Differences in bone mineral density between normal-weight children and children with overweight and obesity: a systematic review and meta-analysis

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ABSTRACT

Objective

To examine the differences in bone mineral density between normal-weight children and children with overweight or obesity.

Methods

A systematic review and meta-analysis of observational studies (published up to June 22nd 2016) on the differences in bone mineral density between normal weight children and overweight and obese children was performed. Results were pooled when possible and mean differences were calculated between normal-weight and overweight and normal-weight and obese children for bone content and density measures at different body sites.

Results

Twenty-seven studies, with a total of 5958 children, were included. There was moderate and high quality of evidence that overweight (MD 213 grams; 95%CI 166, 261) and obese children (MD 329 grams; 95%CI 229, 430) have a significantly higher whole body bone mineral content than normal-weight children. Similar results were found for whole body bone mineral density. Sensitivity analysis showed the association was stronger in girls.

Conclusions

Overweight and obese children have a significantly higher bone mineral density compared to normal-weight children.

Since there was only one study included with a longitudinal design, the long term impact of childhood overweight and obesity on bone health at adulthood is not clear.

INTRODUCTION

Obesity in both children and adolescents has been increasing dramatically worldwide (1). In 1990 it was estimated that 32 million children under the age of 5 were overweight or obese, and this number has risen to 41 million children in 2014 (1). Of all continents, Europe has the highest prevalence (13%) of children having overweight (1). These numbers indicate that childhood obesity is a growing problem, and even more so with the knowledge that obese children are more likely to stay obese into adulthood (1).

It has been shown that childhood obesity can, among other diseases, lead to diabetes, pulmonary complaints and cardiovascular diseases like hypertension, with symptoms of these diseases already apparent during childhood, and carrying on to adulthood (2, 3). In addition it has been shown that childhood obesity increases the chance of developing musculoskeletal complaints, injuries and fractures as early as in childhood (4, 5).

The mechanism behind the increased injury and fracture risk in obese children is not clear and therefore different theories have been proposed. Childhood obesity is associated with a decline in motor skills, these children may therefore be more prone to falling with injuries or fractures as a result (6). Furthermore, attaining a high peak bone mass by bone mass accrual during childhood, and maintaining bone mass through life is associated with a lower fracture risk later in life (7, 8). It is however unknown whether children with obesity have a normal bone mass accrual during childhood.

Furthermore, several studies have investigated the role of overweight and obesity on bone mineral content (BMC) and bone mineral density (BMD) in adults(9, 10). These studies show a positive relationship between BMI and BMC and BMD. These relationships have been studied less extensively in children, and the mechanism and factors influencing bone density in children seems more complex.

Research that has been conducted on children suggests that more adipose tissue in obese children is related to greater total bone mineral density by causing a greater mechanical load on the bone, however this relation is still under investigation (11, 12, 13). On the other hand, the lower physical activity levels in obese children, may contribute to a lower BMD in obese children compared to children with a normal weight (8, 14). Because of this contradictory uncertainty in the literature and the many studies performed on the association between BMD and weight status, this review will provide a systematic overview and meta-analysis on the differences in BMD between normal-weight children and children with overweight and obesity, in order to be able to draw a more uniform conclusion on this suggested association.

METHODS

Search methods

We searched the following databases for relevant articles available for all years up to June 22nd 2016: Medline (OVID), Embase, Cochrane, Web of Science (WoS), Cinahl ebsco, Pubmed publisher and Google scholar. The search string contained the terms obesity, BMD and children. The search string (see Appendix 1) was adapted to the different databases to facilitate a comprehensive search.

A study had to fulfill the following criteria to be included in this review:

Study design

Cross-sectional and longitudinal studies that investigated the differences in BMD between normal-weight children and overweight and obese children were included.

Participants

Participants had to be children aged between 2 and 18.

Exposure

The exposure was childhood overweight or obesity, with children of normal weight as control group. The definition of the different weight groups, i.e. normal-weight, overweight and/or obese, based on BMI, fat percentage or body weight had to be clarified in the study and children had to be categorized in these groups by each individual study.

Outcome

The outcome measure had to be BMD in g/cm^2, BMAD (bone mineral apparent density) in g/cm^3, or bone mineral content (BMC) expressed in kg's or grams, measured by dual x-ray absorptiometry (DEXA) or volumetric BMD (vBMD) in mg/cm^3 or mg/mm^3 measured by peripheral quantitative computed tomography (pQCT). The outcome measures could be measured at any site of the body. All outcome measures had to be reported on a continuous scale.

Exclusion criteria

Studies including children with any underlying (chronic/ systemic) disease including growth hormone deficiency, diabetes type 2, cystic fibrosis, kidney disease, liver disease or transplantation, inflammatory bowel disease and eating disorders were excluded. Studies including children with genetic defects were also excluded. Articles written in a language other than English or Dutch were excluded.

Study selection

Four reviewers (JvL, BK, MvM, WP) independently screened the relevant articles identified by the search strategy on in-and exclusion criteria. After the first screening, based on title and abstract, the full texts of the remaining articles were reviewed. Any discrepancies between the reviewers were resolved by discussing the original article and reaching consensus.

Risk of bias assessment

Three reviewers (JvL, MvM, BK) performed a risk of bias assessment, using an adjusted version of the quality assessment score of Paulis et al. (5) and the Newcaste-Ottowa Scale (NOS) (15) (see Appendix 2). The quality assessment list contained 16 criteria to assess the risk of bias, of which 14 are applicable to cross-sectional studies and all 16 items apply to longitudinal studies (see Appendix 2). The studies were then rated on these 16 items as 'positive', 'negative', or 'unclear'. Disagreements between the authors were resolved by a discussion. The final risk of bias was calculated by adding up the items with positive scores and dividing them by the total number of items. If more than 50% of the items were scored positive, the risk of bias was arbitrarily rated as low.

Data management

Data were extracted by three independent researchers (JvL, MvM, BK) using a standardized data extracting form. Study characteristics extracted were: study design, setting, country in which the study was performed, number of participants, mean age of participants, gender, weight status assessment, weight status definition, BMC and BMD assessment, sites of BMC and BMD assessment and BMC and BMD definition.

The bone mineral density measures (means and standard deviations) at different body sites for each weight group were extracted.

If standard deviations were not reported we used the confidence intervals to calculate the standard deviation. If the confidence interval was also not reported, an estimation of the standard deviation was made based on study data of comparable studies in terms of measurements and sample size.

If studies only reported their outcome as graphs, the means and (when shown) standard deviations were estimated from these graphs.

Data analysis

Data were pooled of studies which were clinically homogeneous and reported on the same outcome measures. Mean differences with 95% confidence intervals (CI) between overweight and normal-weight, and obese and normal-weight children were calculated. If a study grouped overweight and obese children into one group, this group was used as an 'overweight' group in the analyses, but additional analyses were performed to investigate potential differences between overweight and obese children when possible. Sensitivity analysis were performed to investigate potential differences between overweight and normal weight, and obese and normal weight children by gender.

For pooling we used the random effects model. Review manager 5.0 software was used to calculate the total mean differences with accompanying 95%CI. Statistical heterogeneity was tested with the chi^2 and I^2 test. For the pooled studies, we used funnel plots to analyze potential publication bias. If the funnel plot was symmetrical no publication bias was considered. If outcome measures were presented on different scales, the outcome measure was transformed to the most frequently reported scale. If pooling was not possible, data were analyzed descriptively.

Strength of evidence

In order to evaluate the strength of evidence of the pooled results, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used (16). The rating of evidence started at high quality, because observational studies were the most appropriate design for the current review. The quality of evidence was downgraded by one level if there was inconsistency (I^2>40%), uncertainty (n < 400), or probability of bias (>25% of patients come from a study with a high risk of bias, or the funnel plot indicated publication bias). It was upgraded by one level if strong evidence of associations was found (MD >2SD). The following levels of evidence were distinguished.

- High: further research is unlikely to change the level of evidence. There are no known or suspected reporting biases
- Moderate: further research is likely to have an important impact on confidence of the estimate of effect and may change the estimate
- Low: further research is likely to have an important impact on confidence of the estimate of effect and is likely to change the estimate
- Very low: the estimate of effect is very uncertain

RESULTS

Study selection

From our search we obtained 5028 articles (Figure 1). After screening on title and abstract, 282 articles remained for potential inclusion for which full text was assessed. Finally, 27 articles were included in this systematic review (12, 17-42).

Study characteristics

Of the 27 included studies, five had a longitudinal design and the other 22 studies had a cross-sectional or case-control design. Of four of the five longitudinal studies (31, 38,

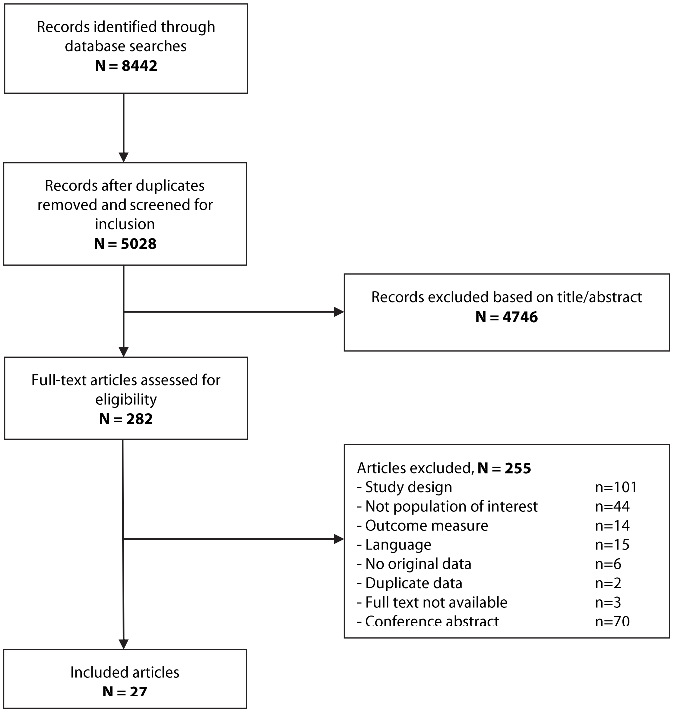


Figure 1 – Flowchart of selected papers.

41, 42) only baseline data were used since our outcome of interest was not reported at follow-up. These were therefore considered as cross-sectional.

The study characteristics of the included studies are shown in Table 1. The 27 included studies were conducted in 17 different countries across the world. Children were recruited in different settings, ranging from a random selection from an open population to schools and outpatient clinics. The most frequently reported outcomes were total body BMC (g), total body BMD (g/cm2), lumbar spine BMD (g/cm2) and femoral neck BMD (g/cm2). Only two studies did not report on any of these outcomes, but only on bone densities at different body sites (31, 39). The cross sectional studies included a total of 5126 children aged four to 18 years. The longitudinal study included 832 children.

Risk of bias assessment

Table 2 shows the final risk of bias assessment with 26 studies with a cross-sectional or case control design and one study with a longitudinal design. The reviewers agreed on 89.6% of the items of the 27 included studies (403 of 450), and reached consensus on all items after discussing them. Of the 27 included studies, 23 had a low risk of bias. Most studies (n=20) scored negative on the inclusion of at least 50 cases. Nearly all studies (n=26) reported a clear weight status and BMD definition.

Table 1 – study characteristics of included studies

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assessment	Sites of BMD assessment	BMD definition
De la Torre 1990	Not described	Case-control	Not described	11`	Control: 10.3 (1.7) Obese: 10.5 (1.7)	Not described	Not described	Not described	DXA	Whole body	BMD (g/cm^2)
Dimitri 2015	United Kingdom	Case-control	Tertiary pediatric endocrine unit and open population	36	Lean: 12.9 (2.0) Obese: 12.6 (1.9)	Not `described	BMI measured, cut-off based on Cole (43)	BMI <91st percentile is lean, BMI > 98th percentile is obese	High resolution peripheral quantitative computed tomography (HR-pQCT),	Non-dominant distal radius and non-dominant distal tibia	Total density (Dtot) (mg/cm^3), cortical density (CoD) (mg/cm^3), trabecular density (TrD) (mg/cm^3)
Ducher 2009	Australia	Cross-sectional	Schools	427	Range: 7-10 Normal-weight: 8.4 (0.4) Overweight: 8.3 (0.4)	48%	BMI measured, cut-off based on Cole (44)	Corresponds to adult percentile: BMI < 25 is non-overweight, BMI ≥ 25 overweight/obese	Peripheral quantitative computed tomography	Non-dominant distal forearm and contralateral distal lower leg	BMC (g/cm), Trabecular density (TrD) (mg/cm^3), Cortial density (CoD) (mg/cm^3)
El-Dorry 2015	Egypt	Case-control	Outpatient clinics	80	Range: 6-10	Not described	BMI measured, cut off according to Egyptian Growth Charts (45)	BMI 5th-85th percentile is non-obese, BMI >95th percentile is obese	DXA	Whole-body	BMC (g), BMD (g/cm^2)

Table 1 – study characteristics of included studies (continued)

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assessment	Sites of BMD assessment	BMD definition
Ellis 2003	USA	Cross-sectional	Pediatricians	865	Males: Normal-weight: 11.2 (4.1) Overweight: 11.0 (3.8) Obese: 11.6 (2.4) Females: Normal-weight: 11.4 (3.3) Obese: 12.2 (3.3) Obese 12.1 (3.4)	49%	% Fat by DXA	<25% fat is normal 25-20% fat is overweight >30% is obese	DXA	Whole-body	BMC (g)
Eriksson 2008	Sweden	Cross-sectional	Schools	96	Overall: 8.17 (0.34) Normal-weight: 8.17 (0.36) Overweight/obese: 8.20 (0.20)	56%	BMI measured, cut-off based on Cole (44)	Corresponds to adult percentile: BMI < 25 is non-overweight, BMI ≥ 25 overweight/obese	DXA	Whole-body, lumbar spine (ls), femoral neck (fn)	BMC (g), BMD (g/cm^2)
Fintini 2011	Italy	Cross-sectional	Outpatient clinic	151	14.5 (2.4)	46%	BMI measured, cut-off baed on BMI-SD scores (46)	BMD-SDS <2.0 is normal, BMD-SDS >2.0 is obese	DXA	Whole-body, Lumbar spine	BMD (g/cm^2),

Table 1 – study characteristics of included studies (continued)

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assessment	Sites of BMD assessment	BMD definition
Fischer 2000	Chili	Cross-sectional, case control	Outpatient clinic	32	Range: 5-13	50%	BMI measured, cut off based on National Center for Health Statistics (47)	More than 2 standard deviations of height/weight ratio is obese	DXA	Total body, Lumbar spine, femoral neck	BMD (g/cm^2), BMC (g)
Gracia-Marco 2011	Spain	Cross-sectional	Open population	330	Range: 12.5-17.5 Boys: 14.7 (1.3) Girls: 14.7 (1.1)	51%	BMI measured, cut off based on Cole (44, 48)	Corresponds to adult percentile: BMI < 25 is non-overweight, BMI ≥ 25 overweight/obese	DXA	Whole body, total hip, femoral neck and lumbar spine	BMC (g), BMD (g/cm^2)
Hanks 2015	USA	Cross-sectional	Participants at research at department of nutrition sciences	69	Range: 7-12 Overall: 9.5 (1.8) Non-obese: 9.2 (2.0) Obese: 9.8 (1.3)	38%	BMI-z score measured, using CDC growth charts (49)	BMI z-score < 1.64 is non-obese, BMI z-score ≥ 1.64 is obese	DXA	Whole body	BMC (kg), BMD (g/cm^3)

Table 1 – study characteristics of included studies (continued)

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assess-ment	Sites of BMD assessment	BMD definition
Haroun 2005	United Kingdom	Case-control	Hospitals, community clinic, ongoing studies in, obesity clinics	50	Range: 7-14 Boys: Control: 11.1 (1.6) Obese: 10.4 (2.1) Girls Control: 11.9 (2.0) Obese: 10.8 (2.2)	46%	BMI measured, converted to SDS using UK reference data (43)	BMI standard deviation scores (SDS)-2 to 1.61 is normal, BMI > 95th percentile, 1.61BMI SDS is obese.	DXA	Whole body	BMC (kg)
Hasano-glu 2000	Turkey	Cross-sectional	Not described	74	Range: 5-15 Control: 10.5 (2.8) Obese: 10.2 (3.2)	59%	BMI measured, cut off based on Hammer et al. (50)	BMI>95th percentile, and weight-length index >120 is obese	DXA	Lumbar spine	BMD (g/cm^2)
Ivuškāns 2014	Estonia	Cross-sectional	Schools	264	Range: 11-13 Normal-weight: 12.1 (0.8) Overweight: 12.0 (0.8)	100%	% body fat, cut-off based on McCarthy (51)	< 21.3-22.8 fat is normal ≥ 21.3-22.8 is overweight	DXA	Whole-body, lumbar spine (LS), femoral neck (FN)	BMD (g/cm^2), BMC (g)

Table 1 – study characteristics of included studies (continued)

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assess-ment	Sites of BMD assessment	BMD definition
Jeddi 2015	Iran	Cross-sectional	Schools	472	Range: 9-18	50%	BMI measured, cut off based on IOTF (44)	BMI <85th percentile is normal, BMI 85-95th percentile is overweight BMI ≥ 95th percentile is obese	DXA	Whole body BMD, lumbar spine (LS), femoral neck (FN)	BMD (g/cm^2), BMC (g)
Klein 1998	USA	Cross-sectional	Not described	48	Non-obese: 10.0 (1.9) Obese: 8.9 (1.8)	52%	BMI measured, cut off based on Frisch et al. (52)	BMI <85th percentile is non-obese, BMI > 95th percentile is obese	DXA	Whole body	BMD (g/m^2)
Kouda 2012	Japan	Longitudinal, but can only use baseline data (no-f-up BMD)	Schools	550	Unknown	52%	BMI, cut off based on Cole (44, 48)	Corresponds to adult: BMI <18.5 is underweight BMI < 25 is non-overweight, BMI ≥ 25 overweight/obese	DXA	Whole body	Bone mineral content index (BMCI) (kg/m^2)

Table 1 – study characteristics of included studies (continued)

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assessment	Sites of BMD assessment	BMD definition
Leonard 2015	USA	Cross-sectional	Hospital and open population	142	Range: 10-15 Non-obese: 14.5 (2.0) Obese: 12.2 (1.2)	36%	BMI measured, cut off on Ogden growth chart (53)	BMI >5th and < 85th percentile is non-obese, BMI > 97th percentile is obese	pQCT	Tibia and radius	CoD (mg/cm^3), TrD (mg/cm^3)
Lucas 2012	Portugal	Prospective cohort	Schools	346	Unknown	0%	BMI measured, cut off based on CDC (54)	BMI < 85th percentile at both timepoints is normal-weight, BMI ≥ 85th percentile at least at one timepoint is overweight	DXA	Nondominant distal forearm	BMD (g/cm^2)
Manzoni 1996	Italy	Cross-sectional	Not reported	115	Range: 5-18 Normal-weight: 11.4 (3.4) Obese: 11.1 (2.9)	50%	Relative body weight (RBW) (55)	RBW 80-120% is normal-weight, RBW > 120% is obese	DXA	Whole body, arms, trunk, legs	BMC (g)
Rocher 2008	France	Cross-sectional	Schools	43	Range: 9-12 Controls: 10.9 (1.1) Obese: 10.7 (1.2)	53%	BMI measured, cut off based on Cole (44)	Corresponds to adult: BMI < 25 is control, BMI ≥ 25 overweight/obese	DXA	Whole body, Lumbar spine	BMC (g), BMD (g/cm^2), BMAD (g/cm^3)

Table 1 – study characteristics of included studies (continued)

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assess-ment	Sites of BMD assessment	BMD definition
Rocher 2013	France	Cross-sectional	Schools	77	Range: 7-11 Normal-weight: 10.4 (1.5) Obese: 10.3 (1.4)	42%	BMI measured, cut off based on Cole (44)	Not reported	DXA	Whole body, lumbar spine (ls), nondominant forearm (tf), nondominant hip (th)	BMC (g), BMD (g/ cm^2)
Shin 2011	Korea	Case-control	High schools	60	Unknown	0%	Kg	<51 kg is light weight 51-56.9kg is middle weight >57 is heavy weight	DXA	Lumbar spine, femoral neck	BMD (g/cm^2)
Temple-ton 2010	USA	Longi-tudinal, use only baseline data	Previous studies	96	Normal-weight: 11.55 (2.18) Overweight: 12.32 (2.34) Obese: 11.3 (2.5)	64%	BMI measured	BMI <85^{th} percentile is normal-weight, BMI ≥ and < 95^{th} percentile is overweight, BMI ≥95^{th} percentile is obese	DXA	Whole body, arm, leg, trunk	BMC (kg)
Tubíc 2012	Sweden	Cross-sectional	Schools	41	Rage: 4-5 Normal-weight: 4.45 (0.36) Obese: 4.57 (0.32)	68%	BMI measured, cut off based on Karlberg et al. (56)	Not described	DXA	Heel	BMC (g), BMD (g/ cm^2), BMAD (g/ cm^3)

Table 1 – study characteristics of included studies (continued)

Study	Country	Design	Setting	N	Age (years), range and/or mean (sd)	Gender %male	Weight status assessment	Weight status definition	BMD assessment	Sites of BMD assessment	BMD definition
Uusi-Rasi 2012	Finland	Prospective cohort	Radomly selected from national population register	832	12 at baseline, mean 36.1(2.7) at follow up	45%	BMI measured at age 12.5, cut-off based on Cole (44)	Males: BMI >21.56 is overweight Females: BMI > 22.14 is overweight	pQCT	Distal radius, distial tibia, tibia shaft and radial shaft.	TrD (mg/cm^3), CoD (mg/cm^3)
Vaitkeviciute 2014	Estonia	Longitudinal, but use only baseline data	Schools	206	Underweight: 11.7 (0.47) Normal-weight: 12.1 (0.69) Overweight: 11.9 (0.74) Obese: 12.1 (0.95)	100%	BMI measured, cut-off based on Cole et al. (48)	BMI < 15.35 is underweight, BMI ≥ 15.35-21.22 is normal-weight, BMI ≥ 21.22-26.02 is overweight, BMI > 26.02 is obese	DXA	Whole body, lumbar spine (ls), femoral neck (fn)	BMD (g/cm^2)
Wetzsteon 2008	Canada	Longitudinal, but only use baseline data	Schools	445	Normal-weight: 10.2 (0.6) Overweight: 10.1 (0.6)	51%	BMI measured, cut-off based on CDC (54)	BMI ≤ 75^{th} percentile is healthy weight, BMI ≥ 85^{th} percentile is overweight	pQCT	Left tibia at 8% (total density), 50% and 66% site	Total density (mg/mm^3), CoD (mg/mm^3)

Table 2 – Quality assessment scores of included studies. Scoring options were positive (1), negative (0), unclear (2), or not applicable (na).

Study	Study groups are clearly defined	Participation ≥ 70%	Number of cases ≥ 50	Weight status definition	Assessment of weight status	Weight status assessment by independent person	BMD definition	Assessment of BMD	Blind for weight status	Longitudinal design	Inclusion and exclusion criteria	Follow-up period ≥1 year	Information completers vs withdrawals	Data presentation	Consideration of confounders	Control for confounding	Total percentage
								Cross-sectional studies									
De la Torre 1990	0	2	0	0	0	2	1	0	2	0	0	na	na	1	0	0	14
Dimitri 2015	1	2	0	1	1	1	1	1	2	0	1	na	na	1	1	1	71
Ducher 2009	1	1	1	1	1	1	1	1	2	0	0	na	na	1	1	1	79
El-Dorry 2015	0	2	0	1	1	1	1	1	2	0	1	na	na	0	0	0	43
Ellis 2003	1	2	0	1	1	1	1	1	2	0	0	na	na	1	1	1	64
Eriksson 2008	1	1	0	1	0	1	1	1	2	0	1	na	na	1	1	0	64
Fintini 2011	1	2	0	1	1	1	1	1	2	0	1	na	na	1	1	1	71
Fischer 2000	1	1	0	1	0	2	1	1	2	0	0	na	na	1	1	1	58
Gracia-Marco 2011	0	1	0	1	0	1	1	1	2	0	0	na	na	0	1	1	50
Hanks 2015	1	2	0	1	1	1	1	1	2	0	1	na	na	1	1	1	71
Haroun 2005	1	1	0	1	1	1	1	1	2	0	0	na	na	1	1	0	64
Hasanoglu 2000	1	1	0	1	0	2	1	1	2	0	0	na	na	1	0	0	43
Ivuskans 2014	1	2	1	1	1	1	0	1	2	0	1	na	na	1	0	0	57
Jeddi 2015	1	2	0	1	1	1	1	1	2	0	1	na	na	1	1	0	64
Klein 1998	1	2	0	1	2	2	1	1	2	0	0	na	na	1	1	1	50
Leonard 2015	1	2	1	1	1	1	1	1	2	0	1	na	na	1	1	1	79
Manzoni 1996	1	2	1	1	1	1	1	1	2	0	2	na	na	1	0	0	57
Rocher 2008	1	2	0	1	1	1	1	1	2	0	1	na	na	1	1	1	71
Rocher 2013	1	2	1	1	1	1	1	1	2	0	1	na	na	1	1	1	79
Shin 2011	1	2	0	1	0	2	1	1	2	0	1	na	na	1	0	0	43
Templeton 2011	1	2	0	1	1	1	1	1	2	1	2	na	na	1	1	1	71
Tubíc 2012	1	2	0	1	1	1	1	1	2	0	1	na	na	1	1	1	71
Kouda 2012	0	1	0	1	1	0	1	1	2	1	1	na	na	1	1	1	71
Lucas 2012	1	1	1	1	1	1	1	1	2	1	1	na	na	1	0	0	79
Vaitkeviciute 2014	1	2	0	1	1	1	1	1	1	1	1	na	na	1	1	1	86
Wetzsteon 2008	1	2	1	1	1	1	1	1	2	1	1	na	na	1	1	1	86
								Longitudinal studies									
Uusi-Rasi 2012	1	0	0	1	2	2	1	1	2	1	0	1	0	1	1	1	56

Mean differences

Prospective study

Uusi-Rasi et al. (40) reported prospective data on the differences in BMD between overweight and non-overweight children. They concluded that childhood overweight may lead to higher trabecular density at the tibia in adult women only with mean difference (MD) 17 mg/cm^3 (95%CI 3.73, 29.27), and adult men have a somewhat lower cortical density at tibia (MD-13 mg/cm^3 (95%CI-13.48,-0.52)).

Cross-sectional studies

Total body bone mineral content(g)

A total of 13 studies reported total body BMC (g) per weight group. Of these, six (20, 21, 24, 28, 29, 38) reported the BMC for normal-weight and overweight children and ten (19, 20, 23, 25, 26, 29, 34, 35, 36, 38) for normal-weight and obese children. Figure 2a shows the pooled results of the differences in BMC between normal-weight and overweight children (MD 214 grams (95%CI 166, 261; I^2=17%)). Low heterogeneity, low uncertainty (n>400) and low probability of bias lead to high quality of evidence showing that overweight children have a significantly higher whole body BMC than normal-weight children.

Pooled data of nine studies comparing whole body BMC between obese and normal-weight children showed a significant MD of 329 grams (95%CI 229, 430) (Figure 2b). The test for heterogeneity showed an I^2 of 63% (p=0.003), therefore the quality of evidence for this significant difference in BMC was downgraded by only one level leading to moderate quality.

Templeton et al. (38) reported BMC for both overweight and obese children, but their results could not be used in both meta-analyses due to different outcome scales, though comparable results were found.

Analysis between overweight and obese children including the results of two studies (20, 29), showed a MD of total body BMC of 112 grams ((95%CI-3, 227), I^2=0% (P=0.88)) leading to high quality of evidence for no significant difference in total body BMC between obese and overweight children (see appendix 3a).

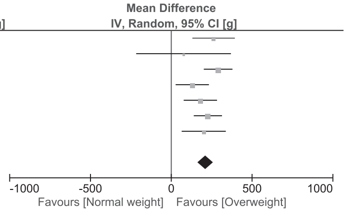
Whole body bone mineral density (g/cm^2)

Six studies (21, 24, 28, 29, 33, 41) reported the BMD for normal-weight and overweight children and pooled results showed a significant MD of 0.04 g/cm^2 (95%CI 0.02, 0.05), I^2=70 (Figure 3a). Pooled data of nine studies (17, 19, 22, 23, 29, 30, 35, 36, 41) showed a significant difference in BMD between normal-weight and obese children (MD 0.05 g/cm^2 (95%CI 0.02, 0.09)) (Figure 3b). Statistical significant heterogeneity (I^2=82) was found and therefore moderate quality of evidence was found for a significant mean difference in BMD between normal weight children and overweight and obese children.

a

Study or Subgroup	Overweight Mean [g]	SD [g]	Total	Normal weight Mean [g]	SD [g]	Total	Weight	Mean Difference IV, Random, 95% CI [g]
Ellis 2003 (1)	1,504	536	96	1,242	533	188	11.1%	262.00 [130.47, 393.53]
Ellis 2003 (2)	1,556	862	37	1,480	855	318	2.5%	76.00 [-217.22, 369.22]
Eriksson 2009	1,286	174	17	996	145	79	21.1%	290.00 [201.32, 378.68]
Gracia-Marco 2012 (3)	1,975	250	30	1,845	300	133	16.7%	130.00 [27.03, 232.97]
Gracia-Marco 2012 (4)	2,225	300	42	2,045	280	125	16.7%	180.00 [76.84, 283.16]
Ivuskans 2014	1,850	374.4	110	1,623.4	332	154	21.5%	226.60 [139.17, 314.03]
Jeddi 2015	1,618.5	505.3	58	1,417.5	420.3	390	10.4%	201.00 [64.43, 337.57]
Total (95% CI)			**390**			**1387**	**100.0%**	**213.52 [166.34, 260.69]**

Heterogeneity: Tau² = 705.26; Chi² = 7.27, df = 6 (P = 0.30); I² = 17%
Test for overall effect: Z = 8.87 (P < 0.00001)

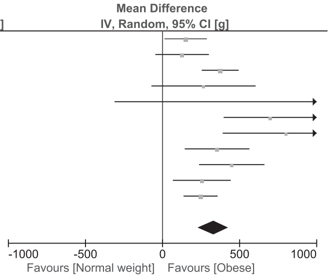


Footnotes
(1) Girls
(2) Boys
(3) Girls. Adjusted for height, calcium intake and sexual maturation
(4) Boys. Adjusted for height, calcium intake and sexual maturation

b

Study or Subgroup	Obese Mean [g]	SD [g]	Total	Normal weight Mean [g]	SD [g]	Total	Weight	Mean Difference IV, Random, 95% CI [g]
El-Dorry 2015	1,200	350	40	1,050	275	40	13.0%	150.00 [12.06, 287.94]
Ellis 2003 (1)	1,607	606	66	1,480	855	318	11.3%	127.00 [-46.80, 300.80]
Ellis 2003 (2)	1,616	596	160	1,242	533	188	13.8%	374.00 [254.28, 493.72]
Fischer 2000	1,684.1	492.38	16	1,418.2	483.48	16	5.8%	265.90 [-72.23, 604.03]
Hanks 2015	2,300	4,000	31	1,200	300	38	0.5%	1100.00 [-311.31, 2511.31]
Haroun 2005 (3)	2,000	400	15	1,300	400	12	6.7%	700.00 [396.36, 1003.64]
Haroun 2005 (4)	2,400	600	13	1,600	400	10	4.4%	800.00 [390.31, 1209.69]
Jeddi 2015	1,771.2	514	24	1,417.5	420.3	390	9.8%	353.70 [143.87, 563.53]
Manzoni 1996	1,927	670	65	1,478	491	50	9.7%	449.00 [236.75, 661.25]
Rocher 2008	1,497.96	347.17	20	1,243.31	269.37	23	10.7%	254.65 [66.85, 442.45]
Rocher 2013	1,313.4	292.7	53	1,066.6	194.1	24	14.2%	246.80 [136.17, 357.43]
Total (95% CI)			**503**			**1109**	**100.0%**	**329.35 [229.00, 429.69]**

Heterogeneity: Tau² = 15259.84; Chi² = 26.68, df = 10 (P = 0.003); I² = 63%
Test for overall effect: Z = 6.43 (P < 0.00001)



Footnotes
(1) Boys
(2) Girls
(3) Girls
(4) Boys

Figure 2 – (a) Pooled results of the studies that reported whole body BMC(g) for normal weight and overweight children. (b) Pooled results of the studies that reported whole body BMC(g) for normal weight and obese children. BMC, bone mineral content.

Analysis between overweight and obese children including the results of two studies (29, 41) showed a MD of total body BMD of 0.05 g/cm^2 (95%CI 0.03, 0.08), I^2=0% (P=0.88). However, since there was uncertainty (n<400), the quality of evidence was downgraded by one level to moderate quality of evidence for a significantly higher BMD in obese children compared to overweight children (see appendix 3b).

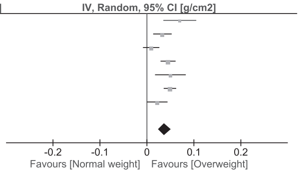
Lumbar spine BMD (g/cm^2)

Six studies (21, 24, 28, 29, 37, 41) reported on the differences in lumbar spine BMD between normal-weight and overweight children and pooled results showed a significant MD of 0.04 g/cm^2 (95%CI 0.01, 0.06), I^2= 75% (Figure 4a). Additionally, pooled data of eight studies (22, 23, 27, 29, 35, 36, 37, 41) comparing lumbar spine BMD between normal-weight and obese children showed a significant MD of 0.08 g/cm^2 (95%CI 0.05, 0.11) (Figure 4b). Statistically significant heterogeneity (I^2 = 73%) was found and therefore moderate quality of evidence was found for a significant mean difference in lumbar spine BMD between normal-weight children and overweight and obese children.

a

Study or Subgroup	Overweight Mean [g/cm2]	SD [g/cm2]	Total	Normal Mean [g/cm2]	SD [g/cm2]	Total	Weight	Mean Difference IV, Random, 95% CI [g/cm2]
Eriksson 2009	0.92	0.07	17	0.85	0.05	79	9.2%	0.07 [0.03, 0.11]
Gracia-Marco 2012 (1)	1.065	0.048	30	1.032	0.057	133	15.2%	0.03 [0.01, 0.05]
Gracia-Marco 2012 (2)	1.065	0.049	42	1.056	0.053	125	16.3%	0.01 [-0.01, 0.03]
Ivuskans 2014	1.007	0.066	110	0.962	0.065	154	17.0%	0.04 [0.03, 0.06]
Jeddi 2015	0.91	0.12	58	0.86	0.11	390	9.9%	0.05 [0.02, 0.08]
Lucas 2012	0.398	0.058	95	0.349	0.052	251	18.2%	0.05 [0.04, 0.06]
Vaitkeviciute 2014	1.001	0.047	22	0.979	0.057	133	14.2%	0.02 [0.00, 0.04]
Total (95% CI)			**374**			**1265**	**100.0%**	**0.04 [0.02, 0.05]**

Heterogeneity: Tau² = 0.00; Chi² = 19.88, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 5.27 (P < 0.00001)

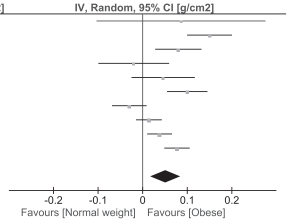


Footnotes
(1) Girls
(2) Boys

b

Study or Subgroup	Obese Mean [g/cm2]	SD [g/cm2]	Total	Normal weight Mean [g/cm2]	SD [g/cm2]	Total	Weight	Mean Difference IV, Random, 95% CI [g/cm2]
De la Torre 1990	0.96	0.09	6	0.874	0.2	5	2.6%	0.09 [-0.10, 0.28]
El-Dorry 2015	0.75	0.12	40	0.6	0.11	40	10.5%	0.15 [0.10, 0.20]
Fintini 2011 (1)	1.08	0.12	40	1	0.12	42	10.4%	0.08 [0.03, 0.13]
Fintini 2011 (2)	1.08	0.12	41	1.1	0.19	28	7.8%	-0.02 [-0.10, 0.06]
Fischer 2000	0.818	0.1	16	0.772	0.105	16	8.5%	0.05 [-0.03, 0.12]
Jeddi 2015	0.96	0.11	24	0.86	0.11	390	11.0%	0.10 [0.05, 0.15]
Klein 1998	0.79	0.06	30	0.82	0.07	18	11.6%	-0.03 [-0.07, 0.01]
Rocher 2008	0.927	0.01	20	0.913	0.07	23	12.5%	0.01 [-0.01, 0.04]
Rocher 2013	0.883	0.069	53	0.845	0.052	24	12.6%	0.04 [0.01, 0.07]
Vaitkeviciute 2014	1.056	0.067	24	0.979	0.057	133	12.5%	0.08 [0.05, 0.11]
Total (95% CI)			**294**			**719**	**100.0%**	**0.05 [0.02, 0.09]**

Heterogeneity: Tau² = 0.00; Chi² = 50.47, df = 9 (P < 0.00001); I² = 82%
Test for overall effect: Z = 3.05 (P = 0.002)



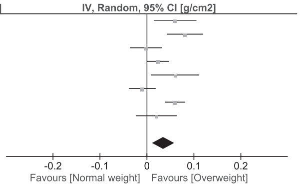
Footnotes
(1) Girls
(2) Boys

Figure 3 – (a) Pooled results of the studies that reported whole body BMD (g/cm2) for normal weight and overweight children. (b) Pooled results of the studies that reported whole body BMD (g/cm2) for normal weight and obese children. BMD, bone mineral density.

a

Study or Subgroup	Overweight Mean [g/cm2]	SD [g/cm2]	Total	Normal weight Mean [g/cm2]	SD [g/cm2]	Total	Weight	Mean Difference IV, Random, 95% CI [g/cm2]
Eriksson 2009	0.741	0.09	17	0.681	0.07	79	10.6%	0.06 [0.01, 0.11]
Gracia-Marco 2012 (1)	1	0.097	30	0.919	0.098	133	11.9%	0.08 [0.04, 0.12]
Gracia-Marco 2012 (2)	0.867	0.098	42	0.869	0.095	125	12.8%	-0.00 [-0.04, 0.03]
Ivuskans 2014	0.839	0.09	110	0.815	0.103	154	15.0%	0.02 [0.00, 0.05]
Jeddi 2015	0.89	0.19	58	0.83	0.16	390	9.5%	0.06 [0.01, 0.11]
Shin 2011 (3)	1.12	0.03	10	1.13	0.035	10	13.9%	-0.01 [-0.04, 0.02]
Shin 2011 (4)	0.93	0.03	10	0.87	0.017	10	15.3%	0.06 [0.04, 0.08]
Vaitkeviciute 2014	0.849	0.097	22	0.829	0.098	133	10.9%	0.02 [-0.02, 0.06]
Total (95% CI)			**299**			**1034**	**100.0%**	**0.04 [0.01, 0.06]**

Heterogeneity: Tau² = 0.00; Chi² = 28.16, df = 7 (P = 0.0002); I² = 75%
Test for overall effect: Z = 2.93 (P = 0.003)

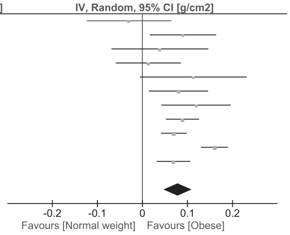


Footnotes
(1) Girls. Adjusted for height, calcium intake and sexual maturation
(2) Boys. Adjusted for height, calcium intake and sexual maturation
(3) Taekwando
(4) Control

b

Study or Subgroup	Obese Mean [g/cm2]	SD [g/cm2]	Total	Normal weight Mean [g/cm2]	SD [g/cm2]	Total	Weight	Mean Difference IV, Random, 95% CI [g/cm2]
Fintini 2011 (1)	0.87	0.13	41	0.9	0.23	28	6.3%	-0.03 [-0.12, 0.06]
Fintini 2011 (2)	0.97	0.18	40	0.88	0.16	42	8.1%	0.09 [0.02, 0.16]
Fischer 2000	0.72487	0.17175	16	0.686	0.13708	16	5.4%	0.04 [-0.07, 0.15]
Hasanoglu 2000 (3)	0.575	0.14	19	0.562	0.079	19	8.2%	0.01 [-0.06, 0.09]
Hasanoglu 2000 (4)	0.746	0.24	18	0.633	0.09	18	4.7%	0.11 [-0.01, 0.23]
Jeddi 2015	0.91	0.16	24	0.83	0.16	390	8.9%	0.08 [0.01, 0.15]
Rocher 2008	0.774	0.16	20	0.655	0.08	23	7.7%	0.12 [0.04, 0.20]
Rocher 2013	0.683	0.093	53	0.594	0.068	24	12.2%	0.09 [0.05, 0.13]
Shin 2011 (5)	1.2	0.03	10	1.13	0.035	10	13.2%	0.07 [0.04, 0.10]
Shin 2011 (6)	1.03	0.045	10	0.87	0.017	10	13.0%	0.16 [0.13, 0.19]
Vaitkeviciute 2014	0.898	0.084	24	0.829	0.098	133	12.2%	0.07 [0.03, 0.11]
Total (95% CI)			**275**			**713**	**100.0%**	**0.08 [0.05, 0.11]**

Heterogeneity: Tau² = 0.00; Chi² = 36.44, df = 10 (P < 0.0001); I² = 73%
Test for overall effect: Z = 5.00 (P < 0.00001)



Footnotes
(1) Boys
(2) Girls
(3) Prepubertal
(4) Pubertal
(5) Taekwando
(6) Control

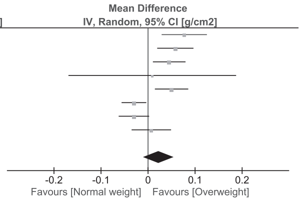
Figure 4 – (a) Pooled results of the studies that reported lumbar spine BMD (g/cm2) for normal weight and overweight children. (b) Pooled results of the studies that reported lumbar spine BMD (g/cm2) for normal weight and obese children. BMD, bone mineral density.

Femoral neck BMD (g/cm^2)

Pooled results of six studies (21, 24, 28, 29, 37, 41) showed an MD of 0.02 g/cm^2 (95%CI -0.01, 0.06), indicating that there is no significant difference in femoral neck BMD between overweight and normal-weight children. The MD of femoral neck BMD between obese and normal-weight children was 0.07 g/cm^2 (95%CI 0.04, 0.09), which was obtained from 5 different studies (23, 29, 36, 37, 41) (Figure 5a and 5b). The heterogeneity for these associations was 81% (P<0.001) and 55% (P=0.05) respectively. This led to a moderate quality of evidence for the non-significant mean difference in femoral neck BMD between normal-weight and overweight children and for the significant mean difference in femoral neck BMD between normal-weight and obese children.

a

Study or Subgroup	Overweight Mean [g/cm2]	Overweight SD [g/cm2]	Overweight Total	Normal weight Mean [g/cm2]	Normal weight SD [g/cm2]	Normal weight Total	Weight	Mean Difference IV, Random, 95% CI [g/cm2]
Eriksson 2009	0.837	0.09	17	0.76	0.1	79	12.3%	0.08 [0.03, 0.13]
Gracia-Marco 2012 (1)	0.889	0.097	30	0.831	0.099	133	13.7%	0.06 [0.02, 0.10]
Gracia-Marco 2012 (2)	0.94	0.1	42	0.895	0.097	125	14.2%	0.04 [0.01, 0.08]
Ivuskans 2014	0.904	0.95	110	0.895	0.101	154	2.8%	0.01 [-0.17, 0.19]
Jeddi 2015	0.75	0.13	58	0.7	0.12	390	14.1%	0.05 [0.01, 0.09]
Shin 2011 (3)	0.8	0.03	10	0.83	0.03	10	15.3%	-0.03 [-0.06, -0.00]
Shin 2011 (4)	1.06	0.025	10	1.09	0.046	10	14.5%	-0.03 [-0.06, 0.00]
Vaitkeviciute 2014	0.913	0.092	22	0.906	0.099	133	13.2%	0.01 [-0.03, 0.05]
Total (95% CI)			**299**			**1034**	**100.0%**	**0.02 [-0.01, 0.06]**

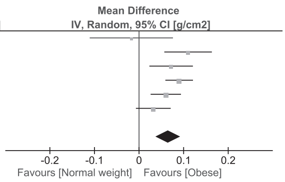


Heterogeneity: Tau² = 0.00; Chi² = 36.52, df = 7 (P < 0.00001); I² = 81%
Test for overall effect: Z = 1.40 (P = 0.16)

Footnotes
(1) Girls. Adjusted for height, calcium intake and sexual maturation
(2) Boys. Adjusted for height, calcium intake and sexual maturation
(3) Control
(4) Taekwando

b

Study or Subgroup	Obese Mean [g/cm2]	Obese SD [g/cm2]	Obese Total	Normal weight Mean [g/cm2]	Normal weight SD [g/cm2]	Normal weight Total	Weight	Mean Difference IV, Random, 95% CI [g/cm2]
Fischer 2000	0.7844	0.11705	16	0.80167	0.15034	16	6.6%	-0.02 [-0.11, 0.08]
Jeddi 2015	0.81	0.13	24	0.7	0.12	390	14.3%	0.11 [0.06, 0.16]
Rocher 2013	0.742	0.108	53	0.67	0.098	24	15.7%	0.07 [0.02, 0.12]
Shin 2011 (1)	0.92	0.04	10	0.83	0.03	10	22.7%	0.09 [0.06, 0.12]
Shin 2011 (2)	1.15	0.03	10	1.09	0.046	10	21.4%	0.06 [0.03, 0.09]
Vaitkeviciute 2014	0.938	0.088	24	0.906	0.099	133	19.3%	0.03 [-0.01, 0.07]
Total (95% CI)			**137**			**583**	**100.0%**	**0.07 [0.04, 0.09]**



Heterogeneity: Tau² = 0.00; Chi² = 11.03, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 4.75 (P < 0.00001)

Footnotes
(1) Control
(2) Taekwando

Figure 5 – (a) Pooled results of the studies that reported femoral neck BMD (g/cm2) for normal weight and overweight children. (b) Pooled results of the studies that reported femoral neck BMD (g/cm2) for normal weight and obese children.

Other outcome measures

Several outcome measures were reported by only one or two individual studies. Outcome measures that were reported by two studies were pooled. A summarized overview of these results are presented in Table 3a (overweight vs normal-weight) and Table 3b (obese vs normal-weight). Overweight children had significantly higher values at all different body sites, except at the distal radius and tibia (CoD) and the lumbar spine and femoral neck (BMC). Obese children showed significantly higher values at all body sites, except at the distal radius and tibia (CoD and TrD), at the forearm (BMD), and for the total bone mineral apparent density.

Sensitivity analyses

Sensitivity analysis on gender for total body BMC, including 3 studies (20, 24, 29), showed that the MD of total body BMC between overweight and normal weight boys was 184 grams ((95%CI 95, 273), I^2=0%, p=0.59). For girls this MD was 172 grams ((95%CI 89, 256), I^2=24%, p=0.27). Both significant MD's had high quality of evidence (see Appendix 4a). The MD of total body BMC between obese and normal weight boys was 353 grams ((95%CI -10, 717), I^2=77%, p=0.01) and for girls 473 grams ((95%CI 300, 645), I^2=50%, p=0.14), based on the same three studies (20, 24, 29). The quality of evidence for these MD's was moderate (see Appendix 4b).

For several other outcome measures, only a maximum of 2 studies reported outcomes for boys and girls separately. A summarized overview of these pooled results are shown in appendix 5.

DISCUSSION

The purpose of this systematic review was to obtain insight in the differences in BMD between normal-weight children and overweight and obese children. The current study shows that overweight and obese children have a significantly higher whole body BMC and BMD than normal-weight children. Measurements of bone density of specific body sites showed an overall trend towards, often significantly, higher bone density values in overweight and obese children. The quality of the evidence found was of moderate or high quality.

For all but two outcome measures there was significant heterogeneity between the studies with an I^2 of 63% to 81%. The heterogeneity was mainly caused by three studies (24, 26, 37). These studies reported outcome measures separately for boys and girls, or for taekwondo and control group, which might partly explain the heterogeneity. When removing these studies from the analyses the heterogeneity dropped substantially and the outcomes remained almost similar. Only for the outcome femoral neck BMD in overweight and normal-weight children, the MD became positive and significant when removing Shin et al. (37) from the analysis (MD 0.05 g/cm^2 (95%CI 0.03, 0.06)). Other possible explanations for heterogeneity could be different cut-off systems used to define the weight groups or the wide age range in the study populations. Overall, the heterogeneity did not seem to impact our results substantially.

Additional analysis between overweight and obese children showed no significant difference for total body BMC between these groups, but moderate quality of evidence was found for a significant difference in total body BMD between overweight and obese children. This indicates that being obese compared to overweight does not have as much impact as being obese or overweight compared to being of normal weight.

Table 3 – (a) Outcome measures overweight vs. non-overweight

Body site with outcome measure	Studies included	N	Mean difference (95%CI)
Radius Metaphysis BMC (g/cm)	1 (12)	427	0.06 (0.04, 0.08)**
Radius Diaphysis BMC (g/cm)	1 (12)	427	0.06 (0.04, 0.08)**
Tibia Metaphysis BMC (g/cm)	1 (12)	427	0.27 (0.19, 0.35)**
Tibia Diaphysis BMC (g/cm)	1 (12)	427	0.28 (0.22, 0.34)**
Distal radius cortical density (g/cm^3)	1 (12)	427	5.10 (-5.07, 15.27)
Distal radius trabecular density (g/cm^3)	1 (12)	427	15.40 (8.54, 22.26)**
Distal tibia cortical density (g/cm^3)	2 (12, 42)	872	-0.44 (-5.01, 4.14)
Distal tibia trabecular density (g/cm^3)	1 (12)	427	15.50 (7.77, 23.23)**
Lumbar Spine BMC (g)	1 (24)	330	0.22 (-2.5, 2.94)
Bone mineral content index (kg/m^2)	1 (31)	482	0.01 (0.01, 0.01)**
Heel BMC (g)	1 (39)	41	0.04 (0.02, 0.06)**
Heel BMD (g/cm^2)	1 (39)	41	0.05 (0.02, 0.08)**
Heel BMAD (g/cm^3)	1 (39)	41	13.30 (3.15, 23.45)*
Total hip BMC (g)	1 (24)	330	1.51 (0.04,2.99*
Total hip BMD (g/cm^2)	1 (24)	330	0.04 (0.02, 0.07)*
Femoral neck BMC (g)	1 (24)	330	0.25 (0.06, 0.44)*

*p < 0.05. **p < 0.001. BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval.

Table 3 – (b) Outcome measures obese vs. normal weight

Body site with outcome measure	Studies included	N	Mean difference (95%CI)
Distal radius cortical density (g/cm^3)	2 (18, 32)	178	-1.67 (-59.24, 55.90)
Distal radius trabecular density (g/cm^3)	2 (18, 32)	178	-0.61 (-10.33, 9.12)
Distal tibia cortical density (g/cm^3)	2 (18, 32)	181	-16.66 (-51.26, 17.93)
Distal tibia trabecular density (g/cm^3)	2 (18, 32)	178	-0.73 (-10.38, 8.93)
Total Bone Mineral Apparent Density (g/cm^3)	2 (25, 35)	112	0.04 (-0.07, 0.15)
Lumbar Spine BMC (g)	2 (35, 36)	120	3.63 (1.77, 5.49)**
Lumbar spine BMAD (g/cm^3)	1 (35)	43	0.02 (0.01, 0.03)**
Arm BMC (g)	1 (34)	115	34.00 (7.31, 60.69)*
Trunk BMC (g)	1 (34)	115	127.00 (55.35, 198.65)**
Leg BMC (g)	1 (34)	115	248.60 (143.90, 353.30)**
Total hip BMC (g)	1 (36)	77	2.66 (0.32, 5.00)*
Total hip BMD (g/cm^2)	1 (36)	77	0.07 (0.02, 0.11)*
Femoral neck BMC (g)	1 (36)	77	0.45 (0.12, 0.78)*
Forearm BMC (g)	1 (36)	77	0.64 (0.24, 1.04)*
Forearm BMD (g/cm2)	1 (36)	77	0.02 (-0.00, 0.04)

*p < 0.05. **p < 0.001. BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; CI, confidence interval.

We decided to include studies with either longitudinal or cross-sectional designs. Surprisingly our search resulted in only one study investigating the long term consequences of obesity on bone mineral density. This study found a higher trabecular density at the tibia in adult women and a somewhat lower cortical density at tibia in adult men who were obese in childhood.

The studies with a cross-sectional design mostly found a significantly higher bone density in overweight and obese children. Given the results of the cross-sectional studies and the lack of evidence on the long term consequences of childhood obesity on BMD, more prospective research should be done in this field in order to gain more knowledge on the long-term consequences of childhood obesity on the quality and strength of the bones.

Some of the cross-sectional studies analyzed girls and boys separately. Therefore, sensitivity analyses for gender were performed. Although only few studies could be included in this analyses, the analyses still showed for most outcome measures more often a significant difference between normal weight and overweight or obese in girls than boys. These findings, in combination with the outcomes of the single longitudinal study, may indicate that overall excess weight in girls leads to a higher bone density than it does in boys. One could suggest that this might be due to the difference in hormonal development in girls and boys.

The results of the current study imply that overall, overweight and obese children develop a higher peak bone mass during childhood than normal weight children. It has been suggested that increased mechanical loading, seen in children with excess weight, increases bone mineral density (12, 13). Furthermore, physical activity has been shown to increase bone mineral density as well (57, 58, 59). However, children with excess weight seem to be less physically active (60, 61). It is therefore questionable whether the effect of increased mechanical loading in overweight and obese children on BMD is as large as the effect of physical activity in normal weight children on BMD, and if the increased mechanical loading in obese children will therefore compensate for the lack of physical activity for the effect on BMD.

To compare the impact of overweight and obesity on BMD with the impact of physical activity on BMD, we compared the results of the current study with studies investigating the BMD in athletes and non-athletes (57, 58, 59). The current review showed a total body BMD MD range of 0.04-0.05 g/cm^2 versus a total body BMD MD of 0.012-0.13 g/cm^2 in studies investigating non-athletes versus athletes (57, 58, 59). The MD at the lumbar spine ranged from 0.04-0.08 g/cm^2 in the current review and from 0.06-0.076 g/cm^2 in the studies on non-athletes and athletes (57, 59). These results indicate that an increased mechanical loading, caused by for instance being overweight or obese, seems to have similar impact in the bone density, especially in the lumbar spine, as does being physically active.

In addition to the different theories mentioned above trying to explain a higher bone density in overweight and obese children, it has also been suggested that obesity may lead to an increase in circulating leptin. The role of leptin in the development of BMD is however still speculative. Leptin is known to have a direct effect on bone density, since it is a growth factor on chondrocytes of skeletal growth centers (18, 62). This could potentially contribute to increased skeletal mass in obese children (63), and to a higher peak bone mass at a younger age compared to non-overweight children (30). However, leptin also has an indirect effect on bone formation by influencing other hormones affecting the bone density (growth hormone, androgens, cortisol) (64). It has also been suggested that leptin alters the microstructure of the bones and that a higher proportion of fat mass is negatively associated with bone strength which both could lead to an increase in the propensity to fracture (12, 18). Moreover, leptin resistance, a state often met in children with obesity, seems to be related to a poorer bone health outcome (64). This may explain why obese children encounter more fractures (4, 5), and in particular fractures of the forearm (65).

Besides leptin, estrogen is also found to play an important role in bone formation and estrogen deficiency leads to increased osteoclast formation (66). One of the main sites of metabolism of estrogen is fat tissue. Since bodies of the overweight and obese contain increased fat tissue, they consequently have increased levels of estrogen (67), which could lead to the growth and positive regulation on bone formation (66).

Strengths and limitations

This is the first systematic review examining the differences in BMD between normal weight children and overweight and obese children. The literature was searched systematically and extensively, and data extraction and risk of bias assessment were done by three independent reviewers. Additionally, meta-analyses were performed to summarize the mean differences of interest.

A large percentage of the included studies reported bodyweight and height as possible confounders. In this review data were not adjusted for confounders, since most included studies only presented unadjusted data. Of the studies that did adjust for potential confounders, only in one study the association between obesity and the outcome measure changed. Confounders that would be of much interest here are for instance muscle mass and physical activity since these, among other factors, are known to play a role in the development of bone mineral density (10, 68, 69), and could therefore have influenced the outcomes in the studies.

Statistical heterogeneity was found in most pooled analyses and is likely to be explained by methodologic differences between studies. In order to deal with the heterogeneity we made use of a random effects model. We interpreted the outcome measures with care by downgrading the level of evidence by one level when heterogeneity was present (I^2 >40%) .

Since most studies included in this review were small studies with less than 50 cases of overweight or obese participants per study, one must be aware of publication bias. The funnel plots for the pooled outcome measures showed some signs of publication bias, since there are only a few larger studies showing a significant effect. The smaller studies however are symmetrically spread around the point estimate, which points to a small risk of publication bias.

It is possible that the classified 'normal weight' children will also include a subgroup of children with underweight. These underweight children could not be separately analyzed but may have had impact on our results by lowering the mean BMI of the normal weight group.

Implications

The relation between overweight and obese children and their BMD has widely been studied. It is now shown that overweight and obese children do have a higher BMC and BMD compared to normal-weight children. However, little is known on the development of bone mass into adulthood, since we only found one study investigating this longitudinal relation. Future research should therefore focus on the potential long-term effects and the development of BMC and BMD in time in both overweight and obese children.

Even though obese children develop a higher bone density during childhood, it is apparent that more injuries and fractures are seen in these children than in normal-weight children (4, 5). These fractures may be caused by increased falling because of clumsiness (6). It could be suggested that the higher bone density in obese children may be a normal adaptation to the increased weight, which is supported by two studies where after adjustment for body weight, no difference between bone density between normal weight and obese children was found (35, 36). However, it has been studied that the quality of the bone in the obese is not as high as in normal weight children and therefore the bones may be insufficient to compensate for the excess body fat and elevated body weight applied to the skeleton (35, 42).

Conclusion

Overweight and obese children have a significantly higher bone mineral density compared to normal-weight children. No conclusions can be drawn on the development of bone density from childhood into adulthood.

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Appendix 1- Search string for embase, medline, cinahl, cochrane, web-of-science, pubmed and google scholar

Embase.com

('obesity'/exp OR 'adipose tissue'/de OR 'abdominal fat'/de OR (('body weight'/de OR 'weight gain'/de OR 'body mass'/de OR 'body composition'/de OR 'body fat'/de OR 'body fat distribution'/exp) AND ('predictive value'/de OR prognosis/de OR 'regression analysis'/exp OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'follow up'/de)) OR (obes* OR overweight* OR adipos* OR ((body OR abdom*) NEXT/1 fat) OR ((BMI OR 'body mass' OR 'body composition' OR 'body weight' OR 'body fat') NEAR/6 (high* OR excess* OR content* OR predict* OR account* OR regression* OR correlat* OR retrospective* OR prospective* OR cohort* OR variable* OR assess* OR associat* OR change* OR effect* OR influen*))):ab,ti) AND ('bone density'/exp OR 'bone densitometry'/exp OR 'bone mineral'/exp OR 'bone mineralization'/exp OR 'bone strength'/de OR ((bone NEAR/3 (densit* OR mineral* OR demineral* OR strength* OR weak* OR microstructure*)) OR bmd):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR pediatrics/exp OR childhood/exp OR 'child nutrition'/de OR 'infant nutrition'/exp OR 'child welfare'/de OR 'child abuse'/de OR 'child advocacy'/de OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'child death'/de OR 'child psychiatry'/de OR 'child psychology'/de OR 'pediatric ward'/de OR 'pediatric hospital'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

Medline ovid

(exp "Overweight"/ OR exp "adipose tissue"/ OR exp "abdominal fat"/ OR ((exp "body weight"/ OR "Body Mass Index"/ OR exp "body composition"/) AND ("prognosis"/ OR exp "regression analysis"/ OR exp "cohort studies"/)) OR (obes* OR overweight* OR adipos* OR ((body OR abdom*) ADJ fat) OR ((BMI OR "body mass" OR "body composition" OR "body weight" OR "body fat") ADJ6 (high* OR excess* OR content* OR predict* OR account* OR regression* OR correlat* OR retrospective* OR prospective* OR cohort* OR variable* OR assess* OR associat* OR change* OR effect* OR influen*))).ab,ti.) AND ("Bone Density"/ OR "Calcification, Physiologic"/ OR ((bone ADJ3 (densit* OR mineral* OR demineral* OR strength* OR weak* OR microstructure*)) OR bmd).ab,ti.) AND (exp child/ OR exp infant/ OR adolescent/ OR exp pediatrics/ OR exp Child Health Services/ OR Hospitals, Pediatric/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti.)

Cinahl ebsco

(MH “Obesity+” OR MH “adipose tissue+” OR MH “abdominal fat+” OR MH “Adipose Tissue Distribution+” OR ((MH “body weight+” OR MH “Body Mass Index+” OR MH “body composition+”) AND (MH “prognosis” OR MH “regression+” OR MH “Prospective Studies+”)) OR (obes* OR overweight* OR adipos* OR ((body OR abdom*) N1 fat) OR ((BMI OR “body mass” OR “body composition” OR “body weight” OR “body fat”) N5 (high* OR excess* OR content* OR predict* OR account* OR regression* OR correlat* OR retrospective* OR prospective* OR cohort* OR variable* OR assess* OR associat* OR change* OR effect* OR influen*)))) AND (MH “Bone Density” OR ((bone N2 (densit* OR mineral* OR demineral* OR strength* OR weak* OR microstructure*)) OR bmd)) AND (MH child+ OR MH adolescence+ OR MH pediatrics+ OR (adolescen* OR infan* OR newborn* OR (new N1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under N1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*))

Cochrane

((obes* OR overweight* OR adipos* OR ((body OR abdom*) NEXT/1 fat) OR ((BMI OR ‘body mass’ OR ‘body composition’ OR ‘body weight’ OR ‘body fat’) NEAR/6 (high* OR excess* OR content* OR predict* OR account* OR regression* OR correlat* OR retrospective* OR prospective* OR cohort* OR variable* OR assess* OR associat* OR change* OR effect* OR influen*))):ab,ti) AND (((bone NEAR/3 (densit* OR mineral* OR demineral* OR strength* OR weak* OR microstructure*)) OR bmd):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

Web-of-science

TS=(((obes* OR overweight* OR adipos* OR ((body OR abdom*) NEAR/1 fat) OR ((BMI OR “body mass” OR “body composition” OR “body weight” OR “body fat”) NEAR/5 (high* OR excess* OR content* OR predict* OR account* OR regression* OR correlat* OR retrospective* OR prospective* OR cohort* OR variable* OR assess* OR associat*

OR change* OR effect* OR influen*)))) AND (((bone NEAR/2 (densit* OR mineral* OR demineral* OR strength* OR weak* OR microstructure*)) OR bmd)) AND ((adolescen* OR infan* OR newborn* OR (new NEAR/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*)))

Pubmed publisher

("Overweight"[mh] OR "adipose tissue"[mh] OR "abdominal fat"[mh] OR (("body weight"[mh] OR "Body Mass Index"[mh] OR "body composition"[mh]) AND ("prognosis"[mh] OR "regression analysis"[mh] OR "cohort studies"[mh])) OR (obes*[tiab] OR overweight*[tiab] OR adipos*[tiab] OR body fat*[tiab] OR abdominal fat*[tiab] OR ((BMI OR "body mass" OR "body composition" OR "body weight" OR "body fat") AND (high*[tiab] OR excess*[tiab] OR content*[tiab] OR predict*[tiab] OR account*[tiab] OR regression*[tiab] OR correlat*[tiab] OR retrospective*[tiab] OR prospective*[tiab] OR cohort*[tiab] OR variable*[tiab] OR assess*[tiab] OR associat*[tiab] OR change*[tiab] OR effect*[tiab] OR influen*[tiab])))) AND ("Bone Density"[mh] OR "Calcification, Physiologic"[mh] OR ((bone AND (densit*[tiab] OR mineral*[tiab] OR demineral*[tiab] OR strength*[tiab] OR weak*[tiab] OR microstructure*[tiab])) OR bmd)) AND (child[mh] OR infant[mh] OR adolescent[mh] OR pediatrics[mh] OR Child Health Services[mh] OR Hospitals, Pediatric[mh] OR (adolescen*[tiab] OR infan*[tiab] OR newborn*[tiab] OR (new born*[tiab]) OR baby OR babies OR neonat*[tiab] OR child*[tiab] OR kid OR kids OR toddler*[tiab] OR teen*[tiab] OR boy*[tiab] OR girl*[tiab] OR minors OR underag*[tiab] OR under ag*[tiab] OR juvenil*[tiab] OR youth*[tiab] OR kindergar*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepubert*[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR school*[tiab] OR preschool*[tiab] OR highschool*[tiab])) AND publisher[sb]

Google scholar

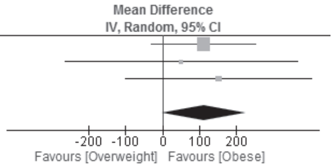
obesity|overweight|bmi prediction|predictive|regression|correlation|retrospective|prospective|longitudinal|cohort "bone density|mineral|mineralization|demineralization" adolescents|adolescence|infants|infancy|children|childhood

Appendix 2 - risk-of-bias assessment

Criteria for quality score	
Study population	
1. **Study groups (according to weight status) are clearly defined**	Positive if at least 2 of the following 3 items in all groups were reported: age, gender, BMI
2. **Participants ≥ 70%**	Positive if the participation of both the overweight and normal weight groups was ≥ 70%
3. **Number of cases ≥ 50**	Positives if the total number of cases was ≥ 50
Assessment of weight status	
4. **Weight status definition**	Positive if cut-off values for weight status definition were mentioned
5. **Assessment of weight status**	Positive if the method of assessment of weight status was described
6. **Blind for weight status assessment**	Positive if the weight status was assessed by an independent person and not based on self-report
Assessment of BMD	
7. **BMD definition**	Positive if the outcome was clearly defined
8. **BMD assessment**	Positive if the method of assessment of BMD was described
9. **Blind for weight status**	Positive if the BMD was assessed while blinded for the weight status
Study Design	
10. **Longitudinal design**	Positive if the study design was longitudinal
11. **Inclusion and exclusion criteria**	Positive if inclusion and exclusion criteria were described
12. **Follow-up period ≥ 1 year**	Positive if the follow-up period was ≥ 1 year
13. **Information on study completers versus withdrawals**	Positive if demographic information was given for completers and withdrawals
Analysis and data presentation	
14. **Data presentation**	Positive if risk estimates were presented or if raw data were given that allow the calculation of risk estimates, such as: odds or prevalence ratios or relative risks
15. **Consideration of confounders**	Positive if the confounders that were considered were described
16. **Control for confounding**	Positive if the method used to control for confounding was described

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Overweight Mean	Overweight SD	Overweight Total	Weight	Mean Difference IV, Random, 95% CI
Ellis 2003	1,616	596	160	1,504	536	96	65.9%	112.00 [-29.51, 253.51]
Ellis 2003	1,607	606	66	1,556	862	37	13.4%	51.00 [-262.88, 364.88]
Jeddi 2015	1,771.2	541	24	1,618.5	505.3	58	20.7%	152.70 [-99.80, 405.20]
Total (95% CI)			**250**			**191**	**100.0%**	**112.25 [-2.63, 227.13]**

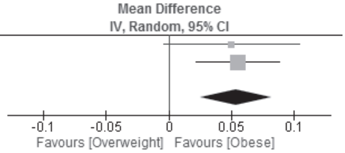
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.06)



Appendix 3a - Total body BMC of overweight and obese children

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Overweight Mean	Overweight SD	Overweight Total	Weight	Mean Difference IV, Random, 95% CI
Jeddi 2015	0.96	0.11	24	0.91	0.12	58	27.6%	0.05 [-0.00, 0.10]
Vaitkeviciute 2014	1.056	0.067	24	1.001	0.047	22	72.4%	0.06 [0.02, 0.09]
Total (95% CI)			**48**			**80**	**100.0%**	**0.05 [0.03, 0.08]**

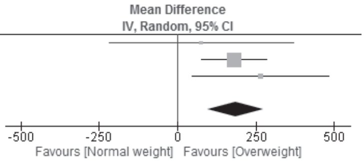
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 3.72 (P = 0.0002)



Appendix 3b - Total body BMD of overweight and obese children

Study or Subgroup	Overweight Mean	Overweight SD	Overweight Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ellis 2003	1,556	862	37	1,480	855	318	9.2%	76.00 [-217.22, 369.22]
Gracia-Marco 2012	2,225	300	42	2,045	280	125	74.3%	180.00 [76.84, 283.16]
Jeddi 2015	1,755	575	29	1,490.4	467.2	195	16.4%	264.60 [45.29, 483.91]
Total (95% CI)			**108**			**638**	**100.0%**	**184.35 [95.40, 273.29]**

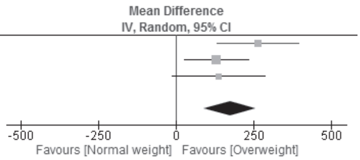
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)



Boys

Study or Subgroup	Overweight Mean	Overweight SD	Overweight Total	Normal weight Mean	Normal weight SD	Normal weight Total	Weight	Mean Difference IV, Random, 95% CI
Ellis 2003	1,504	536	96	1,242	533	188	30.9%	262.00 [130.47, 393.53]
Gracia-Marco 2012	1,975	250	30	1,845	300	133	44.0%	130.00 [27.03, 232.97]
Jeddi 2015	1,482	388.1	29	1,344.6	353.9	195	25.1%	137.40 [-12.33, 287.13]
Total (95% CI)			**155**			**516**	**100.0%**	**172.61 [89.35, 255.86]**

Heterogeneity: Tau² = 1341.19; Chi² = 2.64, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 4.06 (P < 0.0001)

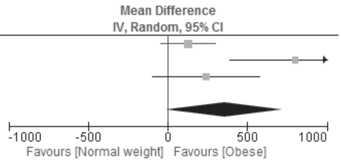


Girls

Appendix 4a - Outcomes of sensitivity analyses for gender for total body BMC normal weight vs overweight

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Normal weight Mean	Normal weight SD	Normal weight Total	Weight	Mean Difference IV, Random, 95% CI
Ellis 2003	1,607	606	66	1,480	855	318	39.9%	127.00 [-46.80, 300.80]
Haroun 2005	2,400	600	13	1,600	400	10	28.2%	800.00 [390.31, 1209.69]
Jeddi 2015	1,732.2	608.1	13	1,490.4	467.2	195	31.9%	241.80 [-95.20, 578.80]
Total (95% CI)			**92**			**523**	**100.0%**	**353.31 [-9.94, 716.55]**

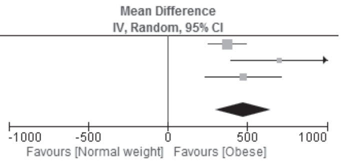
Heterogeneity: Tau² = 78161.65; Chi² = 8.79, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 1.91 (P = 0.06)



Boys

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Normal weight Mean	Normal weight SD	Normal weight Total	Weight	Mean Difference IV, Random, 95% CI
Ellis 2003	1,616	596	160	1,242	533	188	49.7%	374.00 [254.28, 493.72]
Haroun 2005	2,000	400	15	1,300	400	12	21.6%	700.00 [396.36, 1003.64]
Jeddi 2015	1,817.4	399.7	11	1,344.6	353.9	195	28.7%	472.80 [231.43, 714.17]
Total (95% CI)			**186**			**395**	**100.0%**	**472.81 [300.22, 645.40]**

Heterogeneity: Tau² = 11870.44; Chi² = 4.00, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 5.37 (P < 0.00001)



Girls

Appendix 4b - Outcomes of sensitivity analyses for gender for total body BMC normal weight vs obese

Appendix 5 - Outcomes of sensitivity analyses for gender for different outcome measures

Body site with outcome measure	Studies included	N	Mean difference (95%CI)
Total body BMD normal weight vs overweight			
Males	2(27, 32)	391	0.02 (-0.01, 0.06)
Females	2(27, 32)	387	0.03 (0.01, 0.05)**
Total body BMD normal weight vs obese			
Males	2(25, 32)	277	0.02 (-0.05, 0.09)
Females	2(25, 32)	288	0.10 (0.05, 0.14)**
Lumbar spine BMD normal weight vs overweight			
Males	2(27, 32)	391	0.03 (-0.05, 0.11)
Females	2(27, 32)	387	0.07 (0.04, 0.11)**
Lumbar spine BMD normal weight vs obese			
Males	2(25, 32)	277	0.01 (-0.07, 0.09)
Females	2(25, 32)	288	0.11 (0.06, 0.16)**
Femoral neck BMD normal weight vs overweight			
Males	2(27, 32)	391	0.04 (0.01, 0.07)*
Females	2(27, 32)	387	0.06 (0.03, 0.09)**

*p<0.05, **p<0.001