Nutrient and food intakes in early life and risk of childhood fractures: a systematic review and meta-analysis[1,2]

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ABSTRACT

Background: The identification of detrimental dietary patterns early in life may contribute to reducing the high incidence of fracture among healthy children. However, information based on a systematic review of the effect of various dietary foods and nutrients on fracture risk is lacking.

Objective: We conducted a systematic review and meta-analysis of observational studies that examined the association between dietary intake or serum nutritional concentrations and childhood fractures.

Design: Studies published up until June 2015 were identified on the basis of a literature search in Medline, Web of Science, and Scopus databases and by hand searching references by first author based on predefined inclusion criteria. A meta-analysis was carried out for case-control studies that examined differences in mean calcium intake 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.

Results: From a total of 1960 articles, we identified 18 observational studies, which were primarily case-control in design. Randomized controlled trials were absent, potentially because of unethical aspects related to the enrollment of children randomly assigned to certain dietary exposures and later fracture rates. Overall, fracture risk seemed to be associated with milk avoidance, high energy intake, high cheese intake, high intake of sugar-sweetened beverages, and no breastfeeding. The pooled effect size of the 9 case-control studies that examined mean calcium intake, which had appropriate data for the meta-analysis, showed no association ($P = 0.99$) with fair heterogeneity ($I^2 = 69.3\%$, $P = 0.001$) with the use of the random-effects model.

Conclusions: On the basis of a systematic review of studies that were 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. The results may be inflated by selection bias, bias in diet reporting, or residual confounding. More high-quality longitudinal observational or intervention studies are needed on the subject. *Am J Clin Nutr* 2015;102:1182–95.

Keywords: bone, epidemiology, fracture, nutrition, public health

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 (1–4), although a few studies from northern Europe have suggested a leveling off or even a decrease in incidence (5, 6). Nevertheless, the overall incidence of pediatric fractures is high, is most pronounced among boys (1, 2, 7), and occurs especially during the growth spurt, which subsides at ages 12–15 y (1, 2, 8). Moreover, in addition to country and region, the incidence of pediatric fractures varies with ethnicity and season (2, 6–10).

Fracture risk in healthy children can be influenced by both genetic and environmental factors. Thus, several studies have shown that impaired bone health (11, 12) as well as sociodemographic factors [e.g., parental age, marital status (13)] 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

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[8]], 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 ex-
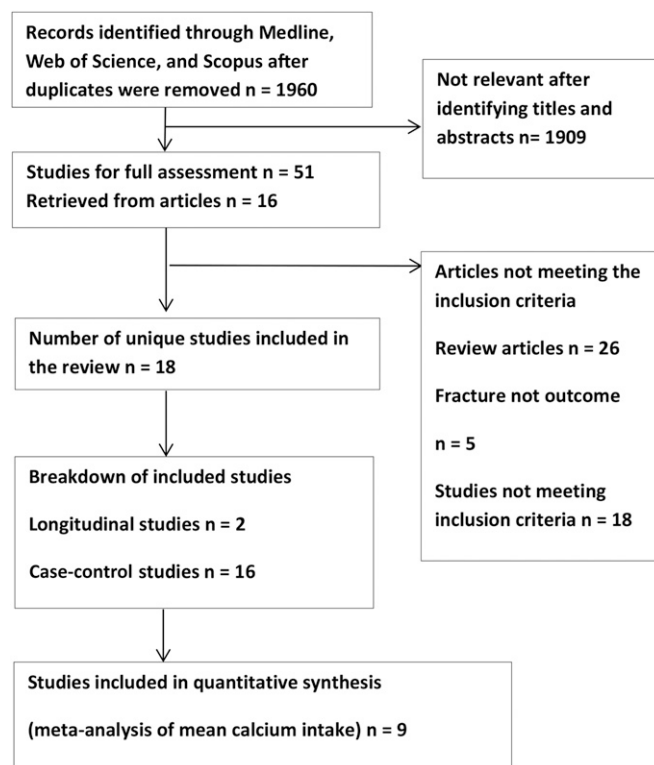
cluded. The review protocol was prepared on the basis of the Evidence Analysis Manual published by the Academy of Nutrition and Dietetics (14). A flowchart of the included studies is presented in **Figure 1**.

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. This was mainly related to how withdrawals were handled and described (i.e., dropouts, loss to follow-up, attrition rate, and missing data). The fourth category evaluated the control for confounding 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

FIGURE 1 Flowchart of included studies.

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[8] 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/m^2) 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; $\chi^2 = 31.0$, $P = 0.001$, 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

TABLE 1
Overview of included studies

Exposure and study type	Included studies, n	Studies in fracture cases with		
		Lower intake	Higher intake	No significant association
Dairy products				
Case-control	6	3	(1 cheese only)	3
Beverages				
Case-control	3	—	3	—
Calcium				
Case-control	9	1 (+1 from milk only)	1	7
Longitudinal	2	—	1	1
Vitamin D				
Case-control	4	1	—	3
Longitudinal	1	—	—	1
Energy				
Case-control	2	—	1	1
Longitudinal	1	—	—	1
Protein				
Case-control	1	—	—	1
Fat				
Case-control	1	—	—	1
Breastfeeding				
Case-control	2	1	—	1
Longitudinal	1	—	—	1

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 of 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: −62.81, 63.81; $P = 0.99$) with fair heterogeneity ($I^2 = 69.3\%$, $P = 0.001$) by using the random-effects model (**Figure 2**). Nevertheless, the meta-analysis revealed that there were 2 fairly recent studies from 2012 that showed contradictory results (12, 31). One of these studies, judged to be of high quality, showed that forearm fracture case black children from the United States had a higher calcium intake (889.8 ± 405.8 mg/d) than did nonfracture control black children (680.5 ± 333.5 mg/d) ($P = 0.001$) (31). In the other study, also judged to be of high quality, conducted in white children from Finland with either single or recurrent fractures of any kind, a lower dietary calcium intake was found among cases compared with nonfracture control white children (990 ± 410 compared with 1190 ± 330 mg/d; $P = 0.04$), but the analysis did not control for body weight or size (12). One other case-control study, judged to be of high quality, found no significant differences in overall mean dietary calcium intake between the case and control groups; however, the authors did find a significant difference for children aged 3–7 y with regard to current dairy calcium intake, which was lower among fracture cases than among fracture-free control children (372 ± 193 compared with 509 ± 310 mg/d; $P < 0.02$) (19). 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.

TABLE 2
Case-control studies on the effect of dairy intake on upper and lower limb fracture in children 2–13 y of age[1]

First author, y (ref)	n	Age, y	Sex, % F	BMI, kg/m²	Main findings[2]	Risk assessment	Quality
			Participants				
Goulding, 2004 (20)	MA: 50; CCs: >1000	FCs: 6.7 ± 2.1[3]; NFCs: 5.8 ± 2.0	60	FCs: 18.1 ± 3.0; NFCs: 17.0 ± 2.4	FCs vs. CCs: 16 observed vs. 6 expected[4] ($\chi^2 = 31.0$, df = 5)***	MA associated with increased risk	Ø
Ma, 2004 (24)	FCs: 206; NFCs: 206	FCs: hand, 13.1 ± 2.1; NFCs: hand, 13.1 ± 2.1	33	FCs: hand, 20.7 ± 3.1; NFCs: hand, 21.4 ± 4.5	1.36 (0.83, 2.23)[5]	No	+
		FCs: wrist-forearm, 12.0 ± 2.0; NFCs: wrist/forearm, 12.1 ± 2.1		FCs: wrist-forearm, 19.9 ± 3.4; NFCs: wrist/forearm, 19.7 ± 3.5	0.79 (0.59, 1.06)[6]		
		FCs: upper arm, 12.6 ± 2.2; NFCs, upper arm, 12.8 ± 2.3		FCs: upper arm, 20.3 ± 3.1; NFCs: upper arm, 20.7 ± 4.3	1.05 (0.68, 1.63)[7]		
Petridou, 1997 (13)	FCs: 100; NFCs: 100	Not reported	26	Not reported	0.5 (variance not reported)[8] (χ for trend: -0.15)	No	+
					2.6 (variance not reported)[9] (χ for trend: 2.18)*	Cheese intake associated with increased risk	
Manias, 2006 (26)	NFCs: 50	NFCs: 9.7 ± 3.3	26–58	FCs: 19.18 ± 0.34; NFCs: 17.71 ± 0.25	FCs: 0.41 ± 0.34 L/d; NFCs: 0.49 ± 0.3 L/d[10]	Low milk intake associated with recurrent fractures	Ø
	FCs, 1 fracture: 50	FCs, 1 fracture: 9.6 ± 3.2		FCs, 1 fracture: 18.59 ± 0.36	FCs, 1 fracture: 0.5 ± 0.4 L/d[10]		
	FC, recurrent: 50	FCs, recurrent: 11.7 ± 3.0		FCs, recurrent: 19.76 ± 0.31	FCs, recurrent: 0.33 ± 0.3 L/d[10–12,*]		
Pires, 2005 (27)	FCs: 23; NFCs: 23	Not reported	0	Not reported	FCs: 1.5 ± 1.2 glasses/d; NFCs: 2.7 ± 1.2 glasses/d[4,**]	Low milk intake associated with increased risk	Ø
Ryan, 2012 (31)	FCs: 76; NFCs: 74	FCs: 6.9 ± 1.4; NFCs: 7.0 ± 1.5	42/46	Not reported	FCs: 7.4 ± 6.8 servings of milk/wk; NFCs: 7.0 ± 6.2 servings of milk/wk[13]	No	+

[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 $\pm$ 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 ≥ 90 units/mo. The units were not specified in the study.

[9] OR for cheese and other milk products ≥ 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.

With regard to sex differences, Mäyränpää 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 3
Case-control studies on the effect of beverage intake on upper and lower limb fracture in children 2–13 y of age[1]

First author, y (ref)	Participants				Main findings[2]	Risk assessment	Quality
	n	Age, y	Sex, % F	BMI, kg/m²			
Ma, 2004 (24)	FCs: 206; NFCs: 206	FCs, hand: 13.1 ± 2.1[3]; NFCs, hand: 13.1 ± 2.1	33	FCs, hand: 20.7 ± 3.1; NFCs, hand: 21.4 ± 4.5	1.41 (0.71, 2.82)[4] 1.11 (0.71, 1.74)[5]	No No	+
		FCs, wrist-forearm: 12.0 ± 2.0; NFCs, wrist-forearm: 12.1 ± 2.1		FCs, wrist-forearm: 19.9 ± 3.4; NFCs, wrist-forearm: 19.7 ± 3.5	1.39 (1.01, 1.91)[6] 1.14 (0.89, 1.46)[7]	High cola intake associated with increased risk in wrist and forearm fractures No	
		FCs, upper arm: 12.6 ± 2.2; NFCs, upper arm: 12.8 ± 2.3		FCs, upper arm cases: 20.3 ± 3.1; NFCs, upper arm: 20.7 ± 4.3	0.36 (0.36, 1.17)[8] 1.00 (0.63, 1.58)[9]	No No	
Petridou, 1997 (13)	FCs: 100; NFCs: 100	Not reported	26	Not reported	2.2 (variance not reported)[10] (χ for trend: 1.68)	No	+
					4.8 (variance not reported)[11] (χ for trend: 3.39)**	High cola intake associated with increased risk	
					3.4 (variance not reported)[11] (χ for trend: 2.51)*	High noncarbonated beverage intake associated with increased risk	
Manias, 2006 (26)	NFCs: 50	NFCs: 9.7 ± 3.3	26–58	FCs: 19.18 ± 0.34; NFCs: 17.71 ± 0.25	FCs: 0.25 ± 0.44 L/d;[12] NFCs: 0.13 ± 0.17 L/d	High carbonated drink intake associated with recurrent fractures	Ø
	FCs, 1 fracture: 50	FCs, 1 fracture: 9.6 ± 3.2		FCs, 1 fracture: 18.59 ± 0.36	FCs, 1 fracture: 0.16 ± 0.19 L/d[13]		
	FCs, recurrent: 50	FCs, recurrent: 11.7 ± 3.0		FCs, recurrent: 19.76 ± 0.31	FCs, recurrent: 0.33 ± 0.57 L/d[14]*		

[1] *$P < 0.05$, **$P < 0.01$. FC, fracture case; 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).

[4,6,8] OR for cola drinks/wk: [4] hand fractures, [6] wrist/forearm fractures, [8] upper arm fractures.

[5,7,9] OR for carbonated drinks/wk: [5] hand fractures, [7] wrist/forearm fractures, [9] upper arm fractures.

[10] OR for carbonated non-cola ≥28 cans/mo.

[11] OR for noncarbonated beverages ≥42 cans/mo.

[12] FCs, all, compared with FCs, 1 fracture; $P < 0.02$ (t and F tests).

[13] FCs, recurrent, compared with FCs, 1 fracture; $P < 0.04$ (t and F tests).

[14] FCs, recurrent, compared with NFCs; $P < 0.02$ (t and F tests).

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). 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.

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]

First author, y (ref)	Participants				Main findings,[2] mg/d or HR (95% CI)	Risk assessment	Quality
	n	Age, y	Sex, % F	BMI, kg/m²			
Clark, 2008 (25)	Total: 2692; FCs: 193	6.8 (diet assessment); 10–12 (fracture assessment)	53	17.5 ± 2.8[3]	898 ± 295[4]	No	+
					0.9 (0.75, 1.08)[5]		
Wren, 2012 (32)	Total: 1470	White: 10.8 ± 3.1; nonwhite: 11.1 ± 3.0	50–51	Not reported	White: 967 ± 491; nonwhite: 890 ± 620	—	+
					1.26 (1.01, 1.57)[6]	High calcium intake associated with fracture risk (adjusted model: no)	
					1.1 (0.72, 1.67)[7]	No	
					0.93 (0.69, 1.26)[8]	No	
					1.24 (0.75, 2.05)[9]	No	

[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 proportianal hazard model for first fracture.
[7] Cox proportianal hazard model for entire cohort.
[8] Cox proportianal hazard model for no previous fracture.
[9] Cox proportianal hazard model for previous fracture history

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, showed 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 the 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

TABLE 5
Case-control studies on the effect of calcium intake (mg/d) on upper and lower limb fracture among children 2–13 y of age[1]

First author, y (ref)	Participants				Main findings, mg/d	Risk assessment	Quality
	n	Age, y	Sex, % F	BMI, kg/m²			
Chan, 1984 (30)	FCs: 15/17; NFCs: 17	6.4 ± 0.8[2]	47	Not reported	FCs: 787 ± 137; NFCs: 810 ± 57[3]	No	Ø
Goulding, 1998 (19)	FCs: 100; NFC: 100	Not reported	100	Not reported	FCs: 858 ± 432; NFCs: 829 ± 332[4]	No	+
		FCs, 3–7 y: 5.87 ± 1.3; NFCs, 3–7 y: 5.91 ± 1.24		FCs, 3–7 y: 15.71 ± 2.12; NFCs, 3–7 y: 5.31 ± 1.2	FCs: 372 ± 193; NFC: 509 ± 310[4,5,*]	Low calcium intake from milk associated with fracture risk	
		FCs, 8–10 y: 9.67 ± 0.78; NFCs, 8–10 y: 9.63 ± 0.73		FCs, 8–10 y: 19.16 ± 2.88; NFCs, 8–10 y: 17.52 ± 2.83	FCs: 451 ± 251; NFCs: 395 ± 207[4,5]	No	
Goulding, 2001 (11)	FCs: 100; NFC: 100	FCs: 12.0 ± 3.7; NFCs: 12.0 ± 3.7	0	FCs: 20.21 ± 4.22; NFCs: 19.03 ± 3.03	FCs: 1136 ± 538; NFCs: 1278 ± 618[4]	No	Ø
Goulding, 2004 (20)	FCs, MA: 16	FCs, MA: 6.7 ± 2.1; NFCs: 5.8 ± 2.0	60	FCs, MA: 18.1 ± 3.0; NFCs: 17.0 ± 2.4	FCs: 438 ± 189; NFCs: 449 ± 250[4]	No	Ø
Mäyränpää, 2012 (12)	FCs, prone: 64; NFCs: 64	FCs, prone: 10.9 ± 2.9; NFCs: 11.2 ± 2.7	33	Not reported	FCs: 990 ± 410*; NFCs: 1190 ± 330[6]	Low calcium intake associated with fracture risk	+
Olney, 2008 (33)	FCs, recurrent: 68; NFCs: 57	FCs: 12.0 ± 3.0; NFCs: 11.1 ± 3.2	20/30	Not reported	FCs: 957 (562, 1550)[7]; NFCs: 906 (485, 1481)[8]	No	Ø
Ryan, 2012 (31)	FCs: 76; NFCs: 74	FCs: 6.9 ± 1.4; NFCs: 7.0 ± 1.5	42/46	Not reported	FCs: 889.8 ± 405.8**; NFCs: 680.5 ± 333.5[9]	High calcium intake associated with increased risk	+
Sierra, 2009 (29)	FCs: 160; NFCs: 160	Not reported	50	FCs: 19.14 ± 3.5; NFCs: 17.46 ± 2.67	FCs: 883.48 ± 332.46; NFCs: 851.15 ± 374.19[6]	No	Ø
Valerio, 2012 (28)	FCs: 449; NFCs: 130	FCs: 8.7 ± 2.9; NFCs: 8.3 ± 2.9	35	FCs: 20.5 ± 4.5; NFCs: 19.4 ± 4.9	FCs: 1141 ± 404; NFCs: 1137 ± 431[6]	No	+

[1]*$P < 0.05$, **$P < 0.01$. FC, fracture case; MA, milk avoiding; NFC, nonfracture control; ref, reference; Ø, medium; +, positive.
[2]Mean ± SD (all such values).
[3]Unclear reporting on statistical analysis.
[4]Chi-square test.
[5]Calcium from milk only.
[6]t test.
[7]10th, 90th percentile (all such values).
[8]Mann-Whitney rank-sum test.
[9]ANOVA.

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

TABLE 6
Case-control studies on calcium intake (mg/d) less than the RDA on frequency of upper and lower limb fracture among children 2–13 y of age[1]

First author, y (ref)	Participants				Main findings, % <RDA	Risk assessment	Quality
	n	Age, y	Sex, % F	BMI, kg/m²			
Chan, 1984 (30)	FCs: 17; NFCs: 17	6.4 ± 0.8[2]	47	Not reported	FCs: 27; NFCs: 0[3,4]	Higher frequency of low calcium intake among FCs	Ø
Goulding, 1998 (19)	FCs: 100; NFCs: 100	Not reported	100	Not reported	FCs: 19; NFCs: 21[5]	No	+
Goulding, 2001 (11)	FCs: 100; NFCs: 100	FCs: 12.0 ± 3.7; NFCs: 12.0 ± 3.7	0	FCs: 20.21 ± 4.22; NFCs: 19.03 ± 3.03	FCs: 50; NFCs: 39[5,6]	Higher frequency of low calcium intake among FCs	Ø
Goulding, 2004 (20)	FCs, MA: 50; CCs: >1000	FCs: 6.7 ± 2.1; NFCs: 5.8 ± 2.0	60	FCs: 18.1 ± 3.0; NFCs: 17.0 ± 2.4	FCs: 31; NFCs: 27[5,7]	No	Ø
Goulding, 2005 (21)	FCs, recurrent: 90; NFCs: 200	FCs, girls: 12.3 ± 2.9; FCs, boys: 12.2 ± 3.5	52	FCs, girls: 20.6 ± 4.2; FCs, boys: 20.3 ± 4.4	FCs: 20; NFCs: 4.5[5,8,**]	Higher frequency of low calcium intake among FCs	Ø
Mäyränpää, 2012 (12)	FCs, prone: 64; NFCs: 64	FCs: 10.9 ± 2.9; NFCs: 11.2 ± 2.7	33	Not reported	FCs: 31; NFCs: 8[5,**]	Higher frequency of low calcium intake among FCs	+

[1]**P < 0.01. CC, control from the community; FC, fracture case; MA, milk avoiding; NFC, nonfracture control; RDA, Recommended Daily Allowance; ref, reference; Ø, medium; +, positive.
[2]Mean ± SD (all such values).
[3]Unclear reporting on statistical analysis.
[4]Less than 60% of the RDA (1000 mg/d).
[5]Chi-square test.
[6]P value not reported.
[7]Intake <300 mg/d.
[8]Less than 66% of the RDA (1000 mg/d).

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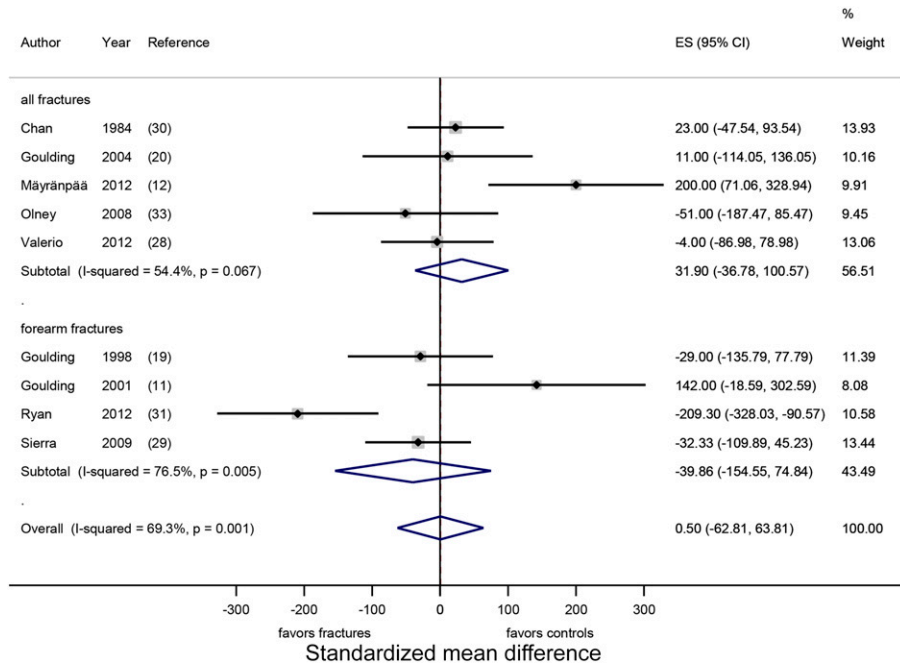
FIGURE 2 Effect of calcium intake on fractures. Random-effects analysis based on the effect estimates based on differences in mean calcium intakes between cases and controls. ES, effect size.

(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

TABLE 7
Studies on the effect of vitamin D intake on upper and lower limb fracture in children 2–13 y of age[1]

| First author, y (ref) | Participants | | | | Main findings, $\mu g/d$ | Risk assessment | Quality |
	n	Age, y	Sex, % F	BMI, kg/m^2			
Longitudinal studies							
Clark, 2008 (25)	Total: 2692; FCs: 193	6.8 (diet assessment); 10–12 (fracture assessment)	53	17.5 ± 2.8[2]	2.87 ± 1.30[3]	No	+
					$0.97 (0.84, 1.13)$[4]		
Case-control studies							
Chan, 1984 (30)	FCs: 17; NFCs: 17	6.4 ± 0.8	47	Not reported	Not reported	No	Ø
Olney, 2008 (33)	FCs, recurrent: 68; NFCs: 57	FCs, recurrent: 12.0 ± 3.0; NFCs: 11.1 ± 3.2	20/30	Not reported	FCs, recurrent: 4.73 (1.38, 13.2); NFCs: 3.74 (0.84, 10.9)[5]	No	Ø

[1]FC, fracture case; NFC, nonfracture control; ref, reference; Ø, medium; +, positive.
[2]Mean $\pm$ 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.

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[1]

First author, y (ref)	Participants				Main findings (serum concentration)	Risk assessment	Quality
	n	Age, y	Sex, % F	BMI, kg/m^2			
Serum calcium							
Chan, 1984 (30)	FCs: 15/17; NFCs: 17	6.4 ± 0.8[2]	47	Not reported	FCs: 9.0 ± 0.1 mg/dL; NFCs: 9.1 ± 0.1 mg/dL[3]	No	Ø
Serum 25(OH)D							
Chan, 1984 (30)	FCs: 17; NFCs: 17	6.4 ± 0.8	47	Not reported	FCs: 28 ± 1 ng/mL; NFCs: 31 ± 2 ng/mL[3]	No	Ø
Mäyränpää, 2012 (12)	FCs, prone: 64; NFCs: 64	FCs: 10.9 ± 2.9; NFCs: 11.2 ± 2.7	33	Not reported	FCs: 42 ± 13 nmol/L; NFCs: 43 ± 12 nmol/L[4]	No	+
Ryan, 2012 (31)	FCs: 76; NFCs: 74	FCs: 6.9 ± 1.4; NFCs: 7.0 ± 1.5	42/46	Not reported	FCs: 21.9 ± 7.3 ng/mL; NFCs: 22.6 ± 7.2 ng/mL[5]	No	+
					FCs: 47.1%; NFCs: 40.8%[6]	No	
					3.46 (1.09, 10.94)[7,8]	Deficiency of 25(OH)D associated with fracture risk	
					0.92 (0.85, 0.99)[9]	Low 25(OH)D associated with fracture risk	

[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.

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 9
Studies on the effect of energy, protein, and fat intake on upper and lower limb fracture in children 2–13 y of age[1]

First author, y (ref)	Participants				Main findings	Risk assessment	Quality
	n	Age, y	Sex, % F	BMI, kg/m^2			
Longitudinal studies							
Clark, 2008 (25)	Total: 2692; FCs: 193	6.8 (diet assessment); 10–12 (fracture assessment)	53	17.5 ± 2.8[2]	Energy intake: 7689 ± 1744 kJ/d[3]	No	+
					Energy: 1.2 (0.99, 1.45)[4]		
Case-control studies							
Chan, 1984 (30)	FCs: 15/17; NFCs: 17	6.4 ± 0.8	47	Not reported	Energy: FCs, 1275 ± 105 kcal/d; NFCs, 1251 ± 80 kcal/d[5]	No	Ø
					Protein: FCs, 46 ± 5 g/d; NFCs, 45 ± 4 g/d[5]	No	
					Fat: FCs, 47 ± 6 g/d; NFCs, 50 ± 5 g/d[5]	No	
Ryan, 2012 (31)	FCs: 76; NFCs: 74	FCs: 6.9 ± 1.4; NFCs: 7.0 ± 1.5	42/46	Not reported	Energy: FCs, 2311.9 ± 1117.0 kcal/d[6,***]; NFCs, 1742.0 ± 699.3 kcal/d	High energy intake associated with fracture risk	Ø

[1]***$P < 0.001$. 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 ($P = 0.293$).
[4]Logistic regression, adjusted OR test for trend for fractures in quartiles of energy intake. 95% CI in parentheses (all such values).
[5]Unclear reporting on statistical analysis.
[6]ANOVA.

(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

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[1]

First author, y (ref)	Participants				Main findings: breastfeeding (yes/no)	Risk assessment	Quality
	n	Age, y	Sex, % F	BMI, kg/m^2			
Longitudinal studies							
Jones, 2004 (22)	FCs, prepubertal: 156	Not reported	37	Not reported	1.04 (0.86, 1.23)[2]	No	Ø
Case-control studies							
Ma 2002 (23)	FCs: 32; NFCs: 292	FCs: 8.32 ± 0.34[3]; NFCs: 8.19 ± 0.3.3	28/37	Not reported	0.44 (0.2, 0.97)[4]	No breastfeeding associated with fracture risk	Ø
					FCs: 38%; NFCs: 56%[5]	No	
Manias 2006 (26)	NFCs: 50	NFCs: 9.7 ± 3.3	26–58	FCs: 19.18 ± 0.34; NFCs: 17.71 ± 0.25	$\chi^2 = 5.91$, $P = 0.052$, df = 2[6]	No	Ø
	FCs, 1 fracture: 50; FCs, recurrent: 50	FCs, 1 fracture: 9.6 ± 3.2; FCs, recurrent: 11.7 ± 3.0		FCs, 1 fracture: 18.59 ± 0.36; FCs, recurrent: 19.76 ± 0.31			

[1]FC, fracture case; NFC, nonfracture control; ref, reference; Ø, medium.
[2]Logistic/binominal regression, RRs for fractures if breastfeeding (yes/no). 95% CI in parentheses (all such values).
[3]Mean ± SD (all such values).
[4]Logistic regression, OR for fractures if breastfeeding (yes/no).
[5]t test.
[6]Chi-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 over-estimated 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 more high-quality longitudinal cohort studies are needed, particularly studies that include follow-up by retrieving fracture records or linkage to health registries and claim databases.

REFERENCES

1. Khosla S, Melton LJ III, Dekutoski MB, Achenbach SJ, Oberg AL, Riggs BL. Incidence of childhood distal forearm fractures over 30 years: a population-based study. JAMA 2003;290:1479–85.
2. Hedström EM, Svensson O, Bergstrom U, Michno P. Epidemiology of fractures in children and adolescents. Acta Orthop 2010;81:148–53.
3. Hagino H, Yamamoto K, Ohshiro H, Nose T. Increasing incidence of distal radius fractures in Japanese children and adolescents. J Orthop Sci 2000;5:356–60.
4. de Putter CE, van Beeck EF, Looman CW, Toet H, Hovius SE, Selles RW. Trends in wrist fractures in children and adolescents, 1997-2009. J Hand Surg Am 2011;36:1810–5.e2.
5. Mäyränpää MK, Makitie O, Kallio PE. Decreasing incidence and changing pattern of childhood fractures: a population-based study. J Bone Miner Res 2010;25:2752–9.
6. Tiderius CJ, Landin L, Duppe H. Decreasing incidence of fractures in children: an epidemiological analysis of 1,673 fractures in Malmo, Sweden, 1993-1994. Acta Orthop Scand 1999;70:622–6.
7. Ryan LM, Teach SJ, Searcy K, Singer SA, Wood R, Wright JL, Chamberlain JM. Epidemiology of pediatric forearm fractures in Washington (DC). J Trauma 2010;69:S200–5.
8. Brudvik C, Hove LM. Childhood fractures in Bergen, Norway: identifying high-risk groups and activities. J Pediatr Orthop 2003;23: 629–34.
9. Wareham K, Johansen A, Stone MD, Saunders J, Jones S, Lyons RA. Seasonal variation in the incidence of wrist and forearm fractures, and its consequences. Injury 2003;34:219–22.
10. Lyons RA, Sellstrom E, Delahunty AM, Loeb M, Varilo S. Incidence and cause of fractures in European districts. Arch Dis Child 2000;82: 452–5.
11. Goulding A, Jones IE, Taylor RW, Williams SM, Manning PJ. Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy X-ray absorptiometry study. J Pediatr 2001; 139:509–15.
12. Mäyränpää MK, Viljakainen HT, Toiviainen-Salo S, Kallio PE, Makitie O. Impaired bone health and asymptomatic vertebral compressions in fracture-prone children: a case-control study. J Bone Miner Res 2012; 27:1413–24.
13. Petridou E, Karpathios T, Dessypris N, Simou E, Trichopoulos D. The role of dairy products and non alcoholic beverages in bone fractures among schoolage children. Scand J Soc Med 1997;25:119–25.
14. Research and Strategic Business Development: Evidence analysis manual: steps in the academy evidence analysis process. Chicago (IL): Academy of Nutrition and Dietetics. 2012.
15. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 2007;36: 666–76.
16. von Elm E. Commentary: assessing the quality of observational studies—or a lesson from Mars. Int J Epidemiol 2007;36:677–8.
17. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate: a practical guide to its calculation, use and limitations. Int J Obes Relat Metab Disord 2000; 24:1119–30.
18. Börnhorst C, Huybrechts I, Ahrens W, Eiben G, Michels N, Pala V, Molnar D, Russo P, Barba G, Bel-Serrat S, et al. Prevalence and determinants of misreporting among European children in proxy-reported 24 h dietary recalls. Br J Nutr 2013;109:1257–65.
19. Goulding A, Cannan R, Williams SM, Gold EJ, Taylor RW, Lewis-Barned NJ. Bone mineral density in girls with forearm fractures. J Bone Miner Res 1998;13:143–8.
20. Goulding A, Rockell JE, Black RE, Grant AM, Jones IE, Williams SM. Children who avoid drinking cow's milk are at increased risk for prepubertal bone fractures. J Am Diet Assoc 2004;104:250–3.
21. Goulding A, Grant AM, Williams SM. Bone and body composition of children and adolescents with repeated forearm fractures. J Bone Miner Res 2005;20:2090–6.
22. Jones IE, Williams SM, Goulding A. Associations of birth weight and length, childhood size, and smoking with bone fractures during growth: evidence from a birth cohort study. Am J Epidemiol 2004;159:343–50.
23. Ma DQ, Jones G. Clinical risk factors but not bone density are associated with prevalent fractures in prepubertal children. J Paediatr Child Health 2002;38:497–500.
24. Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. Calcif Tissue Int 2004;75:286–91.
25. Clark EM, Ness AR, Tobias JH. Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children. J Bone Miner Res 2008;23:1012–22.
26. Manias K, McCabe D, Bishop N. Fractures and recurrent fractures in children: varying effects of environmental factors as well as bone size and mass. Bone 2006;39:652–7.
27. Pires LA, Souza AC, Laitano O, Meyer F. Bone mineral density, milk intake and physical activity in boys who suffered forearm fractures. J Pediatr (Rio J) 2005;81:332–6.

28. Valerio G, Galle F, Mancusi C, Di OV, Guida P, Tramontano A, Ruotolo E, Liguori G. Prevalence of overweight in children with bone fractures: a case control study. BMC Pediatr 2012;12:166.

29. Sierra SC, Delange SE, Blasco AJ, Navas LVM, Barco GA. Low bone mineral density and other risk factore in prepubertal children with fracture of distal forearm. Ann Pediatr (Barc) 2009;71: 383–90.

30. Chan GM, Hess M, Hollis J, Book LS. Bone mineral status in childhood accidental fractures. Am J Dis Child 1984;138:569–70.

31. Ryan LM, Teach SJ, Singer SA, Wood R, Freishtat R, Wright JL, McCarter R, Tosi L, Chamberlain JM. Bone mineral density and vitamin D status among African American children with forearm fractures. Pediatrics 2012;130:e553–60.

32. Wren TA, Shepherd JA, Kalkwarf HJ, Zemel BS, Lappe JM, Oberfield S, Dorey FJ, Winer KK, Gilsanz V. Racial disparity in fracture risk between white and nonwhite children in the United States. J Pediatr 2012;161:1035–40.

33. Olney RC, Mazur JM, Pike LM, Froyen MK, Ramirez-Garnica G, Loveless EA, Mandel DM, Hahn GA, Neal KM, Cummings RJ. Healthy children with frequent fractures: how much evaluation is needed? Pediatrics 2008;121:890–7.

34. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240–3.

35. Theobald HE. Dietary calcium and health. Nutr Bull 2005;30(3): 237–77.

36. Whiting SJ, Healey A, Psiuk S, Mirwald R, Kowalski K, Bailey DA. Relationship between carbonated and other low nutrient dense beverages and bone mineral content of adolescents. Nutr Res 2001;21:1107–15.

37. Fiorito LM, Marini M, Mitchell DC, Smiciklas-Wright H, Birch LL. Girls' early sweetened carbonated beverage intake predicts different patterns of beverage and nutrient intake across childhood and adolescence. J Am Diet Assoc 2010;110:543–50.

38. Wyshak G, Frisch RE. Carbonated beverages, dietary calcium, the dietary calcium/phosphorus ratio, and bone fractures in girls and boys. J Adolesc Health 1994;15:210–5.

39. Libuda L, Alexy U, Remer T, Stehle P, Schoenau E, Kersting M. Association between long-term consumption of soft drinks and variables of bone modeling and remodeling in a sample of healthy German children and adolescents. Am J Clin Nutr 2008; 88:1670–7.

40. McGartland C, Robson PJ, Murray L, Cran G, Savage MJ, Watkins D, Rooney M, Boreham C. Carbonated soft drink consumption and bone mineral density in adolescence: the Northern Ireland Young Hearts Project. J Bone Miner Res 2003;18:1563–9.

41. Calvo MS, Tucker KL. Is phosphorus intake that exceeds dietary requirements a risk factor in bone health? Ann N Y Acad Sci 2013;1301: 29–35.

42. Ohta M, Ide K, Cheuk G, Cheuk SL, Yazdani M, Nakamoto T, Thomas KA. A caffeine diet can alter the mechanical properties of the bones of young ovariectomized rats. Ann Nutr Metab 2002;46:108–13.

43. Ogur R, Uysal B, Ogur T, Yaman H, Oztas E, Ozdemir A, Hasde M. Evaluation of the effect of cola drinks on bone mineral density and associated factors. Basic Clin Pharmacol Toxicol 2007;100:334–8.

44. Kühn T, Kroke A, Remer T, Schonau E, Buyken AE. Is breastfeeding related to bone properties? A longitudinal analysis of associations between breastfeeding duration and pQCT parameters in children and adolescents. Matern Child Nutr 2014;10(4):642–9.

45. Fewtrell MS, Kennedy K, Murgatroyd PR, Williams JE, Chomtho S, Lucas A. Breast-feeding and formula feeding in healthy term infants and bone health at age 10 years. Br J Nutr 2013;110:1061–7.

46. Harvey NC, Robinson SM, Crozier SR, Marriott LD, Gale CR, Cole ZA, Inskip HM, Godfrey KM, Cooper C. Breast-feeding and adherence to infant feeding guidelines do not influence bone mass at age 4 years. Br J Nutr 2009;102:915–20.

47. Jones G, Riley M, Dwyer T. Breastfeeding in early life and bone mass in prepubertal children: a longitudinal study. Osteoporos Int 2000;11: 146–52.

48. Mølgaard C, Larnkjaer A, Mark AB, Michaelsen KF. Are early growth and nutrition related to bone health in adolescence? The Copenhagen Cohort Study of infant nutrition and growth. Am J Clin Nutr 2011;94: 1865S–9S.

49. Jones G, Hynes KL, Dwyer T. The association between breastfeeding, maternal smoking in utero, and birth weight with bone mass and fractures in adolescents: a 16-year longitudinal study. Osteoporos Int 2013;24:1605–11.

50. Moon RJ, Lim A, Farmer M, Segaran A, Clarke NM, Dennison EM, Harvey NC, Cooper C, Davies JH. Differences in childhood adiposity influence upper limb fracture site. Bone 2015;79:88–93.

51. Cole ZA, Gale CR, Javaid MK, Robinson SM, Law C, Boucher BJ, Crozier SR, Godfrey KM, Dennison EM, Cooper C. Maternal dietary patterns during pregnancy and childhood bone mass: a longitudinal study. J Bone Miner Res 2009;24:663–8.

52. Ganpule A, Yajnik CS, Fall CH, Rao S, Fisher DJ, Kanade A, Cooper C, Naik S, Joshi N, Lubree H, et al. Bone mass in Indian children—relationships to maternal nutritional status and diet during pregnancy: the Pune Maternal Nutrition Study. J Clin Endocrinol Metab 2006;91: 2994–3001.

53. Rakow T, Wright RJ, Spiegelhalter DJ, Bull C. The pros and cons of funnel plots as an aid to risk communication and patient decision making. Br J Psychol 2015;106(2):327–48.