Association between vitamin D level and bronchopulmonary dysplasia: A systematic review and meta-analysis

Hye Won Park,1,2*, Gina Lim,3 Yong-Mean Park,1,2 Misoo Chang,4 Jae Sung Son,1,2 Ran Lee,1,2

1 Department of Pediatrics, Konkuk University Medical Center, Seoul, Republic of Korea, 2 Konkuk University School of Medicine, Seoul, Republic of Korea, 3 Department of Pediatrics, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea, 4 Research Coordinating Center, Konkuk University Medical Center, Seoul, Republic of Korea

* hwwoman@naver.com

Abstract

Neonatal vitamin D deficiency is common and is associated with development of pulmonary disease in children and adults. While the role of vitamin D in normal lung development is well established, the association between vitamin D deficiency and bronchopulmonary dysplasia (BPD) remains unclear. The present meta-analysis was conducted to evaluate the relationship between vitamin D and BPD. We identified relevant studies (n = 8) using the PubMed, EMBASE, Cochrane Library, and KoreaMed databases and applied the Newcastle–Ottawa Scale to assess the methodologic components of each study, and used I² statistic to evaluate heterogeneity. Comprehensive Meta-Analysis software version 3.3 was used for the statistical analysis. A total of 909 infants were included, of whom 251 (27.6%) were diagnosed with BPD. We found that both vitamin D deficiency at birth (four studies; OR 2.405; 95% CI 1.269 to 4.560; p = 0.007) and low levels of vitamin D at birth (four studies; standardized mean difference -1.463; 95% CI -2.900 to -0.027; p = 0.046) were associated with BPD. The compiled data suggest that antenatal vitamin D deficiency and low vitamin D levels are associated with neonatal BPD.

Introduction

Vitamin D is a fat soluble vitamin whose active form, 1,25-dihydroxyvitamin D (1,25[OH]2D), is essential for calcium and phosphorus absorption as well as bone mineralization [1, 2]. Vitamin D receptors are expressed by most cell types [1, 3] and recent evidence also supports roles for vitamin D in cardiovascular disease, chronic respiratory disease, infection, autoimmune disease, and low birth weight, or preterm birth [1, 3–7].

Bronchopulmonary dysplasia (BPD) was first defined by Northway in 1967 in preterm infants with respiratory distress syndrome following prolonged ventilator support [8]. In its classic form, BPD in preterm infants is characterized by airway injury and parenchymal fibrosis leading to chronic respiratory failure and a prolonged oxygen requirement, similar to
chronic obstructive pulmonary disease in adults [9, 10]. BPD in extremely low birth weight infants following the use of surfactant and antenatal steroid was characterized by Jobe [10, 11] as arrest of lung development in both alveolar and vascular development. This disruption of the developmental process occurs during or prior to the late canalicular and saccular stages [9, 12].

Vitamin D deficiency is common in preterm and full term infants [13–16] and is associated with pulmonary diseases such as asthma or respiratory infection in children [17, 18] and adults [19]. Vitamin D deficiency affects lung alveolar and vascular development, immune modulation, repair, and function [4, 5, 19–32]. Recently, the role of vitamin D in normal lung development and in BPD was characterized [20, 33, 34], but the association between vitamin D deficiency and BPD remains controversial.

Thus, we conducted a meta-analysis to assess the relevance of vitamin D deficiency or vitamin D level at birth or within the 24 hours after birth that reflect the serum vitamin D levels of the fetus and mothers to BPD.

Methods

Search strategy and study selection

We searched PubMed, EMBASE, Cochrane Library, and KoreaMed databases using the search terms: “vitamin D” or “25-hydroxyvitamin D” or “25-hydroxyergocalciferol” or “ergocalciferol” or “cholecalciferol” or “hydroxycholecalciferol” or “calcifediol” or “dihydroxycholecalciferol” or “25(OH)D” or “1,25(OH)2-vitD”; and “bronchopulmonary dysplasia” or “chronic lung disease” or “lung injury”; and “prematurity” or “low birth weight infant” or “neonate”. The detailed search strategy for PubMed is presented in S1 Table. There were no restrictions on language, population, or publication year. The last search was performed on June 24, 2019. We initially screened the study titles and abstracts, and subsequently reviewed the full-text articles. Articles were independently reviewed by two reviewers (authors HW Park and G Lim), who applied selection criteria to determine article eligibility for inclusion in the meta-analysis.

Inclusion and exclusion criteria

We included randomized controlled trials, observational studies (including case-control studies), cohort studies, and cross sectional studies in our analysis. BPD was defined as an oxygen dependency at either 28 days of age or 36 weeks of postmenstrual age. BPD was diagnosed in each study according to either the National Institutes of Health consensus [35–38], or other criteria for oxygen dependency, at 36 weeks of postmenstrual age [39], or at 28 days of age [40, 41]. Case reports, case series, single-arm cohort studies, and animal studies were excluded from the meta-analysis.

Data extraction and study quality assessment

Data were independently extracted from the full-text versions of selected studies by the authors (HW Park and G Lim). The collected data included first author name, publication year, study design, study location, study period, study population, time of vitamin D level measurement, definition of BPD, sample size, BPD incidence, and vitamin D level. We also assessed the quality of the included studies using the Newcastle–Ottawa Scale [42]. The Newcastle–Ottawa Scale is based on a “star system” and is composed of eight items evaluating three domains: selection (four items), comparability (one item), and outcomes (three items). One star is awarded for each item, with the exception of the comparability item, which may receive two stars. Using this scale, articles were assigned a quality score between 0 and 9. Based on their
total scores, studies were categorized as ‘low quality’ (≤ 3), ‘moderate quality’ (4–5), and high quality (≥ 6). Any disagreements regarding data interpretation or quality assessment were resolved by discussion with a third reviewer (R Lee); any such study was subsequently reevaluated.

Data synthesis and statistical analyses
The results are presented as summary odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data, and as the standardized mean difference (SMD) and 95% CIs for continuous variables, to demonstrate the relationship between vitamin D and BPD. Among four studies that reported the relationship between vitamin D levels and BPD, three reported the means and standard deviations (SDs) of the 25(OH)D level (a continuous variable); one study did not [43], reporting instead the median and interquartile range (IQR). We tried to contact the author to get the data expressed as mean ± SD to allow the data to be included.

Forest plots were generated to assess between-study heterogeneity. The $I^2$ statistic was used to determine the percentage of variation across studies. The $I^2$ statistic indicates whether the heterogeneity among studies is low (25–50%), moderate (50–75%) or high (>75%). Regardless of the degree of heterogeneity, a random effects model was used for analysis, which is more conservative and has wider CIs than a fixed effect model [44, 45]. Inverse variance weighting was used for weighting the random effects model in this study.

A sensitivity analysis was performed by removing the results of individual studies from the data set and subsequently evaluating the robustness of the combined estimates and the contribution of each study to the pooled OR. To detect temporal trends, a cumulative analysis was performed by adding studies one at a time according to the date of publication.

We performed the Begg and Mazumdar rank correlation test and Egger’s regression test to evaluate publication bias. Publication bias was also evaluated using a funnel plot, which shows the distribution of the effect sizes against the standard error values. The meta-analysis was performed using Comprehensive Meta-Analysis software (version 3.3; Biostat, Englewood, NJ, USA).

Results
Literature search and study selection
The study selection process and exclusion criteria are described in Fig 1. Of the 128 studies identified initially, 120 were excluded based on review of the title, abstract or full text. The reasons for excluding 17 studies [33, 34, 46–60] after full-text review, are provided in Fig 1. The remaining eight studies met the inclusion criteria and were included in the meta-analysis [35, 37, 38, 40, 41, 43, 61, 62].

Characteristics of the included studies
A total of 909 infants were included in this meta-analysis. The mean birth weight of the infants was 1,322.4g and the mean gestational age of all infants (with and without BPD) was 29.1 weeks. One study did not include data regarding gestational age at birth [61]. The characteristics of the study populations are described in Table 1. Among 909 infants, 251 (27.6%) infants were diagnosed with BPD (Table 1). Two studies [40, 41] defined BPD as an oxygen dependency at 28 days of age; the remaining studies [35, 37, 38, 43, 61, 62] defined BPD as oxygen dependency at 36 weeks of postmenstrual age, based on National Institutes of Health consensus [63]. The incidence of BPD vary from 6.6% to 56.8%, 6.6% in the study of Yang et al [61], and 56.8% in the study of Kazzi et al. [38].
Among eight studies, four [38, 40, 41, 62] presented results on the association of vitamin D deficiency with BPD; the other four studies [35, 37, 43, 61] assessed the association of vitamin D level with BPD. The four studies that evaluated vitamin D deficiency used 25(OH)D cutoff values of 20 ng/mL(50 nmol/L) [40, 41], 10 ng/mL [38], or 12 ng/mL(30 nmol/L) [62]. Vitamin D levels were measured from cord blood or at the time of hospital admission or in the 24 hours before intravenous or oral vitamin D administration.

The results of quality assessment of included studies according to the Newcastle–Ottawa Scale are shown in Table 1.

Pooled meta-analysis results
A significant association was detected between vitamin D deficiency and BPD based on oxygen dependency at 28 days of age or at 36 weeks of corrected age (OR 2.405; 95% CI 1.269 to 4.560; p = 0.007; Fig 2), and there was no significant heterogeneity among the studies (p = 0.22; I² = 32.1%). However, as only four studies were included in this part of the meta-analysis, we used a random effects model [44, 45]. Publication bias was not detected by the Begg and Mazumdar rank correlation test (p = 0.089). However, the Egger’s regression test (p = 0.030) and asymmetric funnel plot (S1 Fig) indicated possible publication bias. Thus, we performed a trim and fill adjustment, which yielded the same results (OR 2.405; 95% CI 1.269 to 4.560). The sensitivity analysis showed that no single study changed the pooled results (S2 Fig) and the results of cumulative analysis indicated no temporal effects (S2 Fig).

Vitamin D levels were significantly lower in the BPD infants compared with the controls (SMD = -1.463; 95% CI -2.900 to -0.027; p = 0.046; Fig 3). The heterogeneity assessment
Table 1. Characteristics of studies included in this meta-analysis.

| Studies         | Study design | Population           | Time of vitamin D measurement | Definition of BPD (oxygen dependency) | Definition of vitamin D deficiency (25 (OH) D level) | Study population GA (week), BW (g) expressed as mean ± SD or mean | NOS |
|-----------------|--------------|----------------------|-------------------------------|--------------------------------------|-----------------------------------------------------|----------------------------------------------------------------|-----|
| Onwuneme, 2015  | Prospective  | GA < 32 weeks or birth weight < 1,500 g | Within 24 h of birth          | at 36 weeks of PMA                   | < 12 ng/mL (30 nmol/L)                               | All (n = 94), GA: 28.8 ± 2.09, BW: 1193 ± 375                  | 8   |
|                 |              |                      |                               |                                      |                                                     | BPD (n = 34)                                                    |     |
|                 |              |                      |                               |                                      |                                                     | Vitamin D < 30 nmol/L (n = 60) GA: 28.6 ± 2.3, BW: 1171 ± 363 |     |
|                 |              |                      |                               |                                      |                                                     | Vitamin D > 30 nmol/L (n = 34) GA: 29.1 ± 1.71, BW: 1229 ± 398 |     |
| Yu, 2017        | Prospective  | GA < 34 weeks        | On admission                   | at 28 days of age                    | < 20 ng/mL                                          | All (n = 260), BPD (n = 41)                                     | 8   |
|                 |              |                      |                               |                                      |                                                     | Non-BPD group (n = 219) GA: 31.5 ± 1.6, BW: 1734 ± 359      |     |
|                 |              |                      |                               |                                      |                                                     | BPD group (n = 41) GA: 28.0 ± 1.6, BW: 1141 ± 242          |     |
| Kazzi, 2018     | Prospective  | Birth weight ≤ 1,250 g | Within 24 h of birth           | at 36 weeks of PMA                   | ≤ 10 ng/mL                                          | All (n = 89; 81), BPD (n = 46)                                  | 8   |
|                 |              |                      |                               |                                      |                                                     | Vitamin D ≤ 10 ng/mL group (n = 32) GA: 27 ± 2, BW: 860 ± 262 |     |
|                 |              |                      |                               |                                      |                                                     | Vitamin D > 10 ng/mL group (n = 57) GA: 27 ± 2, BW: 873 ± 210 |     |
| Kim, 2019       | Retrospective| Birth weight < 1,500 g | Within 24 h of birth           | at 28 days of age                    | < 20 ng/mL                                          | All (n = 188), GA: 28.4 ± 3.0, BW: 1104 ± 298.1               | 8   |
|                 |              |                      |                               |                                      |                                                     | BPD (n = 55)                                                    |     |
|                 |              |                      |                               |                                      |                                                     | Vitamin D < 10 ng/mL (n = 83) GA: 28.3 ± 3.3, BW: 1045.2 ± 293.8 |     |
|                 |              |                      |                               |                                      |                                                     | Vitamin D 10–20 ng/mL (n = 67) GA: 28.5 ± 3.2, BW: 1098.3 ± 297.4 |     |
|                 |              |                      |                               |                                      |                                                     | Vitamin D > 20 ng/mL (n = 38) GA: 29.1 ± 2.5, BW: 1245.7 ± 267.1 |     |
| Cetinkay a, 2015| Prospective  | GA ≤ 32 weeks        | On admission                   | at 36 weeks of PMA                   | Measured value†                                      | All (n = 100), GA: 28.4, BW: 1006.5                            | 6   |
|                 |              |                      |                               |                                      |                                                     | Non-BPD group (n = 69) GA: 28.9 ± 2.46, BW: 1063.8 ± 251.1   |     |
|                 |              |                      |                               |                                      |                                                     | BPD group (n = 31) GA: 27.2 ± 2.4, BW: 875.6 ± 247.3         |     |
| Joung, 2016     | Prospective  | GA < 29 weeks        | At birth                       | at 36 weeks of PMA                   | Measured value†                                      | All (n = 44), GA: 26.6, BW: 870                                | 7   |
|                 |              |                      |                               |                                      |                                                     | BPD group (n = 18)                                             |     |
| Mao, 2018       | Prospective  | GA ≤ 32 weeks        | Within 24 h of birth           | at 36 weeks of PMA                   | Measured value†                                      | All (n = 39), GA: 29.5, BW: 1268.9                             | 9   |
|                 |              |                      |                               |                                      |                                                     | Non-BPD group (n = 20) GA: 29.8 ± 0.2, BW: 1323 ± 51.9       |     |
|                 |              |                      |                               |                                      |                                                     | BPD group (n = 19) GA: 29.3 ± 0.3, BW: 1212 ± 50.5           |     |

(Continued)
indicated good heterogeneity among the studies (p < 0.001; I² = 94.20%). Due to the small sample size, publication bias could not be assessed by the funnel plot (S3 Fig). The Begg and Mazumdar rank correlation test (p = 0.734) and Egger’s regression test (p = 0.756) indicated no publication bias. The sensitivity analysis (S4 Fig) and cumulative analysis (S4 Fig) showed that the exclusion of no single study significantly changed the pooled results.

Discussion

The half-life of 25(OH)D is longer than that of 1,25(OH)₂D (15 days vs 10–20 hours [2]) and 1,25(OH)₂D serum levels are influenced by factors other than vitamin D status including, parathyroid hormone, calcium and phosphorus level [46]. Levels of 25(OH)D, which is the most frequently used indicator of vitamin D status [1], were measured at birth or within the 24 hours after birth in all included studies. Serum levels of 25(OH)D measured in the 24 hours before vitamin D supplementation correlated with the serum vitamin D levels of the fetus [38, 41] and the mother [15, 16, 38, 41, 64, 65], which is likely attributable to maternal transfer of vitamin D to the fetus [41].

Vitamin D deficiency has been reported in 40–50% of pregnant females and 45–60% of pre-term infants [66–69]. In our meta-analysis, vitamin D deficiency was observed in 70% (range 33–80%) of preterm infants. Holick et al. [1] defined vitamin D deficiency as a serum 25(OH)D level of less than 20 ng/mL(50 nmol/L). Our analysis included two studies [40, 41] that used 20 ng/mL as the cutoff, one study [38] that used 10 ng/mL (based on the National Institute of...
Health Office of Dietary Supplements recommendations [46]), and one study [62] that used 12 ng/mL (30 nmol/L) (based on the Institute of Medicine report [70]) (Table 1). Four studies did not provide definitions of deficiency and, instead, reported levels of vitamin D [35, 37, 43, 61].

The etiology of BPD is multifactorial [63, 71], thus vitamin D deficiency may not be the only cause of BPD. However, the important role of nutrition in prenatal and postnatal lung growth has been demonstrated in previous reports [57, 59, 72]. Vitamin D has roles in lung development in anatomical [20–22, 25, 26], functional [21, 22, 27, 28, 73], and immunological terms [5, 21, 29], as well as in the development of BPD [20, 74–76] and their recovery therefrom [55].

In animal studies, vitamin D deficiency during lung development was associated with inhibition of alveolar type II cell and fibroblast proliferation, reduced surfactant or antioxidant production, and upregulation of vitamin D receptors [20, 25, 26]. Antenatal vitamin D deficiency is linked to impaired anatomical lung development, including reduced tracheal diameter, irregular cartilage [21, 22], increased airway smooth muscle mass and elevated collagen synthesis [20, 21, 25], as well as to altered pulmonary function, including increased hyperresponsiveness, increased resistance and decreased compliance, obstructive lung disease, and low performance on pulmonary function tests, such as forced vital capacity or forced expiratory volume [21, 22, 27, 28, 73]. Airway inflammation is also found in case of antenatal vitamin D deficiency, demonstrated by elevated neutrophil and decreased lymphocyte counts in bronchoalveolar lavage [21], as well as by decreased expression of IkBa through NFKBIA, and by other indicators of postnatal airway inflammation [5, 21, 29].

The vitamin D pathway also contributes to impaired lung development after endotoxin exposure, where vitamin D receptors and vitamin D catabolic enzymes promote a deficiency-like state [20]. Vitamin D deficiency could contribute to BPD development after endotoxin exposure through increased expression of CYP24A1, a vitamin D regulatory enzyme, and decreased expression of vitamin D receptors and 1α-OHase in the lung [20], and of VEGF expression and secretion, thereby impairing the processes of angiogenesis and vasculogenesis [74–76]. Vitamin D supplementation may help to restore proper alveolar development through suppression of interferon-γ [55].

---

**Table 1**

| Study name   | Std diff In means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|--------------|-------------------|----------------|----------|-------------|-------------|---------|---------|
| Cetinkaya 2015 | -1.919            | 0.255          | 0.065    | -2.419      | -1.418      | -7.517  | 0.000   |
| Joung 2016   | 0.047             | 0.315          | 0.099    | -0.570      | 0.664       | 0.150   | 0.881   |
| Mao 2016     | -3.795            | 0.536          | 0.287    | -4.846      | -2.745      | -7.081  | 0.000   |
| Yang 2018    | -0.343            | 0.392          | 0.154    | -1.111      | 0.425       | -0.874  | 0.382   |

**Fig 3. Meta-analysis of the relationship between vitamin D level and bronchopulmonary dysplasia.** Forest plot of the random effects model, diamonds indicate the effect size of given study, which is proportional to the weight of that study. Std; standardized, BPD; bronchopulmonary dysplasia.

https://doi.org/10.1371/journal.pone.0235332.g003
There have also been studies [25, 73, 77, 78] including systematic reviews reporting a role of vitamin D in fetal and neonatal lung maturation [25, 73, 77] and fetal outcomes during pregnancy [78]. However, these studies did not report the relationship between vitamin D and BPD, but rather the association of vitamin D levels with respiratory infections, and asthma in offspring [78], low birth weight [25, 78], or preterm birth, duration of ventilator support, and duration of oxygen supplementation [25]. In this meta-analysis, we found a significant association between BPD and vitamin D deficiency (OR 2.405; 95% CI 1.269 to 4.560; p = 0.007; Fig 2), and between BPD and low 25(OH)D levels at birth (SMD = -1.463; 95% CI -2.900 to -0.027; p = 0.046; Fig 3). Several studies also reported relationships of vitamin D with BPD and lung development.

There were some limitations to this study. First, as this meta-analysis included a small number of trials (only four studies of vitamin D deficiency and four of vitamin D levels), we must cautiously interpret the results regarding publication bias of the Begg and Mazumdar rank correlation test, Egger’s regression test, and funnel plot (S1 Fig and S3 Fig). Therefore, we did sensitivity analysis and cumulative analysis according to date of publication, and the results showed no temporal effects. Second, although we did not detect significant heterogeneity among the studies (p = 0.22; $I^2 = 32.1\%$) in the analysis of the relationship between vitamin D deficiency and BPD, the possibility of heterogeneity remains. However, we performed the analysis using a random-effect model, which is more conservative, to generate a more accurate estimate with wider CIs [44, 45], compare with fixed effect model.

Our meta-analysis indicated that the vitamin D level at birth, which reflects fetal and maternal vitamin D status during pregnancy, was significantly associated with BPD incidence. Antenatal vitamin D promotes critical lung development during the canalicular and sacellular stages and maternal vitamin D supplementation during pregnancy and for preterm infants is essential for ensuring optimal levels in the fetus, reducing the risk of BPD by promoting healthy lung development. Although postnatal vitamin D supplementation is unable to completely reverse the lung and airway defects caused by fetal vitamin D deficiency, we believe that it may promote postnatal lung development, at least during the first 2 years of life, during which alveolar development occurs [22, 79, 80], as well as reduce airway hyperresponsiveness and inflammation [5, 21, 29]. The dose of vitamin D used as a supplement in preterm and very low birth weight infants varies; 200–400 IU/d is recommended by the American Academy of Pediatrics [81] and 800–1,000 IU/d by the European Society of Pediatric Gastroenterology [82]. A recent meta-analysis [83] found that neither 25(OH)D levels nor BPD incidence differed between these dose ranges. Additional studies are needed to fully evaluate the effects of vitamin D supplementation on maternal and offspring health, including prevention of BPD.

**Supporting information**

S1 Table. MEDLINE search strategy.
(DOCX)

S1 Fig. Funnel plot for the relationship between vitamin D deficiency and bronchopulmonary dysplasia. An asymmetrical funnel plot is displayed.
(TIF)

S2 Fig. Sensitivity analysis (2–1) and cumulative analysis (2–2) for the relationship between vitamin D deficiency and bronchopulmonary dysplasia.
(TIF)

S3 Fig. Funnel plot for the relationship between vitamin D level and bronchopulmonary dysplasia. Due to the small sample size, the publication bias cannot be determined with...
inspection of the funnel plot.

S4 Fig. Sensitivity analysis (4–1) and cumulative analysis (4–2) for the relationship between vitamin D level and bronchopulmonary dysplasia. Std; standardized, BPD; bronchopulmonary dysplasia

**Author Contributions**

**Conceptualization:** Hye Won Park, Yong-Mean Park.

**Data curation:** Gina Lim.

**Formal analysis:** Hye Won Park, Gina Lim, Misoo Chang.

**Investigation:** Hye Won Park, Jae Sung Son, Ran Lee.

**Methodology:** Hye Won Park, Gina Lim, Misoo Chang, Jae Sung Son, Ran Lee.

**Supervision:** Yong-Mean Park, Jae Sung Son, Ran Lee.

**Validation:** Misoo Chang.

**Visualization:** Misoo Chang.

**Writing – original draft:** Hye Won Park.

**Writing – review & editing:** Yong-Mean Park, Jae Sung Son, Ran Lee.

**References**

1. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357(3):266–81. [https://doi.org/10.1056/NEJMra070553 PMID: 17634462].

2. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr. 2008; 88(2):582s–6s. [https://doi.org/10.1093/ajcn/88.2.582s PMID: 18689406].

3. Wierzejska R, Jarosz M, Kleminska-Nowak M, Tomaszewska M, Sawicki W, Bachanek M, et al. Material and Cord Blood Vitamin D Status and Anthropometric Measurements in Term Newborns at Birth. Front Endocrin (Lausanne). 2018; 9:9. [https://doi.org/10.3389/fendo.2018.00009 PMID: 294728924].

4. Ali S, Hirschfeld AF, Mayer ML, Fortuno ES 3rd, Corbett N, Kaplan M, et al. Functional genetic variation in NFKBIA and susceptibility to childhood asthma, bronchiolitis, and bronchopulmonary dysplasia. J Immunol. 2013; 190(8):3949–58. [https://doi.org/10.4049/jimmunol.1201015 PMID: 23487427].

5. Lai G, Wu C, Hong J, Song Y. 1,25-Dihydroxyvitamin D(3) (1,25-(OH)(2)D(3)) attenuates airway remodelling in a murine model of chronic asthma. J Asthma: 2013; 50(2):133–40. [https://doi.org/10.3109/02770903.2012.738269 PMID: 23157452].

6. Fang K, He Y, Mu M, Liu K. Maternal vitamin D deficiency during pregnancy and low birth weight: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2019:1–7. [https://doi.org/10.1080/14767058.2019.1623780 PMID: 31122092].

7. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011; 96(1):53–8. [https://doi.org/10.1203/0b013e3283423ea6b PMID: 21169836].

8. Northway WH Jr., Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967; 276(7):357–68. [https://doi.org/10.1056/NEJM196702162760701 PMID: 5334613].

9. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr. 2011; 23(2):167–72. [https://doi.org/10.1097/MOP.0b013e3283423ea6b PMID: 21169836].

10. Jobe AH. What is BPD in 2012 and what will BPD become? Early Hum Dev. 2012; 88 Suppl 2:S27–8. [https://doi.org/10.1016/s0378-3782(12)70009-9 PMID: 22633907].

11. Jobe AJ. The new BPD: an arrest of lung development. Pediatr Res. 1999; 46(6):641–3. [https://doi.org/10.1203/00006450-199912000-00007 PMID: 10590017].
12. Baker CD, Alvira CM. Disrupted lung development and bronchopulmonary dysplasia: opportunities for lung repair and regeneration. Curr Opin Pediatr. 2014; 26(3):306–14. https://doi.org/10.1097/MOP.0000000000000095 PMID: 24739494.

13. Fort P, Salas AA, Nicola T, Craig CM, Carlo WA, Ambalavanan N. A Comparison of 3 Vitamin D Dosing Regimens in Extremely Preterm Infants: A Randomized Controlled Trial. J Pediatr. 2016; 174:132–8. e1. https://doi.org/10.1016/j.jpeds.2016.03.028 PMID: 27079965.

14. Glorieux FH, Salle BL, Delvin EE, David L. Vitamin D metabolism in preterm infants: serum calcitriol values during the first five days of life. J Pediatr. 1981; 99(4):640–3. https://doi.org/10.1016/s0022-3476(81)80260-6 PMID: 6895088.

15. Monangi N, Slaughter JL, Dawodu A, Smith C, Akinbi HT. Vitamin D status of early preterm infants and the effects of vitamin D intake during hospital stay. Arch Dis Child Fetal Neonatal Ed. 2014; 99(2): F166–8. https://doi.org/10.1136/archdischild-2013-303999 PMID: 23852093.

16. Fallahi M, Afjeh A, Saneifard H, Namazi N, Kazemian M, Tabatabaei S. Comparison of vitamin D level in preterm and term infant–mother pairs: a brief study. IJN 2016; 7(1):32–6.

17. Bantz SK, Zhu Z, Zheng T. The Role of Vitamin D in Pediatric Asthma. Ann Pediatr Child Health. 2015; 3(1):1032. PMID: 25938135.

18. Jat KR, Khairwa A. Vitamin D and asthma in children: A systematic review and meta-analysis of observational studies. Lung India. 2017; 34(4):355–63. https://doi.org/10.4103/0970-2113.209227 PMID: 28671167.

19. Ali NS, Nanji K. A Review on the Role of Vitamin D in Asthma. Cureus. 2017; 9(5):e1288–e. https://doi.org/10.7759/cureus.1286 PMID: 28680776.20.

20. Maniscalco WM, Watkins RH, Pryhuber GS, Bhatt A, Shea C, Huyck H. Angiogenic factors and alveolar vasculature: development and alterations by injury in very premature baboons. Am J Physiol Lung Cell Mol Physiol. 2002; 286(6):L850–9. https://doi.org/10.1152/ajplung.00136.2001 PMID: 12000000.

21. Thiessen JA, Arora A, Pujari A, MacEwen B, Akinbi HT. Vitamin D status of early preterm infants and association with bronchopulmonary dysplasia. J Pediatr. 2011; 158(3):437–41. https://doi.org/10.1016/j.jpeds.2010.08.043 PMID: 20870246.

22. Saadoon A, Ambalavanan N, Zinn K, Ashraf AP, MacEwen M, Nicola T, et al. Effect of Prenatal versus Postnatal Vitamin D Deficiency on Pulmonary Structure and Function in Mice. Am J Respir Cell Mol Biol. 2015; 53(5):664–75. https://doi.org/10.1165/rccmb.2014-0356OC PMID: 25867127.

23. Ramirez AM, Wongtrakool C, Welch T, Steinmeyer A, Zugel U, Roman J. Vitamin D inhibition of pro-fibrotic effects of transforming growth factor beta1 in lung fibroblasts and epithelial cells. J Steroid Biochem Mol Biol. 1994; 50(1):145–52. https://doi.org/10.1016/0960-0760(94)90008-6 PMID: 8148393.

24. Fort P, Salas AA, Nicola T, Craig CM, Carlo WA, Ambalavanan N. A Comparison of 3 Vitamin D Dosing Regimens in Extremely Preterm Infants: A Randomized Controlled Trial. J Pediatr. 2016; 174:132–8. e1. https://doi.org/10.1016/j.jpeds.2016.03.028 PMID: 27079965.

25. Lykkedegny S, Sorensen GL, Beck-Nielsen SS, Christensen HT. The impact of vitamin D on fetal and neonatal lung maturation. A systematic review. Am J Physiol Lung Cell Mol Physiol. 2015; 308(7):L587–602. https://doi.org/10.1152/ajplung.00117.2014 PMID: 25595644.

26. Bantz SK, Zhu Z, Zheng T. The Role of Vitamin D in Pediatric Asthma. Ann Pediatr Child Health. 2015; 3(1):1032. PMID: 25938135.

27. Jat KR, Khairwa A. Vitamin D and asthma in children: A systematic review and meta-analysis of observational studies. Lung India. 2017; 34(4):355–63. https://doi.org/10.4103/0970-2113.209227 PMID: 28671167.

28. Ali NS, Nanji K. A Review on the Role of Vitamin D in Asthma. Cureus. 2017; 9(5):e1288–e. https://doi.org/10.7759/cureus.1286 PMID: 28680776.20.

29. Maniscalco WM, Watkins RH, Pryhuber GS, Bhatt A, Shea C, Huyck H. Angiogenic factors and alveolar vasculature: development and alterations by injury in very premature baboons. Am J Physiol Lung Cell Mol Physiol. 2002; 286(6):L850–9. https://doi.org/10.1152/ajplung.00136.2001 PMID: 12000000.
32. Bhatt AJ, Pryhuber GS, Huyck H, Watkins RH, Metlay LA, Maniscalco WM. Disrupted pulmonary vasculature and decreased vascular endothelial growth factor, Flt-1, and TIE-2 in human infants dying with bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001; 164(10 Pt 1):1971–80. https://doi.org/10.1164/ajrccm.164.10.2101140 PMID: 11734454.

33. Serce Pehlevan O, Karatekin G, Kosalk V, Benzer D, Gursoy T, Yavuz T, et al. Association of vitamin D binding protein polymorphisms with bronchopulmonary dysplasia: a case-control study of gc globulin and bronchopulmonary dysplasia. J Perinatol. 2015; 35(9):763–7. https://doi.org/10.1038/jp.2015.58 PMID: 26067474.

34. Koroglu OA, Onay H, Cakmak B, Bilgin B, YaIaz M, Tunc S, et al. Association of vitamin D receptor gene polymorphisms and bronchopulmonary dysplasia. Pediatr Res. 2014; 76(2):171–6. https://doi.org/10.1038/pr.2014.63 PMID: 24796371.

35. Cetinkaya M, Cekmez F, Erener-Ercan T, Buyukkale G, Demirhan A, Aydemir G, et al. Maternal/neonatal vitamin D deficiency: a risk factor for bronchopulmonary dysplasia in preterms? J Perinatol. 2015; 35(10):813–7. https://doi.org/10.1038/jp.2015.86 PMID: 26226242.36.

36. Yu RQ, Chen DZ, Zhou Q, Wang M, Mei YZ, Jiang SY, et al. Association between serum 25(OH) D levels at birth and bronchopulmonary dysplasia in preterm infants. Zhongguo Dang Dai Er Ke Za Zhi. 2017; 19(10):1051–5. PMID: 29046199.

37. Kim I, Kim SS, Song JI, Yoon SH, Park GY, Lee YW. Association between vitamin D level at birth and respiratory morbidities in very-low-birth-weight infants. Korean J Pediatr. 2019; 62(6):625–32. https://doi.org/10.3345/kjp.2019.62.6.625 PMID: 31471666.

38. Kontopantelis E, Reeves D. Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: A simulation study. Stat Methods Med Res. 2012; 21(4):409–26. https://doi.org/10.1177/0962280211400097 PMID: 21424915.

39. Mohamed Hegazy A, Mohamed Shinkar D, Refaat Mohamed N, Abdalla Gaber H. Association between serum 25 (OH) vitamin D level at birth and respiratory morbidities among preterm neonates. J Matern Fetal Neonatal Med. 2018; 31(20):2649–55. https://doi.org/10.1080/14767058.2017.1350162 PMID: 28670941.

40. Holder M, Salas A. Safety of Early Vitamin D Supplementation in Premature Infants at Risk of Bronchopulmonary Dysplasia (BPD) and Growth Failure (P11-070-19). Curr Dev Nutr. 2019; 3(Suppl 1). https://doi.org/10.1093/cdn/nzx048 PMID: 31224430.

41. Greer FR, McCormick A. Bone mineral content and growth in very-low-birth-weight premature infants. Does bronchopulmonary dysplasia make a difference? Am J Dis Child. 1987; 141(2):179–83. https://doi.org/10.1001/archpedi.1987.04602006090029 PMID: 3812395.

42. PLOS ONE | https://doi.org/10.1371/journal.pone.0235332 July 6, 2020 11 / 13
51. Craig C, Ambalavan N, McNair T. Early vitamin d supplementation for prevention of respiratory morbidity in extremely preterm infants. JIM. 2014; 62(2):492. https://doi.org/10.231/JIM.0000000000000055 CN-01057416.

52. Kabataş EU, Dinlen NF, Zenciroğlu A, Dilli D, Beken S, Okumuş N. Relationship between serum 25-hydroxy vitamin D levels and retinopathy of prematurity. Scott Med J. 2017; 62(4):129–35. https://doi.org/10.1177/0036933017770187 PMID: 28999218.

53. Gaio P, Verlato G, Cavicchio ME, Nardo D, Pasinato A, et al. Incidence of metabolic bone disease in preterm infants of birth weight <1250 g and in those suffering from bronchopulmonary dysplasia. Clin Nutr ESPEN. 2018; 23:234–9. https://doi.org/10.1016/j.clnesp.2017.09.008 PMID: 29460805.

54. Fettah ND, Zenciroğlu A, Dilli D, Beken S, Okumus N. Is higher 25-hydroxyvitamin D level preventive for respiratory distress syndrome in preterm infants? Am J Perinatol. 2015; 32(3):247–50. https://doi.org/10.1055/s-0034-1383489 PMID: 25217734.

55. Liu C, Chen Z, Li W, Huang L, Zhang Y. Vitamin D Enhances Alveolar Development in Antenatal Lipo-polysaccharide-Treated Rats through the Suppression of Interferon-gamma Production. Front Immunol. 2017; 8:1923. https://doi.org/10.3389/fimmu.2017.01923 PMID: 29354129.

56. Surate Solaligue DE, Rodríguez-Castill JA, Ahlbrecht K, Morty RE. Recent advances in our understanding of the mechanisms of late lung development and bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2017; 313(6):L1101–L53. https://doi.org/10.1152/ajplung.00343.2017 PMID: 28971976.

57. Dani C, Poggi C. Nutrition and bronchopulmonary dysplasia. J Matern Fetal Neonatal Med. 2012; 25 (SUPPL. 3):37–40. https://doi.org/10.3109/14767058.2012.712314 PMID: 23016616.

58. Savani RC. Modulators of inflammation in Bronchopulmonary Dysplasia. Semin Perinatol. 2018; 42(7):459–70. https://doi.org/10.1053/j.semp.2018.09.009 PMID: 30446300.

59. Argigliani M, Spinelli AM, Liguori I, Cogo P. Nutrition and lung growth. Nutrients. 2018; 10(7). https://doi.org/10.3390/nu10070919 PMID: 30021997.

60. Ryan S, Congdon PJ, Horsman A, James JR, Truscott J, Arthur R. Bone mineral content in bronchopulmonary dysplasia. Arch Dis Child. 1987; 62(9):889–94. https://doi.org/10.1136/adc.62.9.889 PMID: 29129516.

61. Yang Y, Feng Y, Chen X, Mao XN, Zhang JH, Zhao L, et al. Is there a potential link between vitamin D and pulmonary morbidities in preterm infants? J Chin Med Assoc. 2018; 81(5):482–6. https://doi.org/10.1016/j.jcma.2017.07.011 PMID: 29129516.

62. Onwuneme C, Martin F, McCarthy R, Carroll A, Segurado R, Murphy J, et al. The Association of Vitamin D Status with Acute Respiratory Morbidity in Preterm Infants. J Pediatr. 2015; 166(5):1175–80.e1. https://doi.org/10.1016/j.jpeds.2015.01.055 PMID: 25919726.

63. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001; 163(7):1723–9. https://doi.org/10.1164/ajrccm.163.7.2011060 PMID: 11401896.

64. Hollis BW, Pittard WB 3rd. Evaluation of the total fetomaternal vitamin D relationships at term: evidence for racial differences. J Clin Endocrinol Metab. 1984; 59(4):652–7. https://doi.org/10.1210/jcem-59-4-652 PMID: 6090493.

65. Dawodu A, Nath R. High prevalence of moderately severe vitamin D deficiency in preterm infants. Pediatr Int. 2011; 53(2):207–10. https://doi.org/10.1111/j.1442-200X.2010.03209.x PMID: 20667028.

66. Vandeveijvere S, Amsalkhir S, Van Oyen H, Moreno-Reyes R. High prevalence of vitamin D deficiency in pregnant women: a national cross-sectional survey. PLoS One. 2012; 7(8):e43868. https://doi.org/10.1371/journal.pone.0043868 PMID: 22937114.

67. Bener A, Al-Hamaq AO, Saleh NM. Association between vitamin D insufficiency and adverse pregnancy outcome: global comparisons. Int J Womens Health. 2013; 5:523–31. https://doi.org/10.2147/IJWH.S51403 PMID: 24043954.

68. Molla AM, Al Badawi M, Hammoud MS, Molla AM, Shukkur M, Thalib L, et al. Vitamin D status of mothers and their neonates in Kuwait. Pediatr Int. 2005; 47(6):649–52. https://doi.org/10.1111/j.1442-200x.2005.02141.x PMID: 16354218.

69. Aloia JF. Clinical Review: The 2011 report on dietary reference intake for vitamin D: where do we go from here? J Clin Endocrinol Metab. 2011; 96(10):2987–96. https://doi.org/10.1210/jc.2011-0090 PMID: 21795456.

70. Hayes D Jr, Feola DJ, Murphy BS, Shook LA, Ballard HO. Pathogenesis of bronchopulmonary dysplasia. Respiratio. 2010; 79(5):425–36. https://doi.org/10.1159/000242497 PMID: 19786727.
72. Biniwale MA, Ehrenkranz RA. The role of nutrition in the prevention and management of bronchopulmonary dysplasia. Semin Perinatol. 2006; 30(4):200–8. https://doi.org/10.1053/j.semperi.2006.05.007 PMID: 16860160.

73. Gazibara T, den Dekker HT, de Jongste JC, McGrath JJ, Eyles DW, Burne TH, et al. Associations of maternal and fetal 25-hydroxyvitamin D levels with childhood lung function and asthma: the Generation R Study. Clin Exp Allergy. 2016; 46(2):337–46. https://doi.org/10.1111/cea.12694 PMID: 26399470.

74. Cardus A, Panizo S, Encinas M, Dolce X, Gallego C, Aldea M, et al. 1,25-dihydroxyvitamin D3 regulates VEGF production through a vitamin D response element in the VEGF promoter. Atherosclerosis. 2009; 204(1):85–9. https://doi.org/10.1016/j.atherosclerosis.2008.08.020 PMID: 18834982.

75. Sarkar S, Chopra S, Rohit MK, Banerjee D, Chakraborti A. Vitamin D regulates the production of vascular endothelial growth factor: A triggering cause in the pathogenesis of rheumatic heart disease? Med Hypotheses. 2016; 95:62–6. https://doi.org/10.1016/j.mehy.2016.09.001 PMID: 27692170.

76. Irani M, Seifer DB, Grazi RV, Irani S, Rosenwaks Z, Tal R. Vitamin D Decreases Serum VEGF Correlating with Clinical Improvement in Vitamin D-Deficient Women with PCOS: A Randomized Placebo-Controlled Trial. Nutrients. 2017; 9(4). https://doi.org/10.3390/nu9040334 PMID: 2835032877.

77. Zosky GR, Hart PH, Whitehouse AJ, Kusel MM, Ang W, Foong RE, et al. Vitamin D deficiency at 16 to 20 weeks’ gestation is associated with impaired lung function at asthma at 6 years of age. Ann Am Thorac Soc. 2014; 11(4):571–7. https://doi.org/10.1513/AnnalsATS.201312-423OC PMID: 24601713.

78. Agarwal S, Kovilam O, Agrawal DK. Vitamin D and its impact on maternal-fetal outcomes in pregnancy: A critical review. Crit Rev Food Sci Nutr. 2018; 58(5):755–69. https://doi.org/10.1080/10408398.2016.1220915 PMID: 27558700.

79. Tschanz SA, Burri PH. Postnatal lung development and its impairment by glucocorticoids. Pediatr Pulmonol Suppl. 1997; 16:247–9. https://doi.org/10.1002/ppul.19502308128 PMID: 9443296.

80. Tschanz SA, Damke BM, Burri PH. Influence of postnatally administered glucocorticoids on rat lung growth. Biol Neonate. 1995; 68(4):229–45. https://doi.org/10.1159/000244241 PMID: 8580214.

81. Abrams SA. Calcium and vitamin d requirements of enterally fed preterm infants. Pediatrics. 2013; 131(5):e1676–83. https://doi.org/10.1542/peds.2013-0420 PMID: 23629620.

82. Agostoni C, Buonocore G, Camilli VP, De Curtis M, Darnaoui D, Dececi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010; 50(1):85–91. https://doi.org/10.1097/MPG.0b013e3181adae61 PMID: 19881390.

83. Yang Y, Li Z, Yan G, Jie Q, Rui C. Effect of different doses of vitamin D supplementation on preterm infants—an updated meta-analysis. J Matern Fetal Neonatal Med. 2018; 31(22):3065–74. https://doi.org/10.1080/14767058.2017.1363731 PMID: 28783999.