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Population-based register study of children born in Sweden from 1997-2014 showed an increase in rickets during infancy

Short title: Increase of rickets during infancy

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ABSTRACT

Aim: This population-based study assessed the incidence of rickets in infants up to age of one born in Sweden from 1997-2014. We also examined maternal and perinatal factors and co-morbidity.

Methods: We used Swedish National Board of Health and Welfare registers and data from Statistics Sweden. The outcome measure was an International Classification of Diseases, Tenth Revision, code for rickets

Results: There were 273 cases of rickets, with an incidence of 14.7 per 100,000 and a 10-fold incidence increase between 1997-2014. The majority (78.4%) were born preterm, half were small-for-gestational age (SGA) (birthweight <10th percentile), 4.8% were born to Asian-born mothers and 3.5% to African-born mothers. The adjusted odds ratios by birth week were 182 (95% CI 121-272) before 32 weeks and 10.8 (95% CI 6.72-17.4) by 32-36 weeks. Preterm infants with necrotising enterocolitis had very high odds for rickets and so did SGA term born infants and those born to African-born mothers. The odds for rickets among preterm infants increased considerably during the later years.

Conclusion: Rickets increased 10-fold in Sweden from 1997-2014 and was mainly associated with prematurity, SGA and foreign-born mothers. Possible reasons may include increased preterm survival rates and improved clinical detection and registration.

KEY NOTES

- This population-register study focused on rickets in infants up to age of one born in Sweden from 1997-2014 and examined maternal and perinatal factors and co-morbidity.

- The data showed that there were 273 cases during the study period, with a 10-fold increase.
- Most of the cases (78.4%) were born premature, half were born small-for-gestational and one-tenth had a mother born in Asia or Africa.

KEY WORDS Infants, Incidence, Rickets, Vitamin D deficiency, Metabolic bone disease

INTRODUCTION

Rickets is a nutritional disorder that can present at birth or develop during infancy or childhood (1). Nutritional rickets is caused by dietary deficiencies or malabsorption of vitamin D, calcium or phosphorus. It is still common in infants and toddlers in low-income and middle-income countries and it presents as bone fragility and bone growth disturbances (2). A rising incidence in vitamin D deficiency and nutritional rickets among children high-income countries has also been reported, primarily among ethnic minorities or immigrants (2-5).

Congenital, hereditary, rickets may develop due to genetic disorders (4, 5), foetal deficiency of vitamin D (2, 6, 7) and intrauterine growth retardation (8, 9). In addition, maternal obesity (6) and ethnicity (10) could potentially contribute to fetal vitamin D deficiency. The increase in survival of infants born extremely preterm has led to the recognition of metabolic bone disease of prematurity, which is also called rickets or osteopaenia of prematurity, having decreased bone mineral levels of calcium and phosphorus at birth (9, 11, 12). In addition, twin pregnancies may contribute to metabolic bone disease (13).

We have previously reported that risk factors for long bone and rib fracture in a Swedish setting were maternal obesity, preterm birth and diagnoses of vitamin D deficiency rickets, and calcium disorders, during the first six months of life but not during 6-12 months of life (14). This motivated us to further investigate the occurrence of rickets diagnosis during infancy in a setting with a relatively high survival rate for extremely preterm born children (15) and a high proportion of births to immigrant mothers (16).

The aim of this national population-based register study was to assess the incidence of rickets by time trends, maternal and perinatal risk factors and co-morbidity among infants up to the age of one year.

METHODS

Subjects and data sources

This was a nationwide population-based register study that comprised 1,855,267 uinfants born in Sweden from 1997-2014 and followed up to one year of age. We followed up the infants and their mothers by using data from the health registers maintained by the Swedish National Board of Health and Welfare (17) and Statistics Sweden. The Swedish National Patient Register covers in-patient care during 1997–2015 and specialised outpatient care for the period 2001–2015. During the study period, the National Patient Register applied used diagnosis codes from the International Classification of Diseases, Tenth Revision (ICD-10).

A flow chart of the study design is presented in Figure 1. Out of all children born during the study period 395,812 (21.3%) infants had a diagnosis, entry, in the National Patient Registry. As part of a larger project a selection of diagnoses was made comprising 182,974 (9.9%) infants. For analysis of perinatal and parental factors, four controls were selected for each

infant; these were born the same year and had no diagnoses in the National Patient Register during the first year of life (n=730,971, five cases more than requested), comprising 39.4% of all children during the study period. Data from this sample was linked to the Swedish Medical Birth Register by the personal identity number they were given at birth. The final sample was 908,571 infants.

Exposure

We categorised a number of exposures. The maternal exposures included: maternal age under 20, 20–34 and 35 years plus), parity (up to two or three plus) and body mass index at the start of pregnancy: underweight (<19), normal (19–24), overweight (25–29.9) and obese (30+). We also looked at maternal smoking at pregnancy week 30–32 (none or one of more cigarettes a day), preeclampsia, the mother's region of birth, the family situation (cohabiting/single or other) and years of maternal education (less than 10, 10-14 and more than 14). The infant factors were: sex, single or multiple births, gestational week at birth (less than 32, 32-36 or 37 plus small-for-gestational age (SGA) (<2.5th or <10th percentiles), birth injury to the skeleton, transitory neonatal disorders of calcium and magnesium metabolism, and necrotizing enterocolitis.

Outcome

Rickets was defined by the following ICD-10 diagnoses: rickets, active (E55.0), vitamin D deficiency (E55.9), disorder of bone density and structure, unspecified active (M85.9), and sequelae of rickets (E64.3). We also included disorders of phosphorus metabolism and phosphatases (E83.3), which is recommended in Sweden for diagnosing osteopenia among preterm born infants with vitamin D resistant osteomalacia rickets (Table 1).

Statistical analysis

The incidence proportion and cases of rickets per 100,000 infants born were calculated. For the time trend, namely birth year, we estimated the moving annual average. The Fisher's exact test were applied to assess differences. Multiple logistic regression was performed to evaluate odds with 95% confidence intervals of rickets with the following the categorized covariates: Mother born in Asia or Africa (reference: born in Sweden, Scandinavia, Europe or North America), Maternal age more than 34 years, preeclampsia, gestational week 32-36 or less than 32, birth weight 1500 gr to 2499 gr and less than 1500 gr, SGA less than 2.5^{th} percentile and less than 10^{th}, multiple birth and necrotizing enterocolitis. For the models of adjusted odds ratios were selected as exposure variables those of population and clinical importance, and those having a p-value <0.05: age (35 years of age or more versus others), mother's region of birth (whether born in Africa or Asia, versus others, but Latin American born excluded), pre-eclampsia, multiple birth, gestational week, SGA (10^{th} percentile), necrotizing enterocolitis. Birthweight was excluded from the model because of collinearity. Stratified analysis was performed for preterm-born, term-born and by the periods of children born 1997-2007 and 2008-2014 as the more pronounced increase occurred during the latter period. For the statistical analysis, we used the statistical software package SPSS, version 25.0 (IBM Corp, New York, USA) were used.

The study was approved by the Regional Ethical Committee in Uppsala (2014-11-19, No. 383). This committee approved a waiver of informed consent, considering that the research database contained only coded data.

RESULTS

There were 273 infants born in 1997-2014 with a diagnosis of rickets. From 2001-2014, 58 (26.5%) infants were diagnosed in specialised out-patient care.

There were 282 diagnosis codes for the 273 infants as nine infants had two diagnosis codes. The ICD codes for the whole cohort was: 221 had active rickets (E55.0), 33 had a vitamin D deficiency (E55.9), 18 had vitamin D resistant osteomalacia rickets (E83.3), eight had an unspecified disorder of bone density and structure (M85.9), and two had sequelae of rickets (E64.3).

The incidence proportion was 14.7 per 100,000 infants. The incidence increased from 2.9 in 1997 to 8.4 in 2001, 16.9 in 2009 and 28.7 in 2014 (Fig 2).

Table 2 shows the perinatal and maternal characteristics associated with rickets compared to the population. Having a mother aged above 34 years was associated with rickets, while parity, body mass index, family situation and education were not. We noted that 54 (19.8%) of the mothers had pre-eclampsia. Our findings showed that 214 (78.44%) were preterm born infants: 32 (11.7%) of the total 273 infants were born in gestational weeks 32 to 36, and 182 (66.7%) below gestational age 32. Just less half, 109 (49.8%), were small-for-gestational age with a birthweight below the10^{th} percentile and 56 (20.5%) were multiple births. In addition 11 infants (4.8%) were born to Asian-born mothers and 8 (3.5%) to African-born mothers. During the neonatal period 31 (11.4%) had necrotising enterocolitis and nine (3.3%) had transitory neonatal disorders of calcium and magnesium metabolism.

At the time of their rickets diagnosis, nine had failure to thrive or feeding difficulties, five infants had a diagnosis of other and unspecified convulsions, four had chronic renal disease and three had fractures. There were also three infants with osteogenesis imperfecta and one

with DiGeorge syndrome. Two infants had been diagnosed with abuse with a rib fracture and long bone fracture 80 days and 31 days, respectively, before their rickets diagnosis.

Table 3 presents the crude and adjusted ORs for rickets. Infants born at less than 32 weeks had an aOR of 182 (95% CI 121-272) and at gestational weeks 32–36 the aOR was 10.8 (95% CI 6.72-17.4). The aOR for SGA (<10th percentile) was 2.16 (95% CI 1.53-3.04) and for infants born to an African-born the aOR was 2.64 (95% CI 1.22-5.72). When we only stratified preterm infants born with necrotising enterocolitits the aOR was 18.4 (95% CI 2.42-139). When we only stratified term-born infants, the aOR for infants with an African-born mother increased to 6.91 (95% CI 2.71-17.6) and the SGA (<10th percentile) aOR rose to 2.98 (95% CI 1.53-5.81). When the periods 1997-2007 and 2008-2014 were compared the odds increased considerable for preterm born infants, both for those born in gestational weeks 32-36 and less than 32 weeks. There were no infants with rickets born to African mothers in 1997-2007.

DISCUSSION

The incidence of rickets was 14.7 per 100,000 live births among infants born in Sweden during the study period, with a 10-fold increase in incidence for children born 1997 to 2014. We found that 78.4% was associated with prematurity, 49.8% with SGA (<10th percentile), 4.8% with Asian-born mothers and 3.5% with African-born mothers. The most important risk factor was birth at less than 32 of gestational age, followed by birth at between 32-36 weeks of gestational age. Necrotising enterocolitis was the most prominent risk factor for preterm-born infants. For term-born infants, the risk factors were SGA and having an African-born mother.

Our comparison of the reported incidence during the first year of life with other studies is hampered by differences in study design and definition of cases. A study from the United States reports an incidence of nutritional rickets, defined by a broad definition of rickets-related diagnoses, of 24.1 per 100,000 for children under three years old (4). A study from Canada reported an incidence of 23.9 per 100,000 of nutritional rickets, defined by codes 268 in the ICD, Ninth Revision (ICD-9) and E55 (ICD-10) for term-born children aged less than three years (18). A nationwide register study from Norway reported an incidence of nutritional rickets, defined by ICD-10 codes E55.0 & E55.9 and validated by clinical records, of 0.3 per 10,000 person-years for term-born children aged less than five years, while for those with an immigrant background, the incidence was 3.1 per 10,000 person-years (19). The rising incidence of diagnosis is in accordance with other studies (2-5). Our reported increased incidence may represent a real increase but also may be due to previously undetected cases. Increased survival of extremely preterm born could have added cases during the end of the study period (20). A contributing factor to a real increase might have been immigration, but according to our findings, this was less important. In the present study, the inclusion of outpatient specialised care in the patient register from the year 2001 added cases, one-fourth had only a diagnosis from out-patient care. An increase in detection rate due to increasing clinical awareness during the latter period might also contributed to the increased incidence. New guidelines on osteopaenia among preterm born the Nutrition Group in the Swedish Neonatal Society was first published in 2015 and revised in 2017 (21).

Four-fifths of the cases were associated with prematurity, most probably because of metabolic bone disease of prematurity (9, 11, 12). However, 11.7% of all cases in our study involved infants born during gestational weeks 32–36, warranting alertness that osteopaenia might also occur in this category and not only for preterm borns with birth weight less than 1,500 gr (21).

Small-for-gestational age (<10th percentile) had increased odds for rickets, both for term babies and for preterm-born. The underlying cause could be intra-uterine growth restriction due to impaired placental function, with low transfer of vitamin D and the micronutrients calcium and phosphorus (9, 11, 22-24). Neonatal necrotising enterocolitis is complicated by nutritional deficiencies, which enhance the risk of calcium and phosphorous deficiency related to prematurity, and a determinant of severe metabolic bone disease (12, 25) in line with our finding of high odds for rickets.

Hypocalcaemic seizures is a presenting feature for vitamin D deficiency rickets among infants and toddlers in 11.8% to 40.3% (26). A U.S. population study reported seven cases of seizures as a hypocalcaemic complication at age before of nine months, two of those had rickets present on radiograph (27). The few cases in our study diagnosis with seizures, 1.8% at the same time as rickets, may be explained by that our study design, although only infants, included a variety of cases and maybe not all having overt rickets.

Fractures is reported in 0 to 1.4% as presenting feature of vitamin D deficiency rickets among infants and toddlers (26) comparable to our findings of 1.1%. Clinically silent fractures, occult, are more prevalent in infants with rickets (7, 9, 11, 28). Current diagnostic practice may underestimate prevalence of occult fractures; using x-ray of arms or legs is hampered by uncertainty and is not always combined with laboratory biochemistry. Higher predictivity of osteopaenia is achieved by dual-energy X-ray absorptiometry or quantitative ultrasound (9, 12), preferably the latter which does not expose the infants to radiation.

The increasing odds of rickets in preterm infants of Asian-born mothers and in term infants of African-born mothers shown in our study, do indicate that socio-cultural habits and ethnicity are of importance even during infancy, adding cases of nutritional rickets among children 0–18 years of age (2-5). Our results indicate that at a population level, however, socio-cultural

and ethnicity factors were of minor importance for rickets during first year of life among Swedish born infants.

Maltreatment diagnosis in two infants was associated with rickets diagnosis. Whether these cases were true positive cases for abuse cannot be ascertained by this study design; fractures of the ribs and long bones are reported to be specific for abusive head trauma (29) however at a population level fractures of the ribs and long bones are associated to metabolic bone disease risk factors during the first six months of life (14).

Strengths and weaknesses of the study

The strengths of this study are the population design with national coverage, the prospective data collection, uniform use of the ICD-10 and, probably, high reliability of the detected diagnosis as coming from paediatric care. The dataset, including the controls, included 49% of the 1.85 million children born in Sweden during the study period, implying population representativeness. Moreover, the Swedish Patient Register is considered to have high validity (30). However, none of the ICD codes used in this study for case definition have not been validated. Therefore, a major limitation was that we did not have access to clinical records for further assessment of the diagnosis by skeletal and non-skeletal clinical features (1, 2), laboratory or radiologic findings (9, 11, 12). Another limitation is that only infants born in Sweden was prospectively followed during first year of life. Thus, infants born outside Sweden but with diagnosis of rickets in the National Patient Register were not included in this study, and might have deflated the contribution of rickets from immigrant mothers.

CONCLUSION

Rickets during infancy was mainly associated with prematurity, but also with SGA and, to a lesser extent, with having a foreign-born mother. The incidence was 14.7 per 100,000 infants born in Sweden from 1997-2014. The 10-fold increase may be due to increased survival of extremely preterm born, but also to previously hidden cases because of improved registration and clinical detection.

The new Swedish guidelines of detection and treatment of treatment of osteopaenia among preterm born will probably prevent rickets during infancy. Given the increased interest in vitamin D since the turn of the millennium and the ongoing discussions on undetected vitamin D deficiency it is most probable that rickets was underdiagnosed in the beginning of the studied period. New recommendations with higher D-vitamin supplementation to infants hopefully will provide adequate amounts and decrease the risk of rickets.

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None.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

FIG 1. Flow chart of the study base. Source: The National Patient Register (National Patient Register), the Swedish Medical Birth Register (Medical Birth Register), the Swedish National Board of Health and Welfare, Statistics Sweden.

FIG 2. Rickets in infants up to one year of age, incidence proportion per 100,000 live births in Sweden 1997-2015 (moving annual average).

Table 1. Maternal, perinatal and infant diagnoses, using International Statistical Classification of Diseases, 10th revised edition (ICD-10), Swedish version.

Diagnosis		**ICD-10 code**
Mother		
	Hyperparathyroidism	E21.3
	Pre-eclampsia	O14
Birth	Birth injury to skeleton	P13
	Transitory neonatal disorders of calcium and magnesium metabolism	P71
	Necrotizing enterocolitis of fetus and newborn	P77
Infant diagnoses		
	Rickets, active	E55.0
	Vitamin D deficiency	E55.9
	Disorder of bone density and structure, unspecified[1]	M85.9
	Disorders of phosphorus metabolism and phosphatases (Vitamin-D-resistant: osteomalacia, rickets)	E83.3
	Sequele of rickets	E64.3
	Chronic renal disease	R18
	Other and unspecified convulsions	R56.8
	Failure to thrive	R62.8
	Feeding difficulties and mismanagement	R63.3
	Long bone fracture	S42.2, S42.3, S42.4, S42.7, S42.8, S52, S72, S82
	Rib fracture	S22.3, S22.4
	Osteogenesis imperfecta	Q78.0
	DiGeorge syndrome	D82.1
	Infant abuse diagnosis (observation for suspected abuse, battered baby syndrome, maltreatment syndrome)	Z03.8K, Y07, T74.1, Y06

[1] Swedish version recommended for osteopenia among preterm born

Table 2. Rickets by maternal characteristics, birth, neonatal and infant diagnoses in infants born in Sweden in 1997–2014. Fisher's exact test was used to compare diagnoses between the cases and the population.

		Population (N=908,298)[1]	Rickets (n=273)	
		N (%)	N (%)	p-value
Maternal characteristics				
Age, years	<20	14,586 (1.6)	7 (2.6)	0.209
	20–34	704,033 (77.5)	188 (68.9)	
	35+	189,679 (20.9)	78 (28.6)	0.002
Parity	1	399,449 (44.0)	131 (48.0)	0.204
	2+	508,849 (56.0)	142 (52.0)	
Body Mass Index[2]	Normal (19–24.9)	490,739 (60.3)	119 (56.1)	
	Underweight (<19)	19,791 (2.4)	8 (3.8)	0.247
	Overweight (25–29.9)	204,351 (25.1)	53 (25.0)	0.739
	Obese (30+)	98,289 (12.1)	32 (15.1)	0.745
Smoking[3]	Non-smoking	778,423 (94.5)	179 (65.9)	
	Smoking, pregnancy weeks 30–32	45,595 (5.5)	5 (1.8)	0.111
Pre-eclampsia		38,778 (4.3)	54 (19.8)	<0.001
Mother's region of birth[4]	Sweden/Scandinavia	769,758 (91.0)	196 (85.2)	
	Europe/North America	31,994 (3.8)	14 (6.1)	0.087
	Asia	28,137 (3.3)	11 (4.8)	0.235
	Africa	12,610 (1.5)	8 (3.5)	0.037
	Latin America	2,992 (0.4)	1 (0.4)	1
Family situation	Cohabiting	811,717 (93.9)	207 (75.8)	
	Single/other	52,848 (6.1)	18 (6.6)	0.300
Mothers years in school[5]	15 years+	338,906 (38.4)	99 (37.4)	
	10-14 years	460,864 (52.3)	134 (50.5)	1
	<10 years	82,103 (9.3)	32 (12.1)	0.194
Birth and neonatal diagnoses				
Infant sex	Female	438,952 (48.3)	118 (43.2)	
	Male	469,346 (51.7)	155 (56.8)	0.103
Multiple birth		26 607 (2.9)	56 (20.5)	<0.001
Gestational week[6]	37+	851,504 (93.8)	57 (21.0)	
	32–36	47,377 (5.2)	32 (11.8)	<0.001
	<32	8,962 (1.0)	1824 (67.2)	<0.001
Birth weight (g)[7]	2,500+	866,174 (95.6)	58 (21.4)	
	1,500-2499	32,747 (3,6)	41 (15.1)	<0.001
	<1,500	7,438 (0.8)	172 (63.5)	<0.001
Small-for-gestational age	<2.5th percentile	20,509 (2.3)	65 (30.2)	<0.001
	<10th percentile	94,163 (10.4)	109 (49.8)	<0.001

Birth injury to the skeleton		5,049 (0.27)[8]	2 (0.7)	0.103
Transitory neonatal disorders of calcium and magnesium metabolism		752 (0.04)[8]	9 (3.3)	<0.001
Necrotizing enterocolitis		566 (0.03)[8]	31 (11.4)	<0.001

[1] N= 908,298 (final data set 908 571 minus 273 cases of rickets), [2]Missing data on BMI among referents (n=84,280) and cases (n=61), [3]Missing data on smoking among referents (n=84,280) and cases (n=89), [4]Missing data on mothers region of birth among referents (n=64,807) and cases (n=43), [5]Missing data on Mother years in school among referents (n=24,425) and cases (n=8), [6]Missing information on gestational week among referents (n=455) and cases (n=2), [7]Missing information on birth weight among referents (n=1,939) and cases (n=2) [8]n=1,855,267, all children born live in Sweden 1997-2014,

Table 3. Risk factors for diagnosis of Rickets among infants born in Sweden in 1997–2014. Diagnoses of osteogenesis imperfecta (n=3) and DiGeorge syndrome (n=1) are excluded. Crude ORs and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) are shown.

		Rickets					
Exposure		All infants (n=269)		Preterm-born infants (n=214)	Term-born infants (n=53)	Period 1997-2007 (n=91)	Period 2008-2014 (n=182)
		OR (95% CI)	aOR[1] (95% CI)	aOR[1] (95% CI)	aOR[1] (95% CI)	aOR[1] (95% CI)	aOR[1] (95% CI)
Mother's region of birth	Sweden/Scandinavia/ Europe/North America	1			1	1	
	Asia	1.51 (083-2.78)	1.80 (0.94-4.45)	4.19 (1.46-12.1)	1.88 (0.58-6.11)	1.86 (0.58-6.0)	1.68 (0.77-3.65)
	Afrika	2.15 (1.1.01-4.57)	2.64 (1.22-5.72)	0	6.91 (2.71-17.6)	0	3.52 (1.68-7.37)
Age, years	<35	1					
	35+	1.47 (1.12-1.91)	1.20 (0.86-1.67)	0.81 (0.33-1.98)	0.91 (0.44-1.87)		
Pre-eclampsia		5.63 (4.18-7.59)	1.23 (0.83-1.83)	0.68 (0.23-2.01)	1.05 (0.25-4.36)		

Gestational week	37+	1					
	32–36	10.8 (7.0-16.8)	10.8 (6.72-17.4)	-	-	7.07 (3.07-16.3)	12.1 (6.84-21.7)
	<32	326 (240-443)	182 (121-272)	-	-	123 (63.0-241)	209 (1128-343)
Birth weight (g)	2,500+	1					
	1500-2499	16.5 (11.3-24.1)	-				
	<1,500	293 (222-389)	-				
SGA[4]	<2.5th percentile	18.7 (13.9-25.0)	-	-	-	-	-
	<10th percentile	9.02 (6.89-11.8)	2.16 (1.53-3.04)	3.14 (1.46-6.77)	2.98 (1.53-5.81)	2.03 (1.07-3.82)	2.19 (1.46-3.26)
Multiple birth		8.71 (6.49-11.7)	0.96 (0.65-1.42)	1.33 (0.59-3.01)	0.83 (1.53-5.81)	0.52 (0.21-1.28)	1.10 (0.723-1.1.72)
Necrotizing enterocolitis		208 (142-306)	3.45 (1.93-6.17)	18.4 (2.42-139)	0	4.75 (1.39-16.2)	2.77 (1.43-5.37)

[1]Adjusted odds ratio (age, mother's country/region of birth, pre-eclampsia, multiple birth, gestational week, SGA (10th percentile), necrotizing enterocolitis.