Nutrient and food intakes in early life and risk of childhood fractures: a systematic review and meta-analysis

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Introduction

Fractures during childhood are common among healthy children. Approximately 30–50% of all children experience fractures, and interestingly, those who do often experience recurrent fractures. The pattern in fracture epidemiology indicates that the forearm, hand, and foot are the most common sites of fractures in children; and the incidence of these particular fracture sites seems to be higher among children from the United States, Europe, and Asia, although a few studies from northern Europe have suggested a leveling off or even a decrease in incidence. Nevertheless, the overall incidence of pediatric fractures is high, and pronounced among boys, and occurs especially during the growth spurt, which subsides at ages 12–15 years. Moreover, in addition to country and region, the incidence of pediatric fractures varies with ethnicity and season.

Fracture risk in healthy children can be influenced by both genetic and environmental factors. Thus, several studies have shown that impaired bone health is as well as sociodemographic factors [e.g., parental age, marital status] are related to the risk of pediatric fractures. Childhood growth spurts could be considered a particularly sensitive or vulnerable period in relation to fracture events, and suboptimal nutritional practice during these periods may be correlated to bone health in childhood. From a life-course perspective, poor dietary patterns that track into adulthood may constitute a risk factor for fractures later in life.

This systematic review presents and discusses results from previous observational literature on the influence of childhood food and nutrient intake on pediatric fracture risk. The objective was to identify potential beneficial or detrimental dietary exposures during early life by summarizing and exploring the strengths and limitations of the current evidence base. The outcome was fractures in healthy boys and girls that occurred at approximately 30–50% of all children experience fractures, and...
ages 2–13 y. We anticipate that this systematic review will contribute to a better understanding of the potential dietary determinants of fractures, to help authorities and health care workers in recommending potential lifestyle interventions or beneficial strategies to reduce the risk of (recurrent) pediatric fractures and, by extension, perhaps fractures in adulthood.

METHODS

Search strategy

This systematic review was based on a literature search for original studies with the use of the databases Medline (www.pubmed.com), Web of Science (www.webofknowledge.com), and Scopus (www.scopus.com, including EMBASE) up until June 2015. The search was conducted by one reviewer (MNH). The following keywords were applied as MeSH terms and as a free search: “risk factors”/epidemiology, fractures, bone, pediatric, child*, “all child*”. Separately, the following keywords were added to the search model: diet*, nutri*, food, calorie, energy, macronutrient, micronutrient, vitamin, mineral, beverage, milk, caffeine, breastfeeding, calcium, 25-hydroxyvitamin D [25(OH)D], fruit, vegetables, salt, sodium. The electronic search was supplemented with hand searching reference lists of retrieved articles. The selection of articles was made by one researcher (MNH).

Study selection

We included all experimental and epidemiologic analytic observational studies (intervention studies, retrospective/prospective cohort studies, and case-control studies) that examined associations or influences of any nutritional exposure on pediatric fractures. We excluded cross-sectional studies with no control group, chart reviews, case series, and commentaries (e.g., expert opinion, consensus statements) and studies in all age groups for which we could not separate data on children from those on adolescents. The primary outcome we sought in this medical registration was upper and lower limb fractures, including recurrent fractures, in healthy boys and girls of all ethnic groups aged between 2 and 13 y. The inclusion criteria in terms of exposure data for considering studies eligible for the systematic review were perinatal or childhood diet and nutrient intake (e.g., energy, macronutrients, micronutrients, food or beverages, breastfeeding) thought to potentially increase or decrease the risk of fractures during childhood.

Because of potential growth retardation and/or disturbances in puberty development related to bone mineralization, we excluded studies that specifically addressed patient groups of children with chronic diseases (e.g., asthma, cancer survivors, hospitalized children, rheumatic disorders, eating disorders), children who had a prolonged use of medication/drugs (e.g., antidepressants, corticosteroids), and children who were born preterm. Studies of fractures due to psychiatric risk factors (mental illness), non-accidental injuries (abused children, including injuries caused by parental alcohol abuse), or dental injuries were likewise excluded. The review protocol was prepared on the basis of the Evidence Analysis Manual published by the Academy of Nutrition and Dietetics (14). A flowchart of the included studies is presented in Figure 1.

Quality assessment

The quality of the included studies was assessed by one researcher (MNH) on the basis of 5 quality categories according to criteria assessment. The first category evaluated whether the selection of study participants was free from bias. There were 4 sub questions under the first category related to the specification of inclusion and exclusion criteria, whether or not the criteria were applied equally in all study groups, whether the characteristics of the subjects were fully described, and finally, whether the study group was a representative sample of the relevant population. The second category evaluated the measurement of exposure/outcome variables. Subvalidity questions to aid the evaluation were related to how well the exposure and outcome variables were described; whether the measurements were based on standard, valid, and reliable data collection procedures; and whether the measurements were conducted consistently across groups. The third category evaluated design-specific sources of bias. The studies were evaluated on the basis of whether adequate adjustments had been made for confounding factors that might have affected the outcomes, such as energy intake or other dietary covariates, physical activity level, body composition, socioeconomic indicators, age, sex, and pubertal

Abbreviations used: BMR, basal metabolic rate; FFQ, food-frequency questionnaire; LRNI, lower reference nutrient intake; RDA, Recommended Daily Allowance; 25(OH)D, 25-hydroxyvitamin D.
stage. The fifth category evaluated whether the statistical methods were appropriate for the study design and type of outcome indicators. The subvalidity questions were related to whether the statistical analyses were adequately described, used, and reported and, in case of negative findings, whether type 2 errors and random errors were suitably addressed (15, 16). The criteria were used as a checklist (14). Moreover, we evaluated the quality of the dietary exposure information from the included studies by calculating the ratio between energy intake and the basal metabolic rate (BMR) for all studies that reported on energy intake. BMR was not reported in any of the included studies, and weight was not reported in all of the studies; therefore, age- and sex-specific mean BMR (MJ/d) values from Black (17) were used. The ratio of energy intake to BMR was evaluated against the adapted Goldberg cutoffs for girls (1.5) and for boys (1.55) in the age group 6–10 y (equivalent to a physical activity level of being chair- or bed-bound), which can be used to estimate the mean population bias in reported energy intake (18).

On the basis of the 5 quality categories, the results of the quality evaluation were graded as follows: 1) positive (marked with “+”), indicating that the study addressed issues of random and systematic errors adequately in relation to selection bias and information bias and control for confounding and random error had been addressed (i.e., more than half of the validity questions were addressed adequately, indicating low risk of bias); 2) negative (marked with “−”), indicating that these issues were not adequately addressed (i.e., more than half of the validity questions were addressed inadequately, indicating high risk of bias); and 3) medium (marked with “Ø”), indicating that the study was neither exceptionally strong nor exceptionally weak (i.e., half of the validity questions were addressed adequately, indicating that risk of bias may have occurred).

Finally, the strength of the evidence was graded on the basis of the quality, consistency, quantity, clinical impact, and generalizability within each nutritional topic of interest. The grades given on a 5-point scale were as follows: 1) “good/strong,” 2) “fair,” 3) “limited/weak,” 4) “expert opinion only,” and 5) “grade not assignable” (14).

Statistical methods

Post hoc meta-analyses were performed for case-control studies that examined differences in mean calcium intakes in the case compared with the control group. Random-effects analysis was performed on the basis of the effect estimates derived as the differences in mean calcium intakes between cases and controls. The corresponding SEs were derived on the basis of the standard formula related to differences in means through the use of number of subjects (n) and SDs. When missing the SD of the corresponding available mean, the 10th and 90th percentiles were used to derive the SE.

We used a funnel plot to address the potential risk of publication bias. The analysis was performed by using Stata version 12.1 (StataCorp). A P value of <0.05 was considered to be significant.

RESULTS

Description of studies

Eighteen studies met the criteria for final inclusion in the systematic review, the majority being case-control studies that examined various modifiable childhood dietary exposures among childhood fractures and control children. Only studies from developed countries met the inclusion criteria: 7 studies in New Zealand and Australia (11, 19–24), 7 studies in Europe (12, 13, 25–29), and 4 studies in the United States (30–33).

Selection of study participants

Most of the studies were conducted in white children, with the exception of 2 studies, in which the study populations were of mixed ethnic origin (white, black, Hispanic, and/or Asian) (32, 33). One study exclusively reported on African-American children (31). With regard to sex, one study exclusively reported on girls (19), and 2 studies exclusively reported on boys (11, 27); otherwise, the sex distribution was approximately even between boys and girls (20–22, 25, 26, 29–32) or boys were predominantly represented (>60%) (12, 13, 23, 24, 28, 33). Mean BMI was not reported in all of the studies; however, in the age group of 2–7 y BMI (in kg/m²) generally ranged between 15.3 and 18.1 and in the age group of 8–12 y BMI ranged between 17.5 and 20.6. When considering mean age and by comparing the mean BMI in each study to the cutoffs for BMI proposed by Cole et al. (34), the majority of the children were categorized as being of normal weight, with the exception of Goulding et al. (20) and Valerio et al. (28). In the 2004 study by Goulding et al. (20), the children in the fracture group, but not those in the reference population, were categorized as overweight: the fracture cases had a mean BMI for age 6.7 y of 18.1 (the Cole cutoffs for BMI for age 6.5 y are 17.71 in boys and 17.53 in girls). In one study, both the fracture cases and the nonfracture control group were categorized as overweight; the BMI among cases at a mean age of 8.7 y was 20.5 and BMI among controls at a mean age of 8.3 y was 19.4 (the Cole cutoffs for BMI for age 8.5 y are 18.76 in boys and 18.69 in girls) (28). There were 6 studies that specifically focused on forearm fractures as the outcome (11, 19, 21, 27, 29, 31); the rest considered any fracture in the upper or lower limbs.

Studies on perinatal and childhood dietary and nutritional factors

The dietary exposures considered during childhood were dairy and beverage consumption, calcium intake, vitamin D intake or 25-hydroxyvitamin D [25(OH)D] status, total energy, protein and fat intakes, and breastfeeding. An overview of the results of the included studies is given in Table 1.

Studies related to dairy products and beverage consumption in childhood

There were 6 case-control studies (13, 20, 24, 26, 27, 31) that examined associations between dairy intake and fractures or recurrent fractures (Table 2). On the basis of frequency of fractures in overweight children, avoiding milk seemed to be associated with a higher fracture rate compared with a normal-weight reference population from the community (16 observed compared with 6 expected: χ² = 31.0, P = 0.001, df = 5) in a study judged to be of medium quality (20). Three studies, all judged to be of high quality, found no differences between the fracture case or nonfracture control group in relation to milk intake (24, 31) or dairy intake (13). One small case-control study...
in 7- to 13-y-old boys found lower milk intakes in fracture cases than in the nonfracture control group (1.5 ± 1.2 compared with 2.7 ± 1.2 glasses/d; P = 0.001) (27), but the analysis did not control for body weight or size and the study was judged to be of medium quality. Among recurrent fracture cases, in a study judged to be of medium quality, milk intake was lower compared with controls (0.33 ± 0.3 compared with 0.49 ± 0.3 L/d; P < 0.01) and compared with fracture cases who experienced 1 fracture only (compared with 0.5 ± 0.4 L/d; P < 0.02) (26).

Three studies examined the association between beverage intake, in particular carbonated beverage intake, and fractures among the 9- to 13-y-olds (Table 3). One case-control study, judged to be of high quality, found that excessive beverage consumption of any type (carbonated non-cola, carbonated cola, and noncarbonated drinks) was associated with a higher OR of fractures, but the analysis did not control for body weight or size (13). Another case-control study, judged to be of medium quality, found that carbonated drink intake was higher among fracture and recurrent fracture case groups than among controls (0.25 ± 0.44 compared with 0.13 ± 0.17 L/d; P < 0.02) (26). The third study, judged to be of high quality, found no association between total carbonated beverage or cola intakes and fractures, with the exception of fractures of the wrist and forearm, in which there was a direct association with cola consumption (OR: 1.39; 95% CI: 1.01, 1.91). When stratified by sex, except for hand fractures, no other associations were seen between intake of any types of sweet drinks and fractures (24).

Studies related to calcium intake and status in childhood

In total, 12 studies examined overall calcium intake (Tables 4–6); 9 were case-control studies, 5 of which were judged to be of medium quality (11, 20, 29, 30, 33) and the remaining 4 were judged to be of high quality (12, 19, 28, 31). In the remaining studies, one of the studies had a case-cohort design and judged to be medium quality (25, 32). On the basis of food-frequency questionnaires (FFQs) or 3-d food diaries taken at mean ages between 6 and 11 y, the majority of the case-control studies found no significant differences in mean dietary calcium intake when comparing children who had sustained a fracture with children who were fracture free (11, 19, 21, 28–30, 33). A meta-analysis of the 9 case-control studies, which had appropriate data for the meta-analysis, confirmed that there were no significant differences between the case and control groups in mean calcium intake (pooled effect size: 0.5; 95% CI: −0.20, 0.95; P = 0.19) (25, 26). In the single case-cohort study identified, as well as in the 2 longitudinal studies, judged to be of high quality, calcium intake was not associated with fracture risk.
With regard to sex differences, Mäyrynpää et al. (12), in a study judged to be of high quality, found no significant difference in calcium intake between boys and girls at a mean age of 10.7 y (1010 compared with 950 mg/d; variability was not reported). When comparing the calcium intakes of boys and girls in the milk-drinking control groups (boys compared with girls: 1278 ± 618 compared with 1179 ± 332 mg/d) (11, 19) and in the work of Valerio et al. (28) in a study judged to be of high quality (boy compared with girl cases: 1120 ± 402 compared with 1178 ± 407 mg/d; boy compared with girl controls: 1175 ± 436 compared with 1069 ± 419 mg/d) as well as Sierra et al. (29) in a study judged to be of medium quality, boys

### Table 2

Case-control studies on the effect of dairy intake on upper and lower limb fracture in children 2–13 y of age

<table>
<thead>
<tr>
<th>First author, y (ref)</th>
<th>n</th>
<th>Age, y</th>
<th>Sex, % F</th>
<th>BMI, kg/m²</th>
<th>Main findings</th>
<th>Risk assessment</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goulding, 2004 (20)</td>
<td>60</td>
<td>FCs: 6.7 ± 2.1; NFCs: 5.8 ± 2.0</td>
<td>FCs: 18.1 ± 3.0; NFCs: 17.0 ± 2.4</td>
<td>FCs vs. CCs: 16 observed vs. 6 expected ($\chi^2 = 31.0, df = 5$)*** 1.36 (0.83, 2.23)$^5$</td>
<td>MA associated with increased risk</td>
<td>Ø</td>
<td></td>
</tr>
<tr>
<td>Ma, 2004 (24)</td>
<td>33</td>
<td>FCs: hand, 13.1 ± 2.1; NFCs: hand, 13.1 ± 2.1</td>
<td>FCs: wrist/forearm, 12.0 ± 2.0; NFCs: wrist/forearm, 12.1 ± 2.1</td>
<td>FCs: hand, 20.7 ± 3.1; NFCs: hand, 21.4 ± 4.5</td>
<td>FCs: wrist/forearm, 19.9 ± 3.4; NFCs: wrist/forearm, 19.7 ± 3.5 0.79 (0.59, 1.06)$^6$</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>FPI, 1 fracture: 50</td>
<td>26–58</td>
<td>FCs: 19.18 ± 0.34; NFCs: 17.71 ± 0.25</td>
<td>FCs, 1 fracture: 19.5 ± 0.34 L/d; NFCs: 18.4 ± 0.32 L/d</td>
<td>FCs, 1 fracture: 17.6 ± 0.32 L/d</td>
<td>Ø</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPI, recurrent: 50</td>
<td>11.7 ± 3.0</td>
<td>FCs, recurrent: 19.76 ± 0.31</td>
<td>FCs, recurrent: 19.76 ± 0.31</td>
<td>FCs, recurrent: 19.76 ± 0.31</td>
<td>Low milk intake associated with recurrent fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pires, 2005 (27)</td>
<td>0</td>
<td>Not reported</td>
<td>Not reported</td>
<td>FCs: 1.5 ± 1.2 glasses/d; NFCs: 2.7 ± 1.2 glasses/d$^{*}$</td>
<td>FCs: 1.5 ± 1.2 glasses/d; NFCs: 2.7 ± 1.2 glasses/d$^{*}$</td>
<td>Ø</td>
<td></td>
</tr>
<tr>
<td>Ryan, 2012 (31)</td>
<td>42/46</td>
<td>FCs: 6.9 ± 1.4; NFCs: 7.0 ± 1.5</td>
<td>FCs: 7.4 ± 6.8 servings of milk/wk; NFCs: 7.0 ± 6.2 servings of milk/wk$^{13}$</td>
<td>FCs: 7.4 ± 6.8 servings of milk/wk; NFCs: 7.0 ± 6.2 servings of milk/wk$^{13}$</td>
<td>No</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

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$^1$P < 0.05, **P < 0.01, ***P < 0.001. CC, control from the community; FC, fracture case; MA, milk avoidance; NFC, nonfracture control; ref, reference; Ø, medium; +, positive.

$^2$Values are ORs; 95% CIs in parentheses (derived by using logistic regression) unless otherwise indicated.

$^3$Mean ± SD (all such values).

$^4$Chi-square test.

$^5$–$^7$OR for dairy drinks/wk; $^5$hand fractures, $^6$wrist/forearm fractures, $^7$upper arm fractures.

$^8$OR for milk and yogurt $\geq$90 units/mo. The units were not specified in the study.

$^9$OR for cheese and other milk products $\geq$121 times/mo.

$^{10}$t and F tests.

$^{11}$FCs, recurrent, vs. FCs, 1 fracture (P < 0.02).

$^{12}$FCs, recurrent, vs. NFCs (P < 0.01).

$^{13}$Contingency table analysis.
Hence, to obtain an indication of nutritional inadequacy, we examined further those studies that reported a mean calcium intake below the age-specific LRNI values from the Department of Health, United Kingdom (4–6 y: 275 mg/d; 7–10 y: 325 mg/d; 11–14 y: 480 (boys) and 450 (girls) mg/d) (35). Only one of the included studies, judged to be of medium quality, was found that reported on fracture rates among milk-avoiding children aged ~6 y and with a mean calcium intake <300 mg/d. This study did not find a difference in fracture frequency between fracture cases and controls (20). On the basis of a visual inspection of the funnel plot of the studies on calcium intake, Supplemental Figure 1 resembles a symmetrical inverted funnel; nevertheless, 22% of the studies were placed outside the 95% CI in relation to 5% of the expected distribution of the studies in the case of absence of heterogeneity, suggesting publication bias.

Generally had higher calcium intakes than girls, except at ages 5 and 10 y.

Some studies evaluated calcium intakes in children with a mean age of 6–12 y against the Recommended Daily Allowance (RDA) as an indicator of low intake (age-specific cutoffs according to US, New Zealand, and Nordic references: 1000, 1300, and 900 mg/d, respectively). A single study examined the calcium intake of children below 60% of the RDA (30) (Table 6). Most of the studies, mainly judged to be of medium quality, that used the RDA as a cutoff showed that significantly more children with fractures had a calcium intake below the RDA compared with children without fractures (11, 12, 20, 21, 30). None of the included studies evaluated calcium intake against the lower reference nutrient intake (LRNI).
Studies related to vitamin D intake and 25(OH)D status in childhood

The 6 studies, 3 judged to be of medium and 3 judged to be of high quality, that focused on vitamin D measured during childhood generally did not find an association with fracture prevalence. None of the 6 studies found an association with fracture occurrence from either vitamin D intake measured at the mean ages of 6–12 y (25, 30, 33) (Table 7) or mean serum 25(OH)D measured at the mean ages of 6–11 y (12, 30, 31) (Table 8). However, one case-control study, judged to be of high quality, found an association between vitamin D deficiency in 5- to 9-y-old black children and forearm fractures, both when 25(OH)D concentrations were assessed as below or above 50 nmol/L (adjusted OR: 3.46; 95% CI: 1.09, 10.94) and when assessed as a continuous variable (adjusted OR: 0.9; 95% CI: 0.83, 0.98) (31). Mäyränpää et al. (12) found no significant difference in mean 25(OH)D concentrations between boys and girls measured at a mean age of 10.7 y in a study judged to be of high quality.

Studies related to total energy, protein, and fat intakes in childhood

The results from studies that examined fracture occurrence and energy intake measured during childhood as exposures were inconsistent; one small case-control study, judged to be of medium quality, and one case-cohort study, judged to be of high quality, found no differences in total daily energy intake between children with and without fractures (25, 30) (Table 9). Another case-control study, judged to be of high quality, showed that fracture cases had a higher overall calorie intake (2311.9 ± 1117.0 kcal/d) than did nonfracture control children (1742.0 ± 699.3 kcal/d) (P < 0.001) (31).

When evaluated against the Goldberg cutoffs for girls (1.50) and for boys (1.55) in the age group of 6–10 y, the calculated ratio of energy intake to BMR suggested underreporting of energy intake for 2 studies. First, in the study by Clark et al. (25), the calculated ratio of energy to BMR was 1.60 for girls and 1.35 for boys; and in the study by Chan et al. (30) the calculated ratio of energy to BMR among fracture cases was 1.49 for girls and 1.41 for boys. Among controls, the energy to BMR ratio for girls was 1.46 and for boys was 1.38. Second, from the results in the study by Ryan et al. (31), it appeared that nonfracture controls, but not fracture cases, underreported their energy intakes (fracture cases: girls, 2.0; boys, 1.7; controls: girls, 1.52; boys, 1.28). As shown in Table 9, a single case-control study, judged to be of medium quality, examined overall protein and fat intakes during childhood and found no significant differences in intake between children with fractures and nonfracture control children (30).

Studies related to breastfeeding

With regard to the influence of early-life dietary or nutritional factors, 3 studies with breastfeeding as an exposure (22, 23, 26) were included in the systematic review (Table 10). One of these studies, a cohort study, found no association between breastfeeding and the risk of fractures (RR: 1.04; 95% CI: 0.86, 1.23) (22), whereas a case-control study showed that children who were breastfed had a lower OR for fracture (OR: 0.44; 95% CI: 0.2, 0.97; P < 0.05) (23). The third study, also a case-control study, found a tendency only toward a higher frequency of

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**Table 4**

Longitudinal studies on the effect of mean calcium intake (mg/d) on upper and lower limb fracture in children 2–13 y of age$^1$

<table>
<thead>
<tr>
<th>First author, y (ref)</th>
<th>Participants</th>
<th>Main findings,$^2$ mg/d or HR (95% CI)</th>
<th>Risk assessment</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark, 2008 (25)</td>
<td>Total: 2692; FCs: 193</td>
<td>6.8 (diet assessment); 10–12 (fracture assessment)</td>
<td>53</td>
<td>17.5 ± 2.8$^3$</td>
</tr>
<tr>
<td>Wren, 2012 (32)</td>
<td>Total: 1470</td>
<td>White: 10.8 ± 3.1; nonwhite: 11.1 ± 3.0</td>
<td>50–51</td>
<td>Not reported</td>
</tr>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

$^1$FC, fracture case; ref, reference; +, positive.

$^2$Derived by using Cox regression unless otherwise indicated.

$^3$Mean ± SD (all such values).

$^4$Unclear reporting on statistical analysis: FCs compared with NFCs (P = 0.23).

$^5$Logistic regression, adjusted OR test for trend for fractures in quartiles of calcium intake.

$^6$Cox proportional hazard model for first fracture.

$^7$Cox proportional hazard model for entire cohort.

$^8$Cox proportional hazard model for no previous fracture.

$^9$Cox proportional hazard model for previous fracture history.
valerio, ryan, mayrampa, goulding, goulding, goulding, sierra, olney,
a negative quality score.
of medium quality. None of the studies were classified with
generalizability, data collection, and analysis. Ten studies were
that the study had addressed issues of inclusion/exclusion bias,
table 1
supplemental
positive, medium, or negative quality scores (supplemental
table 1), 8 were graded with a positive quality score, meaning
that the study had addressed issues of inclusion/exclusion bias,
generalizability, data collection, and analysis. Ten studies were
of medium quality. None of the studies were classified with
a negative quality score.

Fractures among children who were never breastfed ($\chi^2 = 5.91,
P = 0.052, df = 2$) (26).

Quality evaluation of all of the included studies

When evaluating the quality of the 18 identified studies by
positive, medium, or negative quality scores (supplemental
table 1), 8 were graded with a positive quality score, meaning
that the study had addressed issues of inclusion/exclusion bias,
generalizability, data collection, and analysis. Ten studies were
of medium quality. None of the studies were classified with
a negative quality score.

Six of the 8 studies with a positive quality score were case-
control studies (12, 13, 19, 24, 28, 31) and the remaining 2 were
longitudinal cohort studies (25, 32). Among the studies with
a medium quality score, 8 were case-control studies (11, 21, 23,
26, 27, 29, 30, 33), one was a case-cohort study (20), and one was
a longitudinal study (22). The studies with the medium quality
score lacked a detailed description in relation to evaluating the
risk of selection bias (11, 20, 22, 26, 33) and/or whether the
assigned groups were comparable (e.g., including baseline
descriptive information and potential confounding factors) (20, 21,
24, 27, 29, 30, 33). Potential key confounding factors considered
in the included studies were not consistent. Among biological
covariates most commonly used were age, sex, anthropometric measurements (11, 12, 19–26, 29, 31, 32), and, to some degree, pubertal stage (13, 21, 25, 26); only one study added birth weight to the model (25). Among sociologic covariates, educational level, family size, and ethnicity (25, 26, 31, 32) were taken into account; and finally, among behavioral covariates, diet, physical activity (13, 23–26, 31), medicine use, and breastfeeding (23) were adjusted for. A few studies did not report on any of the covariates being controlled for (27, 28, 30, 33).

The strength of evidence for the association between breastfeeding, dietary or nutritional risk factors, and fractures was evaluated as 1) “good/strong,” 2) “fair,” 3) “limited/weak,” 4) “expert opinion only,” or 5) “grade not assignable” (Supplemental Table 2). On the basis of the strength of the study design, the unexplained discrepancy in the results, a limited number of studies, the low number of subjects included, and some doubts about the significance and generalizability of the results, the strength of evidence for breastfeeding, energy intake, macronutrients, and vitamin D was graded as limited. In the studies with dairy, beverage, and calcium intakes as the exposure, the strength of evidence was graded as fair.

DISCUSSION

In this systematic review of 18 original peer-reviewed articles, we identified only a limited number of studies with significant results. These findings suggest that some nutritional factors, in particular milk avoidance, high cheese intake, high sugar-sweetened beverage intake, high energy intake, or no breastfeeding, may be associated with an increased risk of pediatric fractures. It cannot be excluded that these associations may be underestimated due to residual confounding. Although there were no significant differences in calcium intake between the prevalence of fractures in the case and control groups in the pooled meta-analysis results, the literature identified in the present review generally suggests that there may be a threshold effect for intakes of calcium below the RDA (20, 26, 27). The threshold effect premise is strengthened by the lack of studies with subjects having a mean calcium intake below the LRNI, suggesting that adverse events may already occur below the reference nutrient intake, ranging from 900 to 1300 mg/d depending on country, age, and sex (35). Perhaps there is even a U-shaped association with increased risk of fractures at both low and high intakes.

A similar U-shaped association may also be suggested on the basis of the results of those studies that examined associations between dairy products and fractures. However, here, differences in study designs made meta-analysis inappropriate.

When avoiding milk, the drink replacement seems to be either noncarbonated or carbonated beverages rather than water (36, 37). Hence, hypothetically, the replacement will increase the risk of sustaining fractures, as also seen in the 3 studies included in this systematic review (13, 24, 26). Comparing these results to studies that examined the correlation between beverages and fractures among adolescents, a single study found a higher OR for fractures in relation to cola consumption among adolescent girls.
(OR: 3.59; 95% CI: 1.21, 10.75; \( P = 0.022 \)) (38). Likewise, numerous studies have generally shown inverse relations between the consumption of sugar-sweetened beverages and bone growth and density among both children and adolescents (36, 39, 40). Phosphoric acids in carbonated drinks may lead to hypocalcemia by inhibiting 1α-hydroxylase, which results in reduced conversion of 25-hydroxyvitamin D\(_3\) into 1,25-hydroxyvitamin D\(_3\), which may increase bone resorption (41). Moreover, caffeine in cola drinks seems to affect the content and crystalline size of bone minerals (42). In animal models, the low pH values of cola beverages has also been shown to cause renal acid load, which may have a direct association with bone resorption due to osteoclast stimulation, which was found to be negatively associated with bone mineral density (43).

As in the 3 studies that examined breastfeeding and fracture risk identified in this systematic review (22, 23, 26), studies that examined the association between breastfeeding and skeletal variables in children were also inconclusive. Some studies did not find significant associations (44–46), whereas a few others showed a direct association between months of breastfeeding and bone measures (47, 48) or a lower odds of fracture at the age

### FIGURE 2
Effect of calcium intake on fractures. Random-effects analysis based on the effect estimates based on differences in mean calcium intakes between cases and controls. ES, effect size.

### TABLE 7
Studies on the effect of vitamin D intake on upper and lower limb fracture in children 2–13 y of age

<table>
<thead>
<tr>
<th>First author, y (ref)</th>
<th>n</th>
<th>Age, y</th>
<th>Sex, % F</th>
<th>BMI, kg/m(^2)</th>
<th>Main findings, (\mu g/d)</th>
<th>Risk assessment</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longitudinal studies</strong></td>
<td></td>
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</tr>
<tr>
<td>Clark, 2008 (25)</td>
<td>Total: 2692; FCs: 193</td>
<td>6.8 (diet assessment); 10–12 (fracture assessment)</td>
<td>53</td>
<td>17.5 ± 2.8(^2)</td>
<td>2.87 ± 1.30(^3)</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Chan, 1984 (30)</td>
<td>FCs: 17; NFCs: 17</td>
<td>6.4 ± 0.8</td>
<td>47</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No</td>
<td>Ø</td>
</tr>
<tr>
<td>Olney, 2008 (33)</td>
<td>FCs, recurrent: 68; NFCs: 57</td>
<td>12.0 ± 3.0; NFCs: 11.1 ± 3.2</td>
<td>20/30</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No</td>
<td>Ø</td>
</tr>
</tbody>
</table>

\(^{1}\)FC, fracture case; NFC, nonfracture control; ref, reference; Ø, medium; +, positive.

\(^{2}\)Mean ± SD (all such values).

\(^{3}\)Unclear reporting on statistical analysis, FCs compared with NFCs (\( P = 0.1 \)).

\(^{4}\)Logistic regression, adjusted OR test for trend for fractures in quartiles of vitamin D intake. 95% CI in parentheses (all such values).

\(^{5}\)Mann-Whitney rank-sum test.
of 16 y (OR: 0.65; 95% CI: 0.48, 0.87) (49). The potential links between breastfeeding and bone health later in childhood are unknown, although several biological mechanisms in relation to changes in bone cell programming induced by breastfeeding have been proposed (47).

Strengths and limitations of the included studies

There are some methodologic aspects that need to be taken into account in evaluating the reviewed studies. First, concerning the identification and selection of the studies, we noted a lack of randomized controlled trials in this area. This was potentially due to the unethical aspects of enrolling and randomly assigned children to no active intervention in the face of nutritional interventions that may be widely held—albeit in the absence of strong direct evidence—to confer skeletal or other benefits. Second, there are obvious limitations in relation to especially selection bias/generalizability due to the heterogeneity of the studies concerning ethnicity (black, white, and Asian), site of fracture (e.g., forearm fractures only compared with fractures in all limbs), and geography. But heterogeneity in the study design (e.g., case-control compared with cohort studies) may explain some of the heterogeneity of the findings. Combined with small sample sizes and too few studies (potentially due to publication bias), a meta-analysis would not be sensible at this point. Third, the measures of the nutritional exposure variables may be biased due to the fact that most of the included studies were based on recall data alone, with the use of FFQs or questionnaires on breastfeeding. In addition to recall bias, the use of FFQs may be particularly challenging when dealing with children, or when an adult is answering on behalf of the children and who may not be paying attention to portion size, frequency of intake, or leftovers. In the studies included in our systematic review, bias in diet reporting was generally not addressed by the authors. Therefore, we attempted to capture signs of misreporting bias by using the Goldberg cutoff for energy intake. Although only a few studies reported on energy intake, our results indicated some underreporting was present. In general, when underreporting energy intake, the direct association with fracture risk may be overestimated. With regard to specificity, accuracy and objectivity to predict dietary intake are higher when using biochemical markers. On the other hand, FFQ measurements are more practical in the sense that they are less onerous, more affordable, and relatively easy to administer, which may be the reason why only a few authors used both a dietary assessment method and biochemical measurement to assess dietary status.

### Table 8
Case-control studies on the effect of serum calcium and vitamin D concentrations on upper and lower limb fracture in children 2–13 y of age

<table>
<thead>
<tr>
<th>First author, y (ref)</th>
<th>Participants</th>
<th>Main findings (serum concentration)</th>
<th>Risk assessment</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan, 1984 (30)</td>
<td>FCs: 15/17; NFCs: 17</td>
<td>Serum calcium: 6.4 ± 0.8(^2)</td>
<td>FCs: 9.0 ± 0.1 mg/dL; NFCs: 9.1 ± 0.1 mg/dL(^3)</td>
<td>No</td>
</tr>
<tr>
<td>Chan, 1984 (30)</td>
<td>FCs: 17; NFCs: 17</td>
<td>Serum 25(OH)D: 6.4 ± 0.8</td>
<td>FCs: 28 ± 1 ng/mL; NFCs: 31 ± 2 ng/mL(^3)</td>
<td>No</td>
</tr>
<tr>
<td>Mäyränpää, 2012 (12)</td>
<td>FCs, prone: 64; NFCs: 64</td>
<td>Calcium: 10.9 ± 2.9; NFCs: 11.2 ± 2.7</td>
<td>FCs: 42 ± 13 nmol/L; NFCs: 43 ± 12 nmol/L(^4)</td>
<td>No</td>
</tr>
<tr>
<td>Ryan, 2012 (31)</td>
<td>FCs: 76; NFCs: 74</td>
<td>Calcium: 6.9 ± 1.4; NFCs: 7.0 ± 1.5</td>
<td>FCs: 21.9 ± 7.3 ng/mL; NFCs: 22.6 ± 7.2 ng/mL(^3)</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>FCs: 47.1%; NFCs: 40.8(^6)</td>
<td>3.46 (1.09, 10.94)(^7,8)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92 (0.85, 0.99)(^9)</td>
</tr>
</tbody>
</table>

\(^{1}\)FC, fracture case; NFC, nonfracture control; ref, reference; 25(OH)D, 25-hydroxyvitamin D; Ø, medium; +, positive.

\(^{2}\)Mean ± SD (all such values).

\(^{3}\)Unclear reporting on statistical analysis.

\(^{4}\)t test.

\(^{5}\)ANOVA.

\(^{6}\)Contingency tables, frequency of 25(OH)D ≤20 ng/mL.

\(^{7}\)Logistic regression, adjusted OR for fractures for 25(OH)D ≤20 ng/mL (dichotomous).

\(^{8}\)OR; 95% CI in parentheses (all such values).

\(^{9}\)Logistic regression, adjusted OR for fractures in 25(OH)D concentration.
(12, 30, 31). Finally, bias due to the definition of outcome (risk of misclassification; e.g., parental report on fractures compared with medical record) must also be taken into consideration. Yet, fractures are rarely left untreated and are hence less likely to be underreported.

As part of the quality assessment we evaluated the studies on the basis of whether or not the analyses addressed confounding. One particularly important confounder for childhood fractures may be body composition, in which most, but not all, studies showed that overweight among children seems to be associated with fracture risk.

### TABLE 9
Studies on the effect of energy, protein, and fat intake on upper and lower limb fracture in children 2–13 y of age

<table>
<thead>
<tr>
<th>First author, y (ref)</th>
<th>n</th>
<th>Age, y</th>
<th>Sex, % F</th>
<th>BMI, kg/m²</th>
<th>Main findings</th>
<th>Risk assessment</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal studies</td>
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</tr>
<tr>
<td>Clark, 2008 (25)</td>
<td>Total: 2692; FCs: 193</td>
<td>6.8 (diet assessment); 10–12 (fracture assessment)</td>
<td>53</td>
<td>17.5 ± 2.8²</td>
<td>Energy intake: 7689 ± 1744 kJ/d³</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Case-control studies</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chan, 1984 (30)</td>
<td>FCs: 15/17; NFCs: 17</td>
<td>6.4 ± 0.8</td>
<td>47</td>
<td>Not reported</td>
<td>Energy: FCs, 1275 ± 105 kcal/d; NFCs, 1251 ± 80 kcal/d⁶</td>
<td>No</td>
<td>Ø</td>
</tr>
<tr>
<td>Ryan, 2012 (31)</td>
<td>FCs: 76; NFCs: 74</td>
<td>FCs: 6.9 ± 1.4; NFCs: 7.0 ± 1.5</td>
<td>42/46</td>
<td>Not reported</td>
<td>Energy: FCs, 2311.9 ± 1117.0 kcal/d; NFCs, 1742.0 ± 699.3 kcal/d</td>
<td>High energy intake associated with fracture risk</td>
<td>Ø</td>
</tr>
</tbody>
</table>

¹Logistic regression, adjusted OR test for trend for fractures in quartiles of energy intake. 95% CI in parentheses (all such values).
²Logistic/binominal regression, RRs for fractures if breastfeeding (yes/no). 95% CI in parentheses (all such values).
³Mean ± SD (all such values).
⁴Uunclear reporting on statistical analysis, FCs compared with NFCs (P = 0.293).
⁵Unclear reporting on statistical analysis.
⁶ANOVA.

### TABLE 10
Longitudinal and case-control studies on the effect of breastfeeding on upper and lower limb fracture in children 2–13 y of age

<table>
<thead>
<tr>
<th>First author, y (ref)</th>
<th>n</th>
<th>Age, y</th>
<th>Sex, % F</th>
<th>BMI, kg/m²</th>
<th>Main findings: breastfeeding (yes/no)</th>
<th>Risk assessment</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal studies</td>
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<tr>
<td>Jones, 2004 (22)</td>
<td>FCs, prepubertal: 156</td>
<td>Not reported</td>
<td>37</td>
<td>Not reported</td>
<td>1.04 (0.86, 1.23)²</td>
<td>No</td>
<td>Ø</td>
</tr>
<tr>
<td>Case-control studies</td>
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</tr>
<tr>
<td>Ma 2002 (23)</td>
<td>FCs: 32; NFCs: 292</td>
<td>FCs: 8.32 ± 0.34¹; NFCs: 8.19 ± 0.33</td>
<td>28/37</td>
<td>Not reported</td>
<td>0.44 (0.2, 0.97)⁴</td>
<td>No breastfeeding associated with fracture risk</td>
<td>Ø</td>
</tr>
<tr>
<td>Manias 2006 (26)</td>
<td>NFCs: 50</td>
<td>NFCs: 9.7 ± 3.3</td>
<td>26–58</td>
<td>FCs: 19.18 ± 0.34; NFCs: 17.71 ± 0.25</td>
<td>FCs: 38%; NFCs: 56%⁵ χ² = 5.91, P = 0.052, df = 2⁶</td>
<td>No</td>
<td>Ø</td>
</tr>
<tr>
<td>FCs, 1 fracture: 50; FCs, recurrent: 50</td>
<td>FCs, 1 fracture: 9.6 ± 3.2; FCs, recurrent: 11.7 ± 3.0</td>
<td>FCs, 1 fracture: 18.59 ± 0.36; FCs, recurrent: 19.76 ± 0.31</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

¹FC, fracture case; NFC, nonfracture control; ref, reference; Ø, medium.
²Logistic/binominal regression, RRs for fractures if breastfeeding (yes/no). 95% CI in parentheses (all such values).
³Mean ± SD (all such values).
⁴Logistic regression, OR for fractures if breastfeeding (yes/no).
⁵Γ test.
⁶Chi-square test, effect of breastfeeding (yes/no) on frequency of fracture.
with fractures (50). If anthropometric measurements are not adjusted for in the analysis, the results may have been inflated. This is prevalent especially in studies in participants with a mean BMI above the normal range. In particular, the effects from high cheese intakes, high beverage consumption (13), low milk intakes (20, 27), and low calcium intakes (12) may have been overestimated because body composition was not controlled for.

Strengths and limitations related to the systematic review and meta-analysis

In the systematic review and meta-analysis we cannot rule out the combined effects of nutrients and bioavailability, but it would seem of interest to examine the risk of fractures among children in relation to an overall healthy diet indicator, such as the “prudent dietary score,” or to individual food groups or supplementation other than dairy and beverages, such as fruit and vegetables, fish, use of multivitamins, food fortification, etc. Some longitudinal studies of an overall healthy maternal diet during pregnancy and bone outcomes in the offspring during childhood have shown results that could support such a hypothesis (51, 52).

The potential for publication bias cannot be eliminated on the basis of the funnel plot (Supplemental Figure 1) in this systematic review. However, some limitations apply to this approach both in respect to the statistical theoretical foundation and especially in relation to communicating risk in medical applications at an individual patient level (53).

Conclusions

In this systematic review of 18 original peer-reviewed articles judged to be of high or medium quality, there is an indication that some nutritional factors seem to be associated with an increased fracture risk among children aged 2–13 y, in particular milk avoidance, high cheese intake, high energy or sugar-sweetened beverage intakes, and no breastfeeding. The results may, in part, be inflated by selection bias, misreporting of dietary intake, or residual confounding. From a public health perspective, the strength of the evidence available from this systematic review can only give a basis for preliminary nutritional conclusions, and its consequences. Injury 2003;34:219–22.

The authors’ responsibilities were as follows—MNH, BLH, and BA: designed the research, wrote the manuscript, and had primary responsibility for the final content; and MNH: conducted the research and analyzed the records or linkage to health registries and claim databases.

REFERENCES


