Original Article

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

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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

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DNA methylation and histone modification which underlie the process of developmental plasticity.[5] 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 31st 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 without 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 I^2 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).

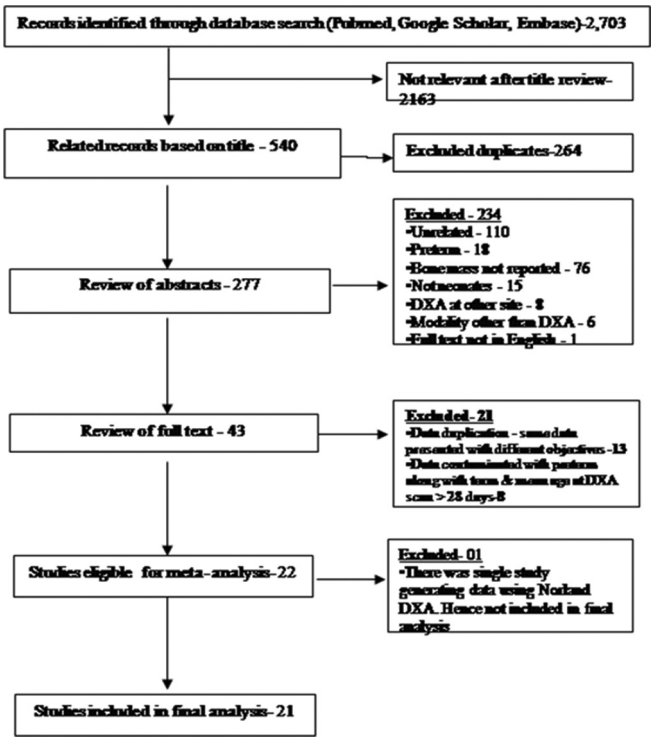

Figure 1: PRISMA diagram for study selection

One study[22] reported bone mass at two gestational ages (38–39 weeks and 40–41 weeks) while another study[13] 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

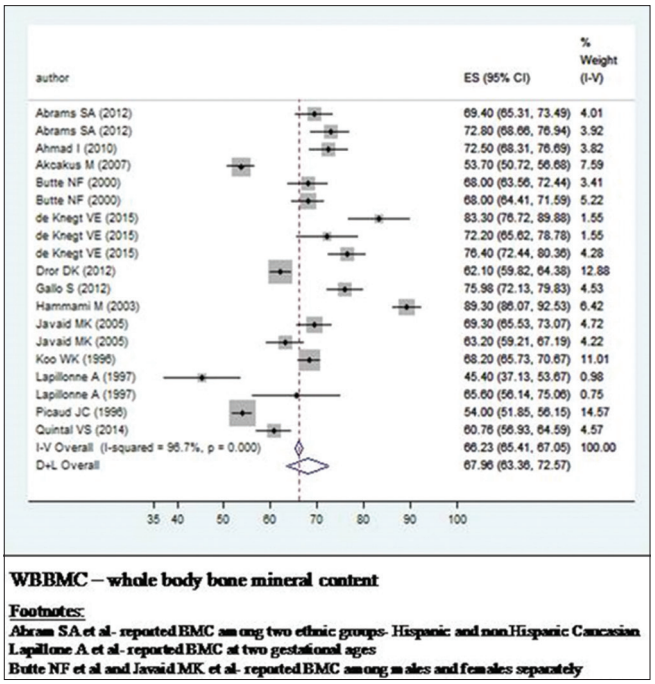

Figure 2: Forest plot of WBBMC by Hologic DXA

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*.[9]	USA	Singleton, AGA term newborn	Cross sectional	Non Hispanic Caucasian & Hispanic	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*.[10]	USA	AGA term 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*.[11]	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*.[12]	France	Term AGA newborn	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*.[13]	USA	Term AGA newborn	Cross sectional	Caucasian, African American, Hispanic Hispanic, Asian	Hologic QDR 2000 (Pencil)	15	Whole body	Male (33) Female (43)	68±13 68±12	-	-
de Knegt VE *et al*.[14]	Denmark	Singleton AGA, full-term newborns	Observational	Danish	Hologic Discovery A (Fan)	1	Whole body	Group* 1 (23) Group 2 (13) Group 3 (28)	83.3±16.1 72.2±12.1 76.4±10.7	0.242±0.03 0.220±0.02 0.229±0.02	341.8±31.6 326.1±24.3 333.3±26.2
Dror DK *et al*.[15]	USA	Singleton AGA newborns	Cross sectional	Multiethinic	Hologic Discovery A (Fan)	8-21	Whole body	120	62.1±12.76	0.2±0.02	-
D. Manousaki *et al*.[16]	Canada	Full-term AGA infants	Cross sectional	Canadian	Lunar (Fan)	30	Lumbar spine	30	-	0.30±0.04	-
Gallo S *et al*.[17]	Canada	Singleton AGA, full-term newborn	Observational	White, First nation, Asian, Black	Hologic QDR 4500A Elite (Fan)	14	Lumbar spine Whole body	62 52	8.86±1.10 75.98±14.17	0.266±0.044 -	- -
Godang K *et al*.[18]	Norway	Singleton AGA newborn	Prospective cohort	Norvegian	GE Lunar Prodigy (Fan)	2	Whole body	202	93±12	0.345±0.042	-
Hammami M *et al*.[19]	USA	Full-term AGA newborns	Observational	White, African American, Hispanic	Hologic QDR 4500A (Fan)	3	Whole body	73	89.3±14.	10.240±0.02	2371±32.7
Holroyd CR *et al*.[20]	UK	Full-term AGA newborns	Population based cohort	European	Lunar DPXL (Fan)	6	Whole body	Male (474) Female (440)	65±15.6 61.3±15.1	0.5±0.03 0.5±0.3	121.4±25.3 118±24.9

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

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)
Javaid MK *et al*.[21]	UK	Full-term AGA new born	Population based cohort	European	Hologic QDR 2000 (Pencil)	14	Whole body	Male (67) Female (50)	69.3±15.76 63.2±14.39	- -	- -
Koo WK *et al*.[22]	USA	Full-term AGA new born	Cross sectional	Memphian	Hologic QDR 1000 (Pencil)	2	Whole body	65	68.2±10.16	0.221±0.017	307.6±26.43
Lapillonne A *et al*.[23]	France	AGA new born	Cross sectional	French	Hologic QDR 1000 (Pencil)	2	Whole body	Group#1 (19) Group 2 (16)	45.4±18.4 65.6±19.3	-	-

Contd...

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/cm^2)	Area (cm^2)
Marta Díaz *et al.*[24]	Spain	Full-term AGA newborns	Cohort	Spanish	Lunar (Fan)	14	Whole body	30	94.4±6 2	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) Females (241)	64.47±15.5 61.91±16.25	0.532±0.026 0.527±0.028	120.5±25.3 116.8±27.1
Picaud JC *et al.*[26]	Belgium	Full-term AGA new born	Cross sectional	Belgian	Hologic QDR 2000 (Pencil)	7	Whole body	30	54±6	-	279±16
Prentice Ann *et al.*[27]	Africa	Full-term AGA new born	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 new born	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 new born	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 new born	Longitudinal population based	Chinese	Norland (Fan)	30	Whole body	Male (516) Female (345)	- - 	0.407±0.066 0.402±0.06	- -

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

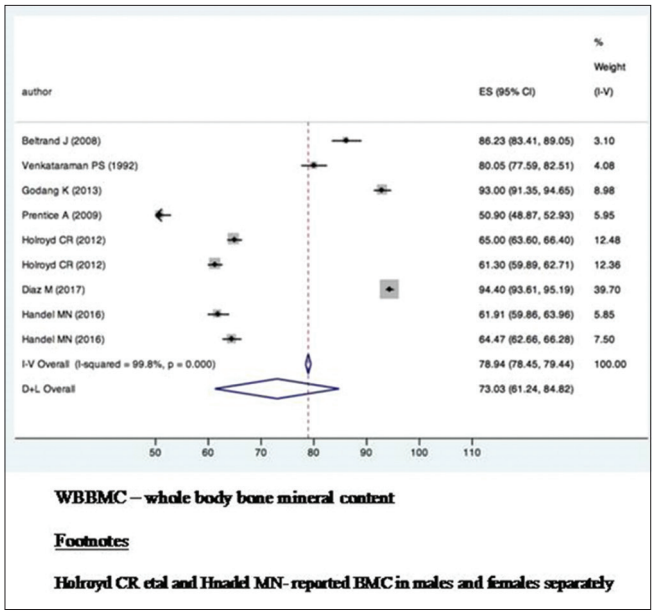

Figure 3: Forest plot of WBBMC by Lunar DXA

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

Table 2: Multivariate meta-regression analysis of newborn mass parameters (whole body BMC, BMD and Area by Hologic DXA)

Characterstics/covariates	Regression coefficient (95% CI)	*P*	Original I^2 unadjusted	Residual I^2 after adjusting for covariates
BMC				
(No of studies=19)				
Continent	0.084 (-5.74 to 5.91)	0.97		
Sex	-7.17 (-15.68 to 1.34)	0.09	96.7	32.6
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.[32]

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.[33] 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.[34] Scientists have suggested a standardization formula for converting parameters from one DXA to another in an attempt to give uniformity and comparison of results.[35] 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.[34] 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.

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.[35] 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 WBBMC 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.[36] 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.

However, gender difference in bone mass has not been reported at birth and volumetric BMD appears similar in male and females.[37]

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.

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Conflicts of interest

There are no conflicts of interest.

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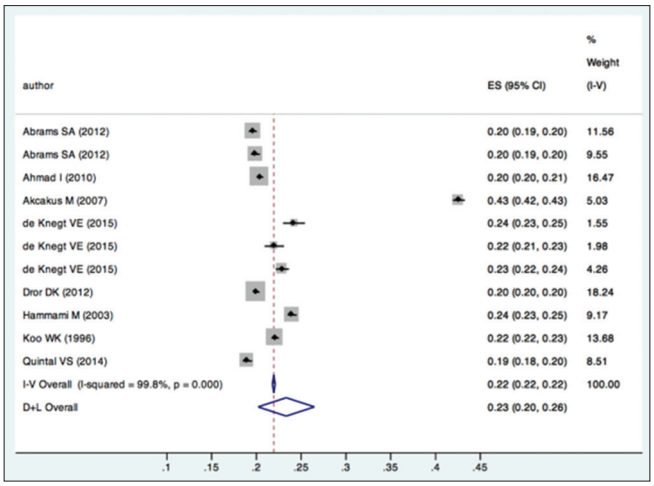

Figure S1: Forest plot of WBBMD by Hologic DXA. WBBMD – whole body bone mineral density.
Abram SA *et al.*- reported BMD among two ethnic groups – Hispanic and non Hispanic Caucasian. de Knegt VE – reported BMC among three three groups of newborns with repositioning between scans

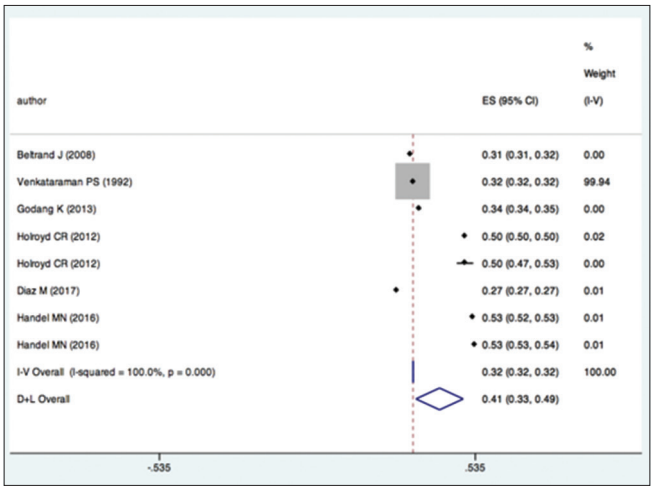

Figure S2: Forest plot of WBBMD by Lunar DXA. WBBMD – whole body bone mineral density.
Holroyd CR *et al.* and Hnadel MN – reported BMD in males and females separately

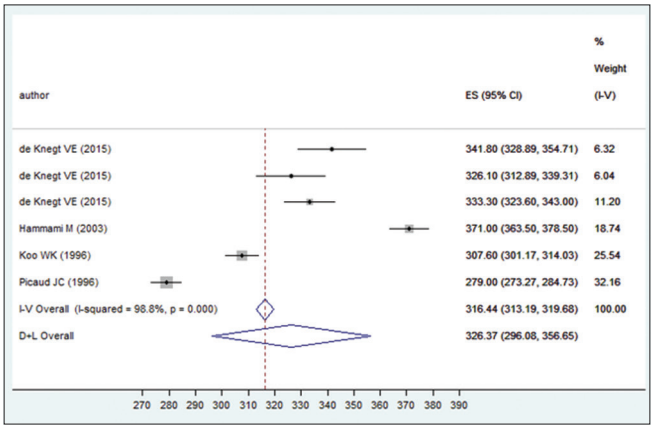

Figure S3: Forest plot of WBArea by Hologic DXA. WBArea - whole body area.
de Knegt VE - reported BMC among three three groups of newborns with repositioning between scans

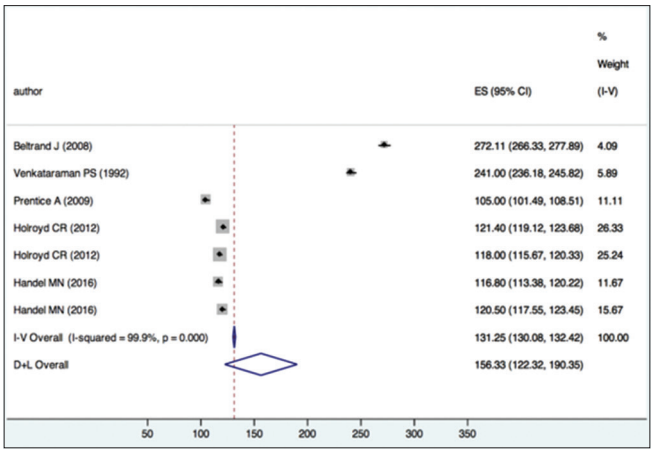

Figure S4: Forest plot of WBArea by Lunar DXA. WBArea- whole body area.
Holroyd CR *et al.* and Hnadel MN- reported area in males and females separately

Table S1: List of excluded studies

Study reference	Study title	Reason for exclusion
Braillon PM *et al*. Pediatr Res. 1992 Jul; 32 (1):77-80.	Dual energy X-ray absorptiometry measurement of bone mineral content in newborns: validation of the technique.	Absolute values of BMC and BMD are not reported, rather provided as range
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-hydroxyvitamin 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*., Am J Perinatol. 2006 Nov; 23 (8):473-80.	The relationship among intrauterine growth, insulinlike growth factor I (IGF-I), 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. (Godang K *et al*., Eur J Endocrinol. 2013; 168 (3):371-8)
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. (Dror DK *et al*., Nutrients. 2012; 4 (2):68-71)
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. (Weiler HA *et al*., Growth Dev Aging. 2008; 71 (1): 35-43)
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. (Gallo S *et al*., J Osteoporos 2012; 672403)

Table S2: Newborn whole body bone mass parameters (BMC, BMD & Area)

Parameter	Hologic DXA machine			Lunar DXA machine		
	No of studies	Mean pooled estimate (95% CI); I^2 (%)		No of studies	Mean pooled estimate (95% CI); I^2 (%)	
		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	73.03 (61.2-84.8)
BMD (g/cm^2)	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	BMC		BMD		AREA	
	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						
Male	2 68.8 (65.9-71.6)	1 64.8 (63.7-65.9)	-	1 0.5 (0.49-0.50)	-	1 121.06 (119.3-122.7)
Female	2 65.9 (63.2-68.5)	1 61.5 (60.3-62.7)	-	1 0.5 (0.47-0.53)	-	2 117.6 (115.7-119.5)
Age Category						
1 Week	9 66.1 (65.1-67.1)	3 88.4 (87.2-89.7)	7 0.22 (0.22-0.23)	3 0.32 (0.32-0.32)	4 316.4 (313.2-319.7)	2 253.7 (250.04-257.4)
2 Week	2 67.2 (65.2-69.2)	4 77.1 (76.6-77.7)	-	3 0.47 (0.47-0.47)	-	3 117.7 (116.4-118.9)
1 month	2 65.7 (63.7-67.7)	-	1 0.20 (0.20-0.20)	-	-	-
Continent						
Asia	1 53.7 (50.7-56.7)	-	1 0.43 (0.42-0.43)	-	-	-
North America	7 70.5 (69.4-71.6)	1 80.05 (77.6-82.5)	5 0.21 (0.21-0.21)	1 0.32 (0.32-0.32)	2 334.4 (329.5-339.3)	1 241 (236.2-245.8)
South America	1 60.7 (56.9-64.6)	-	1 0.19 (0.18-0.20)	-	-	-
Europe	4 62.6 (61.2-64.0)	5 80.7 (80.2-81.3)	1 0.23 (0.22-0.23)	5 0.45 (0.45-0.45)	2 302.1 (297.8-306.5)	3 127 (125.7-128.2)
Africa	-	1 50.9 (48.9-52.9)	-	-	-	1 105 (101.5-108.5)
Beam of DXA machine						
Fan beam	7 71.6 (70.4-72.8)	6 80.7 (80.2-81.2)	6 0.21 (0.20-0.21)	6 0.32 (0.32-0.32)	2 350.2 (345.2-355.2)	4 134.5 (133.3-135.7)
Pencil beam	6 61.4 (60.2-62.5)	1 50.9 (48.9-52.9)	2 0.28 (0.27-0.28)	-	2 291.6 (287.4-295.9)	1 105 (101.5-108.5)