Bone Mass in Newborns Assessed by DXA – A Systematic Review and Meta-analysis

Rekha Ramot, Garima Kachhawa¹, Vidushi Kulshreshtha¹, Shweta Varshney, M. Jeeva Sankar², K. Devasenathipathy³, V. Sreenivas⁴, Rajesh Khadgawat
Departments of Endocrinology and Metabolism, ¹Obstetrics and Gynaecology, ²Paediatrics, ³Radiology and ⁴Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Abstract

Purpose: Peak bone mass - a key determinant of osteoporotic fractures result from bone accretion starting form intrauterine life to early adulthood. Optimal skeletal growth in-utero and infancy may offer protection against osteoporosis in adult life. We attempted to pool the data from available literature to get a consensus on average bone mass among healthy newborns (age ≤30 days after birth). Methods: Systematic review was conducted (PRISMA guidelines) to generate pooled estimates of bone mass parameters at whole body (WB) and lumbar spine (LS), based on both fixed and random effect models of meta-analyses. Two investigators independently carried out a comprehensive literature search using PubMed, Google Scholar and Embase. Meta-regression was applied to further explore causes of heterogeneity. Results: Out of a total 2703 studies, 2682 was excluded leaving 21 studies for final analysis. Thirteen studies reported bone mass by Hologic® and eight by Lunar®. The pooled WBBMC was 66.2g (95% CI 65.4 to 67.05 by fixed effect model, while the corresponding parameter for LS was 2.3g (95% CI 2.2 to 2.4). The subgroup and meta-regression analyses done for controlling potential confounders did not significantly affect heterogeneity. Conclusion: We generated the pooled estimate of bone mass (WBBMC) among healthy newborn subjects. There was high degree of heterogeneity among studies.

Keywords: DXA, Newborn, WBBMC

Introduction

Osteoporosis is a widespread public health problem with devastating health consequences in terms of fragility fractures. Osteoporotic fractures are associated with increased mortality and impaired quality of life, posing a huge financial burden on the economy of a country.[1] Bone mass (a composite measure of bone size and its volumetric mineral density) accumulates from early embryogenesis through intrauterine, infant, childhood, and adult life to reach a peak in the third to fourth decade. The peak bone mass (PBM) achieved is a strong predictor of later osteoporosis risk.[2] Adverse environmental exposures during infancy and puberty may lead to restriction in the growth of appendicular skeleton while that during pre-pubertal period may adversely affect the dimensions of the axial skeleton, which ultimately might affect the PBM.

The studies have suggested that the individuals, who experienced hip fractures in later life, were short at birth but had normal height by 7 years of age. This reflects the phenomenon of endocrine programming wherein hip fracture risk might be particularly elevated among individuals in whom growth of the skeletal envelope is forced ahead of the capacity to mineralise.[3]

There is growing evidence of an interaction between genome and environment in the expression of several chronic diseases including osteoporosis. It is well documented that the human skeleton can be programmed by under-nutrition. Rickets has served as a long-standing example of under-nutrition at a critical stage of early life, leading to persisting changes in structure.[4] The fracture risk might be programmed during intrauterine life through epigenetic mechanisms such as

Address for correspondence: Dr. Rajesh Khadgawat, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi - 110 049, India. E-mail: rajeshkhadgawat@hotmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Ramot R, Kachhawa G, Kulshreshtha V, Varshney S, Sankar MJ, Devasenathipathy K, et al. Bone mass in newborns assessed by DXA - A systematic review and meta-analysis. Indian J Endocr Metab 2019;23:198-205.
DNA methylation and histone modification which underlie the process of developmental plasticity.[9] The phenomenon of developmental plasticity has been demonstrated in experimental studies, stating that alterations in the diet of pregnant animals can produce lasting changes in the offspring’s physiology and metabolism. Epidemiological studies have suggested that maternal smoking and under-nutrition during pregnancy might adversely affect the intrauterine skeletal mineralization. Also, childhood growth rates have been directly linked to the risk of hip fracture.[6] Therefore, appropriate bone mass accumulation is of great significance right from birth. Dual-energy X-ray absorptiometry (DXA) is an ideal method for the accurate assessment of bone mineral content (BMC) in pediatrics as radiation exposure is low and scan time is fast.[7]

There is ample evidence suggesting a link between bone mass in infancy and risk of osteoporosis in later life.[1–3] Appropriate assessment of bone mass in infancy would help not only in better understanding and interpretation of pediatric bone diseases but also in understanding newborn bone mass in individual cases. However, lack of appropriate normative data to define bone mass among newborns makes it difficult to interpret DXA results.

Therefore, we planned this study to systematically review the available literature on bone mass of healthy newborns using DXA to generate pooled estimates of average bone mass among newborns (whole body bone mineral content) using meta-analysis. This might form a basis for generating normative values of bone mass among newborn in further studies.

**Methods**

The PRISMA guidelines were followed for writing this systematic review and the protocol was registered with PROSPERO (CRD42017064774).

**Search strategy**

Two authors independently carried out a comprehensive literature search using PubMed, Google Scholar, and Excerpta Medica database (Embase). The duration of search ranged from 1st January 1990 to 31th March 2018. Each search engine was browsed for related literature using below mentioned keywords and filter (“humans”). The main keywords used were “neonate,” “newborn,” “bone mass,” “bone mineral density,” “bone mineral content,” “reference studies” with Boolean operator “AND”.

**Eligibility criteria and study selection**

We included studies with human newborns (age ≤30 days after birth), singleton pregnancy, term delivery, and reporting bone mass by DXA at whole body and/or lumbar spine whose full text was published in English. Both longitudinal and cross-sectional studies conducted in either community or hospital settings among pregnant women with any major co-morbidity were included. We excluded animal studies, bone mass assessed by modalities other than DXA i.e., QUS, pQCT, similarly bone mass reported in neonates of mothers with systemic illnesses, preterm and SGA newborns and pregnancy complications (gestational diabetes, pre-eclampsia, etc.) were also excluded.

During review process, both authors independently reviewed the title and abstract of the studies which seemed relevant. Further, full text of the studies (seemed relevant after going through abstract), were independently reviewed by both the authors. For studies where full text could not be retrieved, corresponding author was contacted with a request to provide full text of the study. References from the studies were also reviewed for search of further studies. Throughout the process of literature review, all disagreements were resolved by consensus among authors.

**Extraction of data from selected studies: Components of data extraction form**

A standardized form was used to extract data from selected studies, which included following items: study reference (author name, journal name, volume, year, and page number), country where study was conducted, ethnicity of study subjects, continent, study setting (where study was conducted i.e., hospital or community), study design, details of DXA instrument (make and beam), site of DXA scan (whole body or lumbar spine), details of study subjects (total number, age at scan, and gender) mean and standard deviation of BMC, BMD, and bone area. It was also noted that whether investigators had taken steps to prevent movement artifacts during acquisition of scan or not.

Two authors independently worked on extracting data from studies using the standardized data collection form. The data collection forms were filled in hard copies by two authors (RR and SV) separately, cross-checked for any discrepancy by a third author. Discrepancy was sorted by discussion among authors. When the result of bone mass parameters not expressed as mean and SD, values were manually derived (wherever possible). Bone mass parameters estimated by different of DXA instrument (Hologic/Lunar) were analyzed separately.

**Statistical analysis**

Statistical analysis was performed using STATA14 (Stata Corp, College Station, TX). Mean and SD of BMC, BMD and area provided by individual studies were used for calculating pooled estimates by meta-analysis. In case of significant statistical heterogeneity, we pooled the results of studies using both fixed and random effect model. We refrained from pooling the results in the presence of marked clinical heterogeneity (like differences in population, methodology, or outcome). High degree of heterogeneity was defined by either F of more than 60% or a low P value (<0.05).[8] To explore potential causes of heterogeneity, subgroup analyses (based on age category, continent, gender, and beam of DXA machine) were carried out along with meta-regression analysis.
Results

We identified total 2,703 studies through literature search, and after scanning the titles, 2163 studies were not found to be relevant and were excluded. Out of remaining 540 studies, 263 were excluded as duplicate. Thus, abstracts of 277 studies were evaluated in detail and 234 were again excluded as per inclusion/exclusion criteria. This resulted in total 43 studies whose full text was reviewed in detail and another 21 studies were excluded for various reasons [Table S1 in supplement]. Thus, total 22 studies were eligible for meta-analysis. There was a single study reporting bone mass using Norland DXA which was excluded from analysis. Thus, final analysis included 21 studies [Figure 1].

Characteristics of studies included in meta-analysis

Most studies included in the final analysis were cross-sectional. Except for two studies (one each from Turkey and Africa), rest were either from North America or Europe. Thirteen studies used DXA machine of Hologic Inc® while eight used machines made by Lunar Inc®. There were 14 studies used fan beam densitometers while seven used pencil beam densitometer.

Of 21 studies, 19 reported bone mass at whole body, one at lumbar spine and one at both whole body and lumbar spine irrespective of the make of DXA machine. BMC WB was reported in 18 studies, while 16 studies also reported WBBMD and WB area in nine studies. All three bone mass parameters of WB (BMC, BMD, and area) were reported in seven studies. Four studies reported bone mass separately for male and female newborns while one study reported bone mass in different ethnicities (Hispanic & non-Hispanic Caucasian).

One study[22] reported bone mass at two gestational ages (38–39 weeks and 40–41 weeks) while another study[23] reported bone mass among three groups of newborn with repositioning in between scans. Thus, total 30 data sets reported from 21 studies [Table 1] were included in meta-analysis.

The studies selected for meta-analysis had varied objectives: mainly to obtain normal body composition data by DXA; to check the precision and accuracy of DXA-derived body composition measurements and to study association of various maternal, genetic and newborn factors (mainly birth weight) on body composition of infants using DXA, among infants and newborns.

Our meta-analysis was predominantly based on BMC for studies where bone mass was reported at whole body. The pooled estimate for whole body BMC by Hologic DXA [Figure 2] was 66.2 g (95% CI 65.4–67.05); as per fixed effect model, while with Lunar DXA [Figure 3] it was 78.9 g (95% CI 78.4–79.4) as per fixed effect model. The respective forest plots of WBBMD and WBAREA by Hologic and Lunar DXA are provided in supplement as Figures S1-S4.

There was only one study reporting BMC by Hologic DXA at lumbar spine with BMC of 2.3 g (95% CI 2.24–2.45) by fixed effect model. No study reported BMC at lumbar spine by Lunar DXA.

Subgroup analysis was performed based on age, sex, continent, and beam of DXA machine for both Hologic and Lunar DXA separately, to explore the impact of potential confounders on pooled estimates of bone mass parameters. It was performed for studies reporting WB bone mass as there were only few studies reporting lumbar spine parameters. Male subjects had higher
Table 1: Characteristics of studies included for meta-analysis

| Study Ref      | Place of Study | Main inclusion criteria | Study design | Race                              | Make of DXA machine (Beam) | Age at scan (days) | Site | n   | BMC (g)      | BMD (g/cm²) | Area (cm²) |
|----------------|----------------|-------------------------|--------------|-----------------------------------|-----------------------------|--------------------|------|-----|--------------|-------------|------------|
| Abrams SA et al. [10] | USA           | Singleton, Cross AGA term sectional newborns | Cross sectional | Non Hispanic Caucasian & Hispanic American, African | Hologic Delphi (Fan) | 7     | Whole body | Non Hispanic (19) Caucasian Hispanic (19) | 69.4±9.1 | 72.8±9.2 | 0.196±0.01 | 0.199±0.011 | -          |
| Ahmad I et al. [11] | USA           | AGA term Cross infants | Cross sectional | Hispanic, Caucasian, African American, Asian | Hologic Discovery A (Fan) | 3     | Whole body | 39   | 72.5±13.36 | 0.204±0.012 | -          | -          |
| Akcakus M et al. [12] | Turkey        | AGA newborns           | Cross sectional | Turkish                           | Hologic QDR 4500 Elite (Pencil) | 1     | Whole body | 40   | 53.7±9.6  | 0.426±0.022 | -          | -          |
| Beltrand J et al. [13] | France        | Term AGA Cross sectional | Cross sectional | French                           | Lunar Prodigy (Fan) | 3     | Whole body | 182  | 86.23±19.38 | 0.314±0.038 | 272.11±39.79 | -          |
| Butte NF et al. [14] | USA           | Term AGA Cross sectional | Cross sectional | Caucasian, African American, Hispanic Caucasian, Asian | Hologic QDR 2000 (Pencil) | Whole body | 68±13 | -   | 68±12 | -          | -          |
| de Knecht VE et al. [15] | Denmark      | Singleton AGA, full-term newborns | Observational cohort | Danish                           | Hologic Discovery A (Fan) | Group 1 (23) | 8-21 | 120 | 62.1±12.76 | 0.2±0.02 | -          | -          |
| Dror DK et al. [16] | USA           | Singleton AGA newborns | Cross sectional | Multiethnic                        | Hologic Discovery A (Fan) | Group 2 (13) | 8-21 | 120 | 62.1±12.76 | 0.2±0.02 | -          | -          |
| D. Manousaki et al. [17] | Canada       | Full-term AGA newborns | Cross sectional | Canadian                          | Lunar (Fan) | 8-21 | Whole body | 202  | 93±12 | 0.345±0.042 | -          | -          |
| Gallo S et al. [18] | Canada        | Singleton AGA newborns | Observational cohort | White, First nation, Asian, Black | Hologic QDR 4500A Elite (Fan) | Group 3 (28) | 8-21 | 120 | 62.1±12.76 | 0.2±0.02 | -          | -          |
| Godang K et al. [19] | Norway        | Singleton AGA newborns | Prospective cohort | Norwegian                          | GE Lunar Prodigy (Fan) | 8-21 | Whole body | 202  | 93±12 | 0.345±0.042 | -          | -          |
| Hammami M et al. [20] | USA           | Full-term AGA newborns | Observational cohort | White, African American, Hispanic American, Asian | Hologic QDR 4500A (Fan) | 3     | Whole body | 73   | 89.3±14.1 | 10.240±0.02 | 2371±32.7 | -          |
| Holroyd CR et al. [21] | UK            | Full-term AGA newborns | Population based cohort | European                           | Lunar DPXL (Fan) | 6     | Whole body | 474  | 121.4±25.3 | 0.5±0.03 | 118±24.9 | -          |

*Group 1 - scans without repositioning, Group 2 and 3 - scans with repositioning between scans

Contd...
Ramot, et al.: Bone mass among newborns

**Table 1: Contd...**

| Study Ref | Place of study | Main inclusion criteria | Study design | Race | Make of DXA machine (Beam) | Age at scan (days) | Site | n   | BMC (g) | BMD (g/cm²) | Area (cm²) |
|-----------|----------------|-------------------------|--------------|------|---------------------------|------------------|------|-----|---------|-------------|------------|
| Marta Diaz et al.[24] | Spain | Full-term AGA newborns | Cohort | Spanish | Lunar (Fan) | 14 | Whole body | 30 | 94.4±6 | 0.27±0.01 | - |
| M N Handel et al.[25] | UK | Full-term AGA newborns | Population based cohort | European | Lunar (Fan) | 14 | Whole body | Males (282) | 64.47±15.5 | 0.532±0.026 | 120.5±25.3 |
| Females (241) | 61.91±16.25 | 0.527±0.028 | 116.8±27.1 |
| Picaud JC et al.[26] | Belgium | Full-term AGA newborn | Cross sectional | Belgian | Hologic QDR 2000 (Pencil) | 7 | Whole body | 30 | 54±6 | - | 279±16 |
| Prentice Ann et al.[27] | Africa | Full-term AGA newborn | Cross sectional | African | Lunar DPX (Pencil) | 14 | Whole body | 44 | 50.9±11.6 | - | 105±20 |
| V S Quintal et al.[28] | Brazil | Full-term AGA newborn | Longitudinal | Brazilian | Hologic QDR 4500 (Fan) | 1 | Whole body | 14 | 60.76±7.32 | 0.19±0.01 | - |
| Venkataraman PS et al.[29] | USA | Full-term AGA newborn | Cross sectional | White | Lunar (Fan) | 2 | Whole body | 28 | 80.5±6.63 | 0.324±0.0001 | 241±13 |
| Xu H et al.[30] | China | Full-term AGA newborn | Longitudinal population based | Norland (Fan) | 30 | Whole body | Male (516) | - | 0.407±0.066 | 0.402±0.06 | - |
| Female (345) | - | - |

*Group 1 includes newborns at 38-39 weeks gestation, Group 2 includes newborns at 40-41 weeks gestation

**Figure 3:** Forest plot of WBBMC by Lunar DXA

values of WBBMC (male: 68.8 g (95% CI 65.9–71.6); female: 65.9 g (95% CI 63.2–68.5)) irrespective of make of DXA. Similarly, WBBMC was reported to be higher at two weeks of postnatal age compared to 1 week age for Hologic-DXA. Highest WBBMC was seen in newborns from North America followed by Europe and Africa while Asian newborns had lowest WBBMC. Also fan beam densitometers reported higher WBBMC compared to pencil beam. The details of pooled estimates of bone mass and sub group analysis are provided in Tables S2 and S3 in supplementary.

**Meta regression**

On multivariate meta-regression analysis, only the beam of DXA was found to have a significant effect on WBBMC [Table 2]. Meta-regression was not attempted at lumbar spine parameters because of less number of studies.

**Discussion**

Here, we are reporting the pooled estimates of bone mass (WBBMC) among term newborns using both, fixed, and random effect models of meta-analysis. There are evidences from human studies suggesting that optimal bone mass which determines the propensity of osteoporotic fractures in adulthood, is a function of fetal programming and adequate bone mineral accrual right from intrauterine period.[31] Therefore, it is critical to have adequate bone mass accrual right from birth so as to attain optimal peak bone mass which could have a protective effect against osteoporosis later in life.

Measurement of bone mass in pediatric age group has many limitations unlike in adults. ISCD 2013 guidelines suggest that DXA is an appropriate method for clinical densitometry of infants and young children. However, DXA measurements at lumbar spine are more feasible for infants and young children under 5 years of age while whole body BMC measurements for children under 3 years of age. Areal BMD should not be utilized routinely due to difficulty in appropriate positioning. Unlike adult patients in whom the bone volume does not change over time, a child’s bones grow over time and the growth of individual bones is not uniform in three dimensions. Thus, errors resulting from areal measurements of BMD might be introduced with DXA and can make comparison of follow-up
Meta-analysis was carried out separately based on make of DXA i.e., Hologic vs. Lunar since it is not possible to pool the results due to inherent technical variation in both manufacturers. Spine measurements are considered as feasible and reproducible parameters to assess bone mass in infants while measurement of whole body parameters has been suggested for children aged 3 years or more, possibly due to movement artefacts during measurement. However, since there are only two studies (each from different make of densitometers) on lumbar spine; meta-analysis was not feasible. Our meta-analysis predominantly included studies reporting WB BMC by Hologic or Lunar DXA.

There was high heterogeneity in our meta-analysis results for various reasons. The differences in make and beam of DXA (pencil beam in 10 and fan beam in 20 data sets in our studies) are one of the important reasons for heterogeneity of data. On subgroup analysis, fan beam densitometers showed higher values of bone mass compared to pencil beam densitometers (Table S3 in supplement).

The age of newborn at the time of measurement was variable in included studies. Out of 30 data set from 21 studies, 18 measured bone mass within first week after birth, 10 in second week and one in third and fourth week each. During first few months of life, volumetric bone density decreases as much as 30%, often called as physiological osteopenia of infancy. Dependency of newborn on intestinal supply of nutrients especially calcium with total cut-off of placental source has been proposed as one of the important postnatal adaptive changes resulting in physiological osteopenia. This difference could be one of the reasons for variability in bone mass with age and resultant high heterogeneity in the analysis.

Majority of studies reported combined data for both sexes but five studies reported separately for male and female newborns. Higher bone mass was reported in male than female newborns. This could a factor contributing to heterogeneity.

| Characteristics/covariates | Regression coefficient (95% CI) | P  | Original F unadjusted | Residual F after adjusting for covariates |
|---------------------------|---------------------------------|----|-----------------------|-----------------------------------------|
| BMC                       |                                 |    |                       |                                         |
| (No of studies=19)        |                                 |    |                       |                                         |
| Continent                 | 0.084 (-5.74 to 5.91)           | 0.97| 96.7                 | 32.6                                    |
| Sex                       | -7.17 (-15.68 to 1.34)          | 0.09|                       |                                         |
| Age category              | -2.39 (-9.3 to 4.50)            | 0.46|                       |                                         |
| Beam of DXA machine       | 8.12 (2.43 to 13.81)            | 0.008|                      |                                         |
| BMD                       |                                 |    |                       |                                         |
| (no of studies=11)        |                                 |    |                       |                                         |
| Continent                 | -0.047 (-0.07 to -0.022)        | 0.003| 99.8                 | 80.6                                    |
| Age category              | -0.001 (-0.04 to 0.35)          | 0.92|                       |                                         |
| Beam of DXA machine       | -0.024 (-0.055 to 0.007)        | 0.109|                      |                                         |
| Area                      |                                 |    |                       |                                         |
| (No of studies=6)         |                                 |    |                       |                                         |
| Continent                 | 37.26 (8.38 to 66.15)           | 0.026| 98.8                 | 88.6                                    |
| Beam of DXA machine       | 31.7 (14.01 to 49.38)           | 0.01|                       |                                         |

and baseline studies more challenging to interpret in pediatric patients. Measurement of bone mass has always remained area of controversy with many researchers reported bone mass using different techniques. However, over the years, dual energy X-ray absorptiometry (DXA) is considered as gold standard for measurement of bone mass and used in both clinical as well as research studies. The three DXA manufacturers are Hologic Inc. (Bedford, MA, USA), GE-Lunar Inc. (Madison, WI, USA), and Cooper Surgical (Norland; Trumbull, CT, USA). Although the technology used by all three manufacturers is same but bone mass results are different due to different calibration standards, proprietary algorithms to calculate BMD, and differences in regions of interest (ROI). This result in variation in reported parameters for a subject scanned on three different DXA systems. Hologic spine BMD is typically 11.7% lower than GE-Lunar BMD but 0.6% higher than Norland BMD. Scientists have suggested a standardization formula for converting parameters from one DXA to another in an attempt to give uniformity and comparison of results. Attempts have also been made to compare pencil-beam DXA (older versions of DXA) with state-of-the-art fan-beam DXA systems; however, no standardized conversion equation could be derived. Use of these equations have been reported to reduce the difference in bone mass parameters. Although such equations have also been developed for pediatric population but has not been attempted for neonatal age group; hence conversion of bone mass parameters from one to another make becomes practically impossible.

We have found higher values of pooled estimates (for whole body) by fixed effect model than random effect among studies reporting bone mass by Hologic whereas in case of Lunar DXA, values by random effect model were higher.

Table 2: Multivariate meta-regression analysis of newborn mass parameters (whole body BMC, BMD and Area by Hologic DXA)
However, gender difference in bone mass has not been reported at birth and volumetric BMD appears similar in male and females.[33]

Although, racial differences in bone mass have been reported to appear early in life but probably not at birth. Rupich et al. has shown higher WBBMD among healthy black infants at 1–18 months age compared to white infants.[38] Similarly, Prentice et al. observed that the Gambian infants had significantly lower BMC at radius than British infants.[39] In subgroup analysis based on continent, we have also observed that American newborns had greater bone mass as compared to Europeans and Asians. Pooling of data from different geographical regions (continent) might have also contributed to high heterogeneity.

In our analysis, there were few studies reporting bone mass parameters widely differing from the pooled estimate. One study (Akcakus et al.,[11]) reported lowest WBBMC (Hologic) among all other studies; however, reported WBBMD was highest as compared to other studies but bone area was not reported. It seems that all subjects had very less bone area, only then, BMD will be the highest one. However, it seems very unlikely as all newborns had a good birth weight and average birth length. Removing this study from analysis increased the pooled WBBMC from 66.68 g to 67.67 g with minor shift in heterogeneity (96.3% vs. 95.9%).

Similarly, Prentice et al.[27] reported very low WBBMC value (Lunar) while higher BMC is reported by Godang K et al.[18] and Diaz M et al.[24] which varied much from pooled estimate. Higher mean gestational age and birth weight by Godang K et al. and Diaz M et al. compared to Prentice et al. could be a factor resulting in variation.

Strengths and limitations

Our study is probably the first attempt to quantitatively pool the available literature on bone mass among newborn subjects. Majority of the studies reported whole body bone mass in newborns which has not been advised in children under 3 years of age.[33] There are only two studies reporting bone mass at lumbar spine, thereby limiting possibility of meta-analysis. High degree of heterogeneity among studies is another important limitation. However, subgroup analysis based on appropriate categories was carried out to address the issue of high heterogeneity. Similarly, meta-regression analysis was also applied to identify potential confounding factors contributing to heterogeneity.

We have generated pooled estimate of bone mass (WBBMC) among healthy full-term newborns. However, in view of high heterogeneity among studies and fewer studies in each category, there is a need of well-planned high-quality large scale studies to get the true estimate of average bone mass among newborns.

List of abbreviations

- BMC - bone mineral content
- BMD - bone mineral density
- WB BMC/BMD - whole body bone mineral content/bone mineral density
- QUS - quantitative ultrasound
- pQCT - peripheral quantitative computed tomography
- IUGR - intrauterine growth retardation
- AGA - appropriate for gestational age
- SGA - small for gestational age
- SD - standard deviation
- 95%CI - 95% confidence interval.

Declaration of conflict of interest

Rekha Ramot, Garima Kachhawat, Vidushi Kulshreshtha, M. Jeeva Sankar, Devasenathipathy K., V. Sreenivas, and Rajesh Khadgawat declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research work reported.

Author contribution details

RK, JS, RR, GK, VK, KD, and VS: conceived of the project idea and designed the protocol, led the development of the manuscript and have primary responsibility for the final content. RR and SV: designed the proforma for data collection, done extensive literature review, has done screening studies and has captured data from studies that were selected for inclusion in final meta-analysis. VS and JS: analyzed the data, performed the statistical analysis and involved in preparation and approval of final content of manuscript. All authors have read and approved the final manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Harvey N, Dennison E, Cooper C. Epidemiology of osteoporotic fracture. In: Favus MJ, editor. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 7th ed. ASMBR; 2008. p. 198-203.
2. Cooper C, Westlake S, Harvey N, Javaid K, Dennison E, Hanson M. Developmental origins of osteoporotic fracture. Osteoporos Int 2006;17:337-47.
3. Javaid MK, Eriksson JG, Kajantie E, Forsén T, Osmond C, Barker DJP, et al. Growth in childhood predicts hip fracture risk in later life. Osteoporos Int 2011;22:69-73.
4. Godfrey KM. Maternal regulation of fetal development and health in adult life. Eur J Obstet Gynecol Reprod Biol 1998;78:141-50.
5. Earl SC, Harvey NC, Cooper C. The epigenetic regulation of bone mass. JBMS BoneKEy 2010.;7:54-62.
6. Cooper C, Javaid MK, Taylor P, Walker-Bone K, Dennison E, Arden N. The fetal origins of osteoporotic fracture. Calcif Tissue Int 2002;70:391-4.
7. Moras S, Bachrach L, Gilsanz V. Non-invasive techniques for bone mass measurement. In Pediatric Bone: Biology & Diseases. Elsevier Inc.; 2003. p. 303-24.
8. Pai M, McCulloch M, Gorman JD, Pai N, Enanoria W, Kennedy G, et al. Systematic reviews and meta-analyses: An illustrated, step-by-step guide. Natl Med J India 2004;17:86-95.
9. Abrams SA, Hawthorne KM, Rogers SP, Hicks PD, Carpenter TO. Effects of ethnicity and vitamin D supplementation on vitamin D status and changes in bone mineral content in infants. BMC Pediatr 2012;12:6.
10. Ahmad I, Nemet D, Eliakim A, Koeppel R, Grochow D, Coussens M, et al. Body composition and its components in preterm and term newborns: A cross sectional, multimodal investigation. Am J Hum Biol 2010;22:69-75.
11. Akcakus M, Kurtoglu S, Koklu E, Kula M, Koklu S. The relationship between birth weight leptin and bone mineral status in newborn infants. Neonatology 2007;91:101-6.
12. Beltrand J, Alison M, Nicolescu R, Verkaaikenski R, Deehmoun S, Sibony O, et al. Bone mineral content at birth is determined both by birth weight and fetal growth pattern. Pediatr Res 2008;64:86-90.
13. Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ. Body composition during the first 2 years of life: An updated reference. Pediatr Res 2000;47:578-85.
14. de Knegt VE, Carlensen EM, Bech Jensen JE, Lade Rasmussen AM, Prys D. DXA performance in a pediatric population: Precision of body composition measurements in healthy term born infants using dual-energy X-ray absorptiometry. J Clin Densitom 2015;18:117-23.
15. Dorr DK, King JC, Fung EB, Van Loan MD, Gertz ER, Allen LH. Evidence of associations between feto-maternal vitamin D status, cord parathyroid hormone and bone-specific alkaline phosphatase, and newborn whole body bone mineral content. Nutrients 2012;4:68-71.
16. Manousaki D, Rauch F, Chabot G, Dubois J, Fiscaletti M, Alos N. Pediatric data for dual X-ray absorptiometric measures of normal lumbar bone mineral density in children under 5 years of age using the Lunar prodigy densitometer. J Musculoskelet Neuronal Interact 2016;16:247-55.
17. Gallo S, Vanstone CA, Weiler HA. Normative data for bone mass in healthy term infants from birth to 1 year of age. J Osteoporos 2012;2012. doi: 10.1155/2012/672403.
18. Godang K, Frøslie K, Henriksen T, Isaksen GA, Voldner N, Lekva T, et al. Umbilical cord levels of sclerostin, placental weight, and birth weight are predictors of total bone mineral content in neonates. Eur J Endocrinol 2013;168:371-8.
19. Hammani M, Koo WW, Hockman EM. Body composition of neonates from fan beam dual energy X-ray absorptiometry measurement. J Parenter Enter Nutr 2003;27:423-6.
20. Holroyd CR, Harvey NC, Crozier SR, Winder NR, Mahon PA, Ntami G, et al. Placental size at 19 weeks predicts offspring bone mass at birth: Findings from the Southampton Women’s Survey. Placenta 2012;33:623-9.
21. Javaid MK, Godfrey KM, Taylor P, Robinson SM, Crozier SR, Dennisson EM, et al. Umbilical cord leptin predicts neonatal bone mass. Calcif Tissue Int 2005;76:341-7.
22. Koo WW, Walters J, Bush AJ, Chesney RW, Carlson SE. Dual-energy X-ray absorptiometry studies of bone mineral status in newborn infants. J Bone Miner Res 1996;11:997-102.
23. Lapillonne A, Braillon P, Claris O, Chatelain PG, Delmas PD, Salle BL. Body composition in appropriate and in small for gestational age infants. Acta Paediatr 1997;86:196-200.
24. Díaz M, García C, Sebastiani G, de Zegher F, López-Bermejo A, Ibáñez L. Placental and cord blood methylation of genes involved in energy homeostasis: Association with fetal growth and neonatal body composition. Diabetes 2017;66:779-84.
25. Händel MN, Moon RJ, Titcombe P, Abrahamson B, Heitmann BL, Calder PC, et al. Maternal serum retinol and β-carotene concentrations and neonatal bone mineralization: Results from the Southampton Women’s Survey cohort. Am J Clin Nutr 2016;104:1183-8.
26. Picaud JC, Rigo J, Nyamugabo K, Milet J, Senterre J. Evaluation of dual-energy X-ray absorptiometry for body-composition assessment in piglets and term neonates. Am J Clin Nutr 1996;63:157-63.
27. Prentice A, Jarjou LM, Goldberg GR, Bennett J, Cole TJ, Schoenmakers I. Maternal plasma 25-hydroxyvitamin D concentration and birth weight, growth and bone mineral accretion of Gambian infants. Acta Paediatr 2009;98:1360-2.
28. Quintal VS, Diniz EM, Carapbo Vde F, Pereira RM. Bone densitometry by dual-energy X-ray absorptiometry (DXA) in preterm newborns compared with full-term peers in the first six months of life. J Pediatr (Rio J) 2014;90:556-62.
29. Venkataramanan PS, Ahluwalia BW. Total bone mineral content and body composition by X-ray densitometry in newborns. Pediatrics 1992;90:767-70.
30. Xu H, Zhao Z, Wang H, Ding M, Zhou A, Wang X, et al. Bone mineral density of the spine in 11,898 Chinese infants and young children: A cross-sectional study. PLoS One 2013;8:e82098.
31. Cooper C, Javaid K, Westlake S, Harvey N, Dennison E. Developmental origins of osteoporotic fracture: The role of maternal vitamin D insufficiency. J Nutr 2005;135:2728S-34S.
32. Binkovitz LA, Henwood MJ. Pediatric DXA: Technique and interpretation. Pediatr Radiol 2007;37:21-31.
33. Blake GM, Fogelman I. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. Postgrad Med J 2007;83:509-17.
34. Fan B, Lu Y, Genant H, Fuerst T, Shepherd J. Does standardized BMD still remove differences between Hologic and GE-Lunar state-of-the-art DXA systems? Osteoporos Int 2010;21:1227-36.
35. Gordon CM, Leonard MB, Zemel BS. International Society for Clinical Densitometry. 2013 Pediatric Position Development Conference: Executive summary and reflections. J Clin Densitom 2014;17:219-24.
36. Rauch F, Schoenau E. Changes in bone density during childhood and adolescence: An approach based on bone’s biological organization. J Bone Miner Res 2001;16:597-604.
37. Glorieux FH, Pettifor JM, Jappner H. Pediatric Bone: Biology and Diseases. 2nd ed. 32 James Town Road, London, NW 17BY, UK: Academic Press; 2012.
38. Rupich RC, Specker BL, Lieuw-A-Fa M, Ho M. Gender and race differences in bone mass during infancy. Calcif Tissue Int 1996;58:395-7.
39. Prentice A, Ann Laskey M, Shaw J, Cole T, Fraser D. Bone mineral content of Gambian and British children aged 0-36 months. Bone Miner 1990;10:211-24.
**Figure S1:** Forest plot of WBBMD by Hologic DXA. WBBMD – whole body bone mineral density. Abram SA et al. reported BMD among two ethnic groups – Hispanic and non Hispanic Caucasian. de Knecht VE – reported BMC among three groups of newborns with repositioning between scans.

**Figure S2:** Forest plot of WBBMD by Lunar DXA. WBBMD – whole body bone mineral density. Holroyd CR et al. and Hnadel MN – reported BMD in males and females separately.

**Figure S3:** Forest plot of WBArea by Hologic DXA. WBArea - whole body area. de Knecht VE - reported BMC among three three groups of newborns with repositioning between scans.
Figure S4: Forest plot of WBArea by Lunar DXA. WBArea- whole body area.
Holroyd CR et al. and Hnadel MN- reported area in males and females separately
| Study reference            | Study title                                                                                         | Reason for exclusion                                                                 |
|---------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Braillon PM et al.        | Dual energy X-ray absorptiometry measurement of bone mineral content in newborns: validation of the  | Absolute values of BMC and BMD are not reported, rather provided as range          |
| Pediatr. Res. 1992 Jul; 32 (1):77-80. | technique.                                                                                           |                                                                                      |
| Kurl S et al., Clin Physiol Funct Imaging. 2002 May; 22 (3):222-5. | Lumbar bone mineral content and density measured using a Lunar DPX densitometer in healthy full-term infants during the first year of life. | Age at DXA examination is more than one month (0.4±0.17 year)                     |
| Salle BL et al., Acta Paediatr. 1992 Dec; 81 (12):953-8. | Lumbar bone mineral content measured by dual energy X-ray absorptiometry in newborns and infants. | Absolute values of BMD not reported,                                               |
| Zia-Ullah M et al., J Clin Densitom. 2002 Spring; 5 (1):17-25. | Lumbar spine bone measurements in infants: whole-body vs lumbar spine dual X-ray absorptiometry scans. | age at DXA examination ranged from 1-395 days                                      |
| WINSTON W. K. Koo et al., J Bone Miner Res, 1995; 10 (12):1998-2004 | Technical Considerations of Dual-Energy X-Ray Absorptiometry-based Bone Mineral Measurements for Pediatric Studies | Data from same cohort already included in analysis. (Koo WW et al., J Bone Miner Res 1996; 11 (7):997:102) |
| Avila-Díaz M et al., Arch Med Res. 2001 Jul-Aug; 32 (4):288-92. | Increments in whole body bone mineral content associated with weight and length in pre-term and full-term infants during the first 6 months of life. | Age at DXA examination is more than one month (33±4 days)                           |
| Specker BL et al., Pediatrics. 1997 Jun; 99 (6):E12. | Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. | Age at DXA examination is more than one month (4.7±0.5)                             |
| Javaid MK et al., Bone Miner Res. 2004 Jan; 19 (1):56-63. | Umbilical venous IGF-1 concentration, neonatal bone mass, and body composition | Data from same cohort already included in analysis. (Javaid MK et al., Calcif Tissue Int. 2005; 76 (5):341-7) |
| Demarini S et al., Acta Paediatr. 2006 May; 95 (5):594-9. | Bone, lean, and fat mass of newborn twins versus singletons. | Data from same cohort already included in analysis. (Koo WW et al., J Bone Miner Res 1996; 11 (7):997:102) |
| Harvey NC et al., Southampton Women’s Survey Study Group. J Clin Endocrinol Metab. 2008 May; 93 (5):1676-81. | Paternal skeletal size predicts intrauterine bone mineral accrual. | Data from same cohort already included in analysis. (Holroyd CR et al., Placenta. 2012; 33 (8):623-629) |
| Koklu E et al., J Paediatr Child Health. 2007 Oct; 43 (10):667-72. | The relationship between birth weight, oxidative stress and bone mineral status in newborn infants | Data from same cohort already included in analysis. (Akcakus M et al., Neonatology. 2007; 91 (2):101-6) |
| Martin R et al. SWS Study Group. Bone. 2007 May; 40 (5):1203-8. | Placental calcium transporter (PMCA3) gene expression predicts intrauterine bone mineral accrual. | Bone mass values adjusted for gestational age and age at DXA scan                   |
| Godfrey K et al., J Bone Miner Res. 2001 Sep; 16 (9):1694-703. | Neonatal bone mass: influence of parental birth weight, maternal smoking, body composition, and activity during pregnancy | Data from same cohort already included in analysis. (Holroyd CR et al., Placenta. 2012; 33 (8):623-629) |
| Akcakus M et al. Ann Trop Paediatr. 2006 Dec; 26 (4):267-75. | The relationship between birth weight, 25-hydroxvitamin D concentrations and bone mineral status in neonates | Data from same cohort already included in analysis. (Akcakus M et al., Neonatology. 2007; 91 (2):101-6) |
| Akcakus M et al., Acta Paediatr. 2006 Nov; 95 (5):1128-34. | The relationship among intrauterine growth, insulin-like growth factor I (IGF-1), IGF-binding protein-3, and bone mineral status in newborn infants | Data from same cohort already included in analysis. (Akcakus M et al., Neonatology. 2007; 91 (2):101-6) |
| Cooper C, et al. MAVIDOS Study Group. Lancet Diabetes Endocrinol. 2016 May; 4 (5):393.402. | Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial | DXA assessment by Hologic and Lunar instruments but paper reports whole body bone mass without specifying make of DXA instrument |
| Harvey NC et al. J Dev Orig Health Dis. 2010 Feb; 1 (1):35-41. | Maternal predictors of neonatal bone size and geometry: the Southampton Women’s Survey | Data from same cohort already included in analysis. (Holroyd CR et al., Placenta. 2012; 33 (8):623-629) |
| Godang K et al., J Clin Densitom. 2010;13 (2):151-60. | Assessing body composition in healthy newborn infants: reliability of dual-energy X-ray absorptiometry. | Data from same cohort already included in analysis. (Dror DK et al., Nutrients. 2012; 4 (2):68-77) |
| Dror DK et al., Nutrients. 2012 Feb; 4 (2):68-77. | Evidence of associations between feto-maternal vitamin D status, cord parathyroid hormone and bone-specific alkaline phosphatase, and newborn whole body bone mineral content. | Data from same cohort already included in analysis. (Weiler HA et al., Growth Dev Aging. 2008; 71 (1): 35-43) |
| Weiler H et al., CMAJ. 2005 Mar 15;172 (6):757-61. | Vitamin D deficiency and whole-body and femur bone mass relative to weight in healthy newborns. | Data from same cohort already included in analysis. (Gallo S et al., J Osteoporos 2012; 672403) |
| Weiler HA et al., Growth Dev Aging 71: 35-43 | Bone mass in first nations, Asian and white newborn infants | Data from same cohort already included in analysis.                             |
| Table S2: Newborn whole body bone mass parameters (BMC, BMD & Area) |
|---------------------------------------------------------------|
| **Parameter** | **Hologic DXA machine** | **Lunar DXA machine** |
|               | **No of** | **Mean pooled estimate (95% CI); $I^2$ (%)** | **No of** | **Mean pooled estimate (95% CI); $I^2$ (%)** |
|               | **studies** | **Fixed effect model** | **Random effect model** | **Fixed effect model** | **Random effect model** |
| BMC (g)       | 13         | 66.2 (65.4-67.05); 96.7 | 67.7 (63.4-72.6) | 7 | 78.9 (78.4-79.4); 9.8 | 73.0 (61.2-84.8) |
| BMD (g/cm²)   | 8          | 0.22 (0.22-0.22); 9.8 | 0.23 (0.20-0.26) | 6 | 0.32 (0.32-0.32); 100 | 0.41 (0.33-0.49) |
| Area (cm²)    | 4          | 316.4 (313.2-319.7); 98.8 | 326.4 (296.1-356.6) | 5 | 131.3 (130.1-132.4); 99.9 | 156.3 (122.3-190.3) |

| Table S3: Subgroup analysis of newborn bone mass (whole body BMC, BMD and area) |
|--------------------------------------------------------------------------|
| **Variable**                | **Hologic $n$, Mean (95% CI)** | **Lunar $n$, Mean (95% CI)** | **Hologic $n$, Mean (95% CI)** | **Lunar $n$, Mean (95% CI)** | **Hologic $n$, Mean (95% CI)** | **Lunar $n$, Mean (95% CI)** |
| Sex                        | 2 | 68.8 (65.9-71.6) | 1 | 64.8 (63.7-65.9) | - | 0.5 (0.49-0.50) | - | 121.06 (119.3-122.7) |
| Age Category               | 9 | 66.1 (65.1-67.1) | 3 | 88.4 (87.2-89.7) | 2 | 0.22 (0.22-0.23) | 1 | 0.32 (0.32-0.32) | 316.4 (313.2-319.7) | 2 | 253.7 (250.04-257.4) |
| Continent                  | 1 | 53.7 (50.7-56.7) | - | 0.43 (0.42-0.43) | - | 0.23 (0.22-0.23) | 1 | 0.45 (0.45-0.45) | 302.1 (297.8-306.5) | 3 | 127 (125.7-128.2) |
| Beam of DXA machine        | 7 | 34.0 (33.2-34.8) | 6 | 70.5 (69.3-71.7) | 5 | 334.4 (329.5-339.3) | 4 | 33.2 (32.8-33.6) | 3 | 241 (236.2-245.8) |
|                            | 6 | 50.9 (48.9-52.9) | 4 | 61.7 (60.9-62.5) | 1 | 105 (101.5-108.5) | 2 | 105 (101.5-108.5) | 1 | 105 (101.5-108.5) |

| Beam of DXA machine        | 7 | 71.6 (70.4-72.8) | 6 | 80.7 (80.2-81.2) | 6 | 350.2 (345.2-355.2) | 2 | 350.2 (345.2-355.2) | 4 | 134.5 (133.3-135.7) |

| Beam of DXA machine        | 6 | 61.4 (60.2-62.5) | 1 | 50.9 (48.9-52.9) | 2 | 291.6 (287.4-295.9) | 2 | 291.6 (287.4-295.9) | 1 | 105 (101.5-108.5) |