Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Preterm birth and the future risk of orthopedic fracture

Jonathan Michaud[1,2,3], Thuy Mai Luu[4], John C. LeBlanc[5], Jessica Healy-Profitós[2,3], Aimina Ayoub[2,3] and Nathalie Auger[1,2,3]

BACKGROUND: Preterm birth occurs during a critical period of bone mineralization. We assessed whether preterm birth increases the risk of childhood fracture.

METHODS: We analyzed a cohort of 788,903 infants born between 2006 and 2016 in Quebec, Canada. The exposure was preterm birth (<37 weeks). The outcome was any future hospitalization for fracture before 2018. We estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association of prematurity with fractures in adjusted Cox regression models. We determined if the risk of facture varied by the child's age.

RESULTS: The incidence of fracture hospitalizations was higher in preterm children than in term children (17.9 vs. 15.3 per 10,000 person-years). Compared with term, preterm children had 1.27 times the risk of femur fracture hospitalization (95% CI 1.01–1.60) and 2.27 times the risk of assault-related fractures (95% CI 1.37–3.76). Preterm children had 2.20 times the risk of femur fracture between 6 and 17 months of age (95% CI 1.45–3.35).

CONCLUSIONS: Preterm birth is associated with an increased risk of hospitalization for femur fractures and assault-related fractures. Associations are stronger before 18 months of age. Families of preterm children may benefit from counseling and support for fracture prevention during early childhood.

Pediatric Research (2020) 88:466–472; https://doi.org/10.1038/s41390-020-0771-3

INTRODUCTION

Fractures are among the most frequent injuries in children, accounting for 58% of trauma-related hospitalizations in this population.[1] Identifying targets for prevention is challenging, as the determinants of pediatric fractures are poorly understood. Known risk factors such as small bone size, low mineral content, poor nutrition, and genetics explain only a fraction of cases.[2] Preterm birth has the potential to be an important risk factor for fracture, as approximately 80% of bone mineralization occurs in the third trimester of pregnancy.[3] There is some evidence that children born preterm have lower bone mineral content and density at 5–9 years of age than those born at term.[4] The impact of prematurity on risk of childhood fracture is however poorly understood, despite evidence that preterm birth interrupts the development of most body systems.[5]

Previous studies indicate that preterm birth increases the risk of fractures in infancy due to metabolic bone disease of prematurity.[6,7] Whether preterm infants are at risk of fractures beyond the first 6 months of life is less clear. Some data suggest that infants born <32 weeks' gestation with very low birth weight are more prone to fractures due to lower bone mineral content and density in childhood.[4,8] More recent research, however, suggests that preterm birth may not be associated with fractures in the first 5 years of childhood, but the data exclude patients with nonaccidental fractures.[9] Child maltreatment is an important cause of fractures, especially in early childhood.[10,11] Prematurity is a potential risk factor for child maltreatment,[12] as preterm children frequently have morbidities requiring special care that increase parental stress.[5] We sought to determine the relationship between prematurity and risk of orthopedic fracture in childhood using a large population-based cohort of infants.

METHODS

Study design and population

We analyzed a longitudinal cohort of 788,903 neonates born >22 weeks' gestation in hospitals of Quebec, Canada between 2006 and 2016. The cohort included 51,212 preterm births defined as <37 weeks' gestation. We extracted data on the newborns from the Maintenance and Use of Data for the Study of Hospital Clientele registry, an administrative database containing all hospital discharge abstracts for Quebec.[13] The registry includes information on gestational age in completed weeks, type of fracture, accident codes including the presence of assault, up to 41 additional diagnoses, pregnancy comorbidity, and demographic characteristics. Diagnoses are coded using the tenth edition of the International Classification of Diseases. We used health insurance numbers to follow the newborns from birth until the end of the study on March 31, 2018, and identified all hospitalizations for bone fractures.

We excluded newborns with missing or invalid gestational age using the Alexander method.[14] We also excluded newborns without health insurance numbers who could not be followed through time, and newborns who died before discharge or were diagnosed with osteogenesis imperfecta, a genetic disorder known to cause fractures.[15] We did not include infants who had fractures at the initial birth hospitalization, because our goal was

[1]Department of Social and Preventive Medicine, University of Montreal, Montreal, Canada; [2]Health Innovation and Evaluation Hub, University of Montreal Hospital Research Centre, Montreal, Canada; [3]Bureau d'information et d'études en santé des populations, Institut national de santé publique du Québec, Montreal, Canada; [4]Department of Pediatrics, Sainte-Justine Hospital Centre, University of Montreal, Montreal, Canada and [5]Departments of Pediatrics, Psychiatry, and Community Health and Epidemiology, Dalhousie University, Halifax, Canada
Correspondence: Nathalie Auger (nathalie.auger@inspq.qc.ca)

Received: 24 September 2019 Revised: 6 December 2019 Accepted: 11 December 2019
Published online: 22 January 2020

to assess the longitudinal risk of fracture during follow-up, not during the perinatal period.

Preterm birth

The main exposure measure was preterm birth. We used gestational age to classify infants as preterm (<37 weeks) or term (≥37 weeks). We further classified preterm birth as extreme (<28 weeks), very (28−31 weeks), and moderate (32−36 weeks). In Quebec, gestational age is determined by ultrasound in the first or second trimester.

To avoid masking trends by use of aggregate categories of preterm birth, we also analyzed gestational age as a continuous variable. We used restricted cubic splines to model a smooth nonlinear relationship between gestational age and fracture outcomes.[16] We placed knots at 32, 36, and 40 weeks' gestation in the splines, and used 40 weeks as the reference for the comparisons.

Fractures

The main outcome measure included fractures that resulted in morbidity serious enough to require hospitalization. We identified all children hospitalized for traumatic fractures during follow-up, up to 12 years after birth (Supplemental Table S1). Fractures were organized by anatomical location, including head, shoulder-trunk-pelvis, humerus, ulna-radius, hand, femur, and lower leg-foot. We also analyzed children who presented with multiple vs. single fractures, and identified fractures where assault was documented. In this study, we analyzed all fractures requiring treatment in hospital, but did not consider pathologic fractures due to cancer or other lesions. We could not analyze fractures that did not require admission; however, these fractures are less likely to be associated with a high degree of morbidity.

Covariates

We considered several covariates as potential confounders of the association between prematurity and fractures, including infant sex (male, female),[9] maternal age at delivery (<25, 25–34, ≥35 years),[17] multiple birth (yes, no),[17] pregnancy morbidity defined as preeclampsia or gestational diabetes (yes, no; Supplemental Table S1),[18,19] socioeconomic disadvantage (most socioeconomically deprived quintile of neighborhoods for income, employment, and education, not deprived, unknown),[1] and place of residence (rural, urban, unknown).[1] We accounted for infant comorbidities known to be associated with bone fracture, including osteoporosis,[2] vitamin D, calcium and phosphorus deficiency,[6] disorders of bone density and structure,[20] congenital heart defects,[21] cholestasis,[9] and bronchopulmonary dysplasia (Supplemental Table S1).[15]

Data analysis

We estimated the incidence of fractures per 10,000 person-years with 95% confidence intervals (CI). We used Cox proportional hazards regression models to calculate hazard ratios (HR) and 95% CIs for the association of preterm birth with the first fracture hospitalization, comparing preterm with term newborns. The time scale was the number of days from birth to fracture, death, or end of study. We censored children who were never hospitalized for fractures before the study end, and used the Fine and Gray method to handle deaths as a competing event.[22] We adjusted the models for sex, maternal age at delivery, multiple birth, pregnancy morbidity, socioeconomic disadvantage, place of residence, and infant comorbidity, and verified the proportional hazards assumption through time interaction terms.

To further characterize differences in the association between preterm birth and risk of fracture hospitalization at different points in childhood, we stratified the analysis by age at fracture (<6, 6–17, 18–35, ≥36 months). In sensitivity analysis, we removed all children with codes for assault to determine the impact on associations.

We performed the analyses using SAS v9.4 software and assessed the precision of our statistics using 95% CIs. The institutional review board of the University of Montreal Hospital Centre determined that ethical review was not needed for this study as the data were anonymized.

RESULTS

There were 788,903 children in this study, including 51,212 (6.5%) born preterm (Table 1). A total of 8424 children were hospitalized for fractures during 5,432,318 person-years of follow-up. The incidence of fractures was higher in preterm children (17.9 per 10,000 person-years) than in term children (15.3 per 10,000 person-years). The incidence was highest among children born at 32–36 weeks' gestation, with 18.1 fracture hospitalizations per 10,000 person-years, compared with 16.1 at 28–31 weeks and 17.1 at <28 weeks.

Table 1. Incidence of bone fracture hospitalization according to characteristics of children.

	No. infants	No. fractures	Person-years	Fracture incidence per 10,000 person-years (95% confidence interval)
Preterm birth, weeks				
<37	51,212	630	352,103	17.9 (16.5–19.3)
≥37	737,691	7794	5,080,215	15.3 (15.0–15.7)
Severity of preterm birth, weeks				
<28	1621	19	11,115	17.1 (10.9–26.8)
28–31	4009	44	27,319	16.1 (12.0–21.6)
32–36	45,582	567	313,670	18.1 (16.6–19.6)
Infant sex				
Male	404,655	4770	2,785,347	17.1 (16.6–17.6)
Female	384,248	3654	2,646,972	13.8 (13.4–14.3)
Maternal age, years				
<25	126,346	1700	893,187	19.0 (18.1–20.0)
25–34	527,727	5565	3,652,213	15.2 (14.8–15.6)
≥35	134,830	1159	886,918	13.1 (12.3–13.8)
Multiple birth				
Yes	12,506	166	82,619	20.1 (17.3–23.4)
No	776,397	8258	5,349,699	15.4 (15.1–15.8)
Pregnancy comorbidity[a]				
Yes	91,068	899	587,288	15.3 (14.3–16.3)
No	697,835	7525	4,845,030	15.5 (15.2–15.9)
Socioeconomic disadvantage				
Yes	156,050	1794	1,072,008	16.7 (16.0–17.5)
No	602,380	6372	4,178,270	15.3 (14.9–15.6)
Place of residence				
Rural	144,994	2062	1,005,596	20.5 (19.6–21.4)
Urban	630,034	6259	4,352,646	14.4 (14.0–14.7)
Infant comorbidity[b]				
Yes	13,652	231	90,548	25.5 (22.4–29.0)
No	775,251	8193	5,341,770	15.3 (15.0–15.7)
Total	788,903	8424	5,432,318	15.5 (15.2–15.8)

[a]Preeclampsia or gestational diabetes.
[b]Osteoporosis, vitamin D, calcium, and phosphorus deficiency, disorders of bone density and structure, congenital heart defects, cholestasis, and bronchopulmonary dysplasia.

Table 2. Association of preterm birth with risk of bone fracture hospitalization in childhood.

	Preterm <37 gestational weeks		Term ≥37 gestational weeks		Hazard ratio (95% confidence interval)[a]	
	No. fractures	Fracture incidence per 10,000 person-years (95% CI)	No. fractures	Fracture incidence per 10,000 person-years (95% CI)	Unadjusted	Adjusted[b]
Any fracture	630	17.9 (16.5–19.3)	7794	15.3 (15.0–15.7)	1.17 (1.07–1.26)	1.08 (0.99–1.18)
Head	155	4.4 (3.7–5.1)	1806	3.5 (3.4–3.7)	1.24 (1.05–1.46)	1.12 (0.94–1.33)
Shoulder-trunk-pelvis	34	1.0 (0.7–1.3)	236	0.5 (0.4–0.5)	2.08 (1.45–2.97)	1.51 (0.99–2.31)
Humerus	165	4.7 (4.0–5.4)	2245	4.4 (4.2–4.6)	1.06 (0.90–1.24)	1.03 (0.88–1.22)
Ulna-radius	146	4.1 (3.5–4.8)	2136	4.2 (4.0–4.4)	0.98 (0.83–1.16)	0.95 (0.79–1.13)
Hand	29	0.8 (0.6–1.2)	301	0.6 (0.5–0.7)	1.38 (0.95–2.03)	1.31 (0.89–1.94)
Femur	95	2.7 (2.2–3.3)	889	1.7 (1.6–1.9)	1.54 (1.25–1.90)	1.27 (1.01–1.60)
Lower leg-foot	42	1.2 (0.9–1.6)	564	1.1 (1.0–1.2)	1.07 (0.78–1.46)	1.01 (0.73–1.40)
Multiple fractures	30	0.8 (0.6–1.2)	365	0.7 (0.6–0.8)	1.18 (0.82–1.72)	0.99 (0.67–1.46)
Single fracture	603	17.1 (15.8–18.5)	7450	14.7 (14.3–15.0)	1.17 (1.07–1.27)	1.09 (1.00–1.19)
Assault-related fracture	24	0.7 (0.5–1.0)	127	0.2 (0.2–0.3)	2.72 (1.76–4.21)	2.27 (1.37-3.76)
Fracture without assault	608	17.3 (15.9–18.7)	7682	15.1 (14.8–15.5)	1.14 (1.05–1.24)	1.06 (0.97–1.15)

CI confidence interval.
[a]Hazard ratio for preterm vs. term.
[b]Adjusted for sex, maternal age at delivery, multiple birth, pregnancy morbidity, socioeconomic disadvantage, place of residence, and infant comorbidity.

Table 3. Association of preterm birth with risk of bone fracture hospitalization by age.

	Hazard ratio (95% confidence interval)[a]			
	<6 months	6–17 months	18–35 months	≥36 months
Any fracture	1.47 (1.15–1.89)	1.29 (1.01–1.64)	1.12 (0.90–1.39)	0.98 (0.88–1.09)
Head	1.32 (0.98–1.77)	0.96 (0.67–1.39)	1.16 (0.73–1.84)	1.06 (0.78–1.45)
Shoulder-trunk-pelvis	1.62 (0.71–3.68)	1.69 (0.71–4.00)	0.92 (0.22–3.82)	1.56 (0.82–2.96)
Humerus	2.40 (1.09–5.30)	1.07 (0.39–2.93)	1.30 (0.82–2.04)	0.96 (0.80–1.15)
Ulna-radius	5.18 (2.13–12.58)	1.64 (0.57–4.74)	1.09 (0.58–2.04)	0.84 (0.69–1.03)
Hand	6.14 (0.61–61.80)	1.73 (0.42–7.20)	1.21 (0.44–3.27)	1.26 (0.80–1.97)
Femur	1.51 (0.70–3.26)	2.20 (1.45–3.35)	1.14 (0.78–1.66)	0.87 (0.54–1.38)
Lower leg-foot	1.69 (0.56–5.12)	0.76 (0.32–1.80)	0.40 (0.12–1.32)	1.21 (0.82–179)
Multiple fractures	1.78 (0.81–3.90)	1.37 (0.53–3.56)	–	0.70 (0.40–1.24)
Single fracture	1.43 (1.10–1.86)	1.30 (1.02–1.66)	1.15 (0.93–1.44)	0.99 (0.88–1.11)
Assault-related fracture	2.64 (1.42–4.90)	1.75 (0.56–5.48)	1.30 (0.24–7.02)	2.27 (0.31–16.66)
Fracture without assault	1.30 (0.99–1.71)	1.28 (1.01–1.64)	1.11 (0.89–1.39)	0.98 (0.87–1.09)

[a]Hazard ratio for preterm vs. term, adjusted for sex, maternal age at delivery, multiple birth, pregnancy morbidity, socioeconomic disadvantage, place of residence, and infant comorbidity.

Compared with term, preterm children had a higher incidence of most types of fracture except ulna-radius (Table 2). In adjusted regression models, preterm birth was associated with an increased risk of hospitalization for femur (HR 1.27, 95% CI 1.01–1.60) and assault-related fractures (HR 2.27, 95% CI 1.37–3.76). Risks also appeared to be elevated for shoulder-trunk-pelvis and hand fractures, although associations were not statistically significant.

When stratified by age at fracture, associations tended to be stronger among younger children (Table 3). Compared with term infants, preterm infants had 1.47 times the risk of any fracture hospitalization before 6 months (95% CI 1.15–1.89) and 1.29 times the risk of any fracture hospitalization between 6 and 17 months (95% CI 1.01–1.64). An interaction term between gestational age and age at fracture was statistically significant ($p = 0.001$). Before 6 months, preterm birth was associated with 2.40 times the risk of humerus fracture (95% CI 1.09–5.30), 5.18 times the risk of ulna-radius fracture (95% CI 2.13–12.58), and 2.64 times the risk of assault-related fracture (95% CI 1.42–4.90). Between 6 and 17 months, preterm birth was associated with 2.20 times the risk of femur fracture (95% CI 1.45–3.35). Preterm birth was not significantly associated with the risk of any fracture type in children aged ≥18 months.

When analyzed as a *continuous* exposure, lower gestational age was associated with higher risk of hospitalization for several fracture outcomes, especially shoulder-trunk-pelvis, femur, and assault-related fractures (Fig. 1). Compared with 40 weeks, infants born at 33 weeks' gestation had 1.89 times the risk of shoulder-trunk-pelvis (95% CI 1.26–2.83), 1.30 times the risk of femur (95%

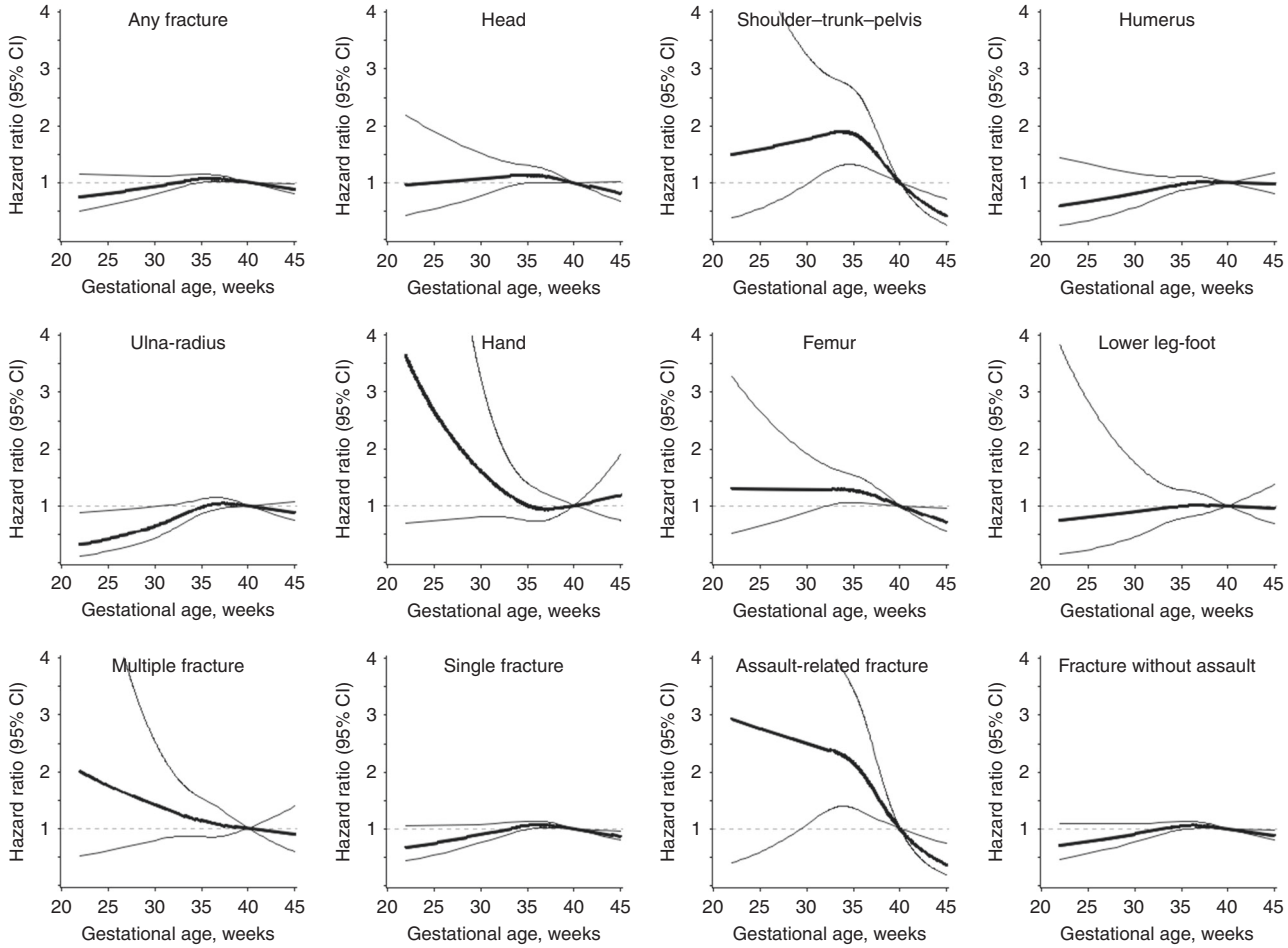

Fig. 1 Association of gestational age with risk of bone fracture hospitalization by site[a]. [a]Hazard ratios are relative to 40 weeks' gestation, and are adjusted for sex, maternal age at delivery, multiple birth, pregnancy morbidity, socioeconomic disadvantage, place of residence, and infant comorbidity.

CI 1.03–1.64), and 2.37 times the risk of assault-related fracture hospitalizations (95% CI 1.37–4.09). Preterm birth was also associated with head, hand, and multiple fractures, although these associations were weaker.

Stratification by age revealed that preterm birth was predominantly associated with fractures before 18 months of age (Fig. 2). Relative to 40 weeks, birth at 33 weeks' gestation was associated with 2.18 times the risk of shoulder-trunk-pelvis (95% CI 1.21–3.93), 1.63 times the risk of femur (95% CI 1.07–2.48), and 2.42 times the risk of assault-related fracture hospitalizations (95% CI 1.31–4.46) before 18 months of age. In sensitivity analysis excluding assaults, associations between preterm birth and fractures remained relatively stable or were slightly attenuated.

DISCUSSION

In this study of 788,903 newborns with 5,432,318 person-years of follow-up, preterm birth was associated with the future risk of fracture hospitalization during early childhood. Using a measure of gestational age on the continuous scale, we found that preterm birth was significantly associated with the risk of femur, shoulder-trunk-pelvis, and assault-related fractures, especially before 18 months of age. Preterm birth was not associated with risk of fracture hospitalization in older children. Although metabolic bone disease may have contributed to some of the associations before 6 months, we cannot rule out the possibility that some were due to assault. Our results suggest that the increased fracture risk in preterm children is not completely explained by metabolic bone disturbances, and that child maltreatment may be an important component, warranting enhanced preventive measures following neonatal discharge.

Metabolic bone disease of prematurity, or osteopenia of prematurity, is relatively common in preterm infants.[7,18] In a retrospective study of 230 infants born <30 weeks' gestation, 30.9% developed radiological evidence of metabolic bone disease.[7] While the exact pathology of metabolic bone disease of prematurity remains to be established, very preterm infants frequently suffer from calcium and phosphate deficiency.[3,18] Metabolic bone disease primarily affects infants born <27 weeks' gestation who miss out on the critical period of bone mineralization,[3] resulting in an increased risk of fractures, particularly of the ribs.[7] Studies suggest that risk factors for metabolic bone disease are associated with up to 16 times the chance of rib and long bone fractures before 6 months of age.[6] It is thought that the risk of fracture disappears at around 6 months of age once a critical bone mass is reached.[6,20] Our results confirm that preterm birth is associated with an elevated risk of fracture hospitalization before 6 months. However, the risk persisted past this time point and was stronger in moderate to late preterm infants, suggesting that pathways beyond metabolic bone disease may be involved.

The association of preterm birth with fractures beyond the first 6 months of life is poorly understood due to the paucity of research.[4,9] One study found that fractures were more common at 5−9 years of age in 20 preterm children who weighed <1500 g at birth, compared with 15 term children.[4] Three of the preterm children had forearm fractures from accidental falls whereas no

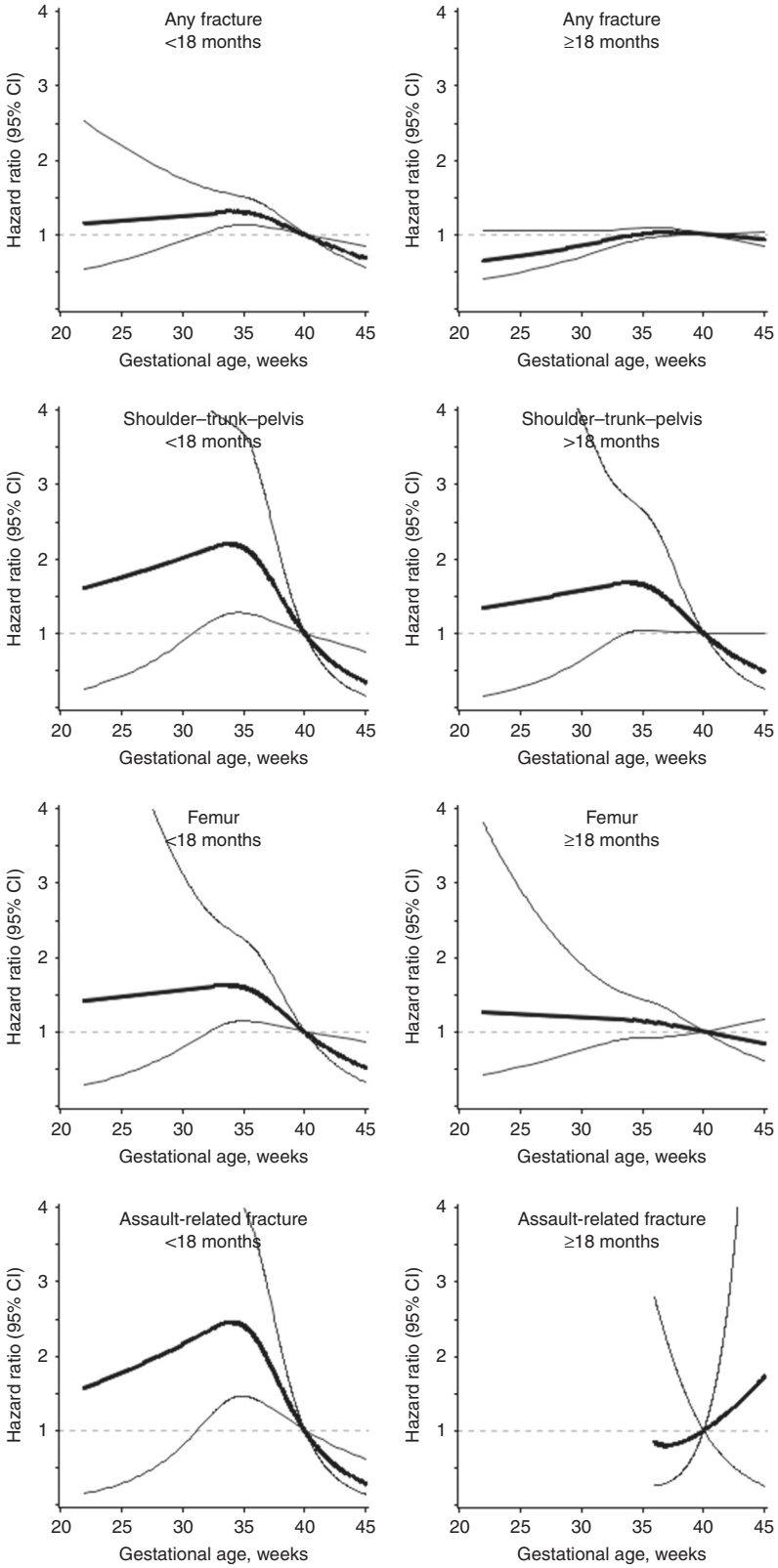

Fig. 2 Association of gestational age with risk of bone fracture hospitalization before and after 18 months of age[a]. [a]Hazard ratios are relative to 40 weeks' gestation, and are adjusted for sex, maternal age at delivery, multiple birth, pregnancy morbidity, socioeconomic disadvantage, place of residence, and infant comorbidity.

children in the term group had fractures. In contrast, a retrospective cohort study of 65,938 infants born at U.S. military treatment facilities found no association between preterm birth and risk of fracture before 5 years of age.[9] The investigators, however, excluded infants with ICD codes for child maltreatment, which eliminated around half of children who ever had fractures.[9] Exclusion of these children may explain the difference with our results, and reinforces the possibility that the increased fracture risk before 18 months is potentially more related to the child's psychosocial environment than to inadequate bone mineralization.

Bone fractures are relatively rare in infancy,[11,23] and many cases are thought to be nonaccidental.[24] Nearly 80% of fractures due to child maltreatment occur before 18 months of age.[15] Accidental fractures due to falls can occur before 18 months, but are still suspicious for maltreatment, as children within this age range are not yet walking and do not normally fall with enough energy to cause fracture.[15,24] Certain fracture sites are also more suggestive of maltreatment. In a systematic review of different fracture types, 71% of rib fractures and 28−43% of femur fractures were thought to be abuse-related.[11] Multiple fractures were also much more commonly seen in abused children.[11] In our study, some of the stronger associations for children under 18 months of age were for multiple fractures, fractures of the shoulder-trunk-pelvis and femur, and assault-related fractures.

Preterm infants may be at risk of child maltreatment for several reasons. Risk factors for preterm birth, such as low maternal education, stress, and drug use,[25–27] are linked with an increased risk of child maltreatment.[10,28] Preterm children are more likely than term children to have special needs,[5] and may have poorly regulated behaviors or difficult temperament making interactions challenging.[5,29] Risk of maltreatment may be greater if there is low parental attachment in conjunction with risk factors such as low socioeconomic status.[12]

This study has some limitations. We did not have data on prescription medications; however, we adjusted the results for diseases that require corticosteroids and diuretics, including congenital heart defects and bronchopulmonary dysplasia.[15,21,30] We accounted for osteoporosis, vitamin D, calcium and phosphorus deficiency, and disorders of bone density and structure, but lacked data on biochemical and radiological findings. Future studies would benefit from including such factors in the analysis. We did not have information on nutrition, although the majority of children under 5 years in Quebec attend childcare facilities with meals that adhere to dietary guidelines.[31,32] Most women breastfeed,[33] and preterm infants have access to donor breastmilk if breastfeeding is not possible.[34] We did not have complete information on smoking and alcohol intake that may be linked with prematurity and bone fractures. We had gestational age in completed weeks, but could not determine the exact age in days. Extremely preterm infants frequently require hospital stays of several months before discharge and may not have the same risk of intentional injuries as term infants who are usually discharged a few days after birth. This problem may weaken the association between prematurity, chance of maltreatment, and fracture risk. Also, child maltreatment is probably underreported in our data, although this is unlikely to vary with gestational age. In cases of severe maltreatment, children may not be taken to hospital for care.[15] We did not analyze fractures treated in an outpatient setting, and future research is needed to determine if the associations in this study generalize to mild fractures. The findings of this study generalize to a population of Canadian children with high-level fractures, although associations may differ in other study settings.

In this study, we found an association between preterm birth and risk of fracture hospitalization in the first 18 months of life, but no significant relationship thereafter. The associations were stronger for assault-related fractures and varied by site. Overall, the findings suggest that metabolic bone disorders do not account for a substantial proportion of fractures among preterm infants, and that psychosocial factors may be more important. The possibility that preterm children and their parents may benefit from counseling or early social interventions should be explored in future fracture prevention studies.

ACKNOWLEDGEMENTS

This work was supported by the Canadian Institutes of Health Research (PJT-162300) and the Fonds de recherche du Québec-Santé (34695). The funders were not involved in the design of the study, collection and analysis of data and decision to publish.

AUTHOR CONTRIBUTIONS

J.M. and N.A. conceived and designed the study. N.A. acquired the data. J.M. analyzed the data, with input from N.A., J.H.-P., and A.A. T.M.L. and J.C.L. helped with the interpretation of data. J.M., N.A., J.H.P., and A.A. drafted the article, and T.M.L. and J.C.L. revised it critically for important intellectual content. All authors approved the final version to be published.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-0771-3) contains supplementary material, which is available to authorized users.

Competing interests: The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. Guice, K. S., Cassidy, L. D. & Oldham, K. T. Traumatic injury and children: a national assessment. *J. Trauma* **63**, S68–S80 (2007).
2. Goulding, A. Risk factors for fractures in normally active children and adolescents. *Med. Sport Sci.* **51**, 102–120 (2007).
3. Chinoy, A., Mughal, M. Z. & Padidela, R. Metabolic bone disease of prematurity: causes, recognition, prevention, treatment and long-term consequences. *Arch. Dis. Child. Fetal Neonatal Ed.* **104**, F560–F566 (2019).
4. Chan, G. M., Armstrong, C., Moyer-Mileur, L. & Hoff, C. Growth and bone mineralization in children born prematurely. *J. Perinatol.* **28**, 619–623 (2008).
5. Behrman, R. E. & Butler, A. S. (eds) *Preterm Birth: Causes, Consequences, and Prevention* (National Academies Press, Washington, DC, 2007).
6. Högberg, U., Andersson, J., Högberg, G. & Thiblin, I. Metabolic bone disease risk factors strongly contributing to long bone and rib fractures during early infancy: a population register study. *PLoS ONE* **13**, e0208033 (2018).
7. Viswanathan, S. et al. Metabolic bone disease: a continued challenge in extremely low birth weight infants. *JPEN J. Parenter. Enter. Nutr.* **38**, 982–990 (2014).
8. Balasuriya, C. N. D. et al. Peak bone mass and bone microarchitecture in adults born with low birth weight preterm or at term: a cohort study. *J. Clin. Endocrinol. Metab.* **102**, 2491–2500 (2017).
9. Wagner, K., Wagner, S., Susi, A., Gorman, G. & Hisle-Gorman, E. Prematurity does not increase early childhood fracture risk. *J. Pediatr.* **207**, 148–153 (2019).
10. Palusci, V. J. Risk factors and services for child maltreatment among infants and young children. *Child. Youth Serv. Rev.* **33**, 1374–1382 (2011).
11. Kemp, A. M. et al. Patterns of skeletal fractures in child abuse: systematic review. *BMJ* **337**, a1518 (2008).
12. Puls, H. T. et al. Newborn risk factors for subsequent physical abuse hospitalizations. *Pediatrics* **143**, e20182108 (2019).
13. Ministry of Health and Social Services. *Med-Echo System Normative Framework—Maintenance and Use of Data for the Study of Hospital Clientele*. (Government of Quebec, Quebec. 2017).
14. Alexander, G. R., Himes, J. H., Kaufman, R. B., Mor, J. & Kogan, M. A United States national reference for fetal growth. *Obstet. Gynecol.* **87**, 163–168 (1996).
15. Flaherty, E. G., Perez-Rossello, J. M., Levine, M. A. & Hennrikus, W. L. Evaluating children with fractures for child physical abuse. *Pediatrics* **133**, e477–e489 (2014).
16. Durrleman, S. & Simon, R. Flexible regression models with cubic splines. *Stat. Med.* **8**, 551–561 (1989).
17. Baker, R., Orton, E., Tata, L. J. & Kendrick, D. Risk factors for long-bone fractures in children up to 5 years of age: a nested case–control study. *Arch. Dis. Child.* **100**, 432–437 (2015).
18. Rustico, S. E., Calabria, A. C. & Garber, S. J. Metabolic bone disease of prematurity. *J. Clin. Transl. Endocrinol.* **1**, 85–91 (2014).

19. Elsori, D. H. & Hammoud, M. S. Vitamin D deficiency in mothers, neonates and children. *J. Steroid Biochem. Mol. Biol.* **175**, 195–199 (2018).
20. Rauch, F. & Schoenau, E. Skeletal development in premature infants: a review of bone physiology beyond nutritional aspects. *Arch. Dis. Child. Fetal Neonatal Ed.* **86**, F82–F85 (2002).
21. Heo, J. H., Rascati, K. L., Lopez, K. N. & Moffett, B. S. Increased fracture risk with furosemide use in children with congenital heart disease. *J. Pediatr.* **199**, 92–98. e10 (2018).
22. Fine, J. P. & Gray, R. J. A proportional hazards model for the subdistribution of a competing risk. *J. Am. Stat. Assoc.* **94**, 496–509 (1999).
23. Taitz, J., Moran, K. & O'Meara, M. Long bone fractures in children under 3 years of age: is abuse being missed in Emergency Department presentations? *J. Paediatr. Child Health* **40**, 170–174 (2004).
24. Agran, P. F. et al. Rates of pediatric injuries by 3-month intervals for children 0 to 3 years of age. *Pediatrics* **111**, e683–e692 (2003).
25. Morgen, C. S., Bjørk, C., Andersen, P. K., Mortensen, L. H. & Nybo Andersen, A. M. Socioeconomic position and the risk of preterm birth—a study within the Danish National Birth Cohort. *Int. J. Epidemiol.* **37**, 1109–1120 (2008).
26. Shapiro, G. D., Fraser, W. D., Frasch, M. G. & Séguin, J. R. Psychosocial stress in pregnancy and preterm birth: associations and mechanisms. *J. Perinat. Med.* **41**, 631–645 (2013).
27. Gouin, K., Murphy, K. & Shah, P. S. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses. *Am. J. Obstet. Gynecol.* **204**, 340.e1–12 (2011).
28. Dubowitz, H. et al. Identifying children at high risk for a child maltreatment report. *Child Abuse Negl.* **35**, 96–104 (2011).
29. Halpern, L. F., Brand, K. L. & Malone, A. F. Parenting stress in mothers of very-low-birth-weight (VLBW) and full-term infants: a function of infant behavioral characteristics and child-rearing attitudes. *J. Pediatr. Psychol.* **26**, 93–104 (2001).
30. Iyengar, A. & Davis, J. M. Drug therapy for the prevention and treatment of bronchopulmonary dysplasia. *Front. Pharmacol.* **6**, 12 (2015).
31. Statistics Canada. Survey on early learning and child care arrangements, 2019. Ottawa. https://www150.statcan.gc.ca/n1/daily-quotidien/190410/dq190410a-eng.pdf (2019).
32. Légis Québec. Educational childcare regulation. Quebec. http://legisquebec.gouv.qc.ca/en/pdf/cr/S-4.1.1,%20R.%202.pdf (2019).
33. Institut national de santé publique du Québec. Allaitement. Montreal. https://www.inspq.qc.ca/sites/default/files/documents/information-perinatale/allaitement.pdf (2018).
34. Héma-Québec. Public mothers' milk bank. https://www.hema-quebec.qc.ca/lait-maternel/donneuses-lait/banque-publique-lait-maternel.en.html (2019).