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Increasing Incidence of Nutritional Rickets: A Population-Based Study in Olmsted County, Minnesota

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Abstract

Objective—To determine temporal trends in incidence and risk factors of nutritional rickets in a community-based population.

Patients and Methods—Rochester Epidemiology Project (REP) data were used to identify all children (<18 years) residing in Olmsted County, Minnesota between January 1, 1970 and December 31, 2009 with diagnostic codes corresponding to rickets, vitamin D deficiency, hypovitaminosis D, rachitis, osteomalacia, genu varum, genu valgum, craniotabes, hypocalcemia, hypocalcemic seizure, and tetany. Record abstraction was performed to select subjects with radiographic confirmation of rickets. Age- and gender-matched controls were identified for evaluation of risk factors. The main outcome measure was radiographic rickets without identifiable inherited, genetic, or non-nutritional causes. Incidence rates were calculated using REP census data.

Results—Of 768 children with eligible diagnostic codes, 23 had radiographic evidence of rickets; of these, 17 children had nutritional rickets. All were younger than 3 years and 13 (76%) were nonwhite. Clinical presentation included poor growth (n=12), leg deformity (n=8), motor delay (n=5), leg pain (n=3), weakness (n=3), and hypocalcemia or tetany (n=2). The incidence of nutritional rickets in children under 3 years was 0, 2.2, 3.7, and 24.1 per 100,000 for the decades beginning in 1970, 1980, 1990, and 2000, respectively (P=.003 for incidence trend). Nutritional rickets was associated with black race, breastfeeding, low birth weight, and stunted growth (P<.05 for all). Four of 13 (31%) who underwent 25-hydroxyvitamin D testing had values less than 10 ng/mL (25 nmol/L).

Conclusion—Nutritional rickets remains rare, but the incidence has dramatically increased after 2000. Not all cases can be attributed to vitamin D deficiency.

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Keywords

bone diseases; metabolic; epidemiology; pediatric; vitamin D

Introduction

Nutritional rickets is characterized by bone pain, leg deformities, and sometimes life-threatening hypocalcemia. It occurs when deficiency of vitamin D or dietary calcium results in impaired mineralization of growing bone.[1] Despite concerns regarding the persistence and possibly increasing incidence of nutritional rickets in the United States and other countries, the actual incidence rate is unknown.[2–5] The primary measure of vitamin D status is serum 25-hydroxyvitamin D (25[OH]D) concentration. Average concentrations of serum 25(OH)D have decreased in the US population between 1994 and 2004, potentially increasing the risk of nutritional rickets due to vitamin D deficiency.[6,7] It is unclear whether the increasing recognition of nutritional rickets is attributable to greater awareness and diagnosis of vitamin D deficiency with laboratory testing or to actual population increases of rickets caused by nutritional or environmental factors. Nevertheless, the prevalence of vitamin D insufficiency in US infants prompted the American Academy of Pediatrics in 2003[8] to recommend that all breastfed infants have a minimum daily vitamin D intake of 200 international units; in 2008,[9] the recommendation was increased to 400 international units per day. One factor that contributes to low 25(OH)D concentrations and the risk of nutritional rickets is northern latitude, which reduces the amount of UV-B exposure that allows vitamin D production in the skin. The prevalence of vitamin D insufficiency (defined as 25[OH]D <20 ng/mL [<50 nmol/L]) in infants and toddlers in Boston (42° north latitude) was 12%.[10] The upper Midwest, which includes Minnesota, generally has lower levels of UV exposure than the rest of the continental United States,[11,12] which may result in a greater risk of vitamin D deficiency.

Case series and chart reviews have reported increased numbers of identified cases of rickets in developed countries in recent years.[13–15] However, much of the data that suggests an increased frequency of nutritional rickets originates from tertiary care centers, which may reflect a change in referral patterns and not a true change in the incidence of rickets. Because the denominator of the total population at risk is unknown, case reports or case series obtained from hospital admissions records cannot establish the incidence or prevalence of rickets. Consequently, no definitive evidence shows that the incidence of nutritional rickets is changing.[16] Population-based data are required to determine temporal trends in the incidence of rickets in children. The primary objectives of this study were 1) to determine the incidence of nutritional rickets in Olmsted County, Minnesota; 2) to describe the clinical characteristics of subjects with nutritional rickets; and 3) to evaluate the temporal trends in incidence during the past 40 years. Our secondary objective was to compare cases of nutritional rickets with controls to identify risk factors associated with nutritional rickets.

Patients and Methods

Olmsted County and the Rochester Epidemiology Project

Olmsted County, Minnesota, is located in the Upper-Midwestern United States (centered at 44° north latitude). The population of Olmsted County has increased from 82,955 in 1970 to 145,225 in 2009. Despite the 75% increase in total population, the number of children younger than 3 years, who are at greatest risk of rickets, had a much smaller increase—from 5,133 in 1970 to 6,277 in 2009 (22% increase). Racial diversity has been increasing. In the 2000 and 2010 censuses, the proportion of Olmsted County children (less than 18 years of

age) classified as African American were 3.8% and 7.3%, respectively, and the proportion classified as white were 86.1% and 78.0%, respectively.

The Rochester Epidemiology Project includes patient and diagnostic data from virtually all medical care providers within Olmsted County, covering 98% of all health care services for Olmsted County residents.[17] The county is served by two large integrated health systems, the Mayo Clinic and the Olmsted Medical Center, including primary through tertiary care, outpatient and hospital care. With more than 100 years of medical records and the full spectrum of local primary to tertiary care services, Olmsted County is ideally suited for long-term, population-based studies of disease incidence, prevalence, risk factors, and outcomes.

Subjects

The institutional review boards of Mayo Clinic and Olmsted Medical Center approved the study. We used the REP database to determine the temporal trend in the incidence of nutritional rickets from January 1, 1970, through December 31, 2009. Children were eligible for study if they were younger than 18 years during the study period, resided in Olmsted County, and had not refused research authorization (n=4). We reviewed medical records of children with any of the following diagnoses: rickets, vitamin D deficiency, hypovitaminosis D, avitaminosis D, rachitis, osteomalacia, genu varum, genu valgum, angulation, bowing, knock-knee, craniotabes, chest deformity, hypocalcemia, hypocalcemic seizure, tetany, and disorders of calcium or phosphorus metabolism, as identified by International Classification of Diseases (ICD) (ninth revision), Hospital International Classification of Diseases Adapted (HICDA), or Berkson codes in the REP databases. The Berkson codes are unique to Mayo Clinic. The HICDA codes were a predecessor of the ICD-9 used widely in the US but modified by Mayo with additional digits to enhance specificity. In total, 57 individual diagnostic codes were used to identify potentially eligible subjects. The broad range of codes was intended to ensure high sensitivity for identifying children with possible nutritional rickets.

Medical records and radiographic data were reviewed to confirm the diagnosis of nutritional rickets. The operational definition for the diagnosis of nutritional rickets was a radiographic interpretation consistent with rickets and no evidence of nonnutritional causes of rickets. Thus, a diagnosis of nutritional rickets was established based on the exclusion of nonnutritional causes of rickets and not always based on the nutrition history or vitamin D concentration. Medical records of the initially identified subjects were searched for a skeletal radiograph at any site with features that were consistent with rickets, as noted on the radiologic report. For subjects who met the radiographic criteria for rickets, the medical records were further reviewed to identify and exclude all patients with an inherited, genetic, or other nonnutritional cause of rickets, including X-linked hypophosphatemic rickets, autosomal dominant and recessive hereditary rickets, hereditary hypophosphatemic rickets with hypercalciuria, vitamin D–dependent rickets types I and II, tumor-induced osteomalacia, renal tubular disorders, renal insufficiency (serum creatinine greater than 3 times the upper limit of normal for age and sex), and hypophosphatasia. Determination of the presence of rickets and likely cause from the radiologic reports and case histories was adjudicated by 3 physicians (T.D.T., P.R.F., P.J.T.) experienced in the diagnosis of children with rickets.

Additional information was abstracted from the medical records of children who met the criteria for nutritional rickets to identify clinical features potentially associated with nutritional rickets: date of diagnosis, age at presentation, sex, race and ethnicity, height or length, weight, breastfeeding status and duration, dietary restrictions, other medical diagnoses, medications, vitamin D or multivitamin supplement use, birth weight and

gestational age at birth, and reported symptoms and their duration. Laboratory values for serum calcium, phosphorus, alkaline phosphatase, 25(OH)D, and parathyroid hormone were recorded.

For each confirmed case, two age- (within one month of date of birth) and sex-matched controls with at least one medical appointment with a primary care provider in the same year as the case's diagnosis of rickets were selected from the REP database. These subjects had the same information abstracted from their medical record as described above (omitting reported symptoms and laboratory values).

Statistical Analysis

The incidence of confirmed cases of rickets in Olmsted County residents at the time of their diagnosis was calculated per 100,000 person-years and then adjusted to 2000 US census data. A Poisson regression model was used to evaluate the association of calendar period with crude incidence. Incidence trends were calculated according to a Poisson regression model using the SAS 9.3 GENMOD procedure (SAS Institute, Inc.; Cary, North Carolina). We imputed the population of black children under 3 years of age in Olmsted County using 2000 and 2010 census proportions for African-American children under 5 years of age (4.7% and 7.4%, respectively). The interpolated proportions between these census years were multiplied by the total population of children under age 3 years in Olmsted county each year to estimate the incidence denominator for black children under age 3 years.

Height and weight percentiles were calculated by using the nutrition program of Epi Info 3.5.3 (Centers for Disease Control and Prevention; Atlanta, Georgia) and standard growth charts.[18] Evaluation of risk factors for rickets was performed for the matched case-control study using a conditional logistic regression analysis with the SAS macro MCSTRAT.[19,20] A univariate analysis of each risk factor was performed, but multivariate analysis could not be conducted because of the small number of cases of nutritional rickets. *P* values less than . 05 were considered statistically significant.

Results

In total, 768 records were identified by the eligible diagnostic codes; diagnoses included leg deformities (n=517), hypocalcemia or tetany (n=131), vitamin D deficiency (n=60), osteomalacia (n=23), rickets (n=27), and craniotabes (n=10). Of the 369 subjects who underwent radiography, 23 (6%) had confirmed rickets and 17 (74%) of these were judged to have nutritional rickets. Of the six excluded cases of confirmed rickets, three had hypophosphatemic rickets, and one each had rickets of prematurity, renal rickets, and Schmid-type metaphyseal chondrodysplasia. Less than half the children (48%) with eligible diagnostic codes underwent radiography to evaluate their condition, a study requirement for confirmation of rickets. Of children with a diagnosis of vitamin D deficiency, the majority (77%) had no radiographic evaluation. The number of children with a medical record diagnosis of either vitamin D deficiency or rickets increased dramatically since 2002 (Figure 1), which corresponded to a greater than 10-fold increase in the volume of 25(OH)D testing at Mayo Clinic (R.J.S., unpublished data, 2008). In fact, of the 60 diagnoses of vitamin D deficiency in the medical record, 59 were made during the decade beginning in 2000. Serum 25(OH)D values were documented in 49 of these subjects, and 32 (65%) had values less than 20 ng/mL, and 11 (22%) had values less than 10 ng/mL.

The Table summarizes patient characteristics at presentation. All children with nutritional rickets presented at less than 3 years of age (Figure 2). Two-thirds of patients presented during the second year of life. The majority (59%) were black. The most common clinical characteristic was poor growth (71%), with a median height for age below the third

percentile. Other frequent symptoms were leg deformities, leg pain, and delayed motor milestones. No significant seasonal variation in the month of presentation of nutritional rickets (P=.18) or in the month of birth (P=.89) was found, although the current study is highly underpowered to detect a statistically significant seasonal variation in the month of presentation of nutritional rickets or in the month of birth. Biochemical features of elevated alkaline phosphatase, hyperparathyroidism, and hypophosphatemia consistent with rickets were frequent but not necessarily present in every child who underwent testing. The median value of 25(OH)D was 13 ng/mL; only 4 of the 13 (31%) who underwent testing had values less than 10 ng/mL, indicating severe vitamin D deficiency.

Compared with control children, a greater proportion of those with nutritional rickets were black, were breastfed (and had a longer duration of breastfeeding), had reduced height and weight, and had a lower birth weight (P<.05 for all). Several potential contributors to the development of rickets were identified in the medical record among children with nutritional rickets. These included poor feeding (n=4), limited sun exposure (n=3), limited milk intake (n=3), a predominantly vegetarian diet (n=2), and prematurity (n=2). None of the children with nutritional rickets had documented vitamin D supplementation before their diagnosis. Two cases of nutritional rickets were considered imported, being identified in new immigrants from Egypt and Saudi Arabia. Four patients with nutritional rickets (since 2000) were US-born infants of recent Somali immigrants.

The incidence of nutritional rickets in children younger than 3 years was relatively stable from 1970 to 2000, but displayed a dramatic increase after 2000 (Figure 1). By aggregated 10-year intervals, the incidence of nutritional rickets was 0, 2.2, 3.7, and 24.1 per 100,000 for the decades beginning in 1970, 1980, 1990, and 2000, respectively (P=.003 for incidence trend by Poisson regression modeling). In the decade beginning in 2000, the incidence of rickets in black children was estimated at 220 per 100,000.

Discussion

As a population-based incidence study over 40 years, this report provides better information regarding the incidence and temporal trends of diagnosed nutritional rickets than previous studies. Unlike other case series, our study had the advantage of a defined population (ie, denominator), and consequently, we were able to determine the actual incidence trend of nutritional rickets without the risk of referral bias. By requiring radiographic evidence of rickets, we avoided disease misclassification by ensuring that all cases had diagnostically confirmed rickets. We showed that the incidence of nutritional rickets has increased significantly during the past 4 decades. However, nutritional rickets still remains rare, despite the region’s relatively northern latitude. While some of the increasing incidence could have been related to increased testing of vitamin D levels during the final decade of the study, most subjects were identified by clinical rather than biochemical abnormalities and most subjects with low vitamin D levels did not have radiographic evidence of rickets. Thus, the increasing incidence of rickets is unlikely to be solely due to temporal changes in laboratory testing.

Little reliable information on the prevalence of nutritional rickets is available, and the prevalence and causative factors may vary between geographic locations.[21] On the basis of a monthly survey of pediatricians from 2002 through 2004, the annual incidence of vitamin D–deficiency rickets in Canada has been estimated at 9 to 12 cases per 100,000 in children younger than 3 years.[22] In the decade beginning in 2000, we found an even greater incidence rate (24.1 per 100,000) in the same age group. On the basis of a postal survey of pediatricians in the United Kingdom, administered in 2001, the incidence of rickets was estimated at 7.5 cases per 100,000 children younger than 5 years.[23] Incidence rates were 38

and 95 per 100,000 in Asian and black children, respectively. In children 0 to 4 years old in Wales, the incidence rate of vitamin D deficiency was 4.3 per 100,000 for 2007–2008,[24] but only half of the 14 children with vitamin D deficiency had radiographic evidence of rickets. Many children with asymptomatic vitamin D deficiency have no radiographic evidence of rickets. Among 40 infants and toddlers with vitamin D deficiency in Boston, only 2 (5%) had radiographic evidence of rickets.[25]

In our case-control analysis, we showed that rickets was associated with black race, breastfeeding, and poor growth, similar to previous reports.[3,26] Black infants are at greater risk of nutritional rickets than white infants, and in our study, 59% of children with nutritional rickets were black. In a chart review at the Children's Hospital of Michigan that identified 58 patients with nutritional rickets (from 1995 through 2005), 81% were African Americans and 14% were Arabic.[13] An increasing number of cases of nutritional rickets were noted after 2000. Similar to our findings, 96% of patients were breastfed, and none received vitamin supplements. Serum 25(OH)D concentrations were below 5 ng/mL in 42% of patients, all of whom were African American. At Children’s Hospital of Wisconsin, 51 cases of nutritional rickets were identified from 1996 through 2004.[27] Skeletal deformities, failure to thrive, fractures, seizures, incidental laboratory findings, tetany, and refusal to walk were the most common presenting features. All were breastfed and 46 (90%) were African American.

The rising incidence of rickets we observed potentially was due to the increasing number of nonwhite (predominantly Somali) immigrants who have settled in Minnesota since 1994.[28] We identified 6 patients with nutritional rickets who were new immigrants or Somali-born children. In a review of 127 children with a diagnosis of vitamin D deficiency in Bristol, United Kingdom, a high proportion (71%) were of Somali origin.[29] A case series of 123 children with rickets in Australia described a steady increase in the frequency of rickets from 1993 through 2003.[14] Affected children were almost exclusively black immigrants, and the frequency of rickets mirrored immigration trends. In a case series of 160 children presenting with symptomatic vitamin D deficiency to the Royal Hospital for Sick Children in Glasgow, Scotland, an increasing number of cases was observed from 2002 through 2008.[15] The vast majority were of African or Middle Eastern ethnic background. Rickets was confirmed by radiographs in 91 children (57%), so not all subjects with vitamin D deficiency had nutritional rickets.

Another reason for an increased incidence of nutritional rickets could be the temporal trend of declining vitamin D status in infants and toddlers. Of 2,731 serum samples from children younger than 18 years who received care at Mayo Clinic (Rochester, Minnesota) from November 2004 through December 2008, 113 (4.1%) had 25(OH)D values less than 10 ng/mL, a level consistent with vitamin D deficiency (R.J.S., unpublished data, 2009). The National Health and Nutrition Examination Surveys[7] found that the prevalence of individuals in the US population with 25(OH)D values less than 30 ng/mL doubled from 1994 to 2004. A downward trend in maternal 25(OH)D values could lead to reduced infant stores at birth, or the decrease could be due to trends in infant vitamin D intake.

Although nutritional rickets is widely assumed to be due to vitamin D deficiency, inadequate dietary calcium intake may also cause nutritional rickets. This has been described previously in African children.[30] Insufficient dietary calcium is a likely and important contributing cause of nutritional rickets in the United States.[31] The combined interaction of suboptimal vitamin D status and limited calcium intake may lead to impaired bone mineralization that results in nutritional rickets.[1] The majority (69%) of children with nutritional rickets in our study who had their serum 25(OH)D concentrations measured did not have evidence of

severe vitamin D deficiency. This suggests that other factors such as a calcium deficient diet may have contributed to the development of rickets in this population of children.

Another temporal trend postulated to have increased the worldwide incidence of rickets is the increased use of sunscreen and implementation of other sun-protection behaviors in recent decades.[32] Sun-protection behaviors are more frequent in fair-skinned than in dark-skinned children, and 83% of parents of children under the age of 2 years engage in sun-protection behaviors.[33] Sun protection is more common with younger children than older children.[34,35] This could account for an increase in rickets among white but probably not in black children.

Potential limitations of our methodology include coding errors or omissions and omission of cases of rickets that were unrecognized or not brought to medical attention. Only 48% of identified patients with potential symptoms or signs of rickets, and 23% of the patients with a diagnosis of vitamin D deficiency had radiographs performed. If radiographs had been performed in these groups, additional cases of nutritional rickets may have been found, and the actual incidence of rickets would be greater than what we report. One important limitation is that we cannot determine the cause of the increasing incidence of rickets. In addition to an increasing immigrant population, other population trends may account for the rising incidence. Furthermore, greater recognition of rickets resulting in a diagnosis would manifest as an increasing incidence. This requires an assumption that milder cases of rickets are undetected and resolve spontaneously. Due to the relatively small number of children with nutritional rickets, our study lacked sufficient power to demonstrate seasonal effects on the occurrence of nutritional rickets.

The generalizability of Olmsted County incidence rates to the entire U.S. population is generally good, but the population of Olmsted County has been less ethnically diverse (90.3% vs 75.1% white), more highly educated, and wealthier compared with the US population as a whole.[36] Given our observation that black children had a nearly 10-fold greater incidence of rickets than the population as a whole, the incidence of rickets would be expected to be greater in populations with a greater proportion of black children than Olmsted County.

Conclusion

We provide population-based evidence that the incidence of rickets has dramatically increased after 2000. Because all cases of nutritional rickets in this study were identified in children younger than 3 years, strategies for rickets prevention should focus on infants and toddlers. These strategies include vitamin D supplementation of breastfed infants and ensuring adequate maternal vitamin D status during pregnancy, particularly in African-American children and in children who have recently entered the US from abroad. Optimizing vitamin D status in all children may be indicated if nonskeletal benefits of vitamin D are established. Nutritional rickets should be suspected in children with evidence of poor growth, particularly if the children are breastfed or are black.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
HICDA	Hospital International Classification of Diseases Adapted
ICD	International Classification of Diseases
REP	Rochester Epidemiology Project
UV	ultraviolet

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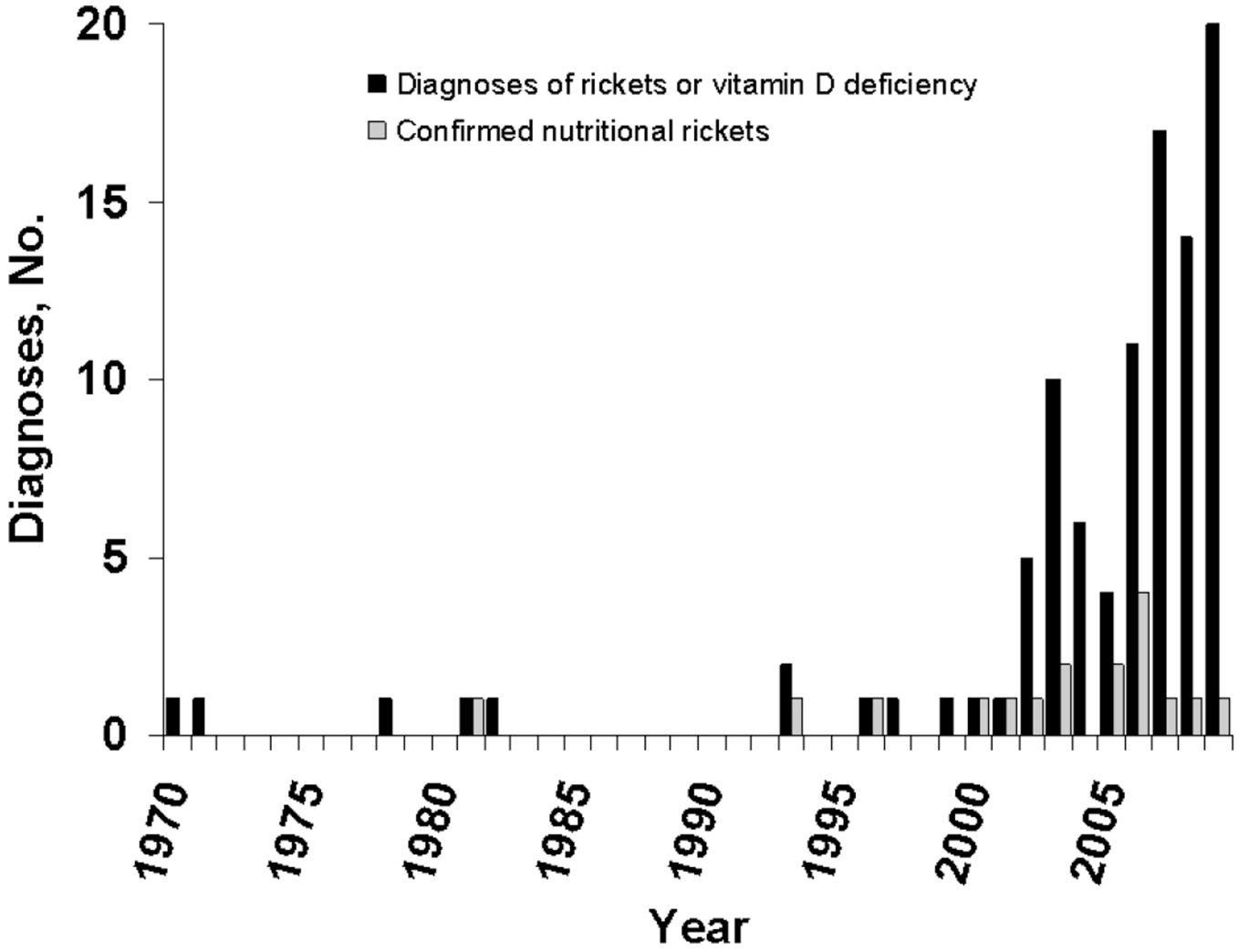

Figure 1.
Diagnoses of Vitamin D Deficiency or Rickets and Confirmed Cases of Nutritional Rickets. Diagnoses are based on medical record coding. Confirmed cases are based on radiographic confirmation and exclusion of non-nutritional causes of rickets.

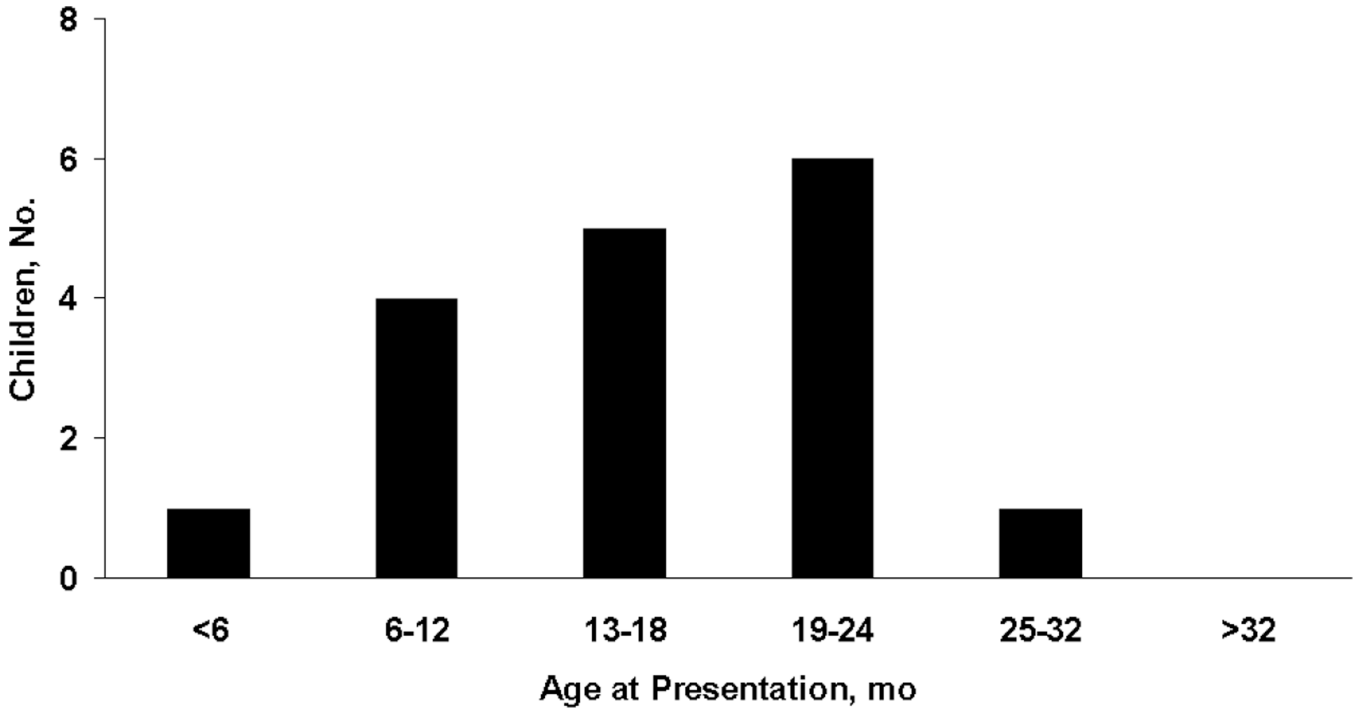

Figure 2.
Age at Presentation with Nutritional Rickets.

Table

Characteristics of Children With Nutritional Rickets and Age- and Sex-Matched Controls[a]

Characteristic	Children with Nutritional Rickets (n=17)	Control Children (n=34)
Age, mo, median (range)	13.3 (5.1–26.6)	14.3 (5.1–26.9)
Male sex, No. (%)	9 (53)	18 (53)
Race, No. (%)		
Black[b]	10 (59)	2 (6)
White[b]	4 (24)	25 (74)
Multiracial	2 (12)	1 (3)
Asian	1 (6)	3 (9)
Unknown	0 (0)	3 (9)
Presentation, No. (%)		
Poor growth	12 (71)	...
Leg deformity	8 (47)	...
Motor delay	5 (29)	...
Leg pain	3 (18)	...
Weakness	3 (18)	...
Hypocalcemia or tetany	2 (12)	...
Height-for-age centile, median (range)[b]	2.7 (<0.01–73.1)	56.9 (0.01–97.6)
<3rd percentile, No. (%)[b]	9/15 (60)	1 (3)
Weight-for-height centile, median (range)[b]	47.6 (8.0–99.6)	0 (0)
<3rd percentile, No. (%)	67.4 (3.4–99.6)	0 (0)
Gestational age at birth, wk, median (range)	38.7 (34.0–42.0)	40.0 (36.3–41.9)
Birth weight, kg, median (range)[b]	3.1 (1.5–4.6)	3.7 (2.7–4.8)
Breastfed, No. (%)[b]	16/16 (100)	22 (65)
Breastfeeding duration, mo, median (range)[b]	12 (1–23)	6 (2–17)
Vitamin D supplementation, No. (%)	0 (0)	1 (2.9)
Month of presentation, No. (%)		
January–March	2 (12)	...
April–June	8 (47)	...
July–September	3 (18)	...
October–December	4 (24)	...
Calcium, mg/dL, median (range)[c]	9.9 (6.8–11.2)	...
<9.6 mgl/dL, No. (%)	5/16 (31)	...
Phosphorus, mg/dL, median (range)[c]	4.7 (1.7–6.5)	...
<4.3 mg/dL, No. (%)	7/16 (44)	...
Alkaline phosphatase, U/L,	602 (305–3586)	...

Characteristic	Children with Nutritional Rickets (n=17)	Control Children (n=34)
median (range)		
>350 U/L, No. (%)	10/14 (71)	...
25-hydroxyvitamin D, ng/mL, median (range)[c]	13 (4–55)	...
<10 ng/mL, No. (%)	4/13 (31)	...
Parathyroid hormone, pg/mL, median (range)[c]	36 (17–353)	...
>65 pg/mL, No. (%)	4/10 (40)	...

[a] Percentages exclude missing data. Percentages may not total 100% because of rounding.

[b] $P<.05$ for comparison with control children.

[c] Conversion factors to International System of Units are as follows: calcium, multiply mg/dL by 0.25 to determine mmol/L; phosphorus, multiply mg/dL by 0.323 to determine mmol/L; 25-hydroxyvitamin D, multiply ng/mL by 2.496 to determine nmol/L; parathyroid hormone, multiply pg/mL by 0.106 to determine pmol/L.