# Prematurity Does Not Increase Early Childhood Fracture Risk

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**Objective** To evaluate the impact of prematurity on fracture by age 5, controlling for medications and comorbidities of prematurity.

**Study design** We performed a retrospective cohort study of infants born in Military Treatment Facilities in 2009-2010 with ≥5 years of follow-up care. Gestational age, low birth weight, comorbidities of prematurity (osteopenia, necrotizing enterocolitis, chronic lung disease, and cholestasis) and fractures were identified by *International Classification of Disease, 9th Edition,* codes. Pharmaceutical records identified treatment with caffeine, diuretics, postnatal corticosteroids, and antacids. Poisson regression analysis determined fracture rate by 5 years of life.

**Results** There were 65 938 infants born in 2009-2010 who received care in the military health system for ≥5 years, including 3589 born preterm; 165 born at ≤28$^{6/7}$ weeks of gestation, 380 born at 29-31$^{6/7}$ weeks of gestation, and 3044 born at 32-36$^{6/7}$ weeks of gestation. Preterm birth at any gestational age was not associated with fracture rate in adjusted models. The fracture rate was increased with cholestasis, proton pump inhibitor exposure, and male sex.

**Conclusions** Prematurity was not associated with fracture rate. Neonatal cholestasis and proton pump inhibitor treatment were associated with increased fractures by age 5. *(J Pediatr 2019;207:148-53).*

Advances in neonatal care have improved preterm infant survival, although preterm birth remains associated with short- and long-term morbidity.[1] Bone health continues to be an area of concern, considering that two-thirds of the total calcium and phosphorus transfer occurs after 25 weeks of gestation, and postnatal nutrition rarely achieves fetal mineral attrition rates.[2] Among infants born at <28 weeks of gestation, metabolic bone disease is estimated to affect ≤55% of extremely low birth weight (ELBW) and ≤25% of very low birth weight (VLBW) preterm infants.[3-6]

Metabolic bone disease is associated with increased early infancy fracture risk, with the majority of fractures occurring during neonatal intensive care unit hospitalization through the first 6 months of life.[3-5,7] An estimated 10% of VLBW infants and 33% of ELBW infants develop fractures during the first 6 months, the majority attributable to prematurity and/or metabolic bone disease.[5,8,9]

Owing to these strong early life associations, fractures occurring in later infancy and early childhood may also be attributed to preterm birth, despite existing evidence demonstrating no association between prematurity and fracture beyond the first 6 months of life.[10-13] Erroneous attribution of fracture to preterm birth has important implications for the identification of child maltreatment and other conditions impacting bone health. No studies have examined fracture risk controlling for comorbidities or medications that may affect bone health. We designed a retrospective cohort study to examine the impact of prematurity on childhood fracture ≤5 years of age, adjusting for comorbidities of prematurity and medications used commonly in neonates, which are thought to affect bone health. We hypothesized that, consistent with the existing literature, prematurity would not impact fracture rate during the first 5 years of life, even after controlling for medications and comorbidities.

## Methods

Using the military healthcare system database, we formed a retrospective cohort of uniformed services beneficiaries born at military treatment facilities. Infants born at military treatment facilities between October 1, 2008, and September 30, 2010 (fiscal years 2009-2010) who received care in the military health system for ≥5 years were identified and included. The military health system provides medical

| | |
|---|---|
| ICD-9-CM | *International Classification of Diseases, Ninth Revision, Clinical Modification* |
| LBW | Low birth weight |
| NEC | Necrotizing enterocolitis |
| PPI | Proton pump inhibitor |

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care to nearly 9.5 million military members, retirees, and dependents. Care is provided at military treatment facilities and civilian facilities domestically and abroad. The military health system database includes records of all inpatient and outpatient care provided, all medications prescribed in the outpatient setting, and all inpatient prescriptions at military treatment facilities. Inpatient prescriptions at civilian facilities are not included in the military health system database, limiting included children to those born and cared for in military hospitals during the neonatal period (the first 28 days of life).

Children born preterm were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for gestational age. The inpatient record included records of any admission that began during the neonatal period. In cases of prematurity, LBW, or illness, admissions could extend beyond the first 28 days of life, but were initiated during this period. ICD-9-CM code categories were used to subcategorize preterm births into gestational age categories, including ≤ $28^{6/7}$ weeks of gestation, 29-$31^{6/7}$ weeks of gestation, and 32-$36^{6/7}$ weeks of gestation. Common comorbidities of prematurity that have been hypothesized to be associated with fracture risk including necrotizing enterocolitis (NEC), chronic lung disease, LBW, and osteopenia also were identified by ICD-9-CM diagnostic codes in the inpatient record.

Inpatient and outpatient prescription data identified children who were treated with histamine-2 receptor blockers ($H_2$ blockers), proton pump inhibitors (PPIs), diuretics, caffeine, or systemic postnatal corticosteroids during the first year of life. Children were classified as ever having taken the medication during the first year of life if they had ≥1prescription for the class of medications.

Childhood fractures during the first 5 years of life were identified by outpatient visits or inpatient admissions with a diagnostic code for fracture as classified by Agency for Healthcare Research and Quality's Clinical Classification System. Agency for Healthcare Research and Quality Clinical Classification System fracture subcategories were used to subclassify fractures as hip, skull, upper limb, lower limb, or other (vertebral column, ribs, or pelvis) fractures. Inpatient or outpatient visits for fracture within 60 days of the original visit for the same type of fracture were excluded and presumed to be follow-up visits. The total fractures over a 5-year period were quantified. Children with ICD-9-CM codes for child maltreatment or osteogenesis imperfecta were excluded, because both are associated with increased fracture risk.

A $\chi^2$ analysis determined group differences between children born term and preterm. Poisson regression analysis, which analyzes the count of events over time, determined the adjusted fracture incidence rate ratios and 95% CIs by preterm birth status. The adjusted model accounted for the effects of sex, medication use including caffeine, $H_2$ blockers, PPIs, diuretics, and postnatal corticosteroids; and comorbidities of prematurity including LBW, osteopenia, NEC, chronic lung disease, and cholestasis. Additional subgroup analyses divided the follow-up period into 2 categories: the first year of life, a time when children generally are not walking, and years 2-5 when children are usually ambulatory.

Stata Intercooled 13 (Stata Corp, College Station, Texas) software was used for all statistical analysis; *P* values of <.05 were considered statistically significant. The study was reviewed and approved by the responsible institutional review boards.

## Results

There were 65 938 children born in the military health system during the study period with ≥5 years of follow-up within the military health system. Overall, 0.7% of children experienced a fracture in the first year of life, and 7% of children experienced ≥1 fracture in the first 5 years of life. There were 505 children excluded owing to diagnosed child maltreatment and one excluded owing to osteogenesis imperfecta. Children excluded owing to maltreatment had a higher fracture rate with 6.5% of excluded children having a fracture in the first year and 14.9% having a fracture in the first 5 years.

Of the remaining 65 432 children, 165 were born at ≤$28^{6/7}$ weeks of gestation, 380 were born at 29-$31^{6/7}$ weeks of gestation, 3044 were born at 32-$36^{6/7}$ weeks of gestation, and 61 843 were born term at ≥37 weeks of gestation. Children born preterm were more likely to be male, be born with LBW, have a neonatal comorbidity (chronic lung disease, NEC, cholestasis, osteopenia), and be treated with caffeine, PPIs, $H_2$ blockers, postnatal corticosteroids, or diuretics (**Table I**). The overall incidence of fracture did not differ significantly between preterm and term children; however, preterm infants had a slightly higher incidence of skull fractures and a lower incidence of upper extremity fractures (**Table II**). There were no cases with ICD-9-CM codes that have been associated with child maltreatment including rib fractures (801.0, 807.1), skull vault fracture (800), or vertebral fracture (805) in the included or excluded children.[14]

In unadjusted analysis, the rate of fracture during the entire 5-year follow-up period was not increased in children born at any degree of prematurity. The unadjusted rate of fracture was increased 9% in males, >800% in infants with cholestasis, >50% in infants treated with PPIs, 67% in infants treated with diuretics, and 12% in those treated with $H_2$ blockers during the first 5 years of life (**Table III**). In unadjusted analysis of the preambulatory group alone (0-1 years), preterm infants born at ≤28 weeks of gestation had 700% as many fractures, but infants born at >28 weeks of gestation did not have increased fractures in the first year of life (**Table III**). Infants with NEC, chronic lung disease, cholestasis, and those treated with caffeine, diuretics, or $H_2$ blockers had increased fracture rates in the first year of life in unadjusted analysis. In the ambulatory group (years 2-5), increased fracture rates were associated with male sex, cholestasis, and PPI use in unadjusted analyses (**Table III**).

In adjusted analysis, the rate of fracture during the entire 5-year follow-up period was not associated with any degree of prematurity. During the 5-year follow-up period, male sex, PPI use, and cholestasis were associated with an increased fracture rate (**Table IV**). During the preambulatory period (age 0-1 years), cholestasis was associated with a 2200% increased rate of fracture; none of the other factors studied was associated with

**Table I. Demographics, medications, and comorbid conditions of children born term and preterm in the military health system in 2009-2010**

| | All children (n = 65 432) | Term > 37 weeks (n = 61 843) | Preterm (n = 3589) | Preterm <28$^{6/7}$ weeks (n = 165) | Preterm 29-31$^{6/7}$ weeks (n = 380) | Preterm 33-36$^{6/7}$ weeks (n = 3044) |
|---|---|---|---|---|---|---|
| Male* | 51.2 | 51.0 | 53.8 | 57.6 | 53.7 | 52.6 |
| LBW* | 3.5 | 0.82 | 49.1 | 96.4 | 96.8 | 40.6 |
| Osteopenia* | 0.11 | 0.03 | 1.5 | 9.7 | 6.3 | 0.46 |
| NEC* | 0.07 | 0.01 | 1.1 | 15.2 | 1.8 | 0.20 |
| Chronic lung disease* | 0.10 | 0.00 | 1.8 | 31.5 | 2.4 | 0.07 |
| Cholestasis* | 0.02 | 0.01 | 0.31 | 3.6 | 0.53 | 0.10 |
| Neonatal medication use | | | | | | |
| Caffeine* | 0.59 | 0.02 | 10.5 | 94.6 | 47.1 | 1.3 |
| Postnatal corticosteroids* | 0.81 | 0.71 | 2.40 | 33.94 | 2.89 | 0.62 |
| Diuretics* | 0.49 | 0.20 | 5.5 | 64.2 | 12.9 | 1.4 |
| PPIs* | 1.6 | 1.4 | 5.3 | 27.9 | 10.5 | 3.4 |
| $H_2$ blockers* | 8.3 | 7.8 | 17.9 | 42.4 | 29.5 | 15.1 |

*Significant difference between preterm versus term group ($P < .05$). Data are percent.

increased fracture in the first year of life. In the ambulatory group (age 2-5 years), male sex was associated with a 9% increased rate of fracture and PPI use during the first year of life was associated with a 47% increased fracture rate. (**Table IV**).

## Discussion

There was no association between prematurity and fracture during the first 5 years of life in our study of children born in 2009 and 2010; this controlled for factors likely to affect bone health. Consistent with previous reported rates, we found that 0.7% of children had a fracture before 12 months of age, 7% had a fracture by 5 years of age, and that rates were not increased in children born preterm.[15-17] Although the unadjusted analysis suggested that birth at ≤28 weeks of gestation may be associated with an increased rate of fracture during the first year of life, this association was not significant once we adjusted for common comorbidities of prematurity and neonatal medications. In our adjusted analysis, male sex, cholestasis, and PPI exposure during the first year of life were all independently associated with an increased rate of fracture during the first 5 years of life.

Our study corroborates the findings of previously published studies suggesting that preterm birth does not confer an increased risk of fracture beyond early infancy.[7,11,12,18,19] Dahlenburg et al published a small, retrospective, case-control study of young children presenting with fractures to an acute care clinic; the authors did not find that children who presented with fractures were more likely to have been born preterm than controls.[12] Similarly, a large Danish cohort study examined the relationship between prematurity or small for gestational age births and hospital admissions for all causes from birth to adulthood; this study found that preterm birth was associated with a decreased risk for hospital admission for fractures or other musculoskeletal injuries.[11] These previous findings, together with our large comprehensive study, suggest that decreased bone mineral density related to prematurity is not likely to translate to an increased risk for sustaining fractures in childhood. Alternatively, it is possible that parents of former preterm infants may be risk adverse and avoid activities associated with accidental injuries. During young adulthood, individuals born preterm display fewer risk-taking behaviors than those born at term; however, it is unknown if this risk aversion occurs in younger children as well, or if these observed behaviors would correlate with a decreased risk of musculoskeletal injuries.[20]

Similar to our findings, other studies have demonstrated that males are at increased risk for fractures during childhood.[21] Chronic lung disease and NEC both have been associated with

**Table II. Fracture incidence and fracture site of children born term and preterm in the military health system in 2009-2010**

| | All children (n = 65 432) | Term > 37 weeks (n = 61 843) | Preterm (n = 3589) | Preterm <28$^{6/7}$ weeks (n = 165) | Preterm 29-31$^{6/7}$ weeks (n = 380) | Preterm 33-36$^{6/7}$ weeks (n = 3044) |
|---|---|---|---|---|---|---|
| Fracture incidence | | | | | | |
| Fracture, 0-5 years | 7.0 | 7.0 | 6.4 | 7.9 | 6.1 | 6.4 |
| Fracture, 0-1 years | 0.69 | 0.69 | 0.70 | 3.0 | 0.53 | 0.59 |
| Fracture, 2-5 years | 6.4 | 6.5 | 5.9 | 5.5 | 5.5 | 6.0 |
| Fracture site | | | | | | |
| Hip | 0.07 | 0.07 | 0.11 | 0.61 | 0 | 0.10 |
| Skull* | 0.48 | 0.47 | 0.75 | 1.2 | 1.1 | 0.69 |
| Upper limb* | 4.7 | 4.7 | 3.9 | 4.9 | 4.0 | 3.9 |
| Lower limb | 2.0 | 2.0 | 1.8 | 1.8 | 1.3 | 1.9 |
| Other/torso | 1.4 | 1.4 | 1.3 | 3.6 | 0.53 | 1.2 |

*Significant difference between preterm versus term group ($P < .05$). Data are percent.

**Table III. Unadjusted incidence rate ratio (and 95% CI) of fracture by age in a cohort of 65 938 infants born in the military health system**

| | 0-5 Years | 0-1 Years | 2-5 Years |
|---|---|---|---|
| Male | *1.09 (1.05-1.16) | 1.13 (0.92-1.38) | *1.09 (1.02-1.16) |
| Gestational age | | | |
| 32-36$^{6/7}$ weeks | 0.90 (0.77-1.05) | 0.86 (0.52-1.42) | 0.90 (0.77-1.06) |
| 29-31$^{6/7}$ weeks | 0.79 (0.51-1.21) | 0.63 (0.16-2.51) | 0.80 (0.51-1.26) |
| ≤28$^{6/7}$ weeks | 1.68 (0.87-3.25) | *7.23 (2.83-18.47) | 1.14 (0.56-2.31) |
| Comorbidities | | | |
| LBW | 0.90 (0.75-1.10) | 1.37 (0.84-2.26) | 0.86 (0.70-1.05) |
| Osteopenia | 0.73 (0.23-2.26) | 3.21 (0.47-21.97) | 0.48 (0.11-2.03) |
| NEC | 2.39 (0.55-10.34) | *13.28 (3.31-53.22) | 1.31 (0.27-6.44) |
| Chronic lung disease | *2.12 (1.15-3.88) | *7.23 (2.36-22.10) | 1.61 (0.72-3.58) |
| Cholestasis | *8.6 (2.6-28.1) | *47.93 (13.14-174.83) | *4.73 (1.20-18.61) |
| Medication use | | | |
| Caffeine | 1.14 (0.72-1.82) | *3.75 (1.64-8.58) | 0.89 (0.56-1.42) |
| PPI | *1.54 (1.22-1.96) | 1.80 (0.99-3.29) | *1.52 (1.18-1.95) |
| Postnatal corticosteroids | 1.33 (0.91-1.92) | 2.04 (0.72-5.77) | 1.25 (0.87-1.81) |
| Diuretics | *1.67 (1.03-2.71) | *4.49 (1.91-10.56) | 1.40 (0.82-2.38) |
| $H_2$ blockers | *1.12 (1.01-1.25) | *1.42 (1.02-1.98) | 1.09 (0.97-1.23) |

*$P < .05$.

an increased risk for fracture during early infancy.[5,8,22] We did not, however, find any association between chronic lung disease or NEC and fracture risk during early childhood, suggesting that any increased risk may be limited to early infancy, or becomes nonsignificant after adjustment for other factors.

Our data show that neonatal cholestasis is associated with an increased fracture rate during the first year of life. Both bowel resection and prolonged parenteral nutrition place affected infants at risk for decreased absorption of vitamin D and other fat-soluble vitamins. Previous studies have suggested that ≤50% of infants with neonatal cholestasis have radiologic evidence of rickets, which is consistent with our finding of increased fracture rates in these children.[23,24] Cholestasis was not associated with fracture rate in children ages 2-5 years, suggesting that the increased fracture risk for infants with cholestasis may not persist.

In our adjusted analysis, the use of diuretics, postnatal corticosteroids, caffeine, or $H_2$ blockers was not associated with an increased rate of early childhood fracture. More than 5% of all preterm infants and >60% of infants born at ≤28 weeks of gestation in our study were treated with diuretics. Furosemide, a diuretic commonly used in the management of chronic lung disease in neonates, causes urinary calcium losses, and its use has been associated with an increased risk of hip fracture in adults.[25] Despite its wide use in our population, we did not find any associations with fracture risk in early childhood. Likewise, although the treatment of chronic lung disease with dexamethasone in preterm infants has been associated with decreased linear growth and decreased bone mineralization, we did not find an association between postnatal corticosteroids and fracture during early childhood.[26-29] Finally, caffeine, used in the neonatal population to treat apnea of

**Table IV. Adjusted incidence rate ratio (and 95% CI) of fracture by age in a cohort of 65 938 infants born in the military health system**

| | 0-5 Years | 0-1 Years | 2-5 Years |
|---|---|---|---|
| Male | *1.09 (1.02-1.16) | 1.10 (0.90-1.35) | *1.09 (1.02-1.16) |
| Gestational age, wk | | | |
| 32-36$^{6/7}$ | 0.90 (0.76-1.07) | 0.79 (0.45-1.41) | 0.92 (0.77-1.09) |
| 29-31$^{6/7}$ | 0.82 (0.44-1.54) | 0.32 (0.09-1.14) | 0.92 (0.48-1.77) |
| <28$^{6/7}$ | 1.10 (0.45-2.69) | 1.07 (0.15-7.49) | 0.97 (0.37-2.54) |
| Comorbidities | | | |
| LBW | 0.93 (0.75-1.17) | 1.02 (0.40-2.61) | 0.92 (0.75-1.13) |
| Osteopenia | 0.66 (0.21-2.13) | 2.43 (0.36-16.55) | 0.46 (0.10-2.13) |
| NEC | 1.62 (0.44-5.92) | 4.24 (0.97-18.56) | 1.06 (0.23-4.78) |
| Chronic lung disease | 1.33 (0.51-3.49) | 1.15 (0.26-5.10) | 1.50 (0.49-4.56) |
| Cholestasis | *6.23 (2.24-17.33) | *22.01 (8.64-56.08) | 3.81 (0.97-14.88) |
| Medication use | | | |
| Caffeine | 0.79 (0.40-1.58) | 1.60 (0.39-6.63) | 0.72 (0.34-1.53) |
| PPI | *1.43 (1.13-1.81) | 1.14 (0.60-2.15) | *1.47 (1.14-1.89) |
| Postnatal corticosteroids | 1.15 (0.82-1.60) | 0.87 (0.40-1.91) | 1.17 (0.81-1.69) |
| Diuretics | 1.40 (0.75-2.61) | 1.28 (0.32-5.10) | 1.42 (0.71-2.82) |
| $H_2$ blockers | 1.07 (0.95-1.20) | 1.34 (0.95-1.89) | 1.05 (0.93-1.18) |

Adjusted for male sex, gestational age, comorbidities, and medication use.
*$P < .05$.

prematurity has been associated with an increased risk of osteoporotic fractures in adult women and is known to decrease intestinal calcium absorption and increase urinary calcium excretion.[30] In our study, caffeine use was not associated with an increased fracture during early childhood.

In our study, 1.6% of all children and >27% of infants born at ≤28$^{6/7}$ weeks of gestation were prescribed a PPI during the first year of life. PPI exposure was associated with an increased rate of fracture, with the greatest effect seen between 2 and 5 years of age. PPIs are used widely in infants despite lack of efficacy in the treatment of gastroesophageal reflux and evidence of potential harm including an increased risk for serious bacterial infections and *Clostridium difficile* infections.[31-34] Recently, PPI use has been associated with an increased risk of fracture in adolescents and older adults.[35-37] Although PPIs do not directly affect calcium absorption, they may alter the function of osteoclasts, which have a proton pump that is critical to their function in bone remodeling and turnover.[38] The association between PPI use during the first year of life and fracture risk during later childhood questions the safety of PPIs in the treatment of infants with gastroesophageal reflux and warrants further study.

The incidence of child maltreatment in our study population, estimated using ICD-9-CM codes for maltreatment, was much lower than the general population and it is unlikely we identified all cases. Additionally, studies have found that vomiting and irritability, which are often used in the diagnosis of gastroesophageal reflux and PPI prescription, are frequent clinical signs in missed cases of nonaccidental trauma.[39-41] Our data suggest a possible association between PPI use and fracture rate, but do not establish causality. A history of PPI use should not be used as an explanation for fracture patterns or histories that are concerning for maltreatment.

There are several limitations of our study. First, ICD-9-CM codes do not indicate disease severity and gestational age dating is imprecise. New fractures may have been misclassified as follow-up and excluded. Although most military beneficiaries and their dependents receive insurance coverage solely through the military health system, care covered by outside insurance providers was not included, creating the possibility that fractures treated outside the military health system were not counted. Finally, medication use was treated as binary data, so subjects were coded as having exposure or not having exposure. We are not able to determine if there are any dose–response relationships between medication exposure and fracture risk.

The strengths of our study include a large sample size with a large cohort of preterm infants cared for in a universal healthcare system which decreases access to care bias, a long follow-up period, and inclusion of pharmaceutical and comorbid covariates. The use of a complete medical database minimizes recall and ascertainment bias.

Our data do not support prematurity as being associated with fracture at ≤5 years of age, but suggests neonatal cholestasis, male sex, and treatment with PPIs during the first year of life are associated with increased fracture rates. Further studies are needed to explore these associations. Efforts should be focused on optimizing bone health in infants with cholestasis and avoiding usage of PPIs in infants. These results support that prematurity should not be used as an explanation for fracture, which is especially important in cases with fracture patterns suspicious for nonaccidental trauma. ■

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## References


1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
2. Moreira A, Jacob R, Lavender L, Escaname E. Metabolic bone disease of prematurity. NeoReviews 2015;16:e631-41.
3. Koo WW, Gupta JM, Nayanar VV, Wilkinson M, Posen S. Skeletal changes in preterm infants. Arch Dis Child 1982;57:447-52.
4. McIntosh N, De Curtis M, Williams J. Failure of mineral supplementation to reduce incidence of rickets in very-low-birthweight infants. Lancet 1986;2:981-2.
5. Viswanathan S, Khasawneh W, McNelis K, Dykstra C, Amstadt R, Super DM, et al. Metabolic bone disease: a continued challenge in extremely low birth weight infants. JPEN J Parenter Enteral Nutr 2014;38:982-90.
6. Bozzetti V, Tagliabue P. Metabolic bone disease in preterm newborn: an update on nutritional issues. Ital J Pediatr 2009;35:20.
7. Fewtrell MS, Williams JE, Singhal A, Murgatroyd PR, Fuller N, Lucas A. Early diet and peak bone mass: 20 year follow-up of a randomized trial of early diet in infants born preterm. Bone 2009;45:142-9.
8. Dabezies EJ, Warren PD. Fractures in very low birth weight infants with rickets. Clin Orthop Relat Res 1997;233-9.
9. Lucas-Herald A, Butler S, Mactier H, McDevitt H, Young D, Ahmed SF. Prevalence and characteristics of rib fractures in ex-preterm infants. Pediatrics 2012;130:1116-9.
10. Bronicki LM, Stevenson RE, Spranger JW. Beyond osteogenesis imperfecta: causes of fractures during infancy and childhood. Am J Med Genet C Semin Med Genet 2015;169:314-27.
11. Á Rogvi R, Forman JL, Greisen G. Prematurity, smallness-for-gestational age and later hospital admissions: a nation-wide registry study. Early Hum Dev 2015;91:299-306.
12. Dahlenburg SL, Bishop NJ, Lucas A. Are preterm infants at risk for subsequent fractures? Arch Dis Child 1989;64:1384-5.
13. Topor LS, Borus JS, Aspinwall S, Gilbert CL, Gordon CM, Huh SY. Fractures among inpatients in a pediatric hospital. Hosp Pediatr 2016;6:143-50.
14. Schnitzer PG, Slusher PL, Kruse RL, Tarleton MM. Identification of ICD codes suggestive of child maltreatment. Child Abuse Negl 2011;35:3-17.
15. Kopjar B, Wichizer TM. Fractures among children: incidence and impact on daily activities. Inj Prev 1998;4:194.
16. Jones IE, Williams SM, Dow N, Goulding A. How many children remain fracture-free during growth? A longitudinal study of children and adolescents participating in the Dunedin Multidisciplinary Health and Development Study. Osteoporos Int 2002;13:990-5.
17. Naranje SM, Erali RA, Warner WCJ, Sawyer JR, Kelly DM. Epidemiology of pediatric fractures presenting to emergency departments in the United States. J Pediatr Orthop 2016;36:e45-8.
18. Chan GM, Armstrong C, Moyer-Mileur L, Hoff C. Growth and bone mineralization in children born prematurely. J Perinatol 2008;28:619-23.
19. Hovi P, Andersson S, Jarvenpaa AL, Eriksson JG, Strang-Karlsson S, Kajantie E, et al. Decreased bone mineral density in adults born with very low birth weight: a cohort study. PLoS Med 2009;6:e1000135.
20. Hille ET, Dorrepaal C, Perenboom R, Gravenhorst JB, Brand R, Verloove-Vanhorick SP. Social lifestyle, risk-taking behavior, and psychopathology in young adults born very preterm or with a very low birthweight. J Pediatr 2008;152:793-800, e1-4.

21. Orton E, Kendrick D, West J, Tata LJ. Independent risk factors for injury in pre-school children: three population-based nested case-control studies using routine primary care data. PLoS ONE 2012;7:e35193.
22. Amir J, Katz K, Grunebaum M, Yosipovich Z, Wielunsky E, Reisner SH. Fractures in premature infants. J Pediatr Orthop 1988;8:41-4.
23. Mohammadi B, Najafi M, Farahmand F, Motamed F, Ghajarzadeh M, Mohammadi J, et al. Prevalence of vitamin D deficiency and rickets in children with cholestasis in Iran. Acta Med Iran 2012;50:482-5.
24. Kobayashi A, Kawai S, Utsunomiya T, Obe Y. Bone disease in infants and children with hepatobiliary disease. Arch Dis Child 1974;49:641-6.
25. Heidrich FE, Stergachis A, Gross KM. Diuretic drug use and the risk for hip fracture. Ann Intern Med 1991;115:1-6.
26. Weiler HA, Paes B, Shah JK, Atkinson SA. Longitudinal assessment of growth and bone mineral accretion in prematurely born infants treated for chronic lung disease with dexamethasone. Early Hum Dev 1997;47:271-86.
27. Eelloo JA, Roberts SA, Emmerson AJ, Ward KA, Adams JE, Mughal MZ. Bone status of children aged 5-8 years, treated with dexamethasone for chronic lung disease of prematurity. Arch Dis Child Fetal Neonatal Ed 2008;93:F222-4.
28. Shrivastava A, Lyon A, McIntosh N. The effect of dexamethasone on growth, mineral balance and bone mineralisation in preterm infants with chronic lung disease. Eur J Pediatr 2000;159:380-4.
29. Ng PC, Lam CW, Wong GW, Lee CH, Cheng PS, Fok TF, et al. Changes in markers of bone metabolism during dexamethasone treatment for chronic lung disease in preterm infants. Arch Dis Child Fetal Neonatal Ed 2002;86:F49-54.
30. Hallstrom H, Wolk A, Glynn A, Michaelsson K. Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women. Osteoporos Int 2006;17:1055-64.
31. Khaver I, Kirmani GL, Pichichero ME, Voloshen T, D'Angio CT. Seven-year follow-up of vaccine response in extremely premature infants. Pediatrics 2002;109:7.
32. Freedberg DE, Lamouse-Smith ES, Lightdale JR, Jin Z, Yang YX, Abrams JA. Use of acid suppression medication is associated with risk for C. difficile infection in infants and children: a population-based study. Clin Infect Dis 2015;61:912-7.
33. Graham PL 3rd, Begg MD, Larson E, Della-Latta P, Allen A, Saiman L. Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. Pediatr Infect Dis J 2006;25:113-7.
34. D'Agostino JA, Passarella M, Martin AE, Lorch SA. Use of gastroesophageal reflux medications in premature infants after NICU discharge. Pediatrics 2016;138:pii: e20161977.
35. Freedberg DE, Haynes K, Denburg MR, Zemel BS, Leonard MB, Abrams JA, et al. Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. Osteoporos Int 2015;26:2501-7.
36. Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016;27:339-47.
37. Elaine WY, Bauer SR, Bain PA, Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. Am J Med 2011;124:519-26.
38. Uzoigwe O. Proton pump inhibitors and fracture: do they do what it says on the tin? Osteoporos Int 2016;27:1671-2.
39. Kondis JS, Muenzer J, Luhmann JD. Missed fractures in infants presenting to the emergency department with fussiness. Pediatr Emerg Care 2017;33:538-43.
40. Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC. Analysis of missed cases of abusive head trauma. JAMA 1999;281:621-6.
41. Letson MM, Cooper JN, Deans KJ, Scribano PV, Makoroff KL, Feldman KW, et al. Prior opportunities to identify abuse in children with abusive head trauma. Child Abuse Negl 2016;60:36-45.