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Does adipose tissue mass positively or negatively influence bone mass in an overweight or obese population? A systematic review and meta-analysis

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ABSTRACT:

Context: Conflicting evidence about the relationship between adiposity and bone in overweight and obese populations exists. **Objective:** To quantify the correlation between adipose mass (absolute and relative) and bone mineral density (BMD) in over-weight and obese populations. **Data Sources and Extraction:** An electronic search of the literature was undertaken using three databases and supplemented through screening the reference lists of relevant articles. Data were extracted from 16 studies which reported a correlation between adipose mass (kg or %BM) and BMD in overweight or obese individuals. Data **Synthesis:** Multi-level modelling indicated opposing relationships between BMD and adiposity, with absolute adiposity positively, and relative adiposity negatively correlated with BMD. Sex and age were the primary moderators of these relationships. Strong evidence was obtained supporting a negative relationship between relative adipose mass and BMD in men (R=-0.37; 95%CI: -0.57,-0.12) and those aged <25 years (R=-0.28; 95%CI: -0.45,-0.08). **Conclusion:** In order to protect bone mass in overweight and obese populations, nutrition and exercise based interventions that focus on a controlled reduction of adipose mass with concomitant preservation of lean mass are recommended.

INTRODUCTION

Increasing obesity prevalence is a global health problem and worldwide statistics have recently estimated that 38% of all adults are overweight, and 13% are obese. [1] In addition to the well-documented health consequences of increasing overweight and obesity levels, [2] obesity also represents a substantial social and economic burden, due to direct (*e.g.,* increased healthcare costs) and indirect (*e.g.,* higher dependence on welfare due to premature retirement and unemployment; increased sick leave) costs. [3] Another worldwide health issue increasing in prevalence and with far-reaching social and economic consequences is osteoporosis. It is estimated that worldwide, osteoporosis causes more than 8.9 million fractures annually, [4] and the worldwide incidence of osteoporosis related hip fracture is predicted to increase by 310% in men, and 240% in women by the year 2050 compared to 1990 statistics. [5] As such, optimal management of these two chronic lifestyle related and nutritionally modulated conditions is required to protect the long-term health of the world population, and to decrease their associated social and economic burden.

More complete understanding of the relationships between the adipose and bone compartments of body composition are essential to the development of management and treatment strategies for obesity and osteoporosis. Obesity has historically been considered to be protective of bone, which was thought to occur as a result of the increased loading afforded by a greater total body mass, mediated through the action of various osteo, adipo and myokines. [6,7] Absolute body mass [8–10] and lean mass in particular, [11] have been reported to be the strongest independent predictors of bone mineral density (BMD), which is the primary determinant in the diagnosis of osteoporosis. The relationship between adipose mass and BMD is more controversial however, with both positive and negative correlations reported. [12,13] A number of studies have reported higher BMD in obese populations, when compared to normal weight controls, [14,15] and a recent meta-analysis conducted on the general population reported a positive correlation between adipose tissue mass and total body BMD (R = 0.28; 95%CI: 0.21, 0.31), [11] leading to the belief that adipose mass exerts a positive influence on bone mass. Conversely, evidence exists supporting a detrimental influence of excess adiposity on bone, which is thought to occur via a number of mechanisms. [16–19] For example, an obese state is associated with increased oxidative stress, [20] which has consequences for bone health. Reactive oxygen species (ROS) act as signalling molecules in the regulation of bone remodelling by mediating osteoclast differentiation. [21,22] Elevated ROS, as occurs in a state of oxidative stress however, could cause a disproportionate increase in bone resorption, increasing the rate of bone loss and contributing to the pathophysiology of a number of bone disorders. [23,24] Both osteoblasts and adipocytes are derived from a common mesenchymal stem cell progenitor and increased adipogenesis may occur at the expense of osteogenesis. [16] In support of this argument is evidence that osteoporosis is associated with an increased prevalence of fat within the bone marrow, [25] although it is not clear whether this is the cause of bone loss or if fat subsequently fills the medullary spaces once bone is already lost. [26] Additionally, obesity typically occurs, at least in part, as a result of a sedentary lifestyle, [27] whereas adaptation to physical activity induced loading increases bone mass and function, [28,29] whilst subsequently reducing adiposity and positively influencing adipose structure and regulation. [30] It appears paradoxical, therefore, to assume that the positive relationship between adiposity and bone mass reported in the general population [11] would also be evident in overweight or obese populations.

The available evidence indicates that adipose tissue mass may exert a “dual” effect on BMD, with both high and low adipose content causing adverse skeletal effects. [31] Both over and underweight states are associated with increased fracture incidence at various sites, [32] suggesting that the relationship between adiposity and bone is biphasic, whereby optimal adiposity exerts a beneficial adaptive effect on bone whilst higher or lower levels are detrimental. Knowledge of the effects of an underweight state on bone health is more developed than the effects of an overweight/obese state. [33] Therefore, the aim of this systematic review and meta-analysis was to quantify the correlation between absolute and relative adipose tissue mass and bone mineral density in over-weight and obese populations and to consider the influence of modifying covariates, including sex, age and BMI category on these correlations.

METHODS

Study Eligibility:

The protocol for this study was designed in accordance with PRISMA guidelines [34] and was prospectively registered in an international register of systematic reviews (PROSPERO, registration number CRD42015024313). Consideration of PICOS (Population; Intervention; Comparator, Outcomes and Study Design) guided the determination of the inclusion and exclusion criteria for this review (see Table 1). The ***population*** was restricted to those who were overweight or obese. This was determined through the selection criteria of the assessed articles. Where appropriate, population specific criteria for overweight or obesity were used, *e.g.* WHO criteria were considered to underestimate obesity prevalence in Chinese adults, [35] and revised criteria were proposed by the Working Group on Obesity in China (WGOC) based on meta-analyses of associations between BMI and cardiovascular disease risk factors and events. [36,37] Chinese criteria for overweight are a BMI between 23.0 and 27.9, and for obesity is > 28.0. In addition, data from paediatric populations were included if the study inclusion criteria classified overweight or obesity based on validated age-specific criteria. If the stated inclusion/exclusion criteria from each study did not confirm that the population were overweight or obese, data were included if the sample mean BMI minus one standard deviation was ≥ 25 $kg \cdot m^{-2}$, indicating that ~ 84% of the sample were overweight according to WHO criteria and assuming that the data were parametrically distributed. Men and women of any age were considered for inclusion within the review. Individuals suffering from medical conditions or taking medications that may be related to the development of secondary osteoporosis, *e.g.*, thyroid dysfunction; hypogonadism; genetic abnormalities (*e.g.*, osteoporosis imperfecta) or physical disabilities were excluded from the study. In addition, athletic populations were also excluded, as regular training may result in a state of overweight or obesity due to high muscularity rather than adiposity. No ***intervention*** or ***comparators*** were identified for this study; however, only studies that reported a correlation between adipose mass and BMD were considered for inclusion. ***Outcome*** measures included a measure of adipose mass (absolute or relative) Absolute adipose mass was defined as the total amount of adipose tissue (kg), while relative adipose mass was defined as the % of adipose tissue relative to total body mass. Adipose mass assessed using dual energy X-ray absorptiometry (DXA) was considered as the primary outcome measure of interest, as DXA has been described as a criterion method for body composition assessment. [38] Indirect methods of body composition assessment (*e.g.,* skinfold assessment) were also considered for inclusion, provided they used validated techniques. Studies were also required to provide data describing BMD of the total body; total hip, femoral neck or lumbar spine assessed by DXA ($g\cdot cm^{-2}$). Only original human studies published in the English language between 1980 and 2016 were considered. The reference lists of the identified review articles were screened for relevant original studies but these reviews were not included. Intervention studies were considered only if the pre-intervention information provided adhered to the inclusion/exclusion criteria outlined above.

Search Strategy:

An electronic search of the literature was independently undertaken by two members of the review team (ED and PAS) from three databases (Medline, Embase and ScienceDirect) using a 3-stage screening process, *i.e.*, 1) Title/Abstract; 2) Full-text screen; 3) Full-text appraisal. The key words "Bone" OR "BMD" within the title were concatenated with "Body Composition" OR "Fat" OR "Lean" OR "Muscle" OR "Fat-Free" OR "Adipose" within the title, abstract or keywords. Results were limited as described within the inclusion/exclusion criteria outlined above and in accordance with the filter options provided within each database. In addition, reference lists of relevant original and review articles were screened in attempts to obtain all relevant studies. The search was completed in July 2016.

Assessment of Methodological Quality and Data Extraction:

Included studies were assessed for methodological validity and data were extracted by two independent reviewers (ED and PAS or JOR) using a pre-piloted template based on the McMaster University critical review form for quantitative studies and adapted for specific use in this review. This tool was selected based on its relevance for all quantitative studies, as opposed to other widely used tools (*e.g.*, CONSORT) that are primarily applicable to randomised controlled trials and of limited relevance for this particular review, which mainly used cross-sectional investigations. Data were extracted regarding study design, participant characteristics (sample size, sex, ethnicity, age and BMI), selection procedures and outcome measures (equipment used, total body, lumbar spine and total hip and femoral neck BMD and adipose mass), along with data analysis and reporting procedures. The primary analysis variable was the bivariate correlation coefficient between adipose mass and BMD (total body, lumbar spine, total hip and femoral neck), although multi-variate coefficients were considered if they controlled for non-lifestyle associated non-modifiable factors (*e.g.*, sex). The two adipose measures included were absolute adipose mass (kg) and relative adipose mass (%BM), thus allowing for a total of 8 correlation coefficients to be extracted. Secondary analyses examined the moderating effect of three subgroups *i.e.* sex, age, and BMI category (overweight and obese). Age categories were included based on a strong body of evidence indicating that physiological stage of development substantially contributes to variation in BMD. [39,40] Three age categories were included within the multi-level model, *i.e.,* <25; 25 – 55 and >55 years. These classifications were selected in order to represent the three main phases of the bone's lifecycle, *i.e.*, development, maintenance and decline. [41] Age categories were assigned based on the mean age reported. Participants were assigned to the obese group if the reported BMI minus one standard deviation was ≥30 $kg \cdot m^{-2}$. In addition, results were considered in relation to sex categories, as evidence indicates that sexual dimorphism may impact the results attained. [42]

Data Synthesis:

Correlation coefficients were converted to Fisher's z scale using the transformation $z = 0.5 \times \ln\left(\frac{1+r}{1-r}\right)$, where r is the correlation coefficient. The variance of z was approximated from $V_z = \frac{1}{n - 3}$, where n was the sample size used to calculate the correlation coefficient. All meta-analyses and meta-regressions were estimated using a three level mixed effects model to account for dependencies within the data as a result of 11 of the 16 included studies reporting correlation coefficients for more than one site. The basic model consisted of three regression equations, one for each level: [43]

$$z_{jk} = \beta_{jk} + \epsilon_{jk} \text{ with } \epsilon_{jk} \sim N\left(0, \sigma^2_{\epsilon jk}\right) \text{ (level1: sample)}$$

The equation at the first level states that z_{jk} the j -th observed transformed correlation from study k is equal to the corresponding population value β_{jk} plus a random deviation, ϵ_{jk}, that is normally distributed with mean zero and variance obtained as described above. The second level equation represents the outcome level and states that the population effects for the different outcomes within a study can be decomposed into a study mean (θ_{0k}) and random residuals v_{jk}.

$$\beta_{jk} = \theta_{0k} + v_{jk} \text{ with } v_{jk} \sim N(0, \sigma_v^2) \text{ (level2: outcome)}$$

The third level is an extension of the common random effects model and states that mean study effects θ_{0k} can vary around an overall mean γ_{00} with the random variation μ_{0k}:

$$\theta_{0k} = \gamma_{00} + \mu_{0k} \text{ with } \mu_{0k} \sim N(0, \sigma_\mu^2) \quad \text{(level 3: study)}$$

The between study variance in the transformed correlations, σ_μ^2, reflects the covariance between measures from the same study. Once summary effects and confidence limits were obtained using Fisher's z metric, values were then converted back to correlations using the transformation $r = \frac{e^{2z} - 1}{e^{2z} + 1}$. Models were extended by incorporating fixed effects in an attempt to further explain the variation in the transformed correlations. The fixed effects assessed included sex, age and BMI classification. All data were analysed using the rma and rma.mv functions in the metafor package [44] in R (R Foundation for Statistical Computing, Vienna Austria). Results were interpreted according to the statistical probabilities of rejecting the null hypothesis and in the following categories: $p > 0.1$: No evidence against H_0; $0.05 < p < 0.1$ Weak evidence against H_0; $0.01 < p < 0.05$: Some evidence against H_0; $0.001 < p < 0.01$: Strong evidence against H_0: $< p < 0.001$ Very strong evidence against H_0.

RESULTS

Search Strategy and Included Study Characteristics:

Sixteen studies, including 2587 participants and 75 correlation coefficients, were included in the meta-analysis. [45–60] A total of 6,631 articles were initially sourced through the database search and the subsequent 3-stage screening process resulted in a total of 15 articles selected for inclusion within the meta-analysis (Figure 1). A secondary screen of the reference lists from relevant original and review articles (n = 32) was also conducted using the same screening process and resulted in the inclusion of one additional article within the review, resulting in 16 articles in total. One article was excluded at the critical appraisal stage, as this study contained the same data set as previously reported within a study already included at an earlier stage. [61] Study characteristics and extracted data from all included articles are reported in Tables 2 and 3. The sample included within this meta-analysis included 1,411 females and 1,176 males, and came from a range of age groups, *i.e.* < 25 years: n = 713; [49,50,53,54,58,60] 25 – 55 years: n = 618; [45,47,48,51,56,57] >55 years: n = 1256. [46,52,55,59]

Primary Analysis:

Results from the meta-analysis showed opposing relationships when BMD was considered in relation to absolute and relative adipose mass, with absolute adipose mass positively, and relative adipose mass negatively correlated with BMD (Tables 4 & 5). Very strong evidence supporting the positive correlation between BMD and absolute adipose mass was obtained at all BMD sites (R = 0.22 to 0.27; p < 0.001 to p = 0.006), whereas no evidence or weak evidence of negative relationships were obtained for BMD and relative adipose mass (R = -0.2 to -0.08; p = 0.058 to 0.424). Comparison between effect sizes estimated across BMD sites demonstrated homogeneity for both absolute and relative adipose mass, with no evidence of differences obtained (p > 0.453 and p > 0.238 respectively). As a result, data across BMD sites were pooled when considering the moderating effects of the subgroup categories.

Secondary Analysis (Sex):

Very strong evidence of a positive correlation between absolute adipose mass and BMD was obtained in women (R = 0.37, 95%CI: 0.26, 0.47). In contrast only weak evidence of a positive correlation between absolute adipose mass and BMD was obtained in men (R = 0.11, 95% CI: -0.02, 0.23). Evidence showing a difference in correlations of BMD and absolute adipose mass between men and women was strong (p < 0.001). Strong evidence of a moderating effect of sex was also identified for the relationship between relative adipose mass and BMD (p = 0.0108). Relative adipose mass was negatively correlated with BMD in men (r = - 0.37; 95%CI: -0.57, - 0.12), while no evidence of a relationship was obtained for women (R = 0.03; 95%CI: -0.19, 0.25).

Secondary Analysis (Age):

Correlations between BMD and absolute adipose mass (kg) was positive for all three age categories (<25, 25 – 55, >55). Correlations did not differ between the groups (p = > 0.737), however evidence supporting a positive relationship was restricted to the age categories <25 (p = 0.010) and 25 – 55 years (p = 0.010) (Table 4). In contrast, correlations between BMD and relative adipose mass were shown to be negative for age categories < 25 and > 55, and positive for age category 25 – 55 years (Table 5). However strong evidence against the null hypothesis was obtained for the negative relationship estimated for the youngest group only (R = -0.28; 95%CI: -0.45, -0.08).

Secondary Analysis (BMI Class):

There was very strong evidence of a positive correlation between absolute adipose mass and BMD in both the overweight and obese subgroups (p < 0.001; Table 4). In addition, no evidence was obtained for a difference in the magnitude of the effect size for each group (p = 0.124). In contrast, evidence of a relationship between relative adipose mass and BMD was obtained for the obese group only (R = -0.20; 95%CI: -0.38, -0.01; Table 5).

Combined Analyses:

As sex and age exerted the primary moderating effects on the correlations reported, combined analyses were conducted to identify if the effects of these variables existed independently of each other. No evidence of interaction effects between the factors was obtained for absolute adipose or relative adipose mass (p = 0.611 and p = 0.741 respectively). When considering the correlation between absolute adipose mass (kg) and BMD, no evidence of a moderating effect of age was obtained after controlling for the effect of sex (p = 0.223), whereas very strong evidence of a moderating effect of sex was obtained after controlling for the effects of age (p < 0.001). Conversely, when considering the correlation between relative adipose mass and BMD, some evidence of a moderating effect of both age and sex remained after controlling for the influence of the other (p < 0.05).

Additional Study Information:

Information related to factors which may act as potential sources of bias are presented as supplementary data in Table S1. All included studies reported simple bivariate correlations between adipose and bone mass, apart from 2 studies, one of which controlled for the linear effects of age, [47] the other which controlled for age and pubertal status. [53] A sensitivity analysis was conducted excluding the data from these two studies and the results obtained made no substantive changes to the model results or interpretation. Fourteen of the 16 studies included within this review assessed adiposity using DXA derived outcome measures (88%). One study assessed relative adiposity using skinfold assessment of subcutaneous adipose tissue, followed by conversion to %BM, [47] while another estimated adiposity from DXA software (GE encore software V.11.10), which predicted adiposity based on lumbar spine and femur DXA images. [52] In order to identify if the inclusion of these studies, which employed different, and potentially less reliable means of assessing body composition, had any impact on the study findings, an additional sensitivity analysis was conducted following the exclusion of these 2 studies. Once again, the results obtained did not make any meaningful changes to the models reported or to the interpretation of results. Participation in physical activity (PA) is known to impact BMD, and may actually alter the relationship between adiposity and bone in certain populations. [62] The majority of studies either excluded participants based upon regular PA participation, or confirmed that BMD was not influenced by PA level, although some did not confirm the PA status of the sample. [48,49,51–53] Selective outcome reporting represents another source of potential bias. One study only reported correlations that were statistically significant. [49] In addition, many of the studies reported correlations between BMD and either absolute or relative adipose mass, but not both (Table 3).

DISCUSSION:

The primary finding of this meta-analysis, was that adipose mass showed an opposing correlation with BMD, which depended on whether adiposity was expressed as an absolute or relative entity. Absolute adipose mass was positively correlated; and relative adipose mass negatively correlated with BMD. Secondary analyses indicated that various factors exerted a moderating influence on these findings, with sex and age predominantly impacting the reported correlations. The relationship between adipose mass and BMD has been the subject of a number of narrative reviews in recent years, [17–19,63] and conflicting findings related to the influence of obesity on bone mass have been reported. [64,65] This is the first study to employ a meta-analytic approach to the quantification of the relationship between adipose tissue and bone mass in overweight and obese populations, allowing many of the limitations of narrative syntheses and single studies to be overcome, and providing a quantitative answer to this contentious question.

Evidence of a positive relationship between absolute adipose mass and BMD was obtained, with this evidence being strongest for women (R = 0.37; 95%CI: 0.26, 0.47). There are a number of potential mechanisms that might explain this finding. In particular, the effect of increased loading caused by the influence of excess adiposity on absolute body mass, or an up-regulation of specific adipokines may exert a beneficial impact on BMD in this population. [6] An alternative explanation might, however, relate to the effect of adipose mass co-linearity with other variables known to exert a positive influence on bone mass (*i.e.*, lean mass and absolute body mass). Positive relationships between adipose tissue and bone mass have been shown to be inverted once absolute body mass was included as a covariate in the model, [66–68] which has been interpreted as illustrating a negative effect of adipose mass *per se*. This interpretation is statistically flawed however, since adipose mass is a major component of absolute body mass, which is positively related to BMD. [69] Further research is required to identify the statistical factors and biological mechanisms underpinning the positive relationships reported between these compartments of body composition. Our results are similar in both direction and magnitude to those previously reported for the general population however, [11] and show that previously reported correlations are not altered in overweight or obese groups.

In contrast to the positive correlation reported between absolute adipose mass and BMD, was the negative correlation reported between relative adipose mass and BMD, with the strongest evidence of this relationship obtained for men and those aged <25 years (Table 5). This shows that excess adiposity exerts a negative influence on bone, but only when accompanied by reduced lean mass and a higher relative proportion of adipose tissue. The primary mediator in the differentiation between adipose and lean mass is physical activity, making it likely that those with a higher level of adiposity and lower lean mass will experience less activity related mechanical loading, which will have negative consequences for BMD. Contrasting results have previously been reported regarding the correlation between relative adiposity and BMD. [61,70,71] It has however been shown that relative adipose mass assumes a negative relationship with BMD between 33 – 38% body fat. [63] Taken collectively, these results indicate a parabolic and bi-phasic relationship between relative adiposity and BMD, with higher relative adiposity levels exerting a negative influence on BMD. Subgroup analyses within the current study showed that this correlation was larger and had a stronger probability of rejecting H_o in the obese (R = -0.20, 95%CI: -0.38, -0.01) compared to the overweight (-0.08. 95%CI: -0.27, 0.11) groups, indicating that the negative impact of relative adiposity on BMD is increased as adiposity increased from overweight to obese levels. These findings support the concept of "*osteosarcopenic obesity*", which is a deterioration of muscle and bone in the presence of, or as a result of excess adiposity. [16] The terms sarcopenia, and osteosarcopenia are associated with age related declines in muscle and bone. [72] The results of the current meta-analysis indicate that the relationship between these three compartments may follow similar patterns at other phases of the life-cycle, *i.e.,* that an increase in adipose mass in overweight or obese populations exerts a negative influence on bone, but only if accompanied by a relative reduction in lean mass, which is particularly apparent in men and in those aged <25 years.

In order to consider the effect of modifying covariates on study findings, sex and age categories were included within the multi-level model. The primary outcome from these analyses was that sex emerged as the primary moderator of the reported correlations. In particular, men were more susceptible to the negative influence of increased relative adipose mass than were women (Table 5). The most likely explanation for this is the influence of female sex hormones, such as estrogen; which is a key systemic regulator of bone homeostasis [73] and is present in greater concentrations in women compared with men. It is plausible that the more positive influence of adiposity on BMD in women compared with men is mediated through estrogen, given that adipose tissue is a key source of aromatase, which contributes to estrogen synthesis from androgen precursors. [74] The finding that men are more susceptible to the negative influence of increased relative adiposity is particularly relevant when considered within the context of the ever-increasing prevalence of male osteoporosis, [5] and highlights the importance of considering sex-specific prevention and treatment options for both obesity and osteoporosis.

No effect of age categorisation was reported when considering the correlation between absolute adipose mass and BMD, but a parabolic element was evident in the relationship between relative adiposity and bone. Negative correlations between bone and relative adiposity were reported in the groups aged < 25 and > 55 years, while weak evidence of a positive correlation was reported in the bone maintenance group (25 – 55 years). These findings suggest that the negative influence of increased relative adiposity is most relevant when bone metabolism is in a state of flux, as evidenced by the negative relationships reported in the bone growth and decline periods. Evidence supporting this negative correlation was strongest in the youngest age category (R = -0.28, 95%CI: -0.45, -0.08). These findings are particularly relevant given that childhood obesity is increasing at an alarming rate, and has been described by the WHO as one of the most serious public health challenges of the 21st century. Interventions designed to reduce childhood obesity, while concurrently protecting bone health, are of paramount importance.

A number of factors should be considered when interpreting the results of this meta-analysis, and their influence accounted for within the design of future studies on this topic. Outcome reporting bias is particularly relevant, as a large number of high-quality studies on the topic area could not be included as they did not meet the specific inclusion criteria of this review. Consideration of such studies may add further insight into the complex relationship between excess adiposity and bone, and the myriad of nutritional, mechanical and metabolic factors that may mediate this relationship. For example, the regional distribution of adipose tissue has been reported to influence BMD, with visceral adiposity showing negative associations with BMD in both general and overweight populations. [75] In addition, bone type (cortical vs trabecular) may also be differentially affected, [76] while factors such as menopausal state and activity level are also likely to exert an influence on the relationship between adipose tissue and bone mass. BMD was used as a primary outcome measure within the current study, due to its clinical relevance, but BMD only accounts for approximately 65% of bone strength, and other factors, including bone geometry and micro-architecture would provide additional insight into bone strength or fragility. Although DXA is a widely used laboratory based measure of body composition assessment, and has been described as a criterion method, [38] it has limitations, including inter and intra-machine and software variation. [77] Its validity may also be reduced in obese individuals, who are often toward the upper end of reference ranges, and may also have practical difficulty in fitting within the scan area.[38] Research into optimal techniques for assessment of body composition is ongoing, and more advanced assessment and imaging techniques, *e.g.,* multi-component modelling, CT and MRI, [78] may provide further insight into the relationships between these compartments of body composition. Currently issues related to availability, radiation exposure and the practicalities of fitting large individuals within scanning machines may preclude the wide-spread use of these technologies, although they do represent an exciting area of on-going research.

Practical Implications:

Our results indicate that increasing adipose mass in overweight or obese populations is negatively correlated with bone mass, but only when accompanied by a relative reduction in lean mass. These findings highlight the importance of optimising the relative proportion between adipose and lean mass, over weight loss *per se*, when considering obesity related interventions that will also protect bone health. We therefore recommend that obesity prevention and management programmes focus on a controlled adipose loss with concomitant preservation of lean muscle mass. A number of strategies have been proposed that may facilitate this. Recently, exercise induced weight loss was reported to induce similar body mass losses to caloric restriction, or a combination between exercise and caloric restriction, but to prevent attenuations in muscle mass. [79] The mechanical loading provided by exercise has long been reported to be osteogenic [28], and we therefore suggest that obesity management programmes should include physical activity components, the exact attributes of which should be determined in relation to the specific requirements of the individual. Energy deficit is required in order to allow oxidation of adipose stores; however a negative energy balance has also been reported to negatively impact bone metabolism. [80] The consumption of a high-protein diet has been suggested to preserve lean mass during times of energy deficiency, [81] provided it is accompanied by an adequate intake of calcium, thereby exerting an indirect and positive impact on bone. In support of this is evidence of a preservation of lean mass and a more positive bone metabolic profile (PINP:CTX ratio) in a group of overweight individuals who were fed a hypocaloric diet comprising high protein and high dairy, during a period of exercise and diet induced weight loss. [82] Dietary strategies should also emphasise nutrient dense food sources, *e.g.*, unprocessed fruits and vegetables, to ensure that micronutrient and phytochemical intakes are adequate.

SUMMARY AND CONCLUSION:

This meta-analysis demonstrates opposing relationships between adiposity and BMD, with absolute adipose mass demonstrating a positive correlation, and relative adipose mass a negative correlation with BMD. Sex and age exerted moderating influences on these correlations, with men and individuals aged <25 years being more susceptible to the negative influence of increasing levels of relative adipose tissue. The results of this meta-analysis should be considered when devising nutritional and training strategies to protect bone while treating obesity and support the importance of maintaining lean mass and reducing the relative proportion of adipose mass, rather than emphasising weight loss *per se*.

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Conflict of Interest:

The authors declare no conflict of interest.

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Table 1: PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion	Exclusion
Population	Overweight or obese participants, including both sexes and all age-groups.	Populations suffering medical conditions, or taking medications related to the development of secondary osteoporosis. Physically disabled populations. Athletes.
Intervention	This review was not based on the evaluation of any specific intervention, but only considered studies which evaluated the correlation between adiposity and bone in overweight or obese groups.	
Comparator	No comparators were identified for this study.	
Outcomes	The correlation (R) between adiposity (expressed as total mass (kg), or relative to total body mass (%BM)) and BMD of the total body, lumbar spine, total femur or femoral neck ($g \cdot cm^{-2}$)	Results from studies which report multi-variate correlations, and did not isolate the correlation between adipose mass and BMD.
Study Design	All study designs were considered for inclusion in this review, provided they adhered to the criteria described above. Cross-sectional designs were considered most likely to contain the required information.	

681 **Table 2:** Characteristics of Included Studies

Author	Participants	N	Gender	Age (Yrs)	BMI ($kg\cdot m^{-2}$)	Adipose Mass (kg)	Adipose Mass (%BM)	Total Body BMD ($g\cdot cm^{-2}$)	Lumbar Spine BMD ($g\cdot cm^{-2}$)	Total Hip BMD ($g\cdot cm^{-2}$)	Femoral Neck BMD ($g\cdot cm^{-2}$)
Abou Samra et al. (2005)* [45]	Obese premenopausal women	48	Female	30.8 ± 10.0	30 – 50.9	28 – 66.1	-	0.97 ± 0.06	1.08 ± 0.1	0.99 ± 0.14	0.88 ± 0.13
Aguirre et al. (2014)* [46]	Elderly, obese, frail	173	Male (81, female 92)	69.5 ± 4.2	36.5 ± 5	41.82 ± 9.53	42.04 ± 6.78	1.224 ± 0.17	1.138 ± 0.189	0.989 ± 0.138	0.826 ± 0.117
Ballard et al. (2010) [47]	Healthy immigrant Hispanic women	84	Female	47.9 ± 7	31.8 ± 6.1	26 ± 7.6	34.7 ± 4.3	-	L2 – 4 0.955 ± 0.11	0.998 ± 0.13	0.843 ± 0.12
Boyanov et al. (2014) [48]	Bulgarian women	180	Female	50.8 ± 9.7	32.7 ± 4.5	36.6 ± 13.0	42.3 ± 6.2	-	L1 – 4 0.954 ± 0.174	-	-
Campos et al. (2012) [49]	Postpubertal obese adolescents	45	Male	16.04 ± 1.87	36.26 ± 4.40	43.1 ± 10.8	40.31 ± 6.41	1.24 ± 0.14	1.06 ± 0.17	0.92 – 1.01	-
Do Prado et al. (2009) [50]	Obese adolescents	41	Male	17.07 ± 1.61	36.03 ± 3.75	39.36 ± 10.35	37.01 ± 7.32	1.17 ± 0.14	-	-	-
Do Prado et al. (2009) [50]	Obese adolescents	68	Female	16.7 ± 1.67	35.09 ± 4.06	40.74 ± 8.83	44.71 ± 5.14	1.14 ± 0.08	-	-	-
Gomez et al. (2009) [51]	Morbidly obese women pre bariatric surgery	25	Female	48 ± 7.6	44.5 ± 3.6	50.2 ± 6.7	45.8 ± 3.6	1.18 ± 0.1	-	-	-
Hawamdeh et al. (2014) [52]	Postmenopausal women	584	Female	63.96 ± 6.71	30.42 ± 4.83	36.14 ± 8.66*	-	-	L1 – 4 0.956 ± 0.161	-	0.784 ± 0.127

Ivuskans et al. (2013) [53]	Overweight boys	110	Male	11.96 ± 0.76	23.1 ± 4.6	19.02 ± 9.57	33.9 ± 7.9	1.007 ± 0.066	L2 – 4 0.839 ± 0.092	-	0.904 ± 0.095
Junior et al. (2013) [54]	Obese children and adolescents	175	Male (83) and female (92)	11.1 ± 2.6	-	-	45.4 ± 5.2	1.044 ± 0.12	-	-	-
Kang et al. (2014) [55]	Overweight Chinese men	225	Male	61.4 ± 16.2	25.9 ± 1.2	20.7 ± 4.2	29.8 ± 5.2	1.173 ± 0.092	L1 – 4 1.115 ± 0.168	1.006 ± 0.131	0.934 ± 0.131
Kang et al. (2014) [55]	Obese Chinese men	140	Male	61.2 ± 14.5	30.1 ± 1.7	27.2 ± 4.8	34.1 ± 4.8	1.198 ± 0.099	L1 – 4 1.119 ± 0.151	1.029 ± 0.121	0.946 ± 0.118
Liu et al. (2014) [56]	African American women with MetS	47	Female	48.8 ± 5.6	34.7 ± 5.5	42.8 ± 13	45.6 ± 5.7	1.295 ± 0.118	L2 – 4 1.231 ± 0.149	1.149 ± 0.147	-
Morberg et al. (2003) [57]	Men with juvenile obesity	234	Male	47.5 ± 5.1	35.9 ± 5.9	38.4 ± 12.2	33.13 ± 6.3	1.32 ± 0.1	-	-	-
Mosca et al. (2014)* [58]	Overweight adolescents	135	Female	13.84 ± 2.34	28.3 ± 5.01	26.03 ± 7.53	36.36 ± 4.63	0.979 ± 0.1	L1 – 4 0.959 ± 0.18	0.969 ± 0.14	-
Mosca et al. (2014)* [58]	Overweight adolescents	84	Male	13.82 ± 1.92	27.6 ± 4.14	23.27 ± 7.1	31.09 ± 6.43	0.946 ± 0.11	L1 – 4 0.827 ± 0.15	0.988 ± 0.16	-
Moseley et al. (2011) [59]	Middle aged men and women with T2 diabetes	56	Female	55.6 ± 6.2	34.4 ± 5	41.9 ± 10.7	44.8 ± 5.4	1.28 ± 0.11	L1 – 4 1.29 ± 0.17	1.12 ± 0.15	1.04 ± 0.15
Moseley et al. (2011) [59]	Middle aged men and women with T2 diabetes	78	Male	56.9 ± 5.9	32.6 ± 4.1	34.7 ± 8.2	33.6 ± 5.1	1.31 ± 0.12	L1 – 4 1.32 ± 0.20	1.16 ± 0.15	1.08 ± 0.162
Remmel et al.	Overweight	55	Male	14.0 ±	26.8 ± 4.5	25.8 ± 12.3	-	1.12 ± 0.10	1.04 ± 0.15		

(2015) [60]	and obese Estonian schoolboys.	0.8

All data is presented as mean ± SD, or as range (maximum – minimum), * represents studies for whom the descriptive data corresponding to the extracted correlation coefficient was not available, and subgroup statistics were subsequently combined to report representative means and standard deviations for the relevant group. BM: Body Mass, BMD: Bone Mineral Density, MetS: Metabolic Syndrome, T2: Type 2.

Table 3: Summary of Correlation Coefficients

Author (date)	N	Total Body BMD VS AAM	Total Body BMD VS RAM	Lumbar Spine BMD VS AAM	Lumbar Spine BMD VS RAM	Total Femur BMD VS AAM	Total Femur BMD VS RAM	Femoral Neck BMD VS AAM	Femoral Neck BMD VS RAM
Abou Samra et al. (2004) [45]	48	0.27	X	0.17	X	0.44	X	0.45	X
Aguirre et al. (2014) [46]	173	X	-0.29	X	-0.29	X	-0.4	X	-0.22
Ballard et al. (2010) [47]	84	X	X	0.32	0.17	0.58	0.43	X	X
Boyanov et al. (2014) [48]	180	X	X	0.425	0.325	X	X	X	X
Campos et al. (2012) [49]	45	0.34	X	X	X	-0.4	X	X	X
Do Prado et al. (2009) [50]	41	-0.392	-0.531	X	X	X	X	X	X
Do Prado et al. (2009) [50]	68	0.146	-0.031	X	X	X	X	X	X
Gomez et al. (2009) [51]	25	-0.193	-0.471	X	X	X	X	X	X
Hawamdeh et al. (2014) [52]	466	X	X	0.28	X	X	X	0.32	X
Hawamdeh et al. (2014) [52]	118	X	X	0.2	X	X	X	0.28	X
Ivuskans et al. (2013) [53]	110	0.615	X	0.455	X	X	X	0.322	X
Junior et al. (2013) [54]	175	X	0.09	X	X	X	X	X	X
Kang et al. (2014) [55]	225	0.069	-0.098	0.058	-0.001	-0.004	-0.12	0.023	-0.122
Kang et al. (2014) [55]	140	0.115	-0.203	0.293	0.108	0.046	-0.22	-0.004	-0.305
Liu et al. (2014) [56]	47	0.343	0.12	0.252	0.127	0.24	-0.041	X	X
Morberg et al. (2003) [57]	234	0.003	X	X	X	X	X	X	X
Mosca et al. (2014) [58]	135	0.496	0.131	0.582	-0.4	0.535	-0.438	X	X
Mosca et al. (2014) [58]	84	-0.128	-0.58	0.084	-0.4	0.022	-0.438	X	X
Moseley et al. (2011) [59]	56	0.57	X	0.2	X	0.44	X	0.41	X
Moseley et al. (2011) [59]	78	0.27	X	0.03	X	0.19	X	0.11	X
Remmel et al. (2015) [60]	55	0.255	X	-0.002	X	X	X	X	X

AAM: Absolute adipose mass; RAM: Relative adipose mass

Table 4: Results of Meta-regressions for Absolute Adipose Mass. Parameter Estimates and Model Outputs.

Moderator		Correlation Estimate	95% CI	Between outcome variance σ_v^2 (% of total variance)	Between study variance σ_u^2 (% of total variance)	QE_{df}
BMD Site	Total Body	0.26*	0.13 - 0.38	0.009 (13.7%)	0.043 (65.2%)	241.3_{42}
	Lumbar Spine	0.23*	0.10 - 0.35			
	Total Femur	0.27*	0.12 - 0.40			
	Femoral Neck	0.22*	0.06 - 0.36			
Age	<25	0.25*	0.06 - 0.43	0.008 (10.8%)	0.049 (69.6%)	220.1_{43}
	25 – 55	0.26*	0.07 - 0.44			
	>55	0.21	-0.04 - 0.44			
BMI Class	Overweight	0.26*	0.13 - 0.38	0.009 (13.5%)	0.042 (65.4%)	228.1_{42}
	Obese	0.25*	0.11 - 0.38			
Gender	Men	0.11	-0.02 - 0.23	0.003 (5.3%)	0.033 (67.1%)	158.4_{44}
	Women	0.37*	0.26 - 0.47			

* $P< 0.05$. †. QE_{df}: Residual heterogeneity test statistic.

Table 5: Results of Meta-regressions for Relative Adipose Mass. Parameter Estimates and Model Outputs.

Moderator		Correlation Estimate	95% CI	Between outcome variance σ_v^2 (% of total variance)	Between study variance σ_u^2 (% of total variance)	QE_{df}
Site	Total Body	-0.13	-0.32, 0.07	0.027 (27.2%)	0.060 (60.7%)	203.8_{25}
	Lumbar Spine	-0.08	-0.28, 0.12			
	Total Femur	-0.20	-0.39, 0.01			
	Femoral Neck	-0.19	-0.44, 0.09			
Age	<25	-0.28*	-0.45, -0.08	0.024 (35.9%)	0.0315 (46.5%)	140.9_{26}
	25 – 55	0.12	-0.11, 0.34			
	>55	-0.21	-0.44, 0.06			
BMI Class	Overweight	-0.08	-0.27, 0.11	0.024 (25.0%)	0.060 (62.5%)	209.9_{27}
	Obese	-0.20*	-0.38, -0.01			
Gender	Men	-0.37*	-0.57, -0.12	0.023 (25.5%)	0.055 (61.3%)	166.3_{22}
	Women	0.03	-0.19, 0.25			

* *P*< 0.05. †. QE_{df}: Residual heterogeneity test statistic

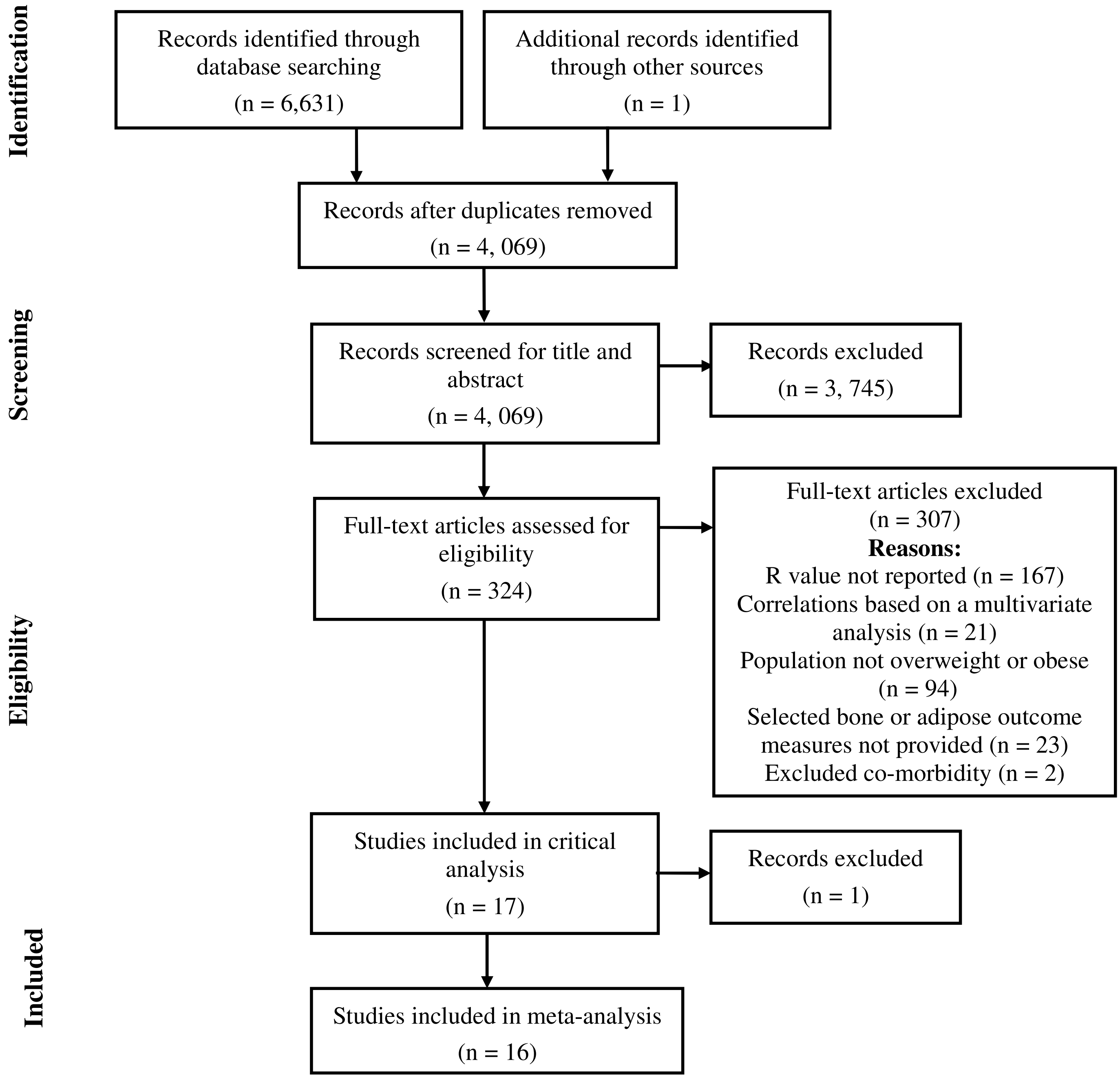

Figure One: Search strategy summary

Text S1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6

Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and	8-10

Section/topic	#	Checklist item	Reported on page #
		confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Table S1: Additional Study Information

Author (date)	Research Question	Study Design	Screening procedures [(a)]	BMD assessment	Adipose assessment	Complete results reported? [(b)]	BMI range	Physical Activity Information	Covariates included.
Abou Samra et al. (2005) [S1]	To investigate the effect of obesity versus the leptin/insulin axis on bone metabolism in insulin resistant and sensitive women.	Cross-sectional	Yes	Hologic 4500A.	DXA	Correlations were reported for absolute adipose mass (kg) but not relative (%BM)	30 – 50.9	Exclusion criteria included participation in strenuous physical activity.	None
Aguirre et al. (2014) [S2]	To determine the influence of body fat and circulating adipokines on BMD in elderly obese frail participants.	Cross-sectional	Yes	Hologic Delphi 4500/w	DXA	Correlations were reported for relative adipose mass (%BM), but not absolute (kg)	Not reported	Inclusion criteria included sedentary lifestyle, defined as not participating in regular exercise more than 2 times per week.	None
Ballard et al. (2010) [S3]	To examine the effects of body composition, behavioural and health history factors on BMD in immigrant Hispanic women.	Cross-sectional	Yes	Hologic Discovery C.	Skinfold thickness of the triceps, suprailiac and thigh converted to body density and fat using the Siri, and Jackson & Pollock equations.	Correlations were reported for total femur BMD but not femoral neck.	Not reported	Assessed by PA questionnaire, descriptives not reported. BMD was not different across PA tertiles.	Correlations corrected for linear effect of age.
Boyanov et al. (2014) [S4]	To test the relative contribution of adipose and lean mass to BMD variability in Bulgarian women.	Cross-sectional	Yes	Hologic QDR 4500 A.	DXA	Yes	Not reported	None reported.	None
Campos et al. (2012) [S5]	To test the relationships between visceral and subcutaneous fat with bone metabolism, anti-inflammatory adipokines and gender in obese	Cross-sectional	Yes	Hologic QDR 4200	DXA	Only reported statistically significant findings.	Not reported	None reported	None

	adolescents.								
Do Prado et al. (2009) [S6]	To explore the combined and independent influence of body composition, leptin, insulin, glucose and HOMA-IR to BMD and BMD in Brazilian obese adolescents.	Cross-sectional	Yes	Hologic QDR4200	DXA	Yes	Not reported	Exclusion criteria included participation in strenuous physical exercise.	None
Gomez et al. (2009) [S7]	To test the relationship between bone, body composition and related proteins and hormones in two cohorts of morbid obese patients, before and after bypass surgery.	Cohort study (data reported from pre-bariatric group only)	Yes	Lunar DXA-IQ, version 4.6c	DXA	Yes	Not reported	None reported.	None
Hawamdeh et al. (2014) [S8]	To assess the relative association between body composition, age and BMD in Jordanian women.	Cross-sectional	Yes	GE iDXA	Estimated from lumbar spine and femur DXA images using GE enCore software version 11.10	Correlations were reported for absolute adipose mass (kg) but not relative (%BM).	17.1 – 43.3	None reported	None
Ivuskans et al. (2013) [S9]	To compare BMD in overweight and normal weight children.	Cross-sectional	Health status of the participants not confirmed.	Lunar Corporation DPX-IQ, software version 3.6	DXA	Correlations were reported for absolute adipose mass (kg) but not relative (%BM).	Not reported	None reported.	Yes, adjusted for age and pubertal status.
Junior et al. (2013) [S10]	To analyze the relationship between abdominal adipose tissue and BMD in obese children and adolescents.	Cross-sectional	Yes	GE Lunar DPX-NT	DXA	Correlations were reported for relative adipose mass (%BM) but not absolute (kg).	Not reported	Exclusion criteria included engagement in regular PA.	None
Kang et al. (2014) [S11]	To test the relationship between body composition and BMD by	Cross-sectional	Yes	GE Lunar DXA.	DXA	Yes	Not reported	Assessed by questionnaire but descriptives not	None

	BMI levels in Northern Chinese men.							reported.	
Liu et al. (2014) [S12]	To test the relationships between body composition and muscular strength with BMD in African American women with metabolic syndrome.	Cross-sectional	Yes	GE iDXA.	DXA	Yes	25.1 – 45.1	Exclusion criteria included participation in exercise, diet or weight loss programs.	None
Morberg et al. (2003) [S13]	To explore the relationship between leptin and BMD in healthy obese and non-obese men.	Cross-sectional	Yes	Lunar DXA-IQ.	DXA	Correlations were reported for absolute adipose mass (kg), but not relative (% BM).	23.2 – 56.4	Recorded by retrospective questionnaire and included in regression models, but descriptive not reported.	None
Mosca et al. (2014) [S14]	To determine the effect of excess adipose tissue on bone mass in overweight and obese adolescents.	Cross-sectional	Yes	Hologic QDR 4500 Discovery A.	DXA	Yes	Not reported	Exclusion criteria included regular practice of physical activity.	None
Moseley et al. (2011) [S15]	To investigate the effects of body composition on BMD in middle-aged men and women with uncomplicated noninsulin dependent diabetes mellitus.	Cross-sectional	Yes	GE Lunar Prodigy.	DXA	Correlations were reported for absolute adipose mass (kg), but not relative (%BM).	Not reported	Exclusion criteria included participation in regular physical activity.	None
Remmel et al. (2015) [S16]	To investigate the association between ghrelin, PYY and bone mineral characteristics in overweight and normal-weight boys.	Cross-sectional	Yes	Lunar DPX-IQ DXA..	DXA	Correlations were reported for absolute adipose mass (kg), but not relative (%BM).	Not reported	Total PA (counts/min assessed by ActiGraph GT1M) was not different between over and normal weight boys, and was not correlated with BMD in either group.	None

[a] Response was yes if screening procedures were described in sufficient detail to ensure that the study population met the inclusion/exclusion criteria of the meta-analysis.
[b] Answered yes if all available results from the study were reported.

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S6. Do Prado WL, De Piano A, Lazaretti-Castro M, et al. Relationship between bone mineral density, leptin and insulin concentration in Brazilian obese adolescents. *J Bone Miner Metab*. 2009;27(5):613-619.

S7. Gomez J, Vilarrasa N, Masdevall C, et al. Regulation of bone mineral density in morbidly obese women: A cross-sectional study in two cohorts before and after bypass surgery. *Obes Surg*. 2009;19(3):345-350.

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