because of lack of bone loss data following weight loss program [10, 21, 23–34]; conducted in children, adolescents, and lactating women [35–41]; repeated publications on the same study [42–46]; lack of randomization [47–52]; surgical and anti-obesity drug intervention [53–56]; lack of data for weight change [57–79]; lacking of access to the full text [80]; not RCT design [81–107]; bone density in whole body or hip or spine were incomplete [108–130]; reporting medication, supplementation, or hormone therapy as an intervention [15, 131–143]; missing control group [14, 29, 144–153]; or no weight loss program [154–157].

Study characteristics of included studies

Table 1 shows a description of the included studies. A total of 32 studies met the inclusion criteria and were assessed in the meta-analysis. Most studies were carried out in North America (22 studies) [158–179]. Four publications were conducted in European countries [180–183], four in Asia [184–187], one in Africa [188], and one Australia [189]. A total of 4471 participants were included. Study duration varied between 2 and 60 months. Sample size of studies ranged from 18 to 1274. Thirteen studies included exercise for weight loss,

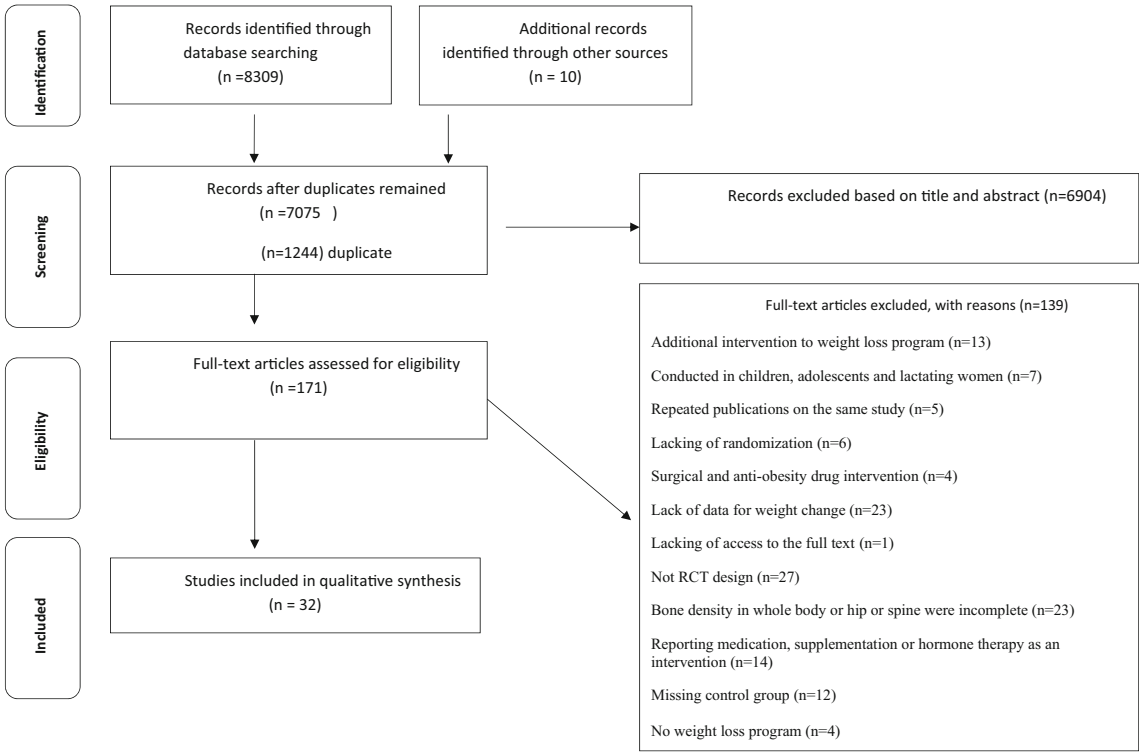

Fig. 1 Flow diagram for study selection process

6 RCTs used calorie restriction, and 13 of studies recommended both exercise and calorie restriction.

Assessment of risk of bias

The risk of bias in the studies is shown in Table 2. Nineteen from the 32 included studies based on Jadad score were classified with good quality. Eleven studies illustrated the randomization scheme and one simply reported the participants were randomized. Twelve studies reported blinding, although its process was not fully described. All of the studies adequately reported dropouts.

Weight loss and BMD

Meta-analysis

In the pooled analysis of 23 trials with 3127 participants [158, 160, 161, 164–175, 181–187, 189], no overall effect of weight loss on total BMD mean differences (MD = 0.007, 95 % CI −0.020–0.034 g/cm^2, $p = 0.608$) was observed (Table 3). In contrast, the meta-analysis (26 studies with 3572 participants) [158, 159, 161, 163–165, 167–180, 182, 183, 185, 186, 188, 189] showed a significant overall effect of reduced body weight on lumbar spine BMD (MD = −0.018 g/cm^2, 95 % CI −0.019 to −0.017 g/cm^2, $p < 0.001$). Additionally, the pooled data of 17 studies with 3193 participants [159, 161, 162, 165–168, 170–174, 177, 179, 186, 188, 189] showed also a significant overall effect of weight loss on hip BMD (MD = −0.008, 95 % CI −0.009–0.006 g/cm^2, $p < 0.001$). There was heterogeneity among studies for the effect of weight loss on total BMD ($I^2 = 99.4$ %, $p < 0.001$), hip BMD ($I^2 = 89.3$ %, $p < 0.001$), and spin BMD ($I^2 = 86.6$ %, $p < 0.001$). Weight loss response following combination of calorie restriction/exercise was (MD = −5.670 kg, 95 % CI −6.007 to −5.333 kg, $p < 0.001$). However, exercise-induced weight loss was rather modest (MD = −0.561 kg, 95 % CI −0.959 to −0.162 kg, $p = 0.006$) compared to diet-induced weight loss (MD = −6.883 kg, 95 % CI −7.314 to −6.453 kg, $p < 0.001$). The largest estimated weight reduction was for hip BMD (MD = −5.163 kg, 95 % CI −6.467 to −3.859 kg, $p < 0.001$). The mean of weight loss was (MD = −4.868 kg, 95 % CI −6.202 to −3.534 kg, $p < 0.001$) for total body and (MD = −4.017 kg, 95 % CI −5.331 to −2.702 kg, $p < 0.001$) for lumbar spine BMD (data not shown).

Subgroup analysis

We explored potential heterogeneity by examining effect sizes in clinical subgroups by predefined categories: participants' age, gender, BMI, trial duration, weight loss approaches for intervention, and supplementation concomitant with intervention. Age, trial duration, baseline BMI, and concomitant supplementation with weight loss did not explain heterogeneity seen between studies for analyses of total BMD. All of the predefining factors were sources of heterogeneity for BMD of the lumbar spine. Age and concomitant supplementation were sources of heterogeneity for

Table 1 Characteristic of randomized controlled trials that evaluated the effect of the weight loss on total, hip, and spine BMD that were eligible to be included in this systematic review

First author, year	No. of participants	Gender and menopausal status	Age	Design	Study duration (months)	Subjects characteristic	Details of intervention	BMD outcome measurement sites	Multi vitamin-mineral supplementation
Svendsen (1993) [183]	118	Post-menopausal women	53.8	Parallel	3	Overweight and obese	Calorie restriction, calorie restriction and exercise program	Total and spin BMD	–
Bassey (1995) [180]	40	Post-menopausal women	54	Parallel	12	Normal and overweight	Exercise program	Spin BMD	–
Kohrt (1997) [164]	39	Post-menopausal women	65	Parallel	11	Normal and overweight	Exercise program	Total and spin BMD	Supplementation
Andersen (1997) [158]	19	Pre- and post- menopausal women	41	Parallel	6	Overweight and obese	Calorie restriction and exercise program	Total and spin BMD	–
Salamone (1999) [177]	241	Pre-menopausal women	46.7	Parallel	18	Normal and overweight	Calorie restriction and exercise program	Hip and spin BMD	supplementation
De Jong (2000) [181]	69	Men and post-menopausal women	76.5	Factorial design	4	Normal weight	Exercise program	Total BMD	–
Rhodes (2000) [176]	38	Post-menopausal women	68.8	Parallel	12	Normal and overweight	Exercise program	Spin BMD	–
Chao (2000) [161]	67	Post-menopausal women	66.3	Parallel	12	Overweight and obese	Calorie restriction	Total, spin and hip BMD	–
Shapses (2001) [169]	24	Men and pre-menopausal women	40	Parallel	6	Overweight and obese	Calorie restriction	Total and spin BMD	–
Jessup (2003) [163]	18	Post-menopausal women	69.1	Parallel	8	Normal and overweight	Exercise program	Spin BMD	supplementation
Englund (2005) [182]	40	Post-menopausal women	72.8	Parallel	12	Normal and overweight	Exercise program	Total and spin BMD	–
Stewart (2005) [171]	104	Men and post-menopausal women	62.7	Parallel	6	Normal and overweight	Exercise program	Total, spin and hip BMD	–
Villareal (2006) [173]	48	Men and post-menopausal women	57.1	Parallel	12	Overweight and obese	Calorie restriction, exercise program	Total, spin and hip BMD	Supplementation
Riedt (2007) [167]	30	Pre-menopausal women	38	Parallel	6	Overweight and obese	Calorie restriction	Total, spin and hip BMD	Supplementation
Park (2007) [186]	373	Pre-menopausal women	46.9	Parallel	60	Normal and overweight	Calorie restriction and exercise program	Total, spin and hip BMD	–
Villareal (2008) [174]	27	Men and post-menopausal women	69.4	Parallel	12	Overweight and obese	Calorie restriction and exercise program	Total, spin and hip BMD	–
Redman (2008) [166]	46	Men and pre-menopausal women	37.5	Parallel	6	Overweight and obese	Calorie restriction and exercise program, calorie restriction	Total and hip BMD	–
Nakata (2008) [185]	35	Pre-menopausal women	42.3	Parallel	3	Overweight and obese	Calorie restriction and exercise program	Total and spin BMD	Supplementation
Warren(2008) [178]	148	Pre-menopausal women	36.4	Parallel	24	Overweight and obese	Exercise program	Spin BMD	–
Singh (2009) [170]	54	Men and pre-menopausal women	40.8	Parallel	10	Normal and overweight	Exercise program	Total, spin and hip BMD	–
Yoo (2010) [175]	21	Post-menopausal women	70.9	Factorial design	3	Normal and overweight	Exercise program	Total and spin BMD	–
Whiteford (2010) [189]	127	Men	64	Parallel	12	Normal and overweight	Exercise program	Total, spin and hip BMD	–
Campbell (2010) [160]	54	Post-menopausal women	59	Parallel	3	Overweight and obese	Calorie restriction	Total BMD	Supplementation
Villareal (2011) [172]	107	Men and post-menopausal women	70	Parallel	12	Overweight and obese	Calorie restriction, exercise program, calorie restriction and exercise program	Total, spin and hip BMD	Supplementation
Schwartz (2012) [168]	1274	Men and pre/post-menopausal women	59	Parallel	12	Overweight and obese	Calorie restriction and exercise program	Total, spin and hip BMD	–
Hosny (2012) [188]	40	Pre-menopausal women	35.9	Parallel	3	Overweight and obese		Spin and hip BMD	–

Table 1 (continued)

First author, year	No. of participants	Gender and menopausal status	Age	Design	Study duration (months)	Subjects characteristic	Details of intervention	BMD outcome measurement sites	Multi vitamin-mineral supplementation
Hamilton (2013) [162]	115	Pre-menopausal women	33.3	Parallel	6	Overweight and obese	Calorie restriction and exercise program Calorie restriction and exercise	Hip BMD	–
Beavers (2014) [159]	284	Men and post-menopausal women	66.1	Parallel	18	Overweight and obese	Calorie restriction and exercise program	Spin and hip BMD	–
Kim (2015) [184]	39	Men	24.8	Parallel	2	Overweight and obese	Exercise program	Total BMD	–
Pop (2015) [165]	38	Men	57.7	Parallel	6	Overweight and obese	Calorie restriction	Total, spin and hip BMD	Supplementation
Villareal (2016) [179]	218	Men and pre-menopausal women	37.9	Parallel	24	Normal weight	Calorie restriction	Spin and hip BMD	Supplementation
Hui (2016) [187]	374	Men and pre/post-menopausal women	45.8	Parallel	3	Normal and overweight	Exercise program	Total BMD	–

BMD of the hip. For studies with both sex (MD = 0.008 g/cm^2, 95 % CI 0.003 to 0.012, $p = 0.001$) and both weight loss approaches (MD = 0.004 g/cm^2, 95 % CI 0.001 to 0.006, $p = 0.009$), the MD for total BMD significantly increased (Table 3). For the BMD of hip, BMD decreased in both genders, in all age categories, after more than 4 months especially in those who were overweight and obese with calorie restriction (Table 3). However, exercise programs increased the BMD of hip (MD = 0.005 g/cm^2, 95 % CI 0.002 to 0.009, $p = 0.004$). In subgroup analysis of lumbar spine, younger (MD = −0.019 g/cm^2, 95 % CI −0.020 to −0.018) non-obese participants (MD = −0.019 g/cm^2, 95 % CI −0.020 to −0.018) with calorie restriction (MD = −0.020 g/cm^2, 95 % CI −0.021 to −0.019) after more than 13 months (MD = −0.020 g/cm^2, 95 % CI −0.021 to −0.019) showed significant decrease in the BMD (Table 3).

Influence analysis

The sensitivity analysis for BMD of the lumbar spine showed that the study by Villareal et al. [179] was responsible for the heterogeneity, and its exclusion did make the pooled results in BMD of the lumbar spine non-significant (figures not shown). Therefore, the significant inverse association between weight loss and BMD of the lumbar spine should be interpreted with caution.

Publication bias

The funnel plots did not show any signs of asymmetry and the Egger's test showed no publication of bias for total BMD ($p = 0.148$, Fig. 2a), BMD of hip ($p = 598$, Fig. 2b), and lumbar spine ($p = 0.434$, Fig. 2c).

Discussion

Previous studies have yielded little consensus concerning the effects of weight loss on BMD. For the first time, the present study evaluated randomized controlled trials to quantitatively assess the effect of all non-pharmacological weight loss programs (weight loss or diet induced) on BMD in adult populations using meta-analysis procedures. Our meta-analysis has revealed weight loss response following calorie restriction resulted in a decrease in hip and lumbar spine bone density, especially after 1 year, whereas an exercise-induced weight loss did not. Moreover, BMD of whole body showed no significant changes in response to weight reduction. However, exercise-induced weight loss was rather modest compared to diet-induced weight loss.

Our findings are in agreement with previous recent meta-analyses which have shown an association between weight reduction and BMD, which existed at the hip site [16]. Conversely, our data are in contrast to this study, reporting

Table 2 Study quality and risk of bias assessment using Jadad tool [20]

First author, year	Randomization	Random description	Blinding	Blinding description	Dropouts	Total	Quality
Svendsen (1993) [183]	1	0	1	0	1	3	Good
Bassey (1995) [180]	1	0	0	0	1	2	Fair
Kohrt (1997) [164]	1	0	0	0	1	2	Fair
Andersen (1997) [158]	1	0	1	0	1	3	Good
Salamone(1999) [177]	1	0	1	0	1	3	Good
De Jong (2000) [181]	1	1	0	0	1	3	Good
Rhodes (2000) [176]	1	0	0	0	1	2	Fair
Chao (2000) [161]	1	0	1	0	1	3	Good
Shapses (2001) [169]	1	0	1	0	1	3	Good
Jessup (2003) [163]	1	0	1	1	1	4	Good
Englund (2005) [182]	1	0	0	0	1	2	Fair
Stewart (2005) [171]	1	1	0	0	1	3	Good
Villareal (2006) [173]	1	0	0	0	1	2	Fair
Riedt (2007) [167]	1	1	1	0	1	4	Good
Park (2007) [186]	1	1	1	0	1	4	Good
Villareal (2008) [174]	1	0	0	0	1	2	Fair
Redman (2008) [166]	1	1	1	0	1	4	Good
Nakata (2008) [185]	1	0	0	0	1	2	Fair
Warren (2008) [178]	1	0	1	0	1	3	Good
Singh (2009) [170]	1	1	1	0	1	4	Good
Yoo (2010) [175]	1	0	0	0	1	2	Fair
Whiteford (2010) [189]	1	1	0	0	1	3	Good
Campbell (2010) [160]	1	0	0	0	1	2	Fair
Villareal (2011) [172]	1	1	0	0	1	3	Good
Schwartz (2012) [168]	1	1	0	0	1	3	Good
Hosny (2012) [188]	1	0	0	0	1	2	Fair
Hamilton (2013) [162]	1	0	0	0	1	2	Fair
Beavers (2014) [159]	1	1	1	0	1	4	Good
Kim (2015) [184]	1	0	0	0	1	2	Fair
Pop (2015) [165]	1	1	0	0	1	3	Good
Villareal (2016) [179]	1	0	0	0	1	2	Fair
Hui (2016) [187]	1	1	0	0	1	3	Good

Studies with a score of 2 or less indicated low quality and studies with a score of 3 or more as high quality study

only minimal lumbar spine bone density loss after at least 13 months weight loss [16].

Our finding showed that the lumbar spine BMD decreased in non-obese adults. Non-obese adults have less FFM compared with obese ones which make them more susceptible to detrimental bone effects following weight loss [190]. We showed the spine BMD was decreased in younger adults. It is possible that loading of the lumbar spine is relatively lower than hip loading during locomotion, the primary loading factor in modern environments. In fact, loading of the hip may be much larger and frequent than at the spine during walking. So it is possible loss of weight will have less of an effect on BMD of the spine so will take longer to occur. So it is possible loss of weight will have less of an effect on BMD of the spine so will take longer to occur. Therefore, it is possible that decreased body weight would have less of an influence on lumbar spine loading than on hip loading thus slowing the loss of lumbar spine BMD.

Our results suggested that weight loss resulted in a decrease in the BMD of hip and lumbar spine but not in the whole body BMD. The more content of spine and hip is trabecular; sites where trabecular bone shown are more sensitive to response turn over factors could be a possible explanation [191]. Moreover, hip and lumbar spine BMD measurement by DXA is the best predictor of future hip fracture risk [192], these site-specific effects of weight reduction could have clinical implications.

Table 3 Meta-analysis showing the effect of weight loss program on total, hip, and spine BMD based on several subgroups (all analyses were conducted using random-effects model)

Study group	Number of participant	MD[1] (95 % CI)	*P* effect	*Q* statistic	*P* within heterogeneity	I^2 (%)	*P* between heterogeneity
Total BMD							
Overall	2753	0.007 (−0.020, 0.034)	0.608	5615.12	<0.001	99.4	–
Gender							
Female	1703	0.00 (−0.003, 0.003)	0.951	80.23	<0.001	80.1	0.007
Male	738	−0.001 (−0.006, 0.004)	0.570	13.41	0.009	70.2	
Both	312	0.008 (0.003, 0.012)	0.001	7.44	0.763	0.00	
Age							
<65 years	2382	0.001 (−0.001, 0.003)	0.372	63.74	<0.001	65.5	0.370
≥65 years	370	0.004 (−0.002, 0.010)	0.205	46.36	<0.001	78.4	
Trial duration							
<3 months	267	−0.002 (−0.006, 0.002)	0.310	25.76	0.001	72.8	0.185
4–6 months	397	−0.004 (−0.001, 0.009)	0.087	49.77	0.00	79.9	
10–12 months	1671	0.003 (−0.001, 0.006)	0.116	30.56	0.004	57.5	
≥13 months	373	0.00 (−0.007, 0.007)	1	0.00	–	–	
Intervention types							
Calorie restriction	242	−0.003 (−0.007, 0.001)	0.143	76.53	<0.001	83.4	0.026
Exercise program	307	0.001 (−0.004, 0.005)	0.843	15.85	0.147	30.6	
Both	939	0.004 (0.001, 0.006)	0.009	11.19	0.191	28.5	
BMI status							
Overweight and obese (BMI ≥ 25 kg/m^2)	1917	0.002 (−0.000, 0.004)	0.111	75.47	<0.001	70.9	0.348
Non-obese	767	0.000 (−0.005, 0.004)	0.854	14.66	0.101	38.6	
Supplementation							
With supplement	342	−0.001 (−0.004, 0.003)	0.764	40.79	<0.001	70.6	0.228
Without supplement	2411	0.002 (−0.00, 0.005)	0.085	68.67	<0.001	70.9	
Hip BMD							
Overall	3193	−0.008 (−0.009, −0.006)	<0.001	214.11	<0.001	89.3	–
Gender							
Female	1775	−0.004 (−0.006, −0.002)	<0.001	43.43	<0.001	86.2	<0.001
Male	663	−0.008 (−0.011, −0.005)	<0.001	30.11	<0.001	90	
Both	755	−0.13 (−0.015, −0.011)	<0.001	214.11	<0.001	89.6	
Age							
<65 years	2690	−0.007 (−0.009, −0.006)	<0.001	120.48	<0.001	86.7	0.072
≥65 years	485	−0.011 (−0.014, −0.007)	<0.001	90.40	<0.001	93.4	
Trial duration							
<3 months	40	0.010 (−0.003, 0.023)	0.136	0.00	–	–	0.006
4–6 months	400	−0.004 (−0.008, 0.00)	0.033	39.87	<0.001	85.0	
10–12 months	1670	−0.008 (−0.010, −0.006)	<0.001	120.55	<0.001	91.7	

Table 3 (continued)

Study group	Number of participant	MD[1] (95 % CI)	*P* effect	*Q* statistic	*P* within heterogeneity	I^2 (%)	*P* between heterogeneity
≥13 months	1083	−0.010 (−0.012, −0.007)	<0.001	41.27	<0.001	90.3	
Intervention type							
Calorie restriction	158	−0.017 (−0.021, −0.013)	<0.001	47.65	<0.001	85.3	<0.001
Exercise program	183	0.005 (0.002, 0.009)	0.004	26.11	<0.001	80.8	
Both	1413	−0.009 (−0.011, −0.008)	<0.001	66.62	<0.001	86.5	
BMI status							
Overweight and obese (BMI ≥ 25 kg/m^2)	2067	−0.011 (−0.013, −0.009)	<0.001	139.76	<0.001	88.6	<0.001
Non-obese	1126	−0.002 (−0.004, 0.000)	0.090	39.30	<0.001	84.7	
Supplementation							
With supplement	673	−0.007 (−0.010, −0.04)	<0.001	70.86	<0.001	88.7	0.538
Without supplement	2520	−0.008 (−0.010, −0.006)	<0.001	142.87	<0.001	90.2	
Spine BMD							
Overall	3354	−0.018 (−0.019, −0.017)	<0.001	247.08	<0.001	86.6	
Gender							
Female	2115	0.003 (−0.002, 0.008)	0.204	94.07	<0.001	80.9	<0.001
Male	699	0.00 (−0.008, 0.008)	0.915	1.63	0.652	0	
Both	758	−0.020 (−0.021, −0.019)	<0.001	42.27	<0.001	76.3	
Age							
<65 years	2931	−0.019 (−0.020, −0.018)	<0.001	107.37	<0.001	81.4	<0.001
≥65 years	641	0.005 (−0.002, 0.012)	0.149	93.27	<0.001	87.1	
Duration							
<3 months	214	−0.001 (−0.013, 0.011)	0.891	1.81	0.771	0	<0.001
4–6 months	282	0.001 (−0.013, 0.016)	0.878	2.62	0.759	0	
7–9 months	18	0.113 (0.063, 0.163)	<0.001	0.00	–	–	
10–12 months	1794	0.004 (−0.001, 0.008)	0.104	74.12	<0.001	85	
≥13 months	1264	−0.020 (−0.021, −0.019)	<0.001	33.30	<0.001	0	
Intervention types							
Calorie restriction	440	−0.020 (−0.021, −0.019)	<0.001	84.06	<0.001	91.7	<0.001
Exercise program	363	0.008 (0.00, 0.016)	0.027	26.44	0.009	50.8	
Both	1187	0.00 (−0.004, 0.004)	0.950	3.25	0.015	0	
BMI status							
Overweight and obese (BMI ≥ 25 kg/m^2)	2259	0.002 (−0.002, 0.006)	0.414	72.76	<0.001	73.9	<0.001
Non-obese	1313	−0.019 (−0.020, −0.018)	<0.001	77.68	<0.001	83.3	
Supplementation							
With supplement	765	−0.019 (−0.018, −0.017)	<0.001	71.02	<0.001	83.1	<0.001
Without supplement	2807	0.001 (−0.003, 0.005)	0.501	79.39	<0.001	74.8	

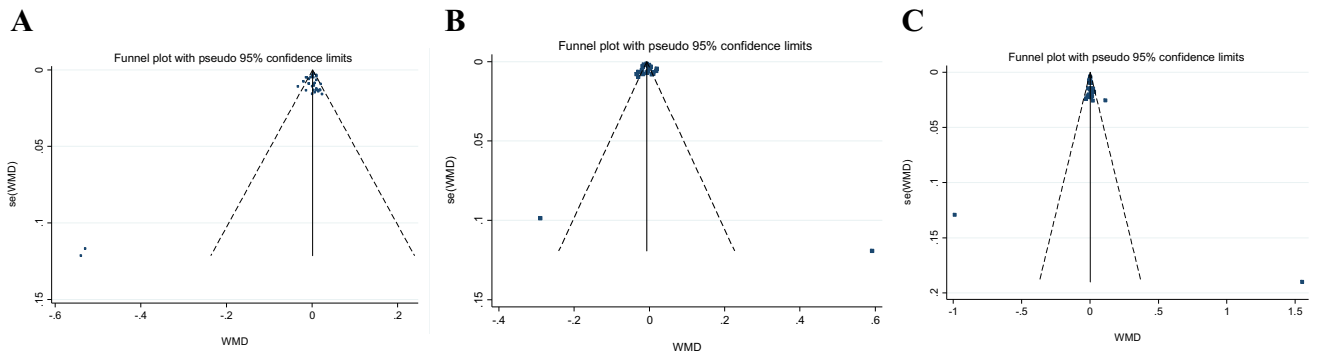

Fig. 2 Egger's funnel plots (with pseudo 95 % CIs) of the mean differences (MDs) versus their SEs (standard errors) for studies that assessed the effect of weight loss program on whole body BMD (**a**), hip BMD (**b**), and spine BMD (**c**). The *horizontal line* shows the pooled MDs calculated with the DerSimonian and Laird random-effects model

The aim of weight loss in obese subjects is loss of fat mass, which may play an important role in regulating BMD [193]. Adipose tissue is a dynamic tissue that secretes a large number of anti and pro inflammatory cytokines called adipokines [194]. Leptin is a well-known adipocyte-derived hormone that its systemic administration to animals and humans increases bone mass [195, 196]. These studies suggest that the anabolic effect of leptin is mediated by stimulant osteoblast proliferation and inhibition of osteoclastogenesis [197, 198]. Adiponectin is another adipokine that increases with moderate weight loss [199]. Result from adiponectin knockout mice suggest that this hormone is related to reduced bone mass [200]. Adiponectin by modulating proliferation and mineralization of osteoblastic cells (then, increasing differentiation of osteoblasts to osteoclasts) [201] enhance the expression of osteoclast receptor activator of nuclear factor-κB ligand [202] and by inhibition of osteoprotegerin exacerbate bone turn over [203]. A reduction in the circulating insulin levels through stimulating insulin sensitivity might also contribute to reduce bone density following weight loss. Insulin resistance, with compensating hyperinsulinemia as a result of obesity, has been suggested to have an anabolic effect on bone mass which may be due to a negative effect on sex hormone-binding globulin and the increase of free sex hormone levels [204, 205]. In addition to this mechanism, insulin, by exerting synergistic effects with insulin-like growth factor-I and parathyroid hormone may prevent decline in BMD [206]. It is essential to point out that the progenitor-mesenchymal stem cells of osteoblasts and adipocytes are in common to each other and their differentiation is regulated by peroxisome proliferators activated receptor-γ (PPAR-γ) and leptin [207]. A reduction in estrogen levels and rise in serum cortisol during weight management program may also explain the bone mass induced by weight loss [208, 209]. Finally, weight loss will be associated with less mechanical loading on the bones during locomotion which may lead to bone loss [15, 173]. Thus, a decrease in body weight that induces concomitant reductions in fat and lean mass could have negative effects on bone mass.

Our results showed that loss of hip BMD due to moderate weight loss was reduced similarly in calorie restriction and combination calorie restriction and exercise program, whereas exercise during energy restriction may minimize loss of BMD. Despite weight loss, the exercise group demonstrated an increase in hip BMD. It should be kept in mind that our result has shown exercise-induced weight loss was rather modest compared to diet-induced weight loss. Inclusion of exercise training during weight loss seems to decrease BMD loss [172], probably due to the combination of greater maintenance of lean mass and increased mechanical loading on the bones [210]. Supporting this, a recent meta-analysis showed that FFM has a larger effect on BMD than FM [90]. It is important to point out that BMD loss following weight loss may not always increase risk of fracture. In fact, at least one study showed that BMD relative to body weight actually increased following a weight loss of approximately 12 kg, showing an improved BMD relative to body weight [162]. Of course exercise training such as walking or running will increase mechanical loading, especially on the hip, and have a positive effect on preventing BMD loss [210].

Significant decreases in hip BMD were observed in present study for interventions longer than 4 months. If intervention induced changes in BMD are to be detected, the time interval between evaluations must be long enough to allow bone remodeling to occur. The complete cycle of bone remodeling takes 4 to 6 months, thus indicating the time interval between two measurements in the same patient should be at least that long to be able to detect BMD changes in clinical trials [211].

Our study has several strengths. The main strength of this meta-analysis is that the RCTs are included to the analysis. RCTs is widely regarded as gold standard to evaluate the effects of an intervention. Moreover, the present meta-analysis has investigated the effect of all non-invasive weight loss programs on BMD, allowing us to explain individually the differences between diet/exercise-induced weight loss on bone quality.

Some limitations in the present study are needed to be considered while interpreting our results. First, there is a large

heterogeneity in hormone replacement therapy in included studies. Indeed, some studies did not take into consideration hormone therapy as exclusion criteria, which are an effective means of attenuating loss of lean mass and bone. Moreover, the majority of studies did not report menopause status separately within their population. Therefore, it was not possible to assess whether differences in menopause status contributed to differences in primary outcomes. Additionally, the degree of participants' compliance with the weight loss program (energy restriction and exercise training), in the most included studies, has not been considered. The weight loss following dietary interventions is usually complex, i.e., differences in macronutrient composition of the diets may influence changes in bone mass. The findings from 16 weeks energy restriction program in overweight adults suggests that a high-protein, calcium-replete diet may protect against bone loss during weight reduction [27]. Furthermore, as blinding is impossible for dietary intervention trials and exercise programs, it is possible that observer bias have influenced on finding of studies.

In conclusion, the present meta-analysis reveals that weight reduction results in reduced BMD at the hip, but has less effect on the spine. Both calorie restriction and a combination of calorie restriction and exercise result in a decrease in hip bone density, whereas weight loss response to exercise training without dietary restriction leads to increased hip BMD.

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Compliance with ethical standards

Conflicts of interest None.

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