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A Systematic Review and Meta-analysis of the Association between Eating Disorders and Bone Density

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Mini Abstract

This meta-analysis investigates the effect of an eating disorder on bone mineral density in two eating disorder subtypes. Following conflicting findings in previous literature, this study finds that not only anorexia nervosa, but also bulimia nervosa has a detrimental effect on BMD. Key predictors of this relationship are discussed.

Supplementary material

Supplemental Table 1: PRISMA 2009 Checklist

Supplemental Figure 1: SMD in Total BMD in the AN Group

Supplemental Figure 2: SMD in Hip BMD in the AN Group

Supplemental Figure 3: SMD in Femoral Neck BMD in the AN Group

Supplemental Figure 4: SMD in Total BMD in the BN Group

Supplemental Figure 5: SMD in Spinal BMD in BN Group. A graph to compare results of BN participants with and without a history of AN

Disclosures

Lauren Robinson, Emma Clark, Madhusmita Misra, Vicki Aldridge, and Nadia Micali declare that they have no conflict of interest

Keywords

Eating Disorder, Anorexia Nervosa, Bulimia Nervosa, Bone, Bone Density, Osteoporosis

Abstract

Purpose: This systematic review and meta-analysis investigates bone mineral density (BMD) in individuals with anorexia nervosa (AN) and bulimia nervosa (BN) in comparison to healthy controls (HCs). AN has been associated with low BMD and a risk of fractures and mixed results have been obtained for the relationship between BN and BMD. Deciphering the effect these two ED subtypes on BMD will determine the effect of low body weight (a characteristic of AN) versus the effects of periods of restrictive eating and malnutrition which are common to both AN and BN.

Methods: We conducted a systematic search through the electronic databases MedLine, EMBASE and PsychInfo and the Cochrane Library to investigate and quantify this relationship. We screened 544 articles and included 27 studies in a random-effects meta-analysis and calculated the standardised mean difference (SMD) in BMD between women with a current diagnosis of AN (n=785) vs HCs (979) and a current diagnosis of BN (n=187) vs HCs (350). The outcome measures investigated were spinal, hip, femoral neck and whole body BMD measured by DXA or DPA scanning. A meta-regression investigated the effect of factors including age, duration since diagnosis, duration of amenorrhea and BMI on BMD.

Results: The mean BMI of participants was 16.65 kg/m² (AN), 21.16 kg/m² (BN) and 22.06 kg/m² (HC). Spine BMD was lowest in AN subjects (SMD, -3.681; 95% CI, -4.738, -2.625; $p<0.0001$), but also lower in BN subjects compared with HCs (SMD, -0.472; 95% CI, -0.688, -0.255; $p<0.0001$). Hip, whole body and femoral neck BMD were reduced to a statistically significant level in AN but not BN groups. The meta-regression was limited by the number of included studies and did not find any significant predictors.

Conclusions: This meta-analysis confirms the association between low BMD and AN and presents a strong argument for assessing BMD not only in patients with AN, but also in patients with BN.

Introduction

Osteoporosis is a condition that weakens bones and makes them prone to fractures. This disease affects almost 3 million in the UK and is typically associated with advancing age (1). Excessive food restriction and malnutrition can lead to secondary osteoporosis and individuals with an eating disorder can present low BMD and osteoporosis at a young age (2, 3). The most studied eating disorders (EDs) in this field are anorexia nervosa (AN) which includes a restricting and binge/ purge subtype and is primarily characterised by excessive food restriction and weight loss, and bulimia nervosa (BN), which is characterised by binge eating and compensatory purging behaviours (4, 5). There has been a recent increase in research to investigate the effect of AN diagnosis on BMD, but there have been no RCTs to date to determine the effect of a BN diagnosis on BMD and the development of osteoporosis in this group.

Anorexia nervosa has been associated with low bone mineral density (BMD), impaired bone structure and an increased risk of bone fractures (6-10). Adolescent AN occurs at a critical time for bone mass acquisition, and limitations in bone accrual at this time can disrupt the attainment of peak bone mass and result in residual bone deficits despite recovery from AN (2, 11, 12). Peak bone mass is typically attained in the middle of the third decade of life and is a major determinant of fracture risk throughout life; individuals with adolescent onset AN have been found to not obtain optimal peak bone mass (13, 14). In contrast, individuals loose bone mass during adulthood may retain the ability to recover without residual bone deficits following complete weight gain, nutritional and menstrual recovery (15).

Fractures are associated with significant pain, disability and loss of work days, and AN patients are 7 times more likely to have bone fractures than age-matched healthy women (16), with an estimated 90% having osteopenia and 40% having osteoporosis at one or more skeletal sites (17). Similar deficits have been reported in sufferers of BN, but studies have been limited by small sample sizes, inconsistent diagnostic criteria and comorbid psychiatric diagnoses of participants (18) which has made it impossible to determine the effect of BN on BMD. The extent to which bone metabolism is affected by malnutrition and weight loss may vary according to anatomical site, and some regions may be more prone to fractures than others (19). Disentangling the causative factors that lead to low bone density in the ED population is a fundamental step towards reducing fractures in this group.

In contrast to AN, women with BN are usually at normal weight and many do not have menstrual abnormalities, and thus studies have suggested that BMD in women with BN is comparable to that in healthy controls (20, 21) and that AN alone is associated with low bone mass (22-24). Others have suggested that although individuals with BN have higher BMD than those with AN, their BMD is lower than in healthy controls (20). Yet others have reported that BN, when coupled with low body weight and secondary amenorrhea, is a strong predictor of fracture risk and osteoporosis (25). A reduced BMD in BN compared to HCs may be associated with amenorrhea (20), low BMI (18) and a previous history of AN, but due to inconsistent methodologies in the available studies the relationship between BN and BMD is unclear.

In girls with AN, bone density measures are reported to be predicted positively by BMI, and inversely by loss of menses and duration of amenorrhea (26). The recovery of menses has been associated with a partial improvement in bone mass following recovery from an ED (27). Oestrogen therapy has been shown to increase BMD in post-menopausal women, in whom the hypo-estrogenic state otherwise results in significant bone loss. For this reason oral contraceptives have been widely used in patients with EDs. However, multiple studies have now shown that oestrogen given orally is not effective in increasing bone density in AN (28, 29). This is likely because of first pass hepatic metabolism resulting in a decrease in IGF-1, a key nutritionally regulated bone trophic hormone that is already low in AN. In contrast, transdermal oestrogen, which does not suppress IGF-1, does increase bone density in AN (13), although complete 'catch up' to a comparable BMD in healthy controls does not occur given that other hormonal deficits persist (27).

Individuals with AN have been observed to have a lower bone mass than women with BN (30), which involves nutritional restriction but not necessarily a low body weight and amenorrhea, and also a lower bone mass than non-ED women with menstrual abnormalities and amenorrhea (17). Investigations into the causal mechanisms behind the low BMD in AN have thus far have focused on alterations in body composition, nutritional factors, and hormones (31-35).

Current inconsistencies in the literature regarding bone consequences of AN vs BN and the role of age and the natural decline of BMD versus the duration and nature of the ED make it important to assess these knowledge gaps in a systematic fashion. Further, a thorough evaluation of the possible determinants of low bone density in patients with EDs, such as age, BMI, duration of amenorrhea and duration since diagnosis, is lacking and has never been studied using a meta-analysis. This systematic review and meta-analysis aims to investigate the relationship between AN, BN and BMD. If BMD is found to be reduced to a similar level in both AN and BN groups, then we may conclude that there are factors other than severe weight loss due to an ED (primarily seen in AN) which contribute to low BMD and secondary osteoporosis. This will be highly useful for informing treatment options for these groups which are currently lacking.

The outcome measures investigated in this meta-analysis are spine, total, hip and femoral neck BMD. We have further investigated the influence of age, BMI, the presence of amenorrhea and the duration since diagnosis on bone mass in EDs.

Materials and Methods

Study Selection

A search criterion was defined to extract research studies investigating the relationship between AN, BN and BMD. A literature search was conducted on bibliographic databases MedLine, EMBASE and PsychInfo and the Cochrane Library. Manual searches were conducted and reference lists were searched of included studies. Reviews on the topics of EDs and bone mineral density were searched to identify key themes and to inform search terms.

We conducted a search using combinations of search terms for eating disorders (Bulimia* Anorexia Nervosa* and Eating Disorders*) and for Osteoporosis we used (Osteoporosis*, Bone Loss *, Bone Density, Bone Mineral Density, Bone Mineral Content, Bone Mass, Fracture) the search was limited to publications in English.

Published articles were eligible if they measured BMD using DXA or DPA scanning in subjects with a current ED, e.g. AN or BN, and a healthy control (HC) group. Participants with AN and a history of BN were excluded; however the BN group included participants with both a history of AN and with exclusively a BN diagnosis, which will later be divided into two sub-groups of BN. Participants identified to have an EDNOS (Eating disorder not otherwise specified) were excluded. Only studies which used female groups were included. We did not limit inclusion by study type, but in the cases of randomized controlled trials and longitudinal studies only baseline measures of BMD were used. When in doubt as to whether two studies had overlapping samples, we contacted the first author to ensure that no participants were used in multiple studies. Study eligibility was assessed by two authors (LR and NM) who discussed the inclusion criteria and reached a consensus based on the *a priori* criteria that studies report independent samples (no sample is used in multiple studies) of participants with either AN or BN and a corresponding healthy control group.

The study selection included the initial screening of title and abstracts against the inclusion criteria using EndNote, and screening of full papers against the inclusion criteria. Studies fitting inclusion criteria were excluded for reasons including replication of participants from other included papers, or patients with AN or BN grouped with other ED participants. In the case of overlapping samples, only one study with the specific sample of participants could be included.

Data Extraction

Data were extracted from included papers using a standardized form. The following data were obtained from each study: Study name, year of publication, number of participants, number of participants with an ED (anorexic and bulimic subgroups), duration of disease, duration of amenorrhea, BMI, age, sample source, method of diagnosis, DXA or DPA scanning methods and BMD data for the spine, hip, femoral neck and whole body where available. Study characteristics including journal, source of funding, geographical location of study, ethnicity of participants, methods, primary outcome measures and key findings were also obtained from each study.

Authors were contacted to retrieve data not published in several studies. Assessment of risk of bias did not justify exclusion of any further studies. The included studies were independently assessed by two reviewers (LR and NM) and any discrepancies in rating were discussed and resolved.

Assessment of Risk of Bias

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. This scale assesses the selection of participants, the comparability of cases and controls and ascertainment of exposure. This includes definition of cases and controls, selection of controls and

representativeness of cases and the comparability of cases and controls. The exposure is assessed as the diagnosis of the ED and the bias of the sample through non-response rate.

The Cochrane collaboration tool for assessing risk of bias was not appropriate as the studies were non-randomised, but relevant aspects of this tool were considered including incomplete outcome data, selective outcome reporting and other potential sources of bias. All the included studies were considered to have a low risk of bias.

Outcome Variables

The outcomes of interest were spine, total, hip and femoral neck BMD.

Statistical Analyses

Meta-Analysis

Statistical analysis was conducted using the STATA 'metan' command. The BMD, BMAD and aBMD values were entered for the AN groups, BN groups and control groups for the spine, hip, femoral neck and whole body (where available). Heterogeneity was suspected in the data and so a random effects meta-analysis was used (36). The standardized mean difference is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways and it is necessary to standardize the results of the studies to a uniform scale before they can be combined. The standardized mean difference expresses the size of the exposure effect in each study relative to the variability observed in that study (37).

Meta-Regression

We used a series of meta-regression analyses in STATA's 'metareg' command to examine the effect of the studies' sample characteristics on spine BMD. The predictors included: mean age, BMI and the duration since diagnosis (years). As different studies contained different predictors, the number of participants in each meta-regression analysis varied. Due to the small number of studies which specified if subjects were of the diagnostic subtype of AN (restricting or binge/purge subtype), it was not possible to perform this subgroup analysis.

Sensitivity Analyses

Heterogeneity was suspected given the use of varying diagnostic tools, diagnostic crossover (between AN and BN), and lack of information on AN subtype in some studies (restricting/ binge-purging subtype). The heterogeneity in the data was assessed using Higgins I^2, and sensitivity analysis was conducted using the trim and fill analysis which aims both to identify and correct for funnel plot asymmetry arising from publication bias to determine if the removal of smaller studies would reduce publication bias (38). Eggers test for small study effects was conducted on spine, hip, femoral neck and whole body BMD data (39).

Results

Search Results

Twenty-five studies measuring BMD in AN, and six studies measuring BMD in BN met the inclusion criteria (Table 1). Four of these included both AN and BN subgroups. Figure 1 is a PRISMA diagram describing the search for eligible items (40). After searching electronic databases, 440 eligible articles were found, of which 119 were identified as relevant based on the title and abstract. Additional searches were conducted based on reference lists and alternative search engines were used. A total of 41 studies met inclusion criteria, with 14 excluded for factors such as replication of data, mixed ED group or for grouping participants with current and recovered EDs together. A total of 27 studies were included in the final meta-analysis.

<Figure 1>

Table 1 includes the 27 eligible studies that were conducted across 11 countries between 1990 and 2014. BMD was assessed in a total of 2359 participants, of which 972 had an ED (785 with AN and 187 with BN). The patients were all outpatients or patient referrals from clinics and all of the participants were female. Six studies assessed patients with BN, and four of these studies included BN participants with a history of AN. The mean age range was 15.9 – 34.3 years for AN studies, 22 – 27.7 years for BN studies and 15.1 – 37.4 years for HCs.

All of the included studies used dual-energy X-ray absorptiometry (DXA) scanning (n=26) or dual photon absorptiometry scanning (DPA) (n=1) to measure BMD (also referred to in some studies as aBMD (areal Bone Mineral Density)), or used DXA measures to derive BMAD (bone mineral apparent density). Both DPA and DXA scanning have been found to have high clinical precision and accuracy (41). Two studies used both DXA and QCT (quantitative computed tomography) methods (42, 43), one used DXA and MRI (8), one used DXA and X-Ray (44) to assess bone health and one used DXA and CT (flat-panel volume computed tomography) scanning to assess bone strength (45). Only the DXA or DPA BMD or BMAD value was used in this meta-analysis. Five studies assessed hormonal parameters in patients and controls by assessing biological concentrations of hormones (12, 13, 34, 46, 47), and one RCT assessed the effect of oestrogen administration on BMD in adolescent girls (48), but only the baseline BMD measures were included in the current meta-analysis.

<Table 1>

Diagnosis of an Eating Disorder

All of the participants had been diagnosed with AN or BN by using the DSM-III, DSM-IV or ICD-10. All ED participants had been previously diagnosed by a health practitioner and referred to an eating disorder clinic where they were recruited, or their diagnosis was confirmed by a study psychiatrist. One study used a structured clinical interview (SCID) for diagnosis (49). The mean BMI (body mass index) of participants was 16.65 kg/m² (AN), 21.16 kg/m² (BN) and 22.06 kg/m² (HC).

Selection of Controls

All of the controls used were normal weight and had no current or past history of EDs. Six studies used age-matched controls, and two used age-matched and bone age-matched controls which is thought to more accurately isolate the effect of an ED on the bone in adolescent studies where girls of the same age could be at a considerably different stage of pubertal development (46, 50). All but nine controls had normal menstruation (51, 52) and all controls were recruited from the same geographical location as their corresponding ED participants. Studies recruited controls through community advertisements (n=5), advertisements across healthcare providers to patients and staff (n=7) and advertisements within universities to staff and students (n=4). The remaining studies did not give details of the recruitment of controls.

Methodological Quality

The Newcastle-Ottawa Scale (NOS) assessments of bias results are presented in Table 2. The general quality of the included studies in this meta-analysis was high, although the lowest scoring studies received only 2 out of 10 stars. The mean score was 4.9* and the scores ranged from 2*-7*. A high quality rating depends on three characteristics: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. There was generally adequate definition of cases and controls and the majority of studies reported a replicable and valid design and analysis. However, none of the studies reported drop-out or non-response rate and only 6 of the studies used the same method of ascertainment for cases and controls. The NOS assessment was not used as a tool for exclusion of studies in this meta-analysis.

<Table 2>

Meta-Analysis Results

Compared with control participants, participants with either ED had an average SMD in spinal BMD of -2.955 (p<0.0001). The results of the meta-analysis are presented in Table 3.

Anorexia Nervosa

The main outcome measure of spine BMD was lowest in subjects with AN. Further, BMD at all anatomical sites was significantly lower in the AN group (see Table 3). Spine BMD (SMD, -3.681; p<0.0001), hip BMD (SMD, -3.337; p<0.0001) and femoral neck BMD (SMD, -3.317; p<0.0001) showed the greatest difference, whereas whole body BMD (SMD, -1.782; p<0.0001) showed a smaller difference in AN. Figure 2 presents the SMD in AN studies which measure spinal BMD (a) and total BMD (b).

Bulimia Nervosa

The BMD is lower in the AN group than the BN group at every anatomical measure of BMD (Table 3). Spine BMD was still statistically significantly lower in the BN group than in healthy controls (SMD, -0.472; p<0.0001). Whole body BMD (SMD, -0.329; p=0.513) and femoral neck BMD (SMD, 0.211; p=0.463) were not significantly lower in the BN group than in healthy controls, although these analyses included few studies (four studies reported whole body BMD and only one study reported femoral neck BMD). No studies

investigated hip BMD in BN vs controls. Figure 3 presents the SMD in BN studies that measure spinal BMD (a) and total BMD (b).

A post-hoc meta-analysis was run exclusively on the BN studies (n=6), and separated those studies with and without participants with a history of AN. Of the studies measuring BMD in BN participants, four included BN participants with a history of AN. BN participants with a history of AN (20, 22, 44, 53) had a significantly lower BMD than HCs (SMD, -0.521; $p<0.0001$). However, the groups including participants with BN and no history of AN (10, 23) did not have a significantly lower BMD than healthy controls (SMD, -0.339; $p=0.108$).

<Table 3>

<Table 4>

Meta-Regression

Table 4 presents the results of the meta-regression which investigated the effects of age, BMI and duration since diagnosis (years) on spinal BMD. The results were statistically non-significant in multiple linear meta-regressions conducted on both AN and BN, although this was limited by the number of studies which could be included. Only 8 AN studies and 6 BN studies included data which could be used in the meta-regression.

<Figure 2>

<Figure 3>

Sensitivity Analyses

The Higgins I^2 heterogeneity statistic (98.3%) indicates that there is heterogeneity in the 27 studies measuring spine BMD. Publication bias is suspected in the analysis, as indicated by the funnel plot in Figure 3, and the Egger test (t=1.84; $p<0.0001$) performed on AN + BN participants' spine BMD measures. The trim and fill correction for missing data was performed and the SMD was converted to an exponential form which remained significant (SMD, 0.052; $p<0.0001$). Karlsson (2000) and Seeman (1992) had particularly large effect sizes; when these two studies were removed from the analysis the SMD reduced and the confidence intervals narrowed (SMD, -2.019; $p<0.0001$), but the significant effect persisted.

Discussion

Low BMD in ED participants can lead to a high prevalence of bone fractures resulting in pain and disability; by disentangling the commonalities and differences between the effects of different ED diagnosis on BMD we have the potential to inform future treatment options in this group based on the overlapping characteristics of the ED subtypes.

We conducted a comprehensive meta-analysis to examine the relationship between EDs and BMD, consisting of two primary meta-analyses on AN groups versus healthy controls and BN groups versus healthy controls. The spinal BMD was statistically lower in the BN groups than healthy controls, but this effect was much smaller than in the AN groups. To investigate this result the BN groups were then separated into studies which included BN participants with a history of AN, and those studies with a criteria for BN with no history of other ED subtypes. Two further meta-analyses were conducted to investigate the spinal BMD in these BN subgroups versus healthy control groups.

Previous research has consistently found a low BMD in participants with AN, but has failed to reliably determine the relationship between BN and BMD. Based on the current study results, there is evidence that patients with both AN and BN have lower spine BMD than healthy controls. We found on average a lower spinal BMD in the AN group than the BN group in comparison to healthy controls, but the effect of BN on spinal BMD was statistically significant. A number of factors were investigated to explain this relationship and the strongest predictor of a low spine BMD in the BN group was the inclusion of participants with a past history of AN in the sample. It is apparent that despite a BMI comparable to HCs, a history of AN was sufficient to produce a statistically significant lower BMD in the BN group, suggesting that acute malnutrition and weight loss can have long lasting and critical effects on the bone.

Our findings support previous research which has found that 92% of patients with AN have BMD 1 SD below controls, and 38% patients have BMD 2.5 standard deviations below controls (17). We found that SMD between AN and controls was greatest for hip BMD and least for whole body BMD. Age and BMI were potentially stronger predictors of low BMD in participants with AN than in BN, although a small number of studies measuring each factor led to lack of power in these analyses and possibly accounted for non-significance of these associations in the meta-regression. Previous research has found age, BMI and both the duration of the ED and the duration of amenorrhea to be significant predictors of BMD in participants with AN (54, 55), and the limited number of studies and the limited number of variables which could be included in this meta-regression is likely to be the reason that we have not found similar results. We could not directly separate participants according to menstrual status in this meta-analysis, and cannot draw conclusions regarding the impact of menstrual status on BMD.

Previous studies have found conflicting results regarding loss of BMD in patients with BN, some studies suggest that BN in combination with low body weight and amenorrhea is predictive of low BMD (20). In other studies, subgroup analysis determined that only those BN participants with a prior history of AN had lower spine BMD than healthy controls (20, 56). In our meta-regression, age, BMI and duration since diagnosis of the ED were not predictive of spine BMD in the BN group, and there were not enough studies measuring whole body and femoral neck BMD to conduct a meta-regression for these endpoints.

We identified methodological issues in the studies included that may be important in the design of future studies, and these are useful in explaining the non-significant results of the meta-regressions. The majority of studies that we excluded from this meta-analysis failed to clearly define the ED diagnosis. Moreover, within

included studies, the wide ranges of age, BMI and illness duration in both subgroups meant that the mean values used in the meta-regression might not capture the large variability within studies. Figure 2 indicates that Karlsson (2000) and Seeman (1992) are outliers in this analysis. Karlsson (2000) included participants who had exclusively received no treatment for their ED, and Seeman (1992) included participants who exclusively had secondary amenorrhea. The variability in characteristics of participants in this meta-analysis limits between-group comparisons and may explain the heterogeneity in the data.

Based on our quality analysis, the studies with the poorest quality assessment rating were limited in their elaboration of the representativeness of cases and controls, and particularly the ascertainment of disorder in cases. Variation in an ED diagnosis may account for the lack of predictors identified for spine BMD in either the AN or BN subgroups. The overall quality of the systematic review was high, meeting 25 of 27 criteria using PRISMA guidelines (57). Despite potential bias in studies included in this review, their results give a consistent representation of the relationship between an ED and BMD.

A recent review on AN and bone loss by Misra (2014) reported that low BMD is a consequence of AN in both sexes and across a wide age range. Studies also suggest that bone health may not fully recover until weight has been regained (58) and normal nutritional status established (59), although the rate of recovery may vary according to the nature and duration of the ED and adolescents may show only partial 'catch-up' (60). However, this study found that despite a BMI similar to healthy controls, the BN sample had a significantly lower spinal BMD. This finding suggests that weight alone does not account for the difference in BMD, and the BN sample has other characteristics including a history of AN, perhaps relapses into AN and a continued poor nutritional status which may contribute to a lower BMD. These findings suggest that both AN and BN patients should be screened for low BMD with a DXA scan at an early age.

Data are lacking regarding the magnitude of the difference in BMD when an ED begins in adolescence versus adulthood, and there are no longitudinal studies that have determined the long-term effects of adolescent onset ED on peak bone mass and BMD in adulthood. The pattern of BMD loss in women with lifetime EDs is still unknown and longitudinal data are necessary to determine if BMD decreases at a consistent rate throughout life, or if there is a rapid decrease in the initial stages of an ED followed by low but stable BMD throughout life.

Although recent studies have shown some evidence for a positive effect of estrogen replacement on bone loss in AN, given the limited treatment options, preventive methods are vital to reduce osteoporosis in this clinical group. This meta-analysis suggests that low BMD occurs in BN as well as AN. We propose that a multi-dimensional approach is needed to fully understand the impact of an ED on BMD.

Impaired nutrition, which causes changes in lean and fat mass and multiple hormonal alterations, contributes to impaired bone metabolism in AN (27). The strongest and most consistent predictor of an increase in BMD following recovery from AN is weight gain; however, no single body composition or hormonal factor can account for this improvement, which is typically incomplete in adolescents. BMD in AN is lower than that predicted by weight loss alone (61), suggesting that there is a cascade of events associated with increased energy

availability (including a normalization of hormone secretion and a positive effect on protein synthesis promoting bone remodelling) which may account for the lower BMD in both AN and BN women, suggesting that common methods of treatment should be used for both ED subtypes which focus on more than weight gain alone (62).

Strengths and Limitations

The objectivity of this meta-analysis is its main strength, provided by a quantitative measurement of BMD in different participant groups. Due to the small number of studies and the heterogeneity within these, it was not possible to make conclusions based on the meta-regression and it was thus difficult to measure trends in participant characteristics relating to the loss of BMD. Furthermore, due to the limited number of BN studies and the lack of adolescent BN participants, it was not possible to make inferences about bone accrual over time.

The meta-analysis compares studies that measure BMD across four anatomical locations in AN participants, and two anatomical locations in BN participants. The varying loss of bone mass in different anatomical locations found in this study provides the foundation for future research to investigate which regions of the skeleton are most vulnerable to the effects of an ED, and factors such as exercise and nutrition that influence bone health.

The significant association between BN and BMD is an important finding of this study, but the varying history of AN in several of the BN samples confounds this finding. This is both a strength and limitation of this meta-analysis. It is beneficial to know that a history of AN puts women with BN at risk for secondary osteoporosis, however the ever-changing nature of psychiatric disorders, and particularly eating disorders, makes it problematic to study one condition in isolation. Thus the very low sample size of women exclusively with BN makes it difficult to determine the effect of BN with no history of AN on BMD.

Finally, several studies report bias in the control groups, including self-selected controls for a study on energy expenditure (63) and for a fitness and dietary study (10). Furthermore, no studies in this meta-analysis screened the control groups using a structural clinical interview for DSM (SCID) (64). A meta-analysis of this kind relies on the accurate formulation of groups to enable optimal group comparisons, and bias in the control groups may influence the accuracy of results.

Conclusion

We found a significant reduction in BMD in both AN and BN ED subtypes. The greater reduction in BMD in the AN group suggests that characteristics particular to this disorder play a key role in the subsequent loss of bone mass. However, the reduced BMD in the BN group, despite a similar BMI to healthy controls, suggests that weight loss alone does not account for the low BMD in participants with an ED. Particular attention should be paid to adolescents with an ED, as loss of bone mass in adolescents may be to some extent irreversible. Future research should accurately determine the key correlates of bone loss and accordingly should develop a multifaceted and targeted treatment plan.

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Table 1: Summary of Study Characteristics

Ref.	ED	Sample Size (n)	Design	ED Population	Controls	Diagnostic Method	Scanning Method	Bone Density Outcome Measures
Bredella (2008)	AN HC	10 10	Case control	ED clinics	Healthy Controls Clinic advertisements	DSM-IV	DXA	Spinal BMD Hip BMD Total BMD
Bredella (2009)	AN HC	10 10	Case-control	Clinic Referrals	Healthy controls Recruited through community advertisements	'Psychiatric diagnostic criteria for AN'	DXA MRI	Spinal BMD Hip BMD Total BMD
Bredella (2012)	AN HC	10 5	Case-control	Clinic Referrals	Healthy Controls. Recruited through community advertisements	DSM-IV	DXA Fluorodeoxyglucose-PET and CT	Spinal BMD Hip BMD Total BMD Femoral neck BMD Lateral spine BMD
Davies, K. M., et al. (1990).	AN BN HC	26 11 211	Case-control	Clinic records of eating disorder patients from medical centre	Healthy controls Some self-select for fitness and diet study. Some DXA and DPA comparison group.	DSM-III DSM-III-R	DPA	Spinal BMD Forearm BMD
Faje (2013)	AN HC	44 23	Cohort	Hospital outpatients	Healthy Controls. 10-90th percentile normal weight.	DSM-IV	DXA	Spinal aBMD Hip aBMD Distal Radius aBMD
Fernandez-Soto (2009)	AN HC	31 25	Cohort	Clinic outpatients	Healthy Controls Caucasian women	DSM-IV	DXA	Spinal BMD Total Body BMD
Guo (2013)	AN HC	26 24	Cohort	Clinic Psychiatrist referrals	Healthy Controls Age-matched	DSM-IV	DXA	Spinal BMD Hip BMD Total BMD
Iketani, T., et al. (1995).	AN BN HC	20 10 10	Cohort	Clinic inpatients and outpatients	Healthy Controls Age matched healthy females.	DSM-III-R	DPA	Spinal BMD Whole Body BMD
Karlsson (2000)	AN HC	77 205	Case-Control	AN Patients untreated with estrogen therapy	Healthy Controls Regular menstrual cycles	ICD-10	DXA	Spinal BMD, aBMD and BMC Femoral neck vBMD, aBMD and BMC
Kooh (1996)	AN HC	22 24	Cohort	Clinic referrals: Adolescent medicine clinic	Healthy Controls School and university students. No oral contraceptives.	DSM-III-R	DXA	Femoral neck BMD Spinal BMD
Naessen, S., et al. (2006)	BN HC	77 56	Cohort	Recruited from hospital advertisements	Healthy Controls Hospital advertising: hospital staff and students. No current diseases or medication prior to 3 months before study.	DSM-IV	DXA	Total BMD Spinal BMD Leg BMD

Ref.	ED	Sample Size (n)	Design	ED Population	Controls	Diagnostic method	Methods	Bone Density Outcome Measures
Newton, J., et al. (1993).	BN HC	20 16	Cohort	ED outpatient treatment program. .	Healthy Controls Age and sex matched controls from hospital staff noticeboards.	DSM-IIIR SCID to assess past AN (64)	DXA	Spinal BMD
Maimoun (2014)	AN HC	98 63	Case-control	Hospital outpatients	Healthy Controls Community advertisement.	DSM-IV	DXA	Whole body aBMD Spinal aBMD Dominant arm radius aBMD Total proximal femur aBMD
Masala (2003)	AN HC	17 27	Cohort	Patients in weight gain program	Healthy Controls Exclusion included medication or illness to affect bone	ICD-10	DXA QCT	Spinal BMD
Misra (2005)	AN HC	23 21	Cohort	Clinic Referrals	Healthy Controls Age matched and bone age matched. Adverts through healthcare providers and newspapers	DSM-IV	DXA	Spinal BMAD Hip BMD
Misra (2007)	AN BN	17 19	Cohort	Paediatrician referrals	Healthy Controls Age matched and bone age matched. Mailings to paediatricians.	DSM-IV	DXA	Spinal BMAD Hip BMD Femoral neck BMAD Total Body BMD Total Body BMC
Misra (2011)	AN HC	120 40	RCT	Hospital outpatient treatment program	Healthy Controls Mailings to paediatricians.	DSM-IV	DXA	Spinal BMD Spinal BMAD Hip BMD
Morris (2004)	AN BN HC	51 26 40	Cohort	ED specialist referrals	Control group data from department of medical physics	DSM-IV	DXA X-Ray	Spinal BMD Whole Body BMD
Olmos (2010)	AN HC	51 40	Prospective longitudinal cohort study.	ED unit outpatients	Healthy Controls Hospital advertisements	DSM-IV	DXA	Spinal BMD Femoral neck BMD Total Hip BMD
Poet (1993)	AN HC	18 36	Cohort	Hospital outpatients	Healthy Controls Volunteers	DSM-III-R	DXA	Spinal BMD
Resch (2000)	AN HC	20 20	Cohort	Hospital outpatients	Healthy Controls Age matched nursing school students.	DSM-III-R	DXA	Spinal BMD Hip BMD

Ref.	ED	Sample Size (n)	Design	ED Population	Controls	Diagnostic method	Methods	Bone Density Outcome Measures
Seeman (1992)	AN HC	65 52	Cohort	Patients with AN	Healthy Controls Volunteers with no illness that affects the bone. No drugs, medication.	DSM-III-R	DXA	Spinal BMD Proximal femur BMD Femoral neck BMD Ward's triangle BMD Trochanter BMD
Soyka (1999)	AN HC	19 19	Cohort	Healthcare provider referrals	Healthy Controls Advertisement in primary care providers and newspapers. BMI 25th-90th centile. One pre-menarche.	DSM-IV	DXA	Spinal BMD Spinal BMC Lateral spine BMD Total BMD
Sundgot-Borgen, J., et al. (1998).	AN BN HC	13 43 17	Case-control	Clinic Referrals	Healthy Controls University information board recruitment. Comprehensive inclusion criteria for dietary, exercise and ED symptoms.	DSM-IV	DXA	Spinal BMD Total BMD Femoral Neck BMD Leg BMD Arm BMD
van Marken (1997)	AN HC	12 16	Cohort	Non-hospitalised outpatients.	Healthy Controls Normal weight participating in a study on energy expenditure.	DSM-III-R	DXA	Total BMD Total BMC
Walsh (2010)	AN HC	8 6	Cohort	Hospital outpatients	Healthy Controls 90-100% ideal weight for age.	DSM-IV	DXA Flat-panel volume computed tomography (CT)	Spinal BMD Hip BMD Femoral neck BMD
Wojcik (2010)	AN HC	15 16	Cohort	Healthcare referrals and community adverts	Healthy Controls Community advertisement recruitment	DSM-IV	DXA	Spinal BMD Hip BMD Femoral neck BMD Total BMD

Table 2: Newcastle Ottawa Scale Results for Quality Assessment

Ref.	Selection	Comparability	Exposure	Total
Bredella 2012	***	*	**	6*
Bredella 2008	****	**	**	8*
Bredella 2009	***	*	*	5*
Davies, K. M., et al. (1990).	***		*	4*
Faje 2013	**	*	*	4*
Fernandez-Soto 2013	**	*	*	4*
Guo 2013	**	*	**	5*
Iketani, T., et al. (1995).	**	**	*	5*
Karlsson 2000	***		*	4*
Kooh1996	**	*	*	4*
Masala 2003	***	*	*	5*
Misra 2005	***	**	*	6*
Misra 2007	***	**	*	6*
Misra 2011	**	*	*	4*
Maimoun 2014	****	*	*	6*
Morris 2004	****		*	5*
Naessen, S., et al. (2006)	**		*	3*
Newton, J., et al. (1993).	****	**	*	7*
Olmos2010	***	*	*	5*
Poet 1992	***	*	*	5*
Resch 2000	***	*	*	5*
Seeman 1992	***	*	*	5*
Soyka 1999	***	*	*	5*
Sundgot-Borgen, J., et al. (1998).	****	**	*	7*
Van Marken1997	**		*	3*
Walsh 2010	**	*	*	4*
Wojkik2010	**	*	*	4*

Table 3: Meta-Analysis Results

Anatomical Site	N	SMD	L 95% CI	U 95% CI	Z	*p*
AN only						
Spinal	22	-3.681	-4.738	-2.625	6.83	<0.0001
Total	13	-1.782	-2.517	-1.047	4.75	<0.0001
Hip	11	-3.337	-4.874	-1.799	4.25	<0.0001
Femoral Neck	11	-3.317	-5.151	-1.484	3.55	<0.0001
All BN Studies						
Spinal	6	-0.472	-0.688	-0.255	4.28	<0.0001
Total	4	-0.329	-0.573	-0.084	2.63	0.513
BN w/o History of AN						
Spinal	2	-0.339	-0.753	0.075	1.61	0.108
Total	N/A					
BN & History of AN						
Spinal	4	-0.521	-0.775	-0.268	4.03	<0.0001
Total	3	-0.259	-0.529	0.011	1.88	0.060

Table 4: Meta-Regression Results

Covariate	Coefficient	L 95% CI	U 95% CI	*p*
AN Studies (N=8)				
Age	-0.609	-2.976	1.757	0.514
BMI	0.942	-2.234	4.118	0.457
ED Duration	0.383	-3.246	4.012	0.784
BN Studies (N=5)				
Age	-0.007	-2.085	2.072	0.974
BMI	-0.070	-5.408	5.268	0.895
ED Duration	0.076	0.633	-1.424	0.633

Figure Legends

Figure 1: Meta-analysis search strategy. AN = anorexia nervosa, BN = Bulimia nervosa

Figure 2: Spinal BMD in AN groups. _ES = effect size, _seES = standard error of effect size

Figure 3: Spinal BMD in BN groups. _ES = effect size, _seES = standard error of effect size

Table Footnotes

Table 1: Study characteristics of included studies in the meta-analysis. PET = positron emission tomography , CT = computerised tomography. 'Spinal' refers to measurement of BMD at the lumbar spine. BMD = Bone Mineral Density, BMAD = Bone Mineral Apparent Density, aBMD = areal Bone Mineral Density. (n) = Number.

Table 2: Quality Analysis of all included studies rated by two trained observers (LR) (VA).

Table 3: Meta-Analysis Standardised Mean Differences and Confidence Intervals for the Anorexia Nervosa and Bulimia Nervosa Groups vs. Healthy Control Groups. N= Number, Z= Z-Scores, *p*= p-value, L= Lower, U = Upper.

Table 4: Meta-Regression Results for the Covariates influencing the Spinal BMD in the Anorexia Nervosa and Bulimia Nervosa Groups. N= Number, *p*= p-value, L= Lower, U = Upper.

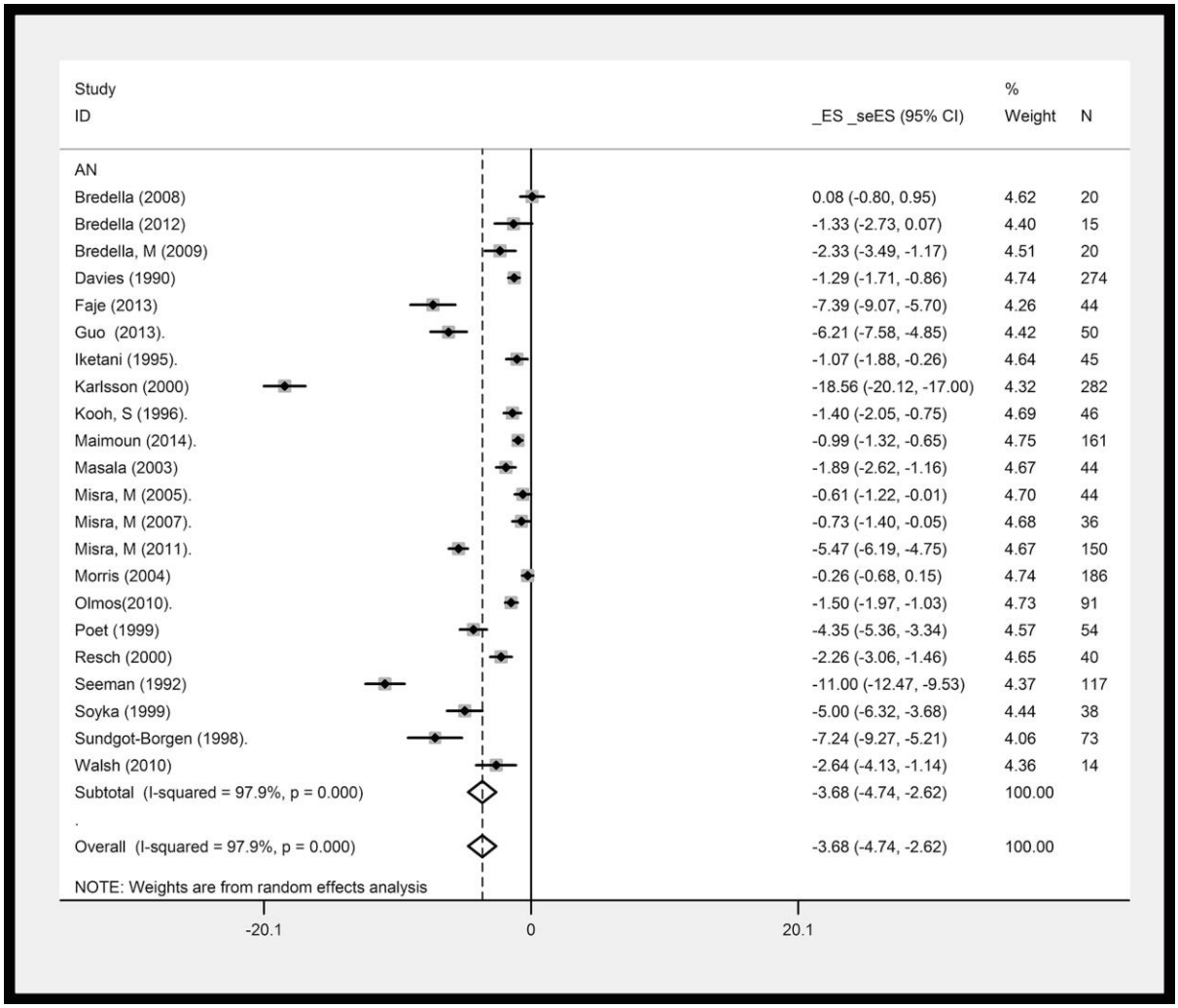
Study
ID
_ES _seES (95% CI)
%
Weight
N
AN
Bredella (2008) 0.08 (-0.80, 0.95) 4.62 20
Bredella (2012) -1.33 (-2.73, 0.07) 4.40 15
Bredella, M (2009) -2.33 (-3.49, -1.17) 4.51 20
Davies (1990) -1.29 (-1.71, -0.86) 4.74 274
Faje (2013) -7.39 (-9.07, -5.70) 4.26 44
Guo (2013). -6.21 (-7.58, -4.85) 4.42 50
Iketani (1995). -1.07 (-1.88, -0.26) 4.64 45
Karlsson (2000) -18.56 (-20.12, -17.00) 4.32 282
Kooh, S (1996). -1.40 (-2.05, -0.75) 4.69 46
Maimoun (2014). -0.99 (-1.32, -0.65) 4.75 161
Masala (2003) -1.89 (-2.62, -1.16) 4.67 44
Misra, M (2005). -0.61 (-1.22, -0.01) 4.70 44
Misra, M (2007). -0.73 (-1.40, -0.05) 4.68 36
Misra, M (2011). -5.47 (-6.19, -4.75) 4.67 150
Morris (2004) -0.26 (-0.68, 0.15) 4.74 186
Olmos(2010). -1.50 (-1.97, -1.03) 4.73 91
Poet (1999) -4.35 (-5.36, -3.34) 4.57 54
Resch (2000) -2.26 (-3.06, -1.46) 4.65 40
Seeman (1992) -11.00 (-12.47, -9.53) 4.37 117
Soyka (1999) -5.00 (-6.32, -3.68) 4.44 38
Sundgot-Borgen (1998). -7.24 (-9.27, -5.21) 4.06 73
Walsh (2010) -2.64 (-4.13, -1.14) 4.36 14
Subtotal (I-squared = 97.9%, p = 0.000) -3.68 (-4.74, -2.62) 100.00
.
Overall (I-squared = 97.9%, p = 0.000) -3.68 (-4.74, -2.62) 100.00
NOTE: Weights are from random effects analysis
-20.1
0
20.1

Figure 2

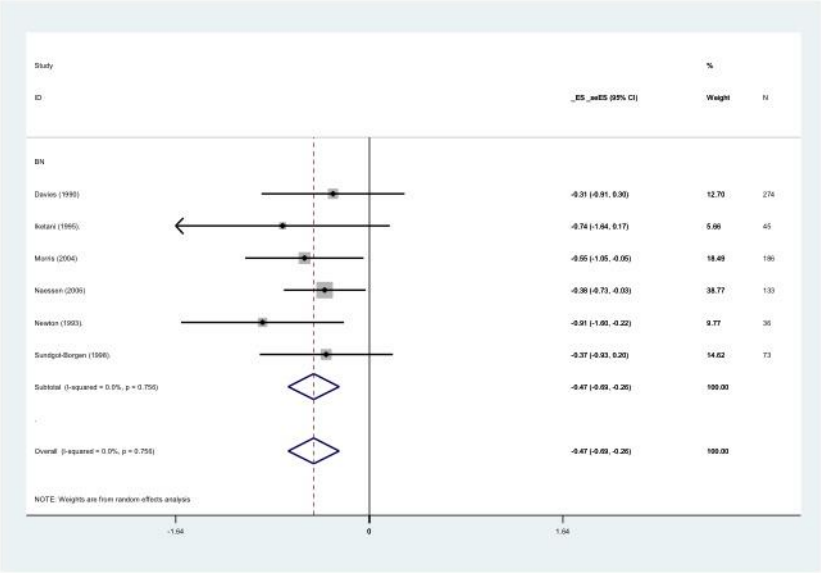
Study
ID
%
Weight
N
BN
Davies (1990)
Ikotani (1995)
Morris (2004)
Naessen (2006)
Newton (1993)
Sundgot-Borgen (1998)
Subtotal (I-squared = 0.0%, p = 0.756)
Overall (I-squared = 0.0%, p = 0.756)
NOTE: Weights are from random-effects analysis
-1.64
0
1.64

Figure 3