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## Original citation & hyperlink:

Brugnara Mello, J, Pedretti, A, García-Hermoso, A, Martins, C, Reis Gaya, A, Duncan, M & Gaya, A 2022, 'Exercise in school Physical Education increase bone mineral content and density: systematic review and meta-analysis', European Journal of Sport Science, vol. 22, no. 10, pp. 1618-1629. https://doi.org/10.1080/17461391.2021.1960426

DOI 10.1080/17461391.2021.1960426 ISSN 1746-1391 ESSN 1536-7290

**Publisher: Taylor and Francis** 

This is an Accepted Manuscript version of the following article, accepted for publication in [European Journal of Sport Science]. [Brugnara Mello, J, Pedretti, A, García-Hermoso, A, Martins, C, Reis Gaya, A, Duncan, M & Gaya, A 2021, 'Exercise in school Physical Education increase bone mineral content and density: systematic review and meta-analysis', European Journal of Sport Science, vol. 22, no. 10, pp. 1618-1629.

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# Exercise in school Physical Education increase bone mineral content and density: systematic review and meta-analysis

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Short title: Physical education and bone health: a meta-analysis

**Conflict of Interest Disclosures**: The authors have no conflicts of interest relevant to this article to disclose.

Funding/Support: No external funding.

**Financial disclosure:** The authors have indicated they have no financial relationships relevant to this article to disclose.

## **Abbreviations:**

BMC – Bone mineral content
BMD – Bone mineral density
aBMD – Areal bone mineral density
PE – Physical education
PRISMA – Preferred Reporting for Systematic Review and Meta-Analysis
PROSPERO – International Prospective Register of Systematic Review Database
DeCS – Descriptors in health sciences
Mendeley – Reference Management Software and Researcher Network
GOFER – Graphical Overview for Evidence Reviews
SMD – Standardized mean differences
CI – Confidence interval
RCT – Randomized controlled trial
DXA – Dual-energy X-ray absorptiometry
pQCTT – Peripheral quantitative computed tomography

**Table of Contents Summary:** This meta-analysis provides insights into the effectiveness of interventions aimed at optimizing PE on bone mass in youth, suggesting type, volume and intensity of activities.

## **Contributors' Statement Page**

Dr Júlio Mello worked in the development of the research question, contributed to the development of inclusion and exclusion criteria, performed the literature search (first coder), screened articles for eligibility, performed data analysis, drafted and critically revised the manuscript.

Dr Augusto Pedretti was the second coder for all reviewed abstracts and full texts, screened articles for eligibility and reviewed the manuscript critically for important intellectual content.

Dr Antonio García-Hermoso was responsible for data checking, data analysis supervisor, drafted and critically revised the manuscript.

Drs Clarice Martins and Anelise Gaya contributed to drafting the manuscript, results' discussion and reviewed it critically for important intellectual content.

Dr Michael Duncan contributed to the development of inclusion and exclusion criteria, drafted and reviewed the manuscript critically for important intellectual content.

Dr Adroaldo Gaya had guided the development of the research question and the inclusion and exclusion criteria, screened articles for eligibility and approved the version to be published.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgments: We would like to acknowledge Coordenadoria de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brazil) for the PhD scholarships of the authors Júlio Mello and Augusto Pedretti. We would like to acknowledge Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) for de researcher scholarship level 1-D of the Adroaldo Gaya. We would like to acknowledge Dr. Will Stahl-Timmins for use of the Graphical Overview for Evidence Reviews (GOfER) software. Dr. García-Hermoso is a Miguel Servet Fellow (Instituto de Salud Carlos III – CP18/0150).

## ABSTRACT

This systematic review and meta-analysis aimed to evaluate the effectiveness of interventions through Physical Education (PE) exercises on bone mineral content (BMC) and density (BMD) of children and adolescents. The research was conducted using the online electronic databases PubMed, Science Direct, Web of Science and Scopus (March 2021). The analysis was restricted to school-based studies that examined the effect of PE interventions on BMC and BMD in schoolchildren (<18 years-old). Standardized mean differences (SMD) with 95% confidence interval (CI) and random effects models were calculated. The heterogeneity and inconsistency of the studies was estimated using Cochran's Q-statistic and I<sup>2</sup>, respectively. Twenty-two studies with 2,556 participants were selected. PE interventions were associated with a significant increase in BMC (SMD=1.348; 95%CI, 1.053-1.643) and BMD (SMD=0.640; 95%CI, 0.417-0.862). Femoral neck subgroup analysis indicate an increase in BMC for boys (SMD=1.527; 95%CI, 0.990-2.065) and girls (SMD=1.27; 95%CI, 0.782-1.767), and in BMD for boys (SMD=0.518; 95%CI, 0.064-0.972) and girls (SMD=0.817; 95%CI, 0.349-1.284). Finally, increases are reported in the lumbar spine BMC for boys (SMD=1.860; 95%CI, 1.018-2.700) and girls (SMD=1.275; 95%CI, 0.782-1.767). This meta-analysis provides insights into the effectiveness of interventions aimed at including physical exercise in PE on bone mass, suggesting that increasing the proportion of curriculum time allocated to PE may improve students' BMD and BMC, especially in the femoral neck and lumbar spine.

Keywords: School-based program; Sports; functional exercise; bone health; children

#### What is already known?

- Bone mass accumulation during childhood and adolescence is an effective way to prevent osteoporosis and maintain bone health in adulthood.
- The annual incidence rate of hip fracture has been estimated as 1.29/1000 person-years in men and 2.24/1000 person-years in women.
- "Osteogenic" physical activities have an effect on bone structure mineral accumulation process by bone tissue's self-organization

#### What are the new findings?

- Interventions in PE, via adding an exercise program increase bone density and content, especially in the femoral neck and lumbar spine, in children and adolescents.
- Boys had greater increases in bone mineral content than girls. However, girls had greater increases in bone mineral density.
- In the majority of interventions, the recurrent feature in PE classes was the insertion of a class period with high or moderate-intensity activities/exercises, comprising 3-5 sessions weekly.
- The exercises most included in interventions were jumping, running, core exercises, coordination activities and different ball games.

## **INTRODUCTION**

Childhood and adolescence are critical periods for bone development. A review<sup>1</sup> focusing on peak bone mass indicated that 85-90% of final adult bone mass is acquired at 18 and 20 years-old in girls and boys, respectively. Therefore, childhood and adolescence (especially in the years around peak height velocity) are critical times for bone mineral acquisition<sup>1,2</sup> in both males and females, as in total, this represents approximately double the amount of bone mineral that will be subsequently lost, from 50 to 80 years of age<sup>2,3</sup>.

Increasing bone mass accumulation during childhood and adolescence, especially during the peak of bone mass phase, has therefore been considered an effective way to prevent osteoporosis and maintain bone health in adulthood<sup>3–5</sup>. Approximately 20% of peak bone mass acquisition depends on environmental and lifestyle factors, such as physical activity, nutrition, physical fitness and sex hormone levels during puberty<sup>6,7</sup>. As a consequence, the WHO 2020 guidelines on physical activity and sedentary behaviour<sup>8</sup> indicate for children and adolescents at least 3 days a week of vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone (in addition to 60 minutes a day of moderate-vigorous physical activity).

However, even if children meet the daily amount of physical activity, a recent crosssectional study<sup>9</sup> showed that the relationship between vigorous physical activity and bone health status is mediated by muscle strength and aerobic physical fitness, sprint speed, and fat mass (in different associations for boys and girls). Therefore, interventions aimed at promoting bone health must take these relationships into account throughout childhood and adolescence. In this sense, interventions with children and adolescents to minimize the decrease bone mass in adult life (tracking) has been proposed<sup>10,11</sup>.

Indeed, school settings may be important for the accomplishment of physical activities, once it is a policy-oriented environment to encourage healthy behaviours. Therefore, the inclusion, on Physical Education (PE) classes, of exercises that assure efforts whose duration and intensity are conducive to the increase of bone mass, could be an important strategy for the health promotion<sup>12</sup>. Besides PE classes, the ingestion of calcium and D-vitamin, and hormonal factors<sup>13–16</sup> appear to be potential approaches to increase peak bone mass for this age group<sup>17,18</sup>. A recent scoping review<sup>19</sup> summarized the evidence of studies that implemented different osteogenic exercises in school PE classes, and although no meta-analysis has been performed, the result indicated that PE classes based on fun, organized and varied approaches, are opportune strategies for bone health promotion. These findings are reinforced by McKay et al. (2005)<sup>20</sup>, Larsen et al. (2018)<sup>21</sup> and MacKelvie et al. (2001)<sup>22</sup>, who reported that the inclusion of simple exercises (e.g. jumps and sprints) and mini-sports-games in PE classes increased different indicators of bone mass.

Despite the existing studies focusing on bone development in different contexts, the potential of PE for enhancing bone health has seemingly been neglected, even knowing that childhood and adolescence are periods in which long-term interventions (such as PE) could promote bone benefits throughout life, reducing the risk of fractures and the osteoporosis development<sup>2,3,5</sup>. To date, no systematic review with meta-analysis has been conducted to examine the association between interventions in PE with health-related bone outcomes. The present study extends the understanding of this research field by quantifying the effects of PE exercises on bone mass using a meta-analytical approach. Without these evidence-based recommendations, improving children's bone health cannot be provided for teachers or public health professionals. Therefore, this systematic review and meta-analysis aimed to evaluate the effectiveness of interventions through PE exercises on BMC and BMD of children and adolescents.

#### **METHODS**

## Protocol and Registration

This systematic review is in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines<sup>23</sup> and registered in the International Prospective Register of Systematic Reviews database (PROSPERO, number CRD42018080311).

## Bibliography research

The strategy was designed around the PICOS question format – Do children and adolescents (Participants) who participate in an exercise-based PE program (Intervention) compared to those who do not (Comparator), differ in BMD and BMC (Outcome) in randomized clinical trials (RCT) or quasi or pre-experimental design (non-RCT) (Study design). The research was conducted using the online electronic databases PubMed, Science Direct, Web of Science and Scopus. No study date or participant demographic restrictions were imposed on the search criteria to ensure literature saturation. The search was conducted in 2018 July and reappointed in 2021 March. The search strategy was concentrated in terms of (i) effects of school-based interventions, (ii) physical education, (iii) BMD and BMC and (iv) children and adolescents (<18 years-old). The four elements were linked by the Boolean operators AND and OR.

For the search procedure, we used the Descriptors in Health Sciences (DeCS): clinical trial; exercise; bone density; child; and adolescent. For the search procedure, the following sequences used for the search strategy in this order: (a) (((("clinical trial") AND (exercise)) AND "bone density") AND (child OR Adolescents)); (b) (((exercise) AND "bone density") AND (child OR adolescents)); (c) ((exercise) AND "bone density"). In the PubMed database, for the search strategy, the title (ti) or title and abstract (tiab) field was used, combined with DeCS terms. E.g. strategy (a) (((("clinical trial"[tiab]) AND ("exercise"[tiab])) AND "bone density" [tiab]) AND ("child"[tiab] OR "Adolescents"[tiab])).

The "a" sequence was use in all databases. If there were no articles selected (result = 0) the sequence "b" was used, as well as later on "c" if there was a need. The searches were export in "bib" format files, which allowed the data to be imported and organize into the free Reference Management Software & Researcher Network (Mendeley) program.

#### Eligibility criteria

Studies were included when the following PICOS criteria were meet: (P) study conducted in healthy (i.e. no obese, disabilities, diagnosed medical condition) children or adolescents aged <18 years-old; (I) interventions characterized by including some physical exercise in PE class or in addition to PE class with objectives for gaining muscular strength, power, velocity, endurance or agility; (C) Studies in which the control group received no structured type of physical exercise (just included the usual care or regular school curriculum); (O) an assessment of at least one of the following variables: BMC or BMD in anywhere in the body; (S) school-based studies with a RCT or non-RCT design; and articles published in English, Portuguese or Spanish. The exclusion criteria included specific studies with obese schoolchildren; bone area or bone metabolism as the only outcomes; and exercise intervention and calcium/D-vitamin intake. Studies with one or more exclusion criteria were excluded.

#### Selection process

Initially, the reviewers (J.M.) and (A.P.) identified through the title/abstract the articles obtained through the search based on the inclusion criteria according to PICO strategy. Then, the complete articles were screen and the exclusion criteria were applied. A third reviewer (A.G.) was request in case of divergence between the first two reviewers. In these cases, reviewer A.G. made a final decision on eligibility.

## Extraction of data

Data extraction was performed in a spreadsheet, in which information was grouped into four domains: (i) descriptive data (sample size, mean age and sex); (ii) methodological (type and quality of the study); (iii) main effects found and (iv) main aspects of the intervention (types of exercises, intensity, volume and intervention period). If data could not be obtained from the full text or if clarification was required, authors were contacted by one reviewer. If sufficient data could not be obtained for a study, the study was excluded. To present the synthesis of study characteristics we use of the Graphical Overview for Evidence Reviews (GOFER) software<sup>24</sup>.

## Risk assessment of bias

Two reviewers (J.M and A.P.) performed the bias risk assessments and in case of disagreement in the final evaluation, a new evaluation was performed by the third reviewer (A.G.) followed by discussion for a consensus.

For the quality assessment of studies, we used the Delphi List<sup>25</sup> as described by Verhagen et al. (1998)<sup>25</sup>, which includes eight questions with three response options 'yes', 'no', or 'do not know' depending on the compliance with key methodological components, and produces a quality score that provides an overall estimate of study quality.

#### Data analysis

The pooled effect estimates were computed from the change scores between the baseline and the end of intervention, their SDs, and the number of participants. Data from intention-to-treat analyses were entered whenever available in the included studies. The authors were contacted through e-mails for unreported data, and if no answer returned or if the data requested were not available, the studies were excluded.

Effect size was expressed as Cohen's  $d^{26}$  and presented as standardized mean differences (SMD – a measure of effect, recommended to be used when a study reports

efficacy of an intervention on continuous measurements, especially in cases of different methods of measurement) and calculations were performed using random effects models. Each study was deleted from the model once in order to analyse the influence of each study on the overall results. In addition, a stratified exploratory analysis was performed using the same procedures as the main analysis, comparing the design type (RCT and non-RCT).

Statistical heterogeneity of treatment effects among studies was evaluated by Cochran's Q-statistic and the I<sup>2</sup> inconsistency test; it was considered that values >50% indicated high heterogeneity<sup>27</sup>. Forest plots were generated to present the pooled effect and the SMD with 95% confidence intervals (CIs). Statistical significance was set at a p-value < 0.05. All analyses were performed using Comprehensive Meta-Analysis Software V.2.

#### RESULTS

#### Study selection

Using the search protocol, we identified 443 potentially eligible articles. Of these, 268 were excluded on the basis of title and abstract. A further one hundred and fifty-eight full-text articles were identified as eligible (read in full). Of those, 136 articles were excluded for different reasons presented (Figure 1). Therefore, 22 studies were included in the systematic review and 21 in the meta-analysis.

## **Insert Figure 1.**

#### Study characteristics

Complete details regarding study characteristics are presented in Figure 2. Several included studies originated from the same research project, so, they were described together in some sections. Seven studies are from POP study<sup>28–34</sup>, six studies are from the same project, but did not have a specific project title<sup>22,35–39</sup>, two studies are from the AS!BC

project<sup>40,41</sup> and two studies are from the BUGSY study<sup>42,43</sup>. The other studies in the review are from different projects.

Data of 2,556 schoolchildren were analysed in experimental groups (1,297 boys, 1,197 girls and 62 children without sex identification). The control groups comprised of 1842 participants (804 boys, 957 girls and 81 children without gender identification). Nine studies were conducted exclusively with girls and two studies with boys.

Some studies presented results from the same research project, making it clear that the same participants are described in more than one study. The participants' ages ranged from 6.8 to 11 years old at the baseline. However, one of the main characteristics is that all studies evaluated and controlled the data analysis by the maturational level of the subjects. Twenty-one studies evaluated maturation by Tanner stages and one study using maturity offset proposed to Mirwald et al. (2002)<sup>44</sup>.

#### Bone mineral content and density measurement

The main variables assessed in all studies were BMC in grams, BMD (g/cm<sup>3</sup>) and aBMD (areal BMD in g/cm<sup>2</sup>), in this study both are described as BMD. The whole body was scanned in all studies, but different parts of the body were evaluated, such as, spine, lumbar spine, L3 vertebra, total body, femoral neck, trochanter, total body less head, proximal femur, narrow neck, distal forearm, calcaneus and distal radius.

Twenty studies <sup>21,22,36–39,42,43,45–48,28–35</sup> assessed bone mass by dual-energy X-ray absorptiometry - DXA [(DPX-L version 1.3z; Lunar®, Madison, WI); (Hologic QDR/4500-A; Hologic, Inc., Waltham, MA, USA); (Luna Pixi, software version: 1.4 CDMDD); (XR800, Norland Medical Systems, USA); (Lunar Prodigy; E Medical Systems, Madison, Wisconsin, USA); and (Hologic Discovery QDR Series; Hologic Inc., Bedford, MA, USA)]. Seven studies<sup>32–34,40,41,45,47</sup> assessed bone mass by peripheral quantitative computed tomography - pQCT [(XCT 2000, Stratec, Pforzheim, Germany); (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany) for main measurement or additional assessments.

#### Characteristics of interventions

Complete details regarding interventions are given in Figure 2. The main characteristic of the intervention programs was the insertion of a period of the PE class with activities of high or moderate-intensity (8 to 20 minutes) or an increase of the weekly volume of physical education classes (3 to 5 times per week) and the standard physical education classes used in the school curriculum (30-50 minutes). Each study described the intervention intensity, even though some studies have not made it clear whether the intensity was assessed objectively or subjectively. In this way, we classified the interventions from each study as moderate, moderate-vigorous or vigorous exercises (Figure 2).

Eight studies<sup>28–34,46</sup> offered an intervention program based on physical activities normally included in the school curriculum (e.g., running, jumping, climbing ropes and playing various ball games). Eleven studies<sup>22,35,48,36–39,42,43,45,47</sup> included exercise programs during, before or after class. These programs involved weight-bearing exercises mainly (e.g., jumping, core movements, coordination and skill activities). Two studies<sup>40,41</sup> increased physical activity opportunities for children throughout the school day (e.g., jumping, dancing and playground activities). And one study<sup>21</sup> used small-sided ball games. *Risk of Bias* 

Fourteen included studies satisfied at least 50% of the quality criteria (four or more quality criteria; Figure 2). Randomization criteria were conducted for 14 studies and 20 studies described the eligibility criteria and presented similar results in the baseline. Just three studies conducted the intention-to-treat analysis. In addition, each question for all

#### 11

studies is described in supplementary table 1. There was a significant publication bias in all analysis (all subgroups), as evidenced by  $I^2$  and Cochran's Q-statistic results.

## Change in bone mineral density and bone mineral content

### General descriptions

BMC was reported in the majority of studies in addition to BMD. Furthermore, the selected studies evaluated different body segments, which makes it difficult to accurately standardize the results. For boys and girls, the femoral neck and lumbar spine were reported in the vast majority of studies, giving data relating to BMC as well as to BMD. Because of this, the BMC in all body sites, femoral neck (BMC and BMD) and lumbar spine (BMC) were the only variables where data were sufficient to conduct a meta-analysis. Figure 2 shows the reported effect of each intervention (just significant or not changes). In the results, the effect size is not presented as authors of each study only presented mean differences between pre and post-test or between experimental and control groups.

## **Insert Figure 2.**

#### Meta-analysis results

Compared with the control conditions, PE interventions were associated with significantly greater values in BMC and BMD (moderate effect size in intervention group). Subgroup analysis revealed that boys demonstrated a larger increase in BMC than girls. These analyses also revealed that girls demonstrated greater increases in BMD than boys and overall results (Table 1 and supplementary figures 1 to 6).

The exploratory analysis showed that the global effect stays the same when stratified by RCTs and non-RCTs. In the RCTs, the effect for BMC was a significant increase (SMD = 1.481; 95% CI, 1.123 to 1.838; p<0.001) and at BMD too (SMD = 0.621; 95% CI, 0.379 to 0.863; p<0.001). In the non-RCTs the effect was a significant increase at

BMC (SMD = 1.077; 95% CI, 0.541 to 1.613; p<0.001) and at BMD (SMD = 0.685; 95% CI, 0.159 to 1.210; p<0.001). In these analyses, heterogeneity remained high (i<sup>2</sup> > 90%).

The subgroup analysis for different parts of the body indicates that for boys' femoral neck was available from 11 studies for BMC and 6 for BMD (Table 1 and supplementary figures 7 and 8). PE interventions were associated with a greater values (large effect size in intervention group) in femoral neck BMC compared with no intervention (SMD= 1.527; 95% CI, 0.990 to 2.065; p<0.001). There was high heterogeneity (I<sup>2</sup> =94%) and the analysis of publication bias for this outcome showed significant bias (p<0.001). Data concerning femoral neck BMD indicated that PE interventions were associated with an increase too (SMD= 0.518; 95% CI, 0.064 to 0.972; p=0.025) with high heterogeneity (I<sup>2</sup> =90%). The analysis of publication bias for this outcome showed significant bias (p<0.001).

The analysis for girls' femoral neck was available from 15 studies for BMC and 10 for BMD (Table 1 and supplementary figures 9 and 10). PE interventions were associated with a greater values (moderate effect size in intervention group) in femoral neck BMC compared with no intervention (SMD= 1.27; 95% CI, 0.782 to 1.767; p<0.001). There was high heterogeneity ( $I^2 = 94\%$ ) and the analysis of publication bias for this outcome showed significant bias (p<0.001). Data concerning femoral neck BMD indicate that PE interventions were associated with an increase too (large effect size in intervention group) (SMD= 0.817; 95% CI, 0.349 to 1.284; p<0.001) and there was high heterogeneity ( $I^2 = 91\%$ ) and the analysis of publication bias for this outcome showed significant bias (p<0.001).

The analysis concerning lumbar spine BMC was available from 8 studies for boys and 12 for girls (Table 1 and supplementary figures 11 and 12). PE interventions were associated with a greater values (large effect size in intervention group) in lumbar spine BMC compared with no intervention for boys (SMD= 1.860; 95% CI, 1.018 to 2.700; p<0.001) with high heterogeneity (I<sup>2</sup> =96%) and a significant bias (p<0.001). For girls, the result showed an increase too (high effect size in intervention group) (SMD= 1.275; 95% CI, 0.782 to 1.767; p<0.001) with high heterogeneity (I<sup>2</sup> =94%) and a significant bias (p<0.001). Conducting analysis for lumbar spine BMD was not possible due to a lack of sufficient studies.

### Insert table 1.

#### DISCUSSION

The purpose of this meta-analysis was to assess the effectiveness of interventions designed to include physical exercise in PE on the BMC and BMD of children and adolescents. The main findings of this study are the following: (1) PE interventions favourably increase BMC and BMD; (2) Subgroup analyses show that the effects of PE interventions are greater in magnitude for boys than girls (i.e., effect sizes values are higher) in BMC; (3) girls show a greater increase than boys in BMD; and (4) the analysis of subgroups for body segments indicates a significant and high increase in neck femoral and lumbar BMC and femoral neck BMD in male and female participants, regardless of age and maturation status (at baseline).

Our meta-analysis evaluated two different outcomes, while BMC is a measure in grams (g) of the amount of mineral present in the bone, BMD is a volumetric measure that involves, in addition to the quantity in grams, the size of the bone (volumetric BMD accessed by pQCT and aBMD accessed by DXA). The current study results indicated that boys seem to be more responsive to PE classes at BMC and girls at BMD. Indeed, the end of childhood is a phase in which boys experience the transition to puberty (approximately between 9 and 11 years old). For girls, this transition occurs earlier (between 7 and 9 years

old)<sup>1,49-50</sup>. In this sense, there is evidence indicating that during puberty, sex hormones are important to bone mass modulators, suggesting an osteogenic effect on trabecular bone<sup>49</sup>.

This life period impacts bone, due to the beginning of the growth spurt (resulting in peak height velocity 2 or 3 years later), characterized mainly by the growth of long bones<sup>49</sup>. As approximately 37% of the total bone mass could be attained in puberty<sup>1</sup>, two factors can explain the different bone changes among boys and girls due to the effects of the interventions, they mature at different ages and proportions. This exponential growth can interfere with BMD measurements since boys naturally increase in size, the necessary amount of bone mineral may not keep pace with the growth rate for some determined time<sup>50</sup> and this was not analysed in the studies included in this review.

In relation to the different growth proportion, during a growth spurt, the peak increment of calcium is greater, occurs later and lasts longer in boys than girls, explaining the fact that boys naturally have greater total accumulation of bone mass<sup>1,4,5</sup>. As a consequence, BMC may be a better variable to observe the intervention effects this time for boys. Conversely, in girls, being in a more advanced process of growth (where growth spurt starts earlier), their bones are probably already balanced in terms of the amount of mineral concerning their size, suggesting that BMD may be a more reliable measure for girls in this age group. Krabbe et al. (1979)<sup>50</sup> observed that after the growth spurt in 301 youths, linear growth slowed considerably while bone mineralisation rose steeply, suggesting that gonadal hormones are the initiators of the short-lived growth, with a visible effect on BMC.

Literature reviews indicate that regions with a greater amount of trabecular bone (e.g., lumbar spine), normally respond better to exercise<sup>51</sup>. Some evidence justifies this by indicating that these regions are possibly more metabolically active<sup>52</sup>. However, other evidence also indicates that the increase in BMD in response to different exercises is

identified in regions with a greater amount of cortical bone (e.g., femur)<sup>37</sup>. These findings are in line with the results of the present meta-analysis, where the most striking results in the subgroup analysis were the neck of the femur (a significant amount of trabecular and cortical bone), for both BMD and BMC, and the lumbar spine only for BMC.

These results are important public health indicators because the annual incidence rate of hip fracture has been estimated as 1.29/1000 person-years in men and 2.24/1000 person-years in women<sup>53</sup>. In addition to the high incidence, the majority of people who suffer from this injury are elderly and the mortality rate in the year following the injury for this population varies from 12 to 27%<sup>54</sup>. In this sense, children and adolescents' physical activity has been described as a strategy to improve the bone profile and prevent osteoporosis and the increased risk of fractures during adulthood<sup>55</sup>, as several studies have reported that active children, in comparison with non-active children, have greater bone mass, both in cross-sectional<sup>56</sup> and longitudinal studies<sup>57</sup>.

However, not all physical activities have equivalent influence on skeletal development<sup>5</sup>. Intense activities, especially those that produce an impact, seem to have a recognized osteogenic effect on bone<sup>14</sup>, due to osteogenic stimuli caused by the gravitational force and the intense action of muscles during impacts (piezoelectric effect of bones)<sup>51</sup>. A recent study<sup>58</sup> investigated the influence of physical activity's intensity and volume on bone mass and geometry in adolescents and adults (17-23 years-old). The authors<sup>58</sup> highlighted that the activity's intensity is key for bone mass, although the volume is important for hip geometry. This evidence indicates that the effect of physical activities on bone occurs specifically in places that support the stress of activity<sup>59</sup>. Therefore, it could be recommended that different high intensity activities should be performed, so that the piezoelectric effect caused by muscle contractions could act on a greater number of bones. These results are corroborated by a recent meta-analysis<sup>12</sup> showing that higher vigorous-

intensity physical activity is positively related to total body BMD among children and adolescents later in life.

Our results indicate that specific activities that include all body segments must be present in school-based interventions, however, the role of different physical-sporting approaches to bone health are not fully understood. Some literature reviews that investigated the effect of different exercises on the bone indicators of obese, adolescents and adults indicate that the effects of interventions may vary according to the type of activity performed and the magnitude, speed and nature of the load applied<sup>17,59–60</sup>.

Gunter et al. (2012)<sup>5</sup> stated that activities with ground reaction force greater than 3.5 times the bodyweight per leg, with peak strength occurring in less than 0.1 seconds, seem to promote greater osteogenic potential. In fact, our results evidence a high heterogeneity of procedures used in the analysed interventions. The intervention strategies of the included studies are very similar to those regularly reported in school-based studies with health outcomes<sup>8</sup>. Some studies have included sports as an addition to physical exercise. This strategy is appropriate because sports practice enhances student engagement in other physical activities.

However, although most of the studies analysed in the present review do not report indicators of ground reaction force, the activities proposed in PE classes were predominantly composed of jumping activities, core exercises, coordination and skill activities, exercise circuit and small-sided games<sup>21,22,36–39,42,43,45–48,28–35</sup>. These intervention strategies seem to be adequate since health promotion, in general, must take into account other health components. Recently, a meta-analysis<sup>12</sup> indicated that both the increase in the number of PE classes and the improvement in the quality of classes are associated with positive effects on several health indicators. This study also indicated that the inclusion of physical exercise circuits (fitness) seems to be the strategy that most promotes the most positive effect on health<sup>12</sup>. These findings are corroborated by the results of the present review, where most studies used the exercise strategies mentioned above.

#### Strengths and limitations

To our knowledge, this study is the first meta-analysis to quantify associations of interventions designed to improve PE with bone health indicators among children and adolescents. The findings of this meta-analysis emphasize the potential of intervention approaches within PE for public health benefit, as they show positive effects of PE on bone health and especially in key regions of the body (femur and spine). This evidence indicates that greater investments in PE may be have the potential to reduce people's hip fractures and osteoporosis in the future.

This study also has limitations: (1) the heterogeneity in the number of PE classes per week in the control groups and its duration; (2) the variety of strategies used during PE classes; (3) the outcomes assessed in different regions of the body, which does not allow accurate evidence from all included studies; (4) BMD was evaluated from different methods, some studies using the volumetric BMD (g/cm<sup>3</sup>) and others areal BMD (g/cm<sup>2</sup>), which makes it difficult to standardize these variables; (5) we were unable to check the ground reaction force of each intervention, what should be considered a limitation; and (6) the role of potential confounders in the meta-analysis (e.g., total physical activity and changes in the maturation level).

## CONCLUSION

Collectively, the results of this systematic review and meta-analysis suggest that interventions conducted within school PE, that aimed to promote bone health, incorporate a combination of specific exercises (e.g., jumping, core movements, coordination and skill activities, dancing and playground activities) and mini-games of high intensity or moderate-vigorous intensity and with a volume of 3 to 5 times a week. The meta-analysis demonstrated a moderate effect in global BMD and BMC. However, boys seem to be more responsive for BMC and girls more responsive for BMD. For both male and females, the results suggest moderate-high effects for the femur region and lumbar spine.

While the current study suggests specific intervention within school PE result in positive benefits for bone health, those studies included presented high publication bias and high heterogeneity. As a consequence, additional, higher-quality studies are needed to provide more robust recommendations as to the most effective exercise prescription to enhance children's bone health through school PE.

## REFERENCES

- 1. Heaney RP, Abrams S, Dawson-Hughes B, et al. Peak bone mass. *Osteoporos Int.* 2000;11(12), 985-1009. doi:10.1007/s001980070020
- 2. Bailey DA, Baxter-Jones ADG, Mirwald RL, et al. Bone growth and exercise studies: The complications of maturation. *J Musculoskel Neuron Interact*. 2003;3(4):335-337.
- 3. Hui SL, Slemenda CW, Johnston CC. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporos Int.* 1990;1(1):30-34. doi:10.1007/BF01880413
- 4. Beck TJ, Oreskovic TL, Stone KL, et al. Structural Adaptation to Changing Skeletal Load in the Progression Toward Hip Fragility: The Study of Osteoporotic Fractures. *J Bone Miner Res.* 2001;16(6):1108-1119. doi:10.1359/jbmr.2001.16.6.1108
- 5. Gunter KB, Almstedt HC, Janz KF. Physical Activity in Childhood May Be the Key to Optimizing Lifespan Skeletal Health. *Exerc Sport Sci Rev.* 2012;40(1):13-21. doi:10.1097/JES.0b013e318236e5ee
- Gracia-Marco L, Vicente-Rodriguez G, Casajus JA, Molnar D, Castillo MJ, Moreno LA. Effect of fitness and physical activity on bone mass in adolescents: the HELENA Study. *Eur J Appl Physiol.* 2011;111(11):2671-2680. doi:10.1007/s00421-011-1897-0
- 7. Turner RT, Kalra SP, Wong CP, et al. Peripheral leptin regulates bone formation. *J Bone Miner Res.* 2013;28(1):22-34. doi:10.1002/jbmr.1734
- 8. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med.* 2020;54:1451-1462. doi: 10.1136/bjsports-2020-102955
- 9. Henriques-Neto D, Magalhães JP, Júdice P, Hetherington-Rauth M, Peralta M. Mediating role of physical fitness and fat mass on the associations between physical activity and bone health in youth. *J Sport Sci.* 2020; 38(24):2811-2818. doi: 10.1080/02640414.2020.1801326
- 10. García-Hermoso A, Ezzatvar Y, Ramírez-Vélez R, Olloquequi J, Izquierdo M. Is device-measured vigorous-intensity physical activity associated with health-related outcomes in children and adolescents? A systematic review and meta-analysis. *J*

Sport Health Sci. 2021;1-12. doi: 10.1016/j.jshs.2020.12.001

- 11. Fritz J, Cöster ME, Nilsson J-Å, Rosengren BE, Dencker M, Karlsson MK. The associations of physical activity with fracture risk—a 7-year prospective controlled intervention study in 3534 children. *Osteoporos Int.* 2016;27(3):915-922. doi:10.1007/s00198-015-3311-y
- García-Hermoso A, Alonso-Martínez AM, Ramírez-Vélez R, Pérez-Sousa MÁ, Ramírez-Campillo R, Izquierdo M. Association of Physical Education With Improvement of Health-Related Physical Fitness Outcomes and Fundamental Motor Skills Among Youths. JAMA Pediatr. April 2020:e200223. doi:10.1001/jamapediatrics.2020.0223
- 13. Specker B, Binkley T. Randomized Trial of Physical Activity and Calcium Supplementation on Bone Mineral Content in 3- to 5-Year-Old Children. *J Bone Miner Res.* 2003;18(5):885-892. doi:10.1359/jbmr.2003.18.5.885
- 14. Bass SL, Naughton G, Saxon L, et al. Exercise and Calcium Combined Results in a Greater Osteogenic Effect Than Either Factor Alone: A Blinded Randomized Placebo-Controlled Trial in Boys. *J Bone Miner Res.* 2007;22(3):458-464. doi:10.1359/jbmr.061201
- 15. Agostinete RR, Lynch KR, Gobbo LA, et al. Basketball Affects Bone Mineral Density Accrual in Boys More Than Swimming and Other Impact Sports: 9-mo Follow-Up. *J Clin Densitom*. 2016;19(3):375-381. doi:10.1016/j.jocd.2016.04.006
- 16. Karpiński M, Popko J, Maresz K, Badmaev V, Stohs SJ. Roles of Vitamins D and K, Nutrition, and Lifestyle in Low-Energy Bone Fractures in Children and Young Adults. *J Am Coll Nutr.* 2017;36(5):399-412. doi:10.1080/07315724.2017.1307791
- Gómez-Bruton A, Matute-Llorente Á, González-Agüero A, Casajús JA, Vicente-Rodríguez G. Plyometric exercise and bone health in children and adolescents: a systematic review. *World J Pediatr*. 2017;13(2):112-121. doi:10.1007/s12519-016-0076-0
- Mello JB, Lemos LFGBP de, Aires LM, et al. Physical activity, sedentary time and bone tissue: effects of an 8-months interdisciplinary program with overweight/obese children. *Rev Bras Atividade Física Saúde*. 2019;23:1-7. doi:10.12820/rbafs.23e0053
- Nguyen VH. School-based exercise interventions effectively increase bone mineralization in children and adolescents. *Osteoporos Sarcopenia*. 2018;4(2):39-46. doi:10.1016/j.afos.2018.05.002
- 20. McKay HA. "Bounce at the Bell": a novel program of short bouts of exercise improves proximal femur bone mass in early pubertal children. *Br J Sports Med.* 2005;39(8):521-526. doi:10.1136/bjsm.2004.014266
- 21. Larsen MN, Nielsen CM, Helge EW, et al. Positive effects on bone mineralisation and muscular fitness after 10 months of intense school-based physical training for children aged 8-10 years: The FIT FIRST randomised controlled trial. *Br J Sports Med.* 2018;52(4):254-260. doi:10.1136/bjsports-2016-096219
- 22. MacKelvie KJ, McKay HA, Khan KM, Crocker PRE. A school-based exercise intervention augments bone mineral accrual in early pubertal girls. *J Pediatr*. 2001;139(4):501-508. doi:10.1067/mpd.2001.118190
- 23. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1. doi:10.1186/2046-4053-4-1
- 24. Graphical Overview for Evidence Reviews software. http://blogs.exeter.ac.uk/gofer/. Accessed May 1, 2020.
- 25. Verhagen AP, de Vet HCW, de Bie RA, et al. The Delphi List. J Clin Epidemiol.

1998;51(12):1235-1241. doi:10.1016/S0895-4356(98)00131-0

- 26. Cohen, J. A power primer *Psychol Bull*. 1992;112(1):155. doi: 10.1037//0033-2909.112.1.155
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ WV. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019).
   In: *The Cochrane Collaboration*. ; 2019. www.training.cochrane.org/handbook.
- 28. Valdimarsson Ö, Linden C, Johnell O, Gardsell P, Karlsson MK. Daily Physical Education in the School Curriculum in Prepubertal Girls during 1 Year is Followed by an Increase in Bone Mineral Accrual and Bone Width—Data from the Prospective Controlled Malmö Pediatric Osteoporosis Prevention Study. *Calcif Tissue Int.* 2006;78(2):65-71. doi:10.1007/s00223-005-0096-6
- 29. Alwis G, Linden C, Stenevi-Lundgren S, et al. A one-year exercise intervention program in pre-pubertal girls does not influence hip structure. *BMC Musculoskelet Disord*. 2008;9(1):9. doi:10.1186/1471-2474-9-9
- Löfgren B, Detter F, Dencker M, Stenevi-Lundgren S, Nilsson J-Å, Karlsson MK. Influence of a 3-year exercise intervention program on fracture risk, bone mass, and bone size in prepubertal children. *J Bone Miner Res.* 2011;26(8):1740-1747. doi:10.1002/jbmr.381
- Lofgren B, Dencker M, Nilsson J-A, Karlsson MK. A 4-Year Exercise Program in Children Increases Bone Mass Without Increasing Fracture Risk. *Pediatrics*. 2012;129(6):e1468-e1476. doi:10.1542/peds.2011-2274
- 32. Detter FTL, Rosengren BE, Dencker M, Nilsson J-Å, Karlsson MK. A 5-Year Exercise Program in Pre- and Peripubertal Children Improves Bone Mass and Bone Size Without Affecting Fracture Risk. *Calcif Tissue Int.* 2013;92(4):385-393. doi:10.1007/s00223-012-9691-5
- Detter F, Rosengren BE, Dencker M, Lorentzon M, Nilsson J-Å, Karlsson MK. A
   6-Year Exercise Program Improves Skeletal Traits Without Affecting Fracture Risk: A Prospective Controlled Study in 2621 Children. J Bone Miner Res. 2014;29(6):1325-1336. doi:10.1002/jbmr.2168
- 34. Fritz J, Rosengren BE, Dencker M, Karlsson C, Karlsson MK. A seven-year physical activity intervention for children increased gains in bone mass and muscle strength. *Acta Paediatr*. 2016;105(10):1216-1224. doi:10.1111/apa.13440
- 35. McKay HA, Petit MA, Schutz RW, Prior JC, Barr SI, Khan KM. Augmented trochanteric bone mineral density after modified physical education classes: A randomized school-based exercise intervention study in prepubescent and early pubescent children. *J Pediatr.* 2000;136(2):156-162. doi:10.1016/S0022-3476(00)70095-3
- 36. Mackelvie KJ, Mckay HA, Petit MA, Moran O, Khan KM. Bone Mineral Response to a 7-Month Randomized Controlled, School-Based Jumping Intervention in 121 Prepubertal Boys: Associations With Ethnicity and Body Mass Index. *J Bone Miner Res.* 2002;17(5):834-844. doi:10.1359/jbmr.2002.17.5.834
- 37. Petit MA, Mckay HA, Mackelvie KJ, Heinonen A, Khan KM, Beck TJ. A Randomized School-Based Jumping Intervention Confers Site and Maturity-Specific Benefits on Bone Structural Properties in Girls: A Hip Structural Analysis Study. *J Bone Miner Res.* 2002;17(3):363-372. doi:10.1359/jbmr.2002.17.3.363
- 38. MacKelvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA. A School-Based Exercise Intervention Elicits Substantial Bone Health Benefits: A 2-Year Randomized Controlled Trial in Girls. *Pediatrics*. 2003;112(6):e447-e452. doi:10.1542/peds.112.6.e447
- 39. MacKelvie KJ, Petit MA, Khan KM, Beck TJ, McKay HA. Bone mass and structure

are enhanced following a 2-year randomized controlled trial of exercise in prepubertal boys. *Bone*. 2004;34(4):755-764. doi:10.1016/j.bone.2003.12.017

- 40. Macdonald HM, Kontulainen SA, Petit MA, Beck TJ, Khan KM, McKay HA. Does a novel school-based physical activity model benefit femoral neck bone strength in pre- and early pubertal children? *Osteoporos Int.* 2008;19(10):1445-1456. doi:10.1007/s00198-008-0589-z
- 41. Macdonald HM, Kontulainen SA, Khan KM, McKay HA. Is a School-Based Physical Activity Intervention Effective for Increasing Tibial Bone Strength in Boys and Girls? *J Bone Miner Res.* 2007;22(3):434-446. doi:10.1359/jbmr.061205
- 42. Fuchs RK, Bauer JJ, Snow CM. Jumping Improves Hip and Lumbar Spine Bone Mass in Prepubescent Children: A Randomized Controlled Trial. *J Bone Miner Res*. 2001;16(1):148-156. doi:10.1359/jbmr.2001.16.1.148
- 43. Fuchs RK, Snow CM. Gains in hip bone mass from high-impact training are maintained: A randomized controlled trial in children. *J Pediatr*. 2002;141(3):357-362. doi:10.1067/mpd.2002.127275
- 44. Mirwald RL, G. Baxter-Jones AD, Bailey DA, Beunen GP. An assessment of maturity from anthropometric measurements. *Med Sci Sport Exerc*. 2002;34(4):689-694. doi:10.1097/00005768-200204000-00020
- 45. Daly RM, Ducher G, Hill B, et al. Effects of a Specialist-Led, School Physical Education Program on Bone Mass, Structure, and Strength in Primary School Children: A 4-Year Cluster Randomized Controlled Trial. *J Bone Miner Res.* 2016;31(2):289-298. doi:10.1002/jbmr.2688
- 46. Hasselstrøm HA, Karlsson MK, Hansen SE, Grønfeldt V, Froberg K, Andersen LB. A 3-Year Physical Activity Intervention Program Increases the Gain in Bone Mineral and Bone Width in Prepubertal Girls but not Boys: The Prospective Copenhagen School Child Interventions Study (CoSCIS). *Calcif Tissue Int.* 2008;83(4):243-250. doi:10.1007/s00223-008-9166-x
- 47. Nogueira RC, Weeks BK, Beck BR. An in-school exercise intervention to enhance bone and reduce fat in girls: The CAPO Kids trial. *Bone*. 2014;68:92-99. doi:10.1016/j.bone.2014.08.006
- 48. Bernardoni B, Thein-Nissenbaum J, Fast J, et al. A school-based resistance intervention improves skeletal growth in adolescent females. *Osteoporos Int.* 2014;25(3):1025-1032. doi:10.1007/s00198-013-2535-y
- 49. Yilmaz D, Ersoy B, Bilgin E, Gümüşer G, Onur E, Pinar E D Bone mineral density in girls and boys at different pubertal stages: relation with gonadal steroids, bone formation markers, and growth parameters. *J Bone Miner Res.* 2005;23(6):476-482. doi: 10.1007/s00774-005-0631-6
- 50. Krabbe S, Christiansen C, Rodbro P, Transbol I. Effect of puberty on rates of bone growth and mineralisation: with observations in male delayed puberty. *Arch Dis Child*. 1979;54(12):950-953. doi:10.1136/adc.54.12.950
- 51. Cadore EL, Brentano MA, Kruel LFM. Efeitos da atividade física na densidade mineral óssea e na remodelação do tecido ósseo. *Rev Bras Med do Esporte*. 2005;11(6):373-379. doi:10.1590/S1517-86922005000600013
- 52. Kemmler W, Eengelke K, Lauber D, Weineck J, Hensen J, Kalender WA. Exercise effects on fitness and bone mineral density in early postmenopausal women: 1-year EFOPS results. *Med Sci Sport Exerc.* 2002;34(12):2115-2123. doi:10.1097/00005768-200212000-00038
- 53. Adams AL, Shi J, Takayanagi M, Dell RM, Funahashi TT, Jacobsen SJ. Ten-year hip fracture incidence rate trends in a large California population, 1997–2006. *Osteoporos Int*. 2013;24(1):373-376. doi:10.1007/s00198-012-1938-5

- 54. Khan SK, Kalra S, Khanna A, Thiruvengada MM, Parker MJ. Timing of surgery for hip fractures: A systematic review of 52 published studies involving 291,413 patients. *Injury*. 2009;40(7):692-697. doi:10.1016/j.injury.2009.01.010
- 55. Nikander R, Sievänen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: A systematic review and meta-analysis for optimising bone strength throughout life. *BMC Med.* 2010;8(1):47. doi:10.1186/1741-7015-8-47
- 56. Nasri R, Hassen Zrour S, Rebai H, et al. Combat Sports Practice Favors Bone Mineral Density Among Adolescent Male Athletes. J Clin Densitom. 2015;18(1):54-59. doi:10.1016/j.jocd.2013.09.012
- 57. Gustavsson A, Thorsen K, Nordström P. A 3-Year Longitudinal Study of the Effect of Physical Activity on the Accrual of Bone Mineral Density in Healthy Adolescent Males. *Calcif Tissue Int*. 2003;73(2):108-114. doi:10.1007/s00223-002-2026-1
- 58. Rowlands AV, Edwardson CL, Dawkins NP, Maylor BD, Metcalf KM, Janz KF. Physical Activity for Bone Health: How Much and/or How Hard? *Med Sci Sports Exerc*. 2020;52(11):2331-2341. doi: 10.1249/mss.00000000002380
- 59. Menkes A, Mazel S, Redmond R a, et al. Strength training increases regional bone mineral density and bone remodeling in middle-aged and older men. *J Appl Physiol*. 1993;74(5):2478-2484. doi:10.1152/jappl.1993.74.5.2478
- 60. Yang X, Zhai Y, Zhang J, Chen J-Y, Liu D, Zhao W-H. Combined effects of physical activity and calcium on bone health in children and adolescents: a systematic review of randomized controlled trials. *World J Pediatr.* January 2020. doi:10.1007/s12519-019-00330-7

Figure 1. PRISMA Flow Diagram.

Figure 2. Graphical Overview for Evidence Reviews

**Table 1.** Synthesis of Pooled Results in general and subgroup analysis.

Outcomes	No. of studies (n)	SMD (95% CI)	p-value	<b>I</b> <sup>2</sup>	Q statistic p-value
	General effects				
BMC	20 (3721)	1.348 (1.053-1.643)	0.000	96.07	0.000
BMD	14 (2690)	0.640 (0.417-0.862)	0.000	90.45	0.000
	General effects - Boys				
BMC	13 (1679)	1.446 (0.969-1.923)	0.000	96.67	0.000
BMD	9 (1303)	0.423 (0.142-0.704)	0.003	87.46	0.000
	General effects - Girls				
BMC	18 (2217)	1.283 (0.901-1.665)	0.000	95.64	0.000
BMD	13 (1666)	0.791 (0.458-1.125)	0.000	91.84	0.000
	Femoral neck effects - Boys				
BMC	11 (1230)	1.528 (0.990-2.066)	0.000	94.79	0.000
BMD	6 (753)	0.519 (0.065-0.973)	0.025	90.93	0.000
	Femoral neck effects - Girls				
BMC	15 (1302)	1.275 (0.783-1.768)	0.000	94.09	0.000
BMD	10 (926)	0.817 (0.350-1.284)	0.001	91.57	0.000
	Lumbar Spine effects in BMC				
BMC – Boys	8 (793)	1.860 (1.019-2.701)	0.000	96.02	0.000
BMC - Girls	12 (900)	1.684 (1.054-2.315)	0.000	94.89	0.000

**Table 1.** Synthesis of Pooled Results in general and subgroup analysis.

n: number of studies; SMD: standardized mean difference; 95% CI: confidence interval of 95%; BMC: bone mineral content; BMD: bone mineral density.



