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Original Contribution

Vitamin D and Fracture Risk in Early Childhood: A Case-Control Study

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The objective of this study was to evaluate the association of vitamin D intake and serum levels with fracture risk in children under 6 years of age. A case-control study was conducted in Toronto, Ontario, Canada. Cases were recruited from the fracture clinic at the Hospital for Sick Children, and matched controls were obtained from the TARGet Kids! primary-care research network. Controls were matched to cases on age, sex, height, and season. Fracture risk was estimated from conditional logistic regression, with adjustment for skin type, fracture history, waist circumference, outdoor free play, neighborhood income, soda consumption, and child's birth weight. A total of 206 cases were recruited during May 2009–April 2013 and matched to 343 controls. Serum 25-hydroxyvitamin D concentration (per 10-nmol/L increment: adjusted odds ratio (aOR) = 0.95, 95% confidence interval (CI): 0.88, 1.03) and intake of cow's milk (<2 cups/day vs. 2 cups/day: aOR = 0.95 (95% CI: 0.60, 1.52); >2 cups/day vs. 2 cups/day: aOR = 1.39 (95% CI: 0.85, 2.23)) were not significantly associated with reduced odds of fracture. A statistically significant association was observed between child use of vitamin D supplements and decreased odds of fracture (yes vs. no: aOR = 0.42, 95% CI: 0.25, 0.69). Vitamin D supplementation, but not serum 25-hydroxyvitamin D level or milk intake, was associated with reduced fracture risk among these healthy young children.

bone fractures; child injury; dietary supplements; 25-hydroxyvitamin D; milk; vitamin D

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

Approximately one-third of children have a bone fracture before the age of 17 years (1). Among girls, the risk of fracture ranges from 27% to 40%, and among boys it ranges from 42% to 64% (2). Known risk factors for childhood fracture include being overweight, lack of exposure to sunlight, milk avoidance, lack of physical activity, use of medications that lead to bone thinning, lower bone mass, and previous history of fracture (3–9). Fractures in healthy children often occur due to injury or trauma, from falls or collisions, or during play or sport (2, 10).

Vitamin D is involved in the regulation of calcium absorption and is important for bone health (11). It has long been known that severe vitamin D deficiency leads to rickets, bone deformities, and poor bone mineralization (9, 11, 12). Low vitamin D levels may also be associated with reduced bone mineralization and low bone density in children and adolescents (13). Yet it is unclear whether lower levels of vitamin D in early childhood are associated with increased risk of fracture (2). Twenty-five-hydroxyvitamin D (25(OH)D) is the preferred biomarker of serum vitamin D level, reflecting both cutaneous production following sunlight exposure and dietary sources of vitamin D (11). The US Recommended Dietary Allowance for vitamin D is 600 IU/day for all children over 1 year of age (14). Vitamin D supplementation and intake of cow's milk are the 2 main modifiable determinants of 25(OH)D concentration in Canadian children (15). Few previous studies have evaluated the association between vitamin D, or its main determinants, and fracture risk in children (2).

Our primary objective in the current study was to evaluate the association between serum 25(OH)D concentration and fracture risk among children younger than 6 years of age.

Our secondary objectives were to evaluate the associations between children's intake of both vitamin D-fortified cow's milk and supplements containing vitamin D and fracture risk.

METHODS

Study design and participants

A case-control study was conducted among children younger than 6 years of age in Toronto, Ontario, Canada. Ethical approval for the study was obtained from the Research Ethics Board at the Hospital for Sick Children and St. Michael's Hospital, and consent was obtained from the parents of all participating children.

Cases

Cases were recruited from the pediatric fracture clinic at the Hospital for Sick Children in Toronto from May 2009 to April 2013. Children were eligible if they were less than 6 years of age with a bone fracture in a lower extremity (femur, tibia, fibula, talus, and metatarsal) or upper extremity (humerus, olecranon, condyle, radius, ulna, clavicle, elbow, forearm, and radius). Fractures were confirmed radiographically.

Controls

Controls were obtained from the TARGet Kids! primary health-care practice-based research network (16). Children under 6 years of age were recruited at their scheduled well-child visit at one of 8 pediatric or family practice primary-care clinics in Toronto (16). Controls were recruited between the years 2008–2012, and a subset were selected for this study by matching them 2:1 to cases on season of blood draw, age, sex, and height. For cases for whom 2 controls could not be matched, 1 matched control was used (see Figure 1).

Exclusion criteria

Children (both cases and controls) were excluded if they had severe chronic health conditions (with the exception of asthma and high-functioning autism), severe developmental delays, or conditions affecting growth, such as cystic fibrosis. Cases and controls were also excluded if they had conditions known to affect bone health, such as osteogenesis imperfecta or Marfan's syndrome, or if they were using medications such as barbiturates and corticosteroids, which may affect 25(OH)D concentrations or bone health.

Exposure variables

The primary exposure, total serum 25(OH)D concentration, was measured from blood samples collected at the fracture clinic for the cases (within a week of injury) and during well-child primary health-care visits for controls. Serum samples for both cases and controls were batch-analyzed for total 25(OH)D using liquid chromatography–tandem mass spectrometry at the Hospital for Sick Children. Samples were analyzed using the 4000 Q TRAP LC/MS/MS system (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, Massachusetts), which was regularly calibrated to the Vitamin D External Assessment Scheme (17). Interassay imprecision was less than 7.5% at 25(OH)D concentrations of 28 nmol/L, 79 nmol/L, and 171 nmol/L, and intraassay imprecision was 3.2%. We evaluated serum 25(OH)D as both a continuous variable and a dichotomous variable using 50 nmol/L as the cutpoint, as recommended by the US Institute of Medicine (14).

The secondary exposures, cow's milk intake and vitamin D supplementation, were measured from the same parent-completed questionnaire for both cases and controls based on the Canadian Community Health Survey (18). Information on intake of cow's milk was obtained by asking parents, "How many cups of each drink does your child have currently in a typical day? (1 cup = 8 ounces = 250 mL)." Response options included 7 checkboxes ranging from zero to 5+. Cow's milk categories were further collapsed based on the recommended daily intake of milk (2 cups/day) into 3 categories: <2 cups/day, 2 cups/day (reference category), and >2 cups/day (19). Children's use of vitamins containing vitamin D was derived from parental responses to the question, "Does your child take any vitamins or supplements regularly?," with a list of vitamins and supplements which included both "vitamin D-containing multivitamin" and "vitamin D supplement."

Other variables

Potential confounders and other covariates were identified a priori through a literature review. Cases and controls were matched on: season of blood draw (winter was defined as October–April and summer was defined as May–September), age (±3 months), sex, and height (±5 cm). Height was measured by trained research assistants using a calibrated stadiometer. We were unable to obtain data on child weight in most fracture cases, as the children were wearing a cast; thus, waist circumference was used as a proxy for adiposity. Waist circumference was age- and sex-standardized to obtain z scores using data on 5,000 children in the full TARGet Kids! cohort, and the mean values and standard deviations were similar to those from the US National Health and Nutrition Examination Survey for children ≥2 years of age (20).

Skin type for the cases and controls was determined by trained research assistants on the basis of the Fitzpatrick scale (21). Neighborhood median after-tax household income was determined using the Statistics Canada Postal Code Conversion Files and information from the 2006 Canadian census (22). Outdoor free play time, child's history of fracture, carbonated soda consumption, and child's birth weight were measured by parental report.

Sample size

Based on preliminary data, the sample size was calculated a priori for the primary outcome, assuming a mean 25(OH)D concentration of 50 nmol/L with a standard deviation of 19.65 nmol/L, using a simple 2-tailed t test with a type I error probability of 0.05. A sample size of 250 cases and a

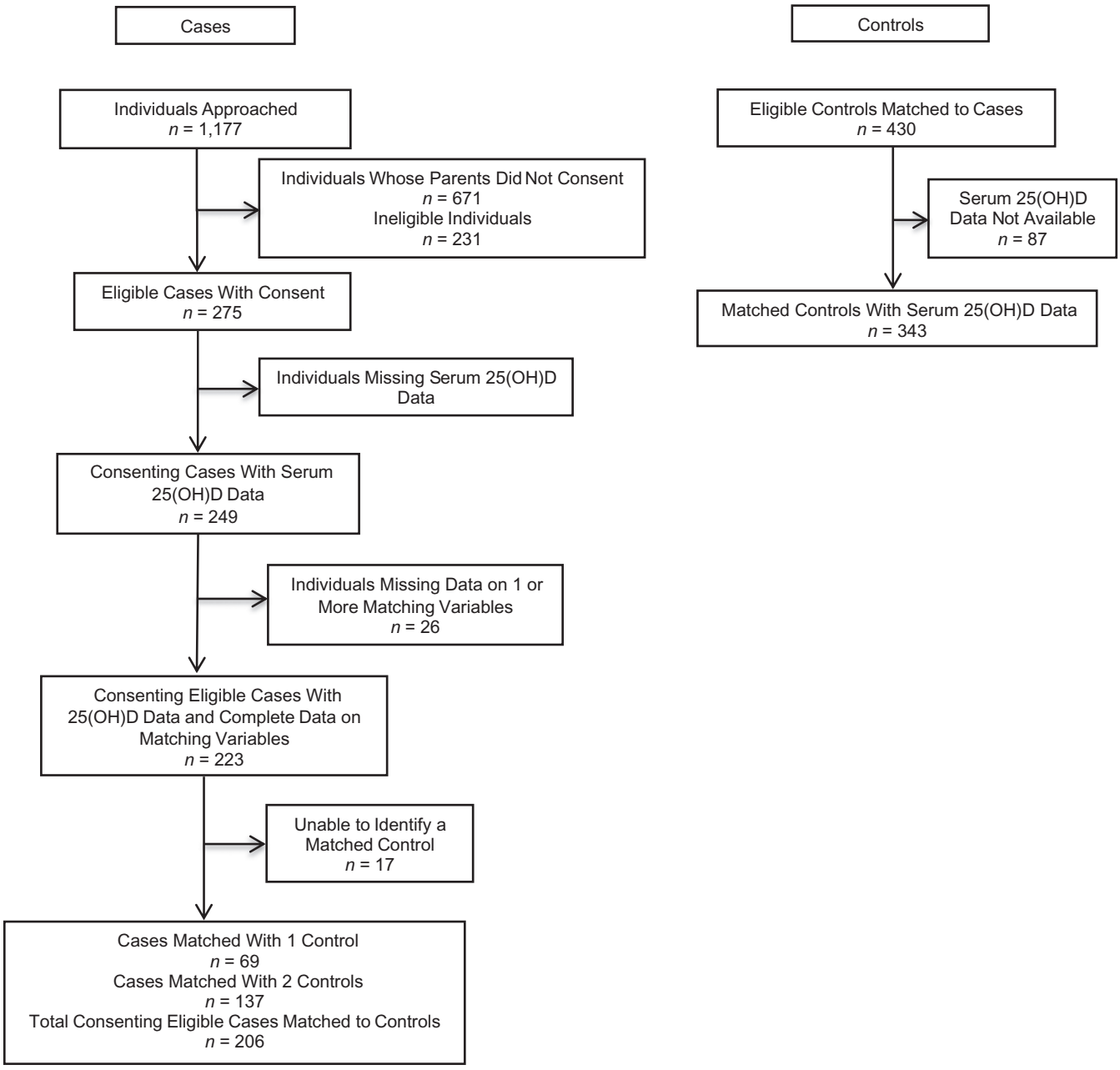

Figure 1. Identification of cases and controls for a study of vitamin D intake and serum levels and early-childhood fracture risk, Toronto, Ontario, Canada, 2009–2013.

minimum of 250 controls would have 80% power to detect a small difference of only 5 nmol/L between cases and controls. Only 125 cases and 125 controls would be required to detect a larger difference in 25(OH)D of 7 nmol/L.

Statistical analysis

Data were analyzed using R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). Descriptive statistics were calculated separately for cases and controls, and differences were evaluated using χ^2 tests for categorical variables and *t* tests for continuous variables. Statistical significance was defined as $P < 0.05$, and all tests were 2-sided. Odds ratios and 95% confidence intervals were obtained from conditional logistic regression, to account for the matching variables, using the "survival" package in R (23). Both unadjusted and fully adjusted multivariable models were created separately for each of the primary

and secondary exposures: 1) continuous 25(OH)D; 2) categorical 25(OH)D (<50 nmol/L vs. ≥50 nmol/L); 3) cow's milk intake; 4) vitamin D supplement use; and 5) multivitamin supplement use. All multivariable models included all potential confounders identified a priori: skin type, standardized waist circumference, history of fracture, outdoor free play time, income based on postal code, birth weight, and soda intake. Missing data were imputed using the multivariate imputation by chained equations (MICE) procedure in R, specifying 15 maximum iterations and 20 multiple imputations (24). The amount of missing data was less than 15% for each variable.

RESULTS

Of the 249 eligible cases whose parents gave consent for them to participate, 206 had 25(OH)D measured and were successfully matched to controls. Of the 430 control children who were eligible for matching, 343 had 25(OH)D data available and were successfully matched to cases (Figure 1). Descriptive statistics for the cases and controls are shown in Table 1. The average age of cases and matched controls was 43 months, and 44% were female. Fracture cases were more likely to have darker skin pigmentation than controls ($P = 0.01$) and more likely to have a history of fracture ($P = 0.01$).

The mean serum 25(OH)D concentration in the cases was 88.5 (standard deviation, 22.4) nmol/L, while the mean concentration in controls was 91.6 (standard deviation, 31.1) nmol/L (Table 2). Among the fracture cases, 16% of parents reported that their child regularly took a vitamin D supplement, as opposed to 31% among the controls.

No statistically significant association was observed between serum 25(OH)D level and fracture risk, and the odds ratio was close to the null (per 10-nmol/L increment in 25(OH)D concentration, adjusted odds ratio (aOR) = 0.95, 95% confidence interval (CI): 0.88, 1.03) (Table 2). The association between low serum 25(OH)D level and fracture risk was also not statistically significant, although the odds ratio was in the expected direction and the 95% confidence interval was very wide (<50 nmol/L vs. ≥50 nmol/L: aOR = 1.36, 95% CI: 0.55, 3.38). Similarly, no statistically significant association was found between cow's milk intake and fracture risk (<2 cups/day vs. 2 cups/day: aOR = 0.95 (95% CI: 0.60, 1.52)); >2 cups/day vs. 2 cups/day: aOR = 1.39 (95% CI: 0.85, 2.23)) (Table 2). However, child use of vitamin D supplements was significantly associated with decreased odds of fracture risk (yes vs. no: aOR = 0.42, 95% CI: 0.25, 0.69), whereas child multivitamin use was not significantly associated with fracture risk (yes vs. no: aOR = 0.76, 95% CI: 0.49, 1.18). The odds ratios were similar in conditional logistic regression models with no adjustment and those with full adjustment (Table 2). We also evaluated a model with minimal adjustment, adjusting only for variables that were independently associated with both vitamin D exposure and fracture outcome: skin type and soda intake. The results of the minimally adjusted model were not different from those of the fully adjusted model (data not shown).

We conducted a sensitivity analysis evaluating the removal of all children under 18 months of age ($n = 50$); this included only 4 children younger than 12 months of age, who ranged in age from 7 months to 11 months. The adjusted odds ratios for 25(OH)D, cow's milk intake, and child vitamin D supplement use were very similar to those from our primary analysis. Further, we explored a model that simultaneously adjusted for both cow's milk intake and vitamin D supplement use, and the adjusted odds ratios for these 2 exposures also did not change (data not shown).

DISCUSSION

Although vitamin D is known to be important for bone health, it has been unclear whether vitamin D is associated with fracture risk in early childhood. We found no statistically significant association between concurrent 25(OH)D concentration and fracture risk. Further, the main dietary source of vitamin D, milk intake, was also not statistically significantly associated with reduced risk of fractures. However, parent-reported children's vitamin D supplement use was associated with a significant reduction in the odds of fracture, and this association was not observed for multivitamin use. The American Academy of Pediatrics Committee on Nutrition recommends supplementation with 400 IU of vitamin D per day for children who drink less than 1 L of vitamin D-fortified milk per day (25).

Despite a large body of literature on the importance of vitamin D for bone health, very few studies have evaluated the association between 25(OH)D concentration and fracture risk (2). In 3 different case series, a high prevalence of 25(OH)D deficiency (<50 nmol/L), ranging from 8% to 59%, was reported among children with fractures; however, none of these studies included a comparison group of children without fractures (9, 26, 27). In one cross-sectional study, Ceroni et al. (28) compared 25(OH)D concentrations among Swiss adolescents (aged 10–16 years) with upper limb fracture, those with lower limb fracture, and healthy controls, and they did not find a statistically significant difference in 25(OH)D across the 3 outcome groups. The only previous case-control study of vitamin D and fracture risk was conducted in African-American children aged 5–9 years (76 cases and 74 controls); in that study, Ryan et al. (29) reported that low serum 25(OH)D concentration was associated with higher fracture risk (aOR = 3.46, 95% CI: 1.09, 10.94). Our null finding is not consistent with this previous study; however, the prevalence of vitamin D deficiency (<50 nmol/L) in that study was high (41% for controls and 47% for cases) (29) relative to our study, where only 5% of cases and 4% of controls had 25(OH)D concentrations less than 50 nmol/L.

Our study also found no statistically significant association between intake of vitamin D-fortified cow's milk and reduced fracture risk. This finding is consistent with several other studies carried out in older children (30, 31), although 2 studies that focused on milk-avoidant children (7) and children with milk allergies (32) found that a complete lack of milk intake was associated with increased fracture risk. Adult studies have had inconsistent findings, with some studies identifying a negative association between cow's milk intake and fracture risk (33) and others finding a positive association with adult (34) or adolescent (35) milk consumption, while a meta-analysis found no overall association (36).

Table 1. Baseline Characteristics of Fracture Cases and Controls in a Study of Vitamin D Intake and Serum Levels and Early-Childhood Fracture Risk, Toronto, Ontario, Canada, 2009–2013

	Cases ($n = 206$)			Controls ($n = 343$)			*P* Value[a]
	Mean (SD)	No. of Children[b]	%	Mean (SD)	No. of Children	%	
Age, months	43.03 (18.79)			42.84 (18.86)			0.91[c]
Neighborhood median after-tax household income, Can$/year	63,133 (29,890)			57,013 (20,693)			0.01
Height, cm	99.90 (13.60)			99.35 (13.19)			0.64[c]
Outdoor free play, minutes/day	69.93 (57.83)			60.73 (61.59)			0.09
Waist circumference *z* score[d]	0.01 (1.47)			0.06 (0.95)			0.64
Child's birth weight, kg	3.39 (0.57)			3.27 (0.67)			0.04
Sex							
Male		116	56		191	56	0.89[c]
Female		90	44		152	44	
Age, months							
<18		20	10		30	9	0.75[c]
18–35		63	31		93	27	
36–60		69	33		128	37	
>60		54	26		92	27	
Season[e]							
Winter		112	54		193	56	0.66[c]
Summer		94	46		150	44	
History of fracture							
No		186	92		321	97	0.01
Yes		17	8		11	3	
Fitzpatrick skin type[f]							
I or II (lightest)		81	39		185	54	0.01
III		56	27		84	24	
IV		35	17		38	11	
V or VI (darkest)		30	15		32	9	
Typical soda intake, cups/day							
0		181	88		292	85	0.04
≥1		19	9		14	4	
Location of fracture[g]							
Lower extremity		77	37		NA		
Upper extremity		129	63		NA		

Abbreviations: NA, not applicable; SD, standard deviation.
[a] The *t* test was used for continuous variables, and the χ^2 test was used for categorical variables.
[b] Values may not sum to totals because of missing data.
[c] Matched variable; no significant difference expected.
[d] Age- and sex-standardized.
[e] Winter was defined as October–April and summer as May–September.
[f] Skin type was determined by trained research assistants on the basis of the Fitzpatrick scale (21).
[g] Lower-extremity fractures included fractures of the femur, tibia, fibula, talus, and metatarsal; upper-extremity fractures included fractures of the humerus, olecranon, condyle, radius, ulna, clavicle, elbow, forearm, and radius.

Consistent with our hypothesis, we found that use of vitamin D supplements was statistically significantly associated with a 58% reduction in the odds of fracture in early childhood. Our results may be supported by those of a previous study showing that vitamin D supplementation in children leads to increased bone mineral density (37). It is somewhat counterintuitive that vitamin D supplementation but not 25(OH)D concentration was associated with reduced fracture

Table 2. Conditional Logistic Regression Analysis of the Association Between Vitamin D Intake and Serum Levels and Early-Childhood Fracture Risk, Toronto, Ontario, Canada, 2009–2013

	Cases ($n = 206$)		Controls ($n = 343$)		OR	95% CI	Adjusted OR[a]	95% CI
	No.[b]	%	No.	%				
Serum 25(OH)D concentration, nmol/L[c]	88.5 (22.4)		91.6 (31.1)					
Serum 25(OH)D concentration, per 10-nmol/L increase					0.96	0.90, 1.03	0.95	0.88, 1.03
Intake of cow's milk, cups/day								
<2	66	32	126	37	0.97	0.64, 1.49	0.95	0.60, 1.52
2	63	31	118	34	1	Referent	1	Referent
>2	72	35	87	25	1.49	0.96, 2.33	1.39	0.85, 2.23
Serum 25(OH)D status, nmol/L								
≥50	195	95	329	96	1	Referent	1	Referent
<50	11	5	14	4	1.30	0.58, 2.95	1.36	0.55, 3.38
Child use of single vitamin D supplement								
No	170	84	229	69	1	Referent	1	Referent
Yes	32	16	105	31	0.42	0.26, 0.66	0.42	0.25, 0.69
Child use of multivitamins								
No	127	63	185	55	1	Referent	1	Referent
Yes	75	37	149	45	0.71	0.47, 1.06	0.76	0.49, 1.18

Abbreviations: CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

[a] Adjusted for fracture history, skin type, age- and sex-standardized waist circumference, outdoor free play time, parental income (based on postal code), birth weight, and soda intake.

[b] Values may not sum to totals because of missing data.

[c] Values are presented as mean (standard deviation).

risk; however, patterns of supplement use in children may be relatively stable, and supplementation may reflect 25(OH)D level in an earlier time window of bone mineralization, which may not be reflected by current 25(OH)D concentration. It is also possible that our finding of a significant protective association for vitamin D supplements was due to residual confounding. Although we adjusted for numerous potential confounders hypothesized a priori and the adjusted results did not differ substantially from the unadjusted results, use of vitamin D supplements may be associated with some unmeasured healthy lifestyle characteristics or protective parenting. If the association was due to residual confounding, a significant inverse association might also be expected for multivitamin use; however, this was not observed. The difference between vitamin D supplements and multivitamins may also be explained by differences in vitamin D dose or frequency of supplement intake, although this information was not available in our study. Further, it may be hypothesized that children who take vitamin D supplements have different patterns of milk consumption; in our study, the mean daily intake of cow's milk was 2.07 cups/day in non–supplement users and 1.83 cups/day in supplement users, and this difference was borderline statistically significant ($P = 0.05$).

To our knowledge, our study was the first to evaluate the associations of vitamin D intake and serum levels with fracture risk in a multiethnic population of young, healthy North American children. Strengths of our study included a relatively large sample of young children with fracture and the inclusion of a healthy control group matched to cases on important suspected confounders. Furthermore, fracture was confirmed by radiography. The matched case-control study design we used allowed us to overcome the feasibility issues involved in obtaining a sufficient number of cases in a prospective cohort study, as fractures in early childhood are relatively rare.

Our study had a number of limitations. Although the sample size was calculated a priori with the goal of 80% power, it is possible that a larger sample size may have revealed more statistically significant associations; however, for the primary exposure, mean 25(OH)D concentrations were similar in cases and controls and the odds ratio was close to 1.0, suggesting no association. Recall bias is possible if the parents of cases differentially reported cow's milk intake or vitamin D supplementation relative to the parents of controls. Further, we did not have detailed information on the duration and frequency of supplement use or the dose of vitamin D. Data on bone mineral density and cause of fracture were also not available. The possibility of selection bias is also a limitation. Controls were recruited through routine primary health-care clinics in the same jurisdiction as the fracture clinic, and they may have been healthier than cases, who may or may not have had the same degree of primary health care. However, controls appeared to have a lower family income than cases, which argues against this possibility. Lastly, 25(OH)D levels in this study population may have been sufficiently high to minimize fracture risk from vitamin D, and our

results may not be generalizable to other populations with lower 25(OH)D levels.

Our findings suggest that serum 25(OH)D level at the time of fracture may not be associated with fracture risk among young children in a population with relatively high 25(OH)D concentrations. However, use of vitamin D supplements was significantly associated with reduced fracture risk; this may have reflected differential 25(OH)D levels at a past time point in bone development or protection against seasonal fluctuation. Future longitudinal studies are needed to elucidate the role of vitamin D in early-childhood fracture risk.

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