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Maternal stress and anxiety disorders and the longitudinal risk of fractures in children

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ABSTRACT

Background: Maternal stress and anxiety are associated with adverse pregnancy outcomes, but the association with future childhood injuries is unclear, especially risk of orthopedic fractures.

Methods: We conducted a longitudinal study of 773,339 newborns in Quebec, Canada between 2006 and 2018. We identified women with stress or anxiety disorders before or after delivery, and computed the incidence of future operative fractures in offspring. We estimated hazard ratios (HR) with 95% confidence intervals (CI) for the association of maternal stress and anxiety disorders with the risk of pediatric fractures, adjusted for maternal and infant characteristics.

Results: Incidence of any fracture was higher for maternal stress (20.5 per 10,000 person-years) and anxiety (19.8 per 10,000 person-years) than no disorder (15.3 per 10,000 person-years). Maternal stress was associated with 1.17 times the risk of pediatric fractures (95% CI 1.00–1.38), and anxiety was associated with 1.26 times the risk (95% CI 1.07–1.47), compared with no disorder. Stress was predominantly linked with fall-related fractures (HR 1.26, 95% CI 1.06–1.50), and anxiety with assault-related fractures (HR 2.97, 95% CI 1.50–5.89). The association of stress with fall-related fractures was more prominent after 36 months of age, whereas anxiety was linked with assault-related fractures before 6 months.

Conclusion: Stress and anxiety disorders before or after delivery are associated with the future risk of fractures in children. Women with a history of stress or anxiety disorders may benefit from counselling and social support for child fracture prevention.

1. Introduction

Fractures comprise a substantial proportion of pediatric injuries [1], but maternal risk factors are poorly understood. Fractures represent nearly 60% of pediatric trauma hospitalizations [1], and are serious injuries [2]. The Centers for Disease Control and Prevention estimated that in 2010, hospitalizations for fractures between 0 and 14 years of age led to lifetime medical costs of $1.5 billion and societal costs of $5.6 billion in the US [3]. Two-thirds of children sustain fractures [4], but maternal risk factors receive little attention and morbidities such as metabolic bone disorders explain only a fraction of cases [5]. A better understanding of how maternal risk factors relate to fractures in children is needed for prevention.

Maternal stress and anxiety disorders are associated with pediatric injuries in general [6–8], but the relationship with fractures, a more serious injury, is understudied. Stress and anxiety may influence the risk of childhood fractures through several pathways, including suboptimal supervision, inadequate safeguarding, and child maltreatment [6,9]. These pathways may be more important for fractures than mild injuries [10]. Stress and anxiety disorders are prevalent in women of reproductive age and reported in up to 25% of pregnant women [11,12]. Yet, only two cohort studies have considered the possibility that stress and anxiety disorders early in a woman's life have the potential to be markers of future fractures in children [7,8]. A Danish study of 975,580 children found that fetal exposure to maternal stress due to a sibling's traumatic death was associated with an elevated risk of any childhood fracture [7]. Similarly, in a British study of 207,048 mothers, child fracture rates were greater during episodes of maternal

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depression and anxiety [8]. However, neither study examined auxiliary factors including anatomical site, cause, and age of fracture. To further the findings of previous studies, we examined the association between maternal stress and anxiety disorders before, during, or after pregnancy and childhood fractures by site, cause, and age.

2. Methods

2.1. Study design

We performed a longitudinal cohort study of 773,339 infants born in hospitals of Quebec, Canada between 2006 and 2016. In Quebec, the majority of births occur in hospital (99%), thus the cohort is population-based. Using de-identified health insurance numbers, we followed the cohort from birth until the end of study on March 31, 2018 to identify hospitalizations for operative bone fractures in childhood. The data were extracted from the Maintenance and Use of Data for the Study of Hospital Clientele registry, a compilation of all discharge summaries in Quebec [13]. Each discharge summary contains demographic data and information on up to 41 diagnoses coded using the tenth revision of International Classification of Diseases (ICD), and 35 procedures coded using the Canadian Classification of Health Interventions. Newborn discharge summaries are linked with the mother, enabling us to identify maternal exposures including stress or anxiety disorders and other morbidities before or after delivery.

We did not include infants who died at birth or had invalid health insurance numbers as they could not be followed over time. We additionally excluded infants with fractures at the delivery admission and infants with osteogenesis imperfecta, a genetic disorder characterized by easily breakable bones. Infants whose mothers had isolated diagnoses of schizophrenic, nonaffective psychotic, mood, neurotic, somatoform, and personality disorders also were not eligible for study inclusion [14].

2.2. Maternal stress and anxiety disorders

In this study, we defined the main exposure measure as maternal stress and anxiety disorders occurring before, during, or after pregnancy (yes, no). Stress disorders included acute and severe stress reactions, post-traumatic stress disorder, and adjustment disorder. Anxiety disorders included phobic, panic, generalized anxiety, obsessive-compulsive, and other disorders. We captured these disorders using diagnostic codes in the ICD, which follow general categories in the Diagnostic and Statistical Manual of Mental Disorders (Supplementary Table 1).

Hospitalization for stress and anxiety disorders indicates serious illness. Stress and anxiety disorder codes were identified on discharge summaries of maternal hospitalizations. Data on the exposure were available for hospitalizations between 1989 and the study end. Admissions before or after delivery allowed us to capture stress and anxiety disorders that were severe enough to require hospitalization, but not disorders that were treated in ambulatory settings. To capture disorders that did not result in hospitalization, we used the discharge summary from the delivery hospitalization which contains information on maternal stress and anxiety disorders treated on an outpatient basis during pregnancy [15].

2.3. Fractures

The main outcome measure included nonpathologic fractures that required treatment in hospital, representing serious pediatric injury. We identified children hospitalized for fractures using ICD codes (Supplementary Table 2). We organized fractures by anatomical site: head (skull, face); spine/thorax/pelvis; upper limb (shoulder, humerus, forearm); lower limb (femur, lower leg/ankle); and hand/foot. We further classified fractures by cause, including fall, assault, transport, mechanical force, and other or unspecified causes.

2.4. Covariates

We considered covariates that may influence the association of maternal stress and anxiety with childhood fractures. Maternal covariates included age at delivery (< 25, 25–34, ≥ 35 years), parity (0, 1, ≥ 2 previous deliveries), illicit drug or alcohol use (yes, no), and pregnancy complications defined as preeclampsia, preexisting or gestational diabetes, multiple birth, and preterm birth (yes, no) (Supplementary Table 1). Infant covariates included sex (male, female), and morbidity defined as osteoporosis, other bone density and structure disorders, congenital heart defects, vitamin D, calcium, and phosphorus deficiency, and bronchopulmonary dysplasia (yes, no) (Supplementary Table 1). Additionally, we accounted for neighbourhood socioeconomic deprivation (poorest population quintile for income, education, and employment, not disadvantaged), place of residence (rural, urban), and time period at cohort entry (2006–2009, 2010–2012, 2013–2016). We had missing data for socioeconomic status ($n = 29{,}866$, 3.9%) and place of residence ($n = 13{,}658$, 1.8%). We used multiple imputation to build five new datasets using the Markov Chain Monte Carlo method [16], and verified the results using a complete case approach excluding patients with missing data.

2.5. Data analysis

We calculated the incidence of fractures per 10,000 person-years with 95% confidence intervals (CI). We verified the proportional hazard assumption in log ($-$log survival) curves, and used Cox proportional hazards regression to estimate the association of maternal stress and anxiety with the first hospitalization for fracture in childhood. These models produced hazard ratios (HR) which reflect the risk of fracture in exposed infants relative to unexposed infants in a given time interval. We adjusted the HRs initially for maternal age at delivery, parity, pregnancy complications, sex, infant morbidity, socioeconomic deprivation, place of residence, and time period. We further adjusted the models for maternal illicit drug or alcohol use, a potential mediator of the relationship of maternal stress and anxiety with pediatric fractures. We accounted for clustering of births in women through robust sandwich estimators. We expressed the time axis in days, beginning at birth and ending at the first fracture event, death, or end of study. Children who were never hospitalized for fractures were censored and death was analyzed as a competing event using the Fine and Gray method. Follow-up was longer for infants who entered earlier in the study. Cox regression can account for differences in the duration of follow-up time through censoring [17].

We estimated HRs and 95% CIs for different types of stress and anxiety disorders and by anatomical site and cause of fractures. We further stratified the analysis by age at fracture, including 0 to 5, 6 to 17, 18 to 35, and 36 months and older. We used these cutoffs to account for metabolic bone disease of prematurity which may lead to fractures before 6 months of age [5], and for child maltreatment which contributes to fractures between 6 and 17 months, as well as between 18 and 35 months of age [10].

We performed sensitivity analyses where we excluded preterm infants at risk of metabolic bone disease. We also examined whether the timing of stress or anxiety disorders affected the associations, by analyzing disorders before, during, and after pregnancy separately.

We used SAS version 9.4 to carry out the analyses and determined statistical significance using 95% CIs. As hospital data were de-identified, the University of Montreal Hospital Centre's institutional review board waived the need for ethical review. The study was in accordance with the 1964 Helsinki declaration and its later amendments, and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, a joint policy of Canada's three federal research agencies.

Table 1
Incidence of fractures according to maternal and infant characteristics.

	No. infants	No. fractures	Total person-years	Incidence rate per 10,000 person-years (95% CI)
Maternal disorder				
Stress	11,266	163	79,425	20.5 (18.4–22.9)
Anxiety	12,026	151	76,367	19.8 (17.7–22.1)
Stress and anxiety	2352	36	16,429	21.9 (17.4–27.6)
No	747,695	7899	5,158,985	15.3 (15.1–15.6)
Age at delivery, years				
< 25	123,455	1656	873,315	19.0 (18.3–19.6)
25–34	517,325	5454	3,584,941	15.2 (14.9–15.5)
≥35	132,559	1139	872,949	13.0 (12.5–13.6)
Parity				
0	379,539	3764	2,627,716	14.3 (14.0–14.7)
1	270,559	2987	1,865,073	16.0 (15.6–16.4)
≥2	123,241	1498	838,415	17.9 (17.2–18.5)
Maternal illicit drug or alcohol use				
Yes	10,817	150	71,058	21.1 (18.9–23.6)
No	762,522	8099	5,260,147	15.4 (15.2–15.6)
Pregnancy complication[a]				
Yes	139,410	1492	925,025	16.1 (15.6–16.7)
No	633,929	6757	4,406,180	15.3 (15.1–15.6)
Sex of infant				
Male	396,680	4672	2,733,227	17.1 (16.8–17.4)
Female	376,659	3577	2,597,979	13.8 (13.5–14.1)
Infant morbidity[b]				
Yes	13,017	213	86,555	24.6 (22.4–27.1)
No	760,322	8036	5,244,650	15.3 (15.1–15.6)
Socioeconomic deprivation				
Yes	159,157	1806	1,087,733	16.6 (16.4–16.8)
No	614,182	6443	4,243,472	15.2 (15.1–15.2)
Place of residence				
Rural	144,273	2034	997,177	20.4 (20.3–20.5)
Urban	629,066	6215	4,334,028	14.3 (14.3–14.4)
Time period of birth				
2006–2009	299,390	4918	2,957,309	16.6 (16.3–17.0)
2010–2012	239,017	2347	1,548,409	15.2 (14.7–15.6)
2013–2016	234,932	984	825,486	11.9 (11.4–12.5)
Total	773,339	8249	5,331,205	15.5 (15.2–15.7)

[a] Preeclampsia, preexisting or gestational diabetes, multiple birth, preterm birth.

[b] Osteoporosis, other bone density and structure disorders, congenital heart defects, vitamin D deficiency, calcium deficiency, phosphorus deficiency, bronchopulmonary dysplasia.

3. Results

In this study, 8249 of 773,339 infants (1.1%) were hospitalized for fractures during 5,331,205 person-years of follow-up (Table 1). The overall incidence of fractures was 15.5 per 10,000 person-years (95% CI 15.2–15.7). The incidence was greater for maternal stress (20.5 per 10,000 person-years) and anxiety disorders (19.8 per 10,000 person-years) than no disorder (15.3 per 10,000 person-years).

In fully adjusted models, maternal stress and anxiety disorders were associated with a greater risk of fracture (Table 2). Compared with no mental disorder, maternal stress and anxiety were associated with 1.22 times the risk of fracture during follow-up (95% CI 1.09–1.36). Maternal stress was just as strongly associated with fractures (HR 1.17, 95% CI 1.00–1.38) as anxiety (HR 1.26, 95% CI 1.07–1.47). Adjustment, panic, and generalized anxiety disorders were more strongly associated with risk of childhood fractures, compared with no disorder. Associations were similar when models were not adjusted for maternal illicit drug or alcohol use.

Maternal stress and anxiety disorders were more strongly associated with facial bone and lower leg/ankle fractures (Table 3). Any stress or anxiety was associated with 1.69 times the risk of facial bone fractures (95% CI 1.20–2.37) and 1.57 times the risk of lower leg/ankle fractures (95% CI 1.07–2.32), compared with no disorder. Significant associations were also present with fractures of the forearm. Stress was most strongly associated with spine/thorax/pelvis fractures (HR 1.93, 95% CI 1.01–3.67), whereas anxiety was most strongly associated with forearm fractures (HR 1.44, 95% CI 1.07–1.94).

Maternal stress and anxiety disorders were closely linked with risk of fractures due to falls and assault (Table 4). Compared with no mental disorder, stress disorders were more strongly associated with fall-related fractures, especially of the upper limb (HR 1.32, 95% CI 1.07–1.62). In contrast, maternal anxiety was more strongly associated with assault-related fractures of the lower limb (HR 2.85, 95% CI 1.02–7.95). Maternal stress was also associated with assault-related fractures of the lower limb (HR 2.84, 95% CI 1.08–7.45).

The association of maternal stress and anxiety with childhood fractures varied with age (Table 5, Supplementary Table 3). Between 0 and 5 months of age, maternal stress and anxiety disorders were associated with 2.67 times the risk of lower limb fractures (95% CI 1.38–5.16), and 2.36 times the risk of spine/thorax/pelvis fractures (95% CI 1.00–5.58), compared with no disorder. Between 6 and 17 months, maternal stress and anxiety were not associated with fractures at any particular anatomical site. Maternal stress and anxiety were, however, associated with the 1.59 times the risk of head fractures between 18 and 35 months (95% CI 1.02–2.50). Moreover, stress and anxiety disorders were more strongly related to assault-related fractures before 6 months (HR 2.55, 95% CI 1.31–4.96). By 36 months of age, the association shifted to fall-related fractures (HR 1.32, 95% CI 1.13–1.55).

In sensitivity analyses, excluding preterm infants slightly attenuated the associations but the general trends persisted. In analyses of timing, stress and anxiety disorders before pregnancy were associated with 1.23 times the risk of fractures (95% CI 1.05–1.46) and during pregnancy with 1.28 times the risk (95% CI 1.03–1.60), compared with no disorder. Stress and anxiety disorders before and during pregnancy were more strongly associated with fractures than disorders after pregnancy (HR 1.15, 95% CI 0.96–1.39).

4. Discussion

In this longitudinal study of 773,339 mother-child pairs, we found that a history of maternal stress and anxiety was associated with 1.2 times the risk of pediatric fractures, compared with no mental disorder. Associations were present for both maternal stress and anxiety, and were more prominent for fall and assault-related fractures. Associations with assault-related fractures were strongest between 0 and 5 months of age, whereas associations with fall-related fractures were more apparent at older ages, especially after 36 months. These findings suggest that maternal stress and anxiety disorders may be associated with risk of future childhood fractures. Identification and treatment of stress and anxiety disorders in women of reproductive age may provide opportunities to reduce the risk of childhood fractures in future offspring, especially fractures due to child maltreatment.

Only a handful of studies have examined the relationship between maternal mental health and the risk of pediatric injuries [6–8,18,19]. While evidence suggests that children whose mothers have poor mental health have a disproportionately high rate of unintentional injuries [6–8,18,19], the association with pediatric fractures was specifically examined in only two studies [7,8]. In Denmark, maternal prenatal stress due to bereavement from a sibling's death was associated with 1.3 times the risk of childhood fractures in a study that linked mothers to children through civil registration numbers [7]. A British study of 207,048 mother-child pairs found that maternal depression and anxiety before and after delivery were associated with 1.2 times the risk of child fractures [8]. However, these studies did not examine the site, cause, and age of fracture, information that is needed to identify strategies for prevention.

In our analyses, maternal stress and anxiety were associated with spine/thorax/pelvis and lower limb fractures, mostly due to assault.

Table 2
Association between maternal stress and anxiety disorders and pediatric fractures.

	No. infants	No. fractures	Hazard ratio (95% CI)		
			Unadjusted	Partially adjusted[a]	Fully adjusted[b]
Any stress or anxiety					
Yes	25,644	350	1.33 (1.20–1.48)	1.24 (1.11–1.38)	1.22 (1.09–1.36)
No	747,695	7899	Referent	Referent	Referent
Type of mental disorder					
Stress	11,266	163	1.34 (1.14–1.56)	1.21 (1.03–1.41)	1.17 (1.00–1.38)
Acute/severe stress reactions	732	11	1.38 (0.77–2.48)	1.22 (0.68–2.20)	1.18 (0.65–2.12)
Post-traumatic stress disorder	375	< 5	0.80 (0.26–2.47)	0.71 (0.23–2.20)	0.69 (0.22–2.14)
Adjustment disorder	10,491	153	1.35 (1.15–1.58)	1.22 (1.04–1.43)	1.18 (1.00–1.39)
Anxiety	12,026	151	1.31 (1.12–1.54)	1.26 (1.08–1.48)	1.26 (1.07–1.47)
Phobic disorder	773	11	1.35 (0.75–2.43)	1.26 (0.70–2.26)	1.24 (0.69–2.23)
Panic disorder	1476	25	1.62 (1.09–2.40)	1.53 (1.03–2.27)	1.52 (1.03–2.26)
Generalized anxiety disorder	2031	30	1.57 (1.10–2.25)	1.54 (1.07–2.20)	1.52 (1.07–2.18)
Obsessive compulsive disorder	642	5	0.74 (0.31–1.78)	0.72 (0.30–1.73)	0.71 (0.30–1.71)
Other	7901	91	1.22 (1.00–1.50)	1.19 (0.96–1.46)	1.18 (0.96–1.45)
Stress and anxiety	2352	36	1.43 (1.03–1.97)	1.28 (0.93–1.77)	1.25 (0.90–1.73)
No	747,695	7899	Referent	Referent	Referent

[a] Adjusted for maternal age at delivery, parity, pregnancy complications, infant sex, infant morbidity, socioeconomic deprivation, place of residence, and time period.
[b] Additionally adjusted for maternal illicit drug or alcohol use.

Associations were apparent under 6 months of age but not at older ages. Causes of fractures in early infancy are not fully established, but often raise suspicion of child maltreatment. Evidence indicates that most battering-related childhood injuries occur between 0 and 5 months [20]. Some data suggest that children whose mothers have anxiety disorders are 1.3 times more likely to be reported to social services for maltreatment and 1.8 times more likely to be placed in foster care, compared with no anxiety disorder [9]. Intergenerational transmission of child maltreatment is also possible, as girls who are maltreated in childhood are more likely to have adult anxiety [21]. Yet, child maltreatment is often overlooked in the differential diagnosis of children who present with fractures, and the proportion of maltreatment-related fractures is therefore likely underestimated [10,22]. Around 20% of fractures before three years of age that are due to child maltreatment may in fact be missed [10,22]. A systematic review revealed that children with multiple rib fractures have a 70% probability of maltreatment, and that femoral fractures due to maltreatment are more common in children who do not yet walk [10].

While we found no association with assault-related fractures at older ages, maternal stress and anxiety after 36 months was associated with fall-related fractures. Falls are the most frequent cause of injury in children [1]. Most fall-related fractures at older ages are attributed to unintentional injuries, although it is possible that some may be due to maltreatment, considering the association of stress and anxiety with assault-related fractures in early childhood. Distinguishing fall-related fractures due to child maltreatment from true unintentional injuries is however difficult, as child activity patterns, energy level, and temperament become more important at older ages [6,23,24]. Moreover, some data suggest that maternal stress is linked with child externalizing behaviours including hyperactivity and impulsivity, which are in turn associated with pediatric injuries [6,25].

Parenting behaviours unrelated to maltreatment may also affect the

Table 3
Association between maternal stress and anxiety disorders and pediatric fractures by anatomical site.

	No. fractures		Hazard ratio (95% CI)[a]		
	Exposed	Unexposed	Any stress or anxiety	Stress[b]	Anxiety
Head	93	1809	1.33 (1.07–1.65)	1.43 (1.08–1.90)	1.20 (0.86–1.67)
Skull	61	1263	1.27 (0.97–1.66)	1.36 (0.95–1.95)	1.16 (0.77–1.74)
Face	38	553	1.69 (1.20–2.37)	1.82 (1.17–2.82)	1.50 (0.86–2.59)
Spine/thorax/pelvis	15	160	1.68 (0.96–2.94)	1.93 (1.01–3.67)	1.30 (0.47–3.54)
Upper limb	187	4388	1.21 (1.04–1.40)	1.15 (0.94–1.41)	1.28 (1.03–1.60)
Shoulder	7	96	1.33 (0.56–3.16)	1.82 (0.68–4.90)	0.56 (0.08–4.02)
Humerus	82	2290	1.02 (0.81–1.28)	0.89 (0.64–1.23)	1.19 (0.87–1.63)
Forearm	106	2133	1.43 (1.17–1.75)	1.42 (1.10–1.84)	1.44 (1.07–1.94)
Lower limb	67	1373	1.28 (0.99–1.65)	1.22 (0.87–1.71)	1.35 (0.94–1.94)
Femur	45	921	1.23 (0.90–1.69)	1.13 (0.74–1.72)	1.36 (0.88–2.10)
Lower leg/ankle	28	479	1.57 (1.07–2.32)	1.54 (0.93–2.55)	1.61 (0.91–2.87)
Hand/foot	13	406	0.85 (0.49–1.48)	0.54 (0.23–1.24)	1.30 (0.64–2.62)

[a] Hazard ratios are relative to no stress or anxiety disorder, adjusted for maternal age at delivery, parity, pregnancy complications, illicit drug or alcohol use, infant sex, infant morbidity, socioeconomic deprivation, place of residence, and time period.
[b] Includes 2352 women with both stress and anxiety disorders.

Table 4
Association between maternal stress and anxiety disorders and pediatric fractures by cause of fracture.

	No. fractures		Hazard ratio (95% CI)[a]		
	Exposed	Unexposed	Any stress or anxiety	Stress[b]	Anxiety
Falls					
Any fracture	252	5879	1.25 (1.10–1.42)	1.26 (1.06–1.50)	1.23 (1.02–1.49)
Head	51	1248	1.10 (0.83–1.47)	1.28 (0.89–1.86)	0.89 (0.56–1.42)
Spine/thorax/ pelvis	< 5	32	0.99 (0.13–7.35)	1.96 (0.27–14.4)	–
Upper limb	166	3703	1.33 (1.13–1.56)	1.32 (1.07–1.62)	1.34 (1.06–1.69)
Lower limb	37	865	1.26 (0.90–1.75)	1.13 (0.71–1.80)	1.40 (0.89–2.21)
Hand/foot	< 5	89	0.38 (0.05–2.76)	–	0.82 (0.11–5.92)
Assault					
Any fracture	18	139	2.12 (1.20–3.74)	1.58 (0.73–3.46)	2.97 (1.50–5.89)
Head	< 5	22	1.85 (0.45–7.65)	0.84 (0.08–8.94)	3.78 (0.86–16.6)
Spine/thorax/ pelvis	7	58	1.98 (0.83–4.75)	2.23 (0.79–6.27)	1.60 (0.38–6.67)
Upper limb	6	56	1.52 (0.57–4.05)	1.10 (0.29–4.24)	2.26 (0.70–7.33)
Lower limb	11	65	2.84 (1.31–6.16)	2.84 (1.08–7.45)	2.85 (1.02–7.95)
Hand/foot	0	9	–	–	–
Transport					
Any fracture	29	526	1.26 (0.85–1.86)	1.06 (0.64–1.77)	1.58 (0.91–2.74)
Head	12	118	2.15 (1.12–4.15)	2.18 (0.99–4.83)	2.10 (0.76–5.77)
Spine/thorax/ pelvis	6	38	2.48 (0.96–6.46)	2.26 (0.78–6.50)	2.96 (0.68–12.8)
Upper limb	6	282	0.54 (0.23–1.26)	0.14 (0.02–1.03)	1.18 (0.49–2.87)
Lower limb	10	121	1.75 (0.89–3.41)	1.88 (0.86–4.12)	1.52 (0.48–4.82)
Hand/foot	< 5	33	0.97 (0.13–7.02)	–	2.21 (0.30–16.3)
Mechanical force					
Any fracture	27	720	0.97 (0.65–1.43)	0.70 (0.39–1.25)	1.35 (0.81–2.25)
Head	12	156	2.12 (1.14–3.94)	1.44 (0.54–3.87)	3.05 (1.44–6.47)
Spine/thorax/ pelvis	0	12	–	–	–
Upper limb	< 5	141	0.31 (0.08–1.26)	0.24 (0.03–1.90)	0.45 (0.07–3.09)
Lower limb	< 5	214	0.47 (0.18–1.28)	0.19 (0.03–1.27)	0.88 (0.28–2.76)
Hand/foot	10	213	1.22 (0.66–2.24)	1.01 (0.45–2.27)	1.50 (0.62–3.65)
Other or unspecified					
Any fracture	31	728	1.04 (0.72–1.52)	1.18 (0.74–1.88)	0.85 (0.46–1.59)
Head	16	265	1.53 (0.92–2.53)	1.79 (0.94–3.42)	1.18 (0.49–2.82)
Spine/thorax/ pelvis	< 5	21	0.68 (0.11–4.05)	1.09 (0.18–6.64)	–
Upper limb	9	241	0.91 (0.46–1.80)	0.98 (0.42–2.26)	0.80 (0.26–2.50)
Lower limb	7	128	1.28 (0.57–2.89)	1.91 (0.76–4.79)	0.46 (0.06–3.29)
Hand/foot	< 5	63	0.44 (0.05–3.52)	–	1.09 (0.15–8.04)

[a] Hazard ratios are relative to no stress or anxiety disorder, adjusted for maternal age at delivery, parity, pregnancy complications, illicit drug or alcohol use, infant sex, infant morbidity, socioeconomic deprivation, place of residence, and time period.
[b] Includes 2352 women with both stress and anxiety disorders.

Table 5
Association between maternal stress and anxiety disorders and pediatric fractures by age at fracture.

	Hazard ratio (95% CI)[a]			
	0–5 months	6–17 months	18–35 months	≥ 36 months
Site of fracture				
Any	1.31 (0.95–1.83)	1.26 (0.92–1.73)	1.11 (0.84–1.47)	1.22 (1.06–1.40)
Head	1.08 (0.71–1.63)	1.12 (0.67–1.87)	1.59 (1.02–2.50)	1.59 (1.09–2.34)
Spine/thorax/ pelvis	2.36 (1.00–5.58)	0.59 (0.10–3.58)[b]	1.17 (0.10–13.1)[b]	1.74 (0.73–4.11)
Upper limb	1.64 (0.76–3.55)	1.68 (0.83–3.40)	0.79 (0.45–1.37)	1.23 (1.04–1.45)
Lower limb	2.67 (1.38–5.16)	1.43 (0.86–2.36)	1.34 (0.83–2.15)	0.92 (0.58–1.46)
Hand/Foot	–	0.53 (0.09–3.12)[b]	1.40 (0.50–3.89)[b]	0.82 (0.41–1.65)
Cause of fracture				
Falls	1.11 (0.72–1.69)	1.28 (0.87–1.88)	0.98 (0.69–1.40)	1.32 (1.13–1.55)
Assault	2.55 (1.31–4.96)	1.03 (0.20–5.36)[b]	2.68 (0.33–21.7)[b]	1.40 (0.18–10.9)[b]
Transport	3.01 (0.79–11.5)[b]	4.63 (0.93–23.1)[b]	1.35 (0.38–4.77)[b]	1.13 (0.72–1.76)
Mechanical force	0.69 (0.13–3.63)[b]	1.09 (0.42–2.81)[b]	1.15 (0.46–2.83)	0.92 (0.55–1.54)
Other or unspecified	1.73 (0.61–4.93)	0.98 (0.39–2.47)	1.42 (0.79–2.56)	0.73 (0.37–1.44)

[a] Hazard ratios are relative to no stress or anxiety disorder, adjusted for maternal age at delivery, parity, pregnancy complications, illicit drug or alcohol use, infant sex, infant comorbidity, socioeconomic deprivation, place of residence, and time period. Sample sizes are shown in Supplementary Table 3.
[b] Fewer than 5 events in the exposed.

risk of fracture. A few studies report that mothers with stress and anxiety disorders are overprotective [26,27], suggesting their children may be less likely to sustain injuries [23,28]. One study found that maternal stress was associated with a lower risk of child injury, a finding attributed to the possibility that stressed mothers act proactively to prevent injuries in their children [24]. However, our findings suggest the opposite as maternal stress and anxiety disorders were associated with a higher risk of fracture. While child maltreatment may be a contributing factor, it is also possible that suboptimal parental supervision or fewer safety practices underlie some of the results. Previous studies indicate that poor maternal mental health may result in lower supervision during child activities and limited injury prevention efforts, including use of safety equipment such as car seats [6,19,24]. Our study supports this plausible pathway as we found a non-negligible risk of fractures at most anatomical sites in children whose mothers had stress or anxiety disorders.

Susceptibility to fractures may also be affected by biologic effects of stress during pregnancy. Prenatal stress is linked with preterm delivery and low birthweight, two factors that predispose children to fractures before 6 months of age due to metabolic bone disease of prematurity [5,29,30]. These factors may explain only part of the findings, however, as associations persisted even when we excluded preterm infants. It may be that prenatal exposure to stress hormones or genetic factors are related to offspring constitution, as infants of stressed pregnant mothers may have more difficult temperament and conduct disorders [30,31]. It is thought that prenatal stress exerts effects on the fetal hypothalamic-pituitary-adrenal (HPA) axis [32]. Maternal stress during pregnancy can increase maternal and fetal levels of cortisol [7,30], a glucocorticoid that may lead to structural changes in the fetal brain and altered offspring behaviour [7]. Several studies show that prenatal stress can alter the expression of genes involved in the fetal HPA axis, including the gene coding the glucocorticoid receptor [32]. Prenatal stress from intimate partner violence has been shown to increase DNA methylation in the glucocorticoid receptor gene of offspring [33]. These pathways could begin even before pregnancy, as stress and anxiety disorders present before conception were also associated with fractures in our data.

There were limitations in this study. We identified women with stress or anxiety disorders using diagnostic codes in administrative data, and misclassification due to coding errors may have occurred. We used the ICD to identify stress and anxiety disorders and did not have codes from the Diagnostic and Statistical Manual of Mental Disorders. Stress or anxiety disorders may be defined differently in other studies [31]. Moreover, we could not capture women with stress and anxiety disorders before pregnancy who did not require hospital admission. Fractures attributable to maltreatment may be underreported in our data [34]. We did not have information on fractures that did not require hospital admission, or on potential confounders such as adverse childhood experiences, physical activity, child behaviour, parenting practices, social support, ethnicity, and prescription drug use. We could not determine the circumstances surrounding the fracture event such as safety of the physical environment and level of supervision. Lastly, while the results of our study are representative of a large Canadian province, our findings may not generalize to other regions with different population demographics.

4.1. Conclusions

Using a cohort of over 770,000 mother-child pairs, we found that maternal stress and anxiety disorders before delivery or postpartum may be risk factors for childhood fractures. Maternal stress and anxiety were more strongly associated with assault-related fractures before 6 months of age and fall-related fractures after 36 months, reflecting a potential shift in the nature of fractures due to maltreatment as children age. While the clinical significance of these findings is difficult to assess, this study suggests that serious maternal stress and anxiety disorders increase the risk of having advanced childhood fractures. Future studies are merited to evaluate the clinical significance of the results and to assess the mediating or moderating role of parenting behaviour in relation to child fractures. Women who present with stress and anxiety disorders before or after delivery may benefit from continued mental health support, counselling, and social resources to reduce fracture risk in children.

Author contributions

NA, GL, and TML conceived and designed the study. GL analyzed the data with input from NA and AA. NL and TML helped interpret the results. NA, GL, and AA drafted the manuscript and NL and TML critically revised it for important intellectual content. NA had full access to all the data in the study and takes responsibility for the integrity of the final content. All authors read and approved the final version of the manuscript.

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Declaration of competing interest

All authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.115143.

References

[1] K.S. Guice, L.D. Cassidy, K.T. Oldham, Traumatic injury and children: a national assessment, J. Trauma 63 (6 Suppl) (2007) S68–S80, https://doi.org/10.1097/TA.0b013e31815acbb6.
[2] P.C. Cryer, S.N. Jarvis, P. Edwards, J.D. Langley, How can we reliably measure the occurrence of non-fatal injury? Int. J. Consum. Prod. Safety 6 (4) (1999) 183–191, https://doi.org/10.1076/icsp.6.4.183.7527.
[3] Centers for Disease Control and Prevention, National Centers for Injury Prevention and Control. Data and Statistics Web-Based Injury Statistics Query and Reporting System (WISQARS): Costs of Injury Reports, https://wisqars.cdc.gov:8443/costT/, (2014).
[4] G. Valerio, F. Gallè, C. Mancusi, V. Di Onofrio, M. Colapietro, P. Guida, G. Liguori, Pattern of fractures across pediatric age groups: analysis of individual and lifestyle factors, BMC Public Health 10 (2010) 656, https://doi.org/10.1186/1471-2458-10-656.
[5] N. Bishop, A. Sprigg, A. Dalton, Unexplained fractures in infancy: looking for fragile bones, Arch. Dis. Child. 92 (3) (2007) 251–256, https://doi.org/10.1136/adc.2006.106120.
[6] S. Hope, J. Deighton, N. Micali, C. Law, Maternal mental health and childhood injury: evidence from the UK Millennium Cohort Study, Arch. Dis. Child. 104 (3) (2019) 268–274, https://doi.org/10.1136/archdischild-2017-313809.
[7] J. Virk, J. Li, J. Lauritsen, J. Olsen, Risk of childhood injuries after prenatal exposure to maternal bereavement: a Danish National Cohort Study, BMJ Open 3 (4) (2013), https://doi.org/10.1136/bmjopen-2012-002357 e002357.
[8] R. Baker, D. Kendrick, L.J. Tata, E. Orton, Association between maternal depression and anxiety episodes and rates of childhood injuries: a cohort study from England, Inj. Prev. 23 (6) (2017) 396–402, https://doi.org/10.1136/injuryprev-2016-042294.
[9] P.L. Kohl, M. Jonson-Reid, B. Drake, Maternal mental illness and the safety and stability of maltreated children, Child Abuse Negl. 35 (5) (2011) 309–318, https://doi.org/10.1016/j.chiabu.2011.01.006.
[10] A.M. Kemp, F. Dunstan, S. Harrison, S. Morris, M. Mann, K. Rolfe, S. Datta, D.P. Thomas, J.R. Sibert, S. Maguire, Patterns of skeletal fractures in child abuse: systematic review, BMJ 337 (2008) a1518, https://doi.org/10.1136/bmj.a1518.
[11] S. Grigoriadis, L. Graves, M. Peer, L. Mamisashvili, G. Tomlinson, S.N. Vigod, C.-L. Dennis, M. Steiner, C. Brown, A. Cheung, H. Dawson, N.A. Rector, M. Guenette, M. Richter, Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis, J. Clin. Psychiatry 79 (5) (2018) 17r12011, https://doi.org/10.4088/JCP.17r12011.
[12] A. Stein, R.M. Pearson, S.H. Goodman, E. Rapa, A. Rahman, M. McCallum, L.M. Howard, C.M. Pariante, Effects of perinatal mental disorders on the fetus and child, Lancet 384 (9956) (2014) 1800–1819, https://doi.org/10.1016/S0140-

6736(14)61277-0.
[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, pp. 1–259.
[14] C.R. Gale, G.D. Batty, D.P. Osborn, P. Tynelius, E. Whitley, F. Rasmussen, Association of mental disorders in early adulthood and later psychiatric hospital admissions and mortality in a cohort study of more than 1 million men, Arch. Gen. Psychiatry 69 (8) (2012) 823–831, https://doi.org/10.1001/archgenpsychiatry.2011.2000.
[15] Collège des médecins du Québec, La tenue des dossiers par le médecin en centre hospitalier de soins généraux et spécialisés, http://www.cmq.org/publications-pdf/p-1-2005-12-01-fr-tenue-des-dossiers-par-medecin-en-centre-hospitalier-de-soins-generaux-et-specialises.pdf, (2005) , Accessed date: 10 May 2019.
[16] J.A. Sterne, I.R. White, J.B. Carlin, M. Spratt, P. Royston, M.G. Kenward, A.M. Wood, J.R. Carpenter, Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls, BMJ 338 (2009) b2393, https://doi.org/10.1136/bmj.b2393.
[17] I. Annesi, T. Moreau, J. Lellouch, Efficiency of the logistic regression and cox proportional hazards models in longitudinal studies, Stat. Med. 8 (12) (1989) 1515–1521, https://doi.org/10.1002/sim.4780081211.
[18] T.G. O'Connor, L. Davies, J. Dunn, J. GoldingALSPAC Study Team, Distribution of accidents, injuries, and illnesses by family type, Pediatrics 106 (5) (2000) E68, https://doi.org/10.1542/peds.106.5.e68.
[19] D.C. Schwebel, C.M. Brezausek, Chronic maternal depression and children's injury risk, J. Pediatr. Psychol. 33 (10) (2008) 1108–1116, https://doi.org/10.1093/jpepsy/jsn046.
[20] P.F. Agran, C. Anderson, D. Winn, R. Trent, L. Walton-Haynes, S. Thayer, Rates of pediatric injuries by 3-month intervals for children 0 to 3 years of age, Pediatrics 111 (6 pt 1) (2003) e683–e692, https://doi.org/10.1542/peds.111.6.e683.
[21] M. Li, C. D'Arcy, X. Meng, Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions, Psychol. Med. 46 (4) (2016) 717–730, https://doi.org/10.1017/S0033291715002743.
[22] E.G. Flaherty, J.M. Perez-Rossello, M.A. Levine, W.L. HennrikusAmerican Academy of Pediatrics Committee on Child Abuse and Neglect, Section on Radiology, American Academy of Pediatrics; Section on Endocrinology, American Academy of Pediatrics, Section on Orthopaedics, American Academy of Pediatrics, Society for Pediatric Radiology, Evaluating children with fractures for child physical abuse, Pediatrics 133 (2) (2014) e477–e489, https://doi.org/10.1542/peds.2013-3793.
[23] D.C. Schwebel, D.L. Roth, M.N. Elliott, M. Windle, J.A. Grunbaum, B. Low, S.P. Cooper, M.A. Schuster, The association of activity level, parent mental distress, and parental involvement and monitoring with unintentional injury risk in fifth graders, Accid. Anal. Prev. 43 (3) (2011) 848–852, https://doi.org/10.1016/j.aap.2010.11.004.
[24] A.L. Damashek, N.A. Williams, K.J. Sher, L. Peterson, T. Lewis, W. Schweinle, Risk for minor childhood injury: an investigation of maternal and child factors, J. Pediatr. Psychol. 30 (6) (2005) 469–480, https://doi.org/10.1093/jpepsy/jsi072.
[25] K.M. Keyes, E. Susser, D.J. Pilowsky, A. Hamilton, A. Bitfoi, D. Goelitz, R.C. Kuijpers, S. Lesinskiene, Z. Mihova, R. Otten, V. Kovess, The health consequences of child mental health problems and parenting styles: unintentional injuries among European schoolchildren, Prev. Med. 67 (2014) 182–188, https://doi.org/10.1016/j.ypmed.2014.07.030.
[26] D.R. Hirshfeld, J. Biederman, L. Brody, S.V. Faraone, J.F. Rosenbaum, Expressed emotion toward children with behavioral inhibition: associations with maternal anxiety disorder, J. Am. Acad. Child Adolesc. Psychiatry 36 (7) (1997) 910–917, https://doi.org/10.1097/00004583-199707000-00012.
[27] S.E. Whaley, A. Pinto, M. Sigman, Characterizing interactions between anxious mothers and their children, J. Consult. Clin. Psychol. 67 (6) (1999) 826–836, https://doi.org/10.1037/0022-006X.67.6.826.
[28] D.C. Schwebel, C.M. Brezausek, S.L. Ramey, C.T. Ramey, Interactions between child behavior patterns and parenting: implications for children's unintentional injury risk, J. Pediatr. Psychol. 29 (2) (2004) 93–104, https://doi.org/10.1093/jpepsy/jsh013.
[29] Y. Sun, P. Hsu, M. Vestergaard, J. Christensen, J. Li, J. Olsen, Gestational age, birth weight, and risk for injuries in childhood, Epidemiology 21 (5) (2010) 650–657, https://doi.org/10.1097/EDE.0b013e3181e94253.
[30] V. Glover, Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done, Best Pract. Res. Clin. Obstet. Gynaecol. 28 (1) (2014) 25–35, https://doi.org/10.1016/j.bpobgyn.2013.08.017.
[31] B.R.H. Van den Bergh, M.I. van den Heuvel, M. Lahti, M. Braeken, S.R. de Rooij, S. Entringer, D. Hoyer, T. Roseboom, K. Räikkönen, S. King, M. Schwab, Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy, Neurosci. Biobehav. Rev. (2017), https://doi.org/10.1016/j.neubiorev.2017.07.003 In press.
[32] L. Cao-Lei, D.P. Laplante, S. King, Prenatal maternal stress and epigenetics: review of the human research, Curr. Mol. Bio. Rep. 2 (1) (2016) 16–25, https://doi.org/10.1007/s40610-016-0030-x.
[33] K.M. Radtke, M. Ruf, H.M. Gunter, K. Dohrmann, M. Schauer, A. Meyer, T. Elbert, Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor, Transl. Psychiatry 1 (2011) e21, https://doi.org/10.1038/tp.2011.21.
[34] J.M. Leventhal, K.D. Martin, A.G. Asnes, Incidence of fractures attributable to abuse in young hospitalized children: results from analysis of a United States database, Pediatrics 122 (3) (2008) 599–604, https://doi.org/10.1542/peds.2007-1959.