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Does dietary calcium have a protective effect on bone fractures in women? A meta-analysis of observational studies

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It is generally accepted that supplemental Ca and/or vitamin D is effective in reducing the incidence of bone fractures; this is supported by numerous randomised controlled trials and meta-analyses. However, a question that has received much less attention is whether dietary Ca, i.e. Ca in physiological doses in normal food intake, also affects bone fracture risk. The present study aims to review the effect of dietary Ca on bone fractures at the hip, spine and radius in women >35 years old, and to compare these results with previous meta-analyses. MEDLINE (1966–1999) and reference lists in papers were searched for observational dietary Ca studies. Data were extracted in duplicate and separately. Heterogeneity and publication bias were tested. Observational studies failed to show any association between dietary Ca intake and risk of hip fracture (risk ratio 1·01, 95 % CI 0·96, 1·07 for each increment of 300 mg dietary Ca intake/d). There is a suggestion that either extremely low Ca intake may increase fracture risk, or that East Asian women may respond differently to increasing Ca intake.

Calcium: Fractures: Meta-analysis

Because of the mortality and morbidity associated with bone fractures, it is more important and more cost-effective to prevent rather than to treat fractures in elderly women (Riggs & Melton, 1988; Chrischilles *et al.* 1994). It is generally accepted that supplemental Ca and/or vitamin D is effective in reducing fracture risk; this is supported by numerous randomised controlled trials and meta-analyses using both clinical fractures and bone mineral density as outcomes (Cumming, 1990; Cumming & Nevitt, 1997; Gillespie *et al.* 2000). However, a question that has received much less attention is whether dietary Ca, i.e. Ca in physiological doses in normal food intake, also affects bone fracture risk. Whereas randomised controlled trials answer the question: 'Does supplemental Ca and/or vitamin D reduce fracture risk?', observational studies answer the question: 'Is Ca at normal dietary doses linked to fracture risk?'. The implication would be that low dietary Ca might be a risk factor for fractures, or alternatively, that Ca at the highest doses seen in normal diets, i.e. short of supplementation, might be protective.

The only previous meta-analysis of observational studies showed that every increment of 300 mg in dietary Ca intake/d was associated with an odds ratio of hip fracture of 0·96 (95 % CI 0·93, 0·99) (Cumming & Nevitt, 1997). This result is qualified by several caveats. Some of the observational study results used in the pooled analysis were based on very low follow-up rates, subjective diagnosis of fracture or a single source of dietary Ca intake. Likewise, the pooled results of observational studies were based on a fixed effects model, even though there was heterogeneity (*P* value for heterogeneity 0·02). These caveats shed doubts on the conclusions.

To clarify the effect of dietary Ca intake on bone fractures, the present review was undertaken. Our aim was to review observational studies (including cohort and case–control studies) to determine if low dietary Ca intake is one of the risk factors for forearm, vertebral and hip fractures in women aged >35 years after adjusting for the effect of age.

Materials and methods

Selection of studies for review

The inclusion criteria for studies were defined as follows:

(1) Observational studies published in English;
(2) Outcomes were hip, forearm or vertebral fractures;
(3) Diagnosis of fracture was objective: e.g. diagnosed by X-ray or other objective test such as computerised tomography, or reported in medical records;
(4) Quantitative dietary Ca intake was derived from at least three types of foods that were rich in Ca;
(5) More than thirty study subjects at entry;
(6) Subjects aged >35 years, and results adjusted for age;

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(7) Studies only in women or, if both male and female subjects were included in a study, data could be extracted for women separately, or adjusted for gender, or conditional logistic regression analysis was used for matched sets;
(8) Follow-up rate for cohort studies or response rate for case–control studies $>50\%$;
(9) Length of follow-up at least 1 year for cohort studies.

Information retrieval

Information retrieval was done by two of the investigators (L. X. and J. A.) with the help of two librarians specialising in database searches. MEDLINE was used to search for studies reported in English from 31 December 1999 using the following search terms: combination of 'fracture*' and 'Ca'; limited to female and human studies.

In addition, studies were identified from the reference lists of obtained papers, editorials and known studies. Authors were contacted if not enough data were included in the paper for analysis. The title and abstract of studies identified in the computerised search were scanned by two of the investigators (L. X. and J. A.) separately to exclude any that clearly did not meet the inclusion criteria. If the abstract and title did not provide sufficient grounds for acceptance or rejection, the original papers were retrieved. Differences were resolved by consensus. The full texts of the papers were retrieved for data extraction.

Data extraction and methodological quality assessment

For each included study, data extraction was performed by L. X. and J. A. separately. Differences were resolved by consensus.

The 'osteoporosis meta-analysis quality assessment form' for cohort and case–control studies derived by Robertson (1995) was modified to assess the methodological quality of the primary observational articles (see Tables 1 and 2 for details of rating scales).

Statistical analyses

Quality scores were used to provide information and explore reasons for heterogeneity, but not to weight studies. The intraclass correlation coefficient was used to examine the level of agreement for the quality scores between the two coders. This was calculated using a two-way ANOVA (Morton & Dobson, 1989) and using the total quality scores of each paper.

Heterogeneity of effect was tested for all studies using a general variance-based method (Sharp & Stern, 1997; Bradburn *et al.* 1998). If the P value was $<0{\cdot}2$, pooling was rejected and reasons for the heterogeneity were examined by regressing the mean effect against each of the following factors individually: age, ethnicity, study design, method of Ca measurement, mean dietary Ca intake level, year of data collection, response rate and/or follow-up rate, follow-up period, continent (Europe or North America) where the study was performed, quality score. These factors were defined *a priori*. Both unweighted and weighted methods (weighting by reciprocals of the variance) were used to check the results.

To check for publication bias, funnel plots were drawn and assessed using Egger's test (Egger *et al.* 1997).

Meta-analysis was performed using the method of Greenland & Longnecker (1992). Estimates of the linear association between dosage of Ca and the natural log of the odds ratio for hip fracture for each study were calculated. The dosage of Ca intake in each study was calculated as the midpoint of each Ca intake category. For the open-ended upper category of Ca intake, the median intake was estimated as the lower bound plus 30 %. The weighted mean values of the individual slopes were pooled to provide the summary risk ratio based on a fixed effects model.

The meta-analysis was done using STATA (version 6.0; Stata Corporation, College Station, TX, USA) and the method of Greenland & Longnecker (1992) was implemented in SAS (version 6.12; Statistical Analysis Systems Inc., Cary, NC, USA).

Results

The intraclass correlation coefficient for scoring agreement between two reviewers was 0·98. The results at different sites studied will be described separately later.

We identified 1582 publications on MEDLINE. Titles and abstracts were scanned to exclude those clearly irrelevant, such as studies addressing bone turnover, pure hormone therapy or cost-effectiveness analysis. The full texts of the remaining papers (n 47) were viewed; fourteen of these observational studies met the inclusion criteria. Two of the fouteen studies (Cummings *et al.* 1995; Schulz *et al.* 1995) were excluded due to duplicate reports. This left twelve studies covering: North America (USA, Canada), Europe (Italy, UK, Sweden, Norway) and East Asia (China). Four were prospective cohort studies and eight were case–control studies. Among eligible studies, one (Cumming *et al.* 1997) investigated hip, forearm and vertebral fractures (data could be extracted separately), one investigated hip and forearm fractures (Kreiger *et al.* 1992; data could be extracted separately), one investigated vertebral fractures (Chan *et al.* 1996) and the remainder investigated hip fractures. Because of the limited number of studies addressing vertebral and forearm fractures, only results of studies analysing the relationship between dietary Ca intake and hip fractures were pooled.

Calcium intake and forearm fractures

The two observational studies regarding Ca intake and forearm fractures (Krieger *et al.* 1992; Cumming *et al.* 1997) arrived at different conclusions: the cohort study by Cumming *et al.* (1997) did not show a protective effect of dietary Ca intake on forearm fractures, while a case–control study (Krieger *et al.* 1992) showed an odds ratio of 0·18 (95 % CI 0·04, 0·81) when Ca intake was >1000 mg/d compared with Ca intake <800 mg/d. Both of these studies took into account Ca supplements in separate analyses.

Table 1. Methodological quality assessment criteria for cohort study

Criteria	Score*
1. Representativeness of the exposed cohort	
Subjects were consecutive or randomly selected from representative group (e.g. community) or hospitalised patients in orthopaedic ward for hip fracture, and response rate ≥70 % of whole original population	2
Selected group (such as volunteers, nurses, hospital patients) or subjects were consecutive or randomly selected, but debatable whether the group is representative of elderly women (e.g. extensive eligibility criteria and no description of non-responders)	1
No description of the derivation of the cohort or response rate ≥70 %	0
2. Selection of the non-exposed cohort	
Drawn from the same community as the exposed cohort	2
Drawn from a different source	1
No description of the non-exposure cohort	0
3. Ascertainment of exposure	
Secure record, e.g. multiple 24 h records (at least three)	3
Structured interview (interviewed FFQ)	2
Written self report-current (self-administered FFQ) or one single 24 h record	1
No description	0
4. Demonstration that outcome of interest was not present at start of study	
Independent or blind assessment stated in the paper; confirmation of the fracture by reference to primary record source, e.g. X-ray or hospital records	2
Fracture with record linkage (derived from ICD codes in database file)	1
No description about the diagnosis of fracture or self-report without reference to any primary record	0
5. Comparability of the exposed and non-exposed cohort	
Risk ratios for Ca intake were adjusted or cohorts closely matched for age, activity, BMI (or weight), smoking, alcohol. Data must be shown for both users and non-users to ensure these criteria are met. Statements of no difference between groups or that differences were not statistically significant are not sufficient for establishing comparability	4
Groups matched or adjusted on age and three other variables	3
Groups matched or adjusted on age and two other variables	2
Groups matched or adjusted on age and one other variable	1
Groups not matched or adjusted on variables, or no description, or age >2 years difference between groups, activity level not comparable between groups, or BMI >5 % (or 1–2 kg/m^2), weight >3 kg difference or not adjusted	0
6. Assessment of outcome (fracture)	
Stated that outcomes were 'blinded' to either user or non-user; confirmation of fracture by reference to X-ray or hospital records	3
Fracture with record linkage (derived from ICD codes in database file)	2
Based on self-report, i.e. there is no reference to original hospital records or X-rays to confirm the outcome	1
No description	0
7. Was follow-up long enough for outcomes to occur	
> 1 year	2
≤ 1 year	0
8. Adequacy of follow-up of cohorts	
Almost complete follow-up (>95 %), intention to treat, statement of no withdrawals	2
Some subjects lost to follow-up, but overall follow-up >80 %, difference of follow-up in two groups <5 %	1
No statement	0

FFQ, food-frequency questionnaire; ICD, International Classification of Diseases.
* Total score 20.

Calcium intake and vertebral fractures

Two studies addressed vertebral fractures (Chan *et al.* 1996; Cumming *et al.* 1997). In a case–control study, Chan *et al.* (1996) found that those with a dietary Ca intake <247 mg/d had an odds radio of vertebral fracture of 2·1 (95 % CI 1·1, 3·9) compared with those whose Ca intake was >382 mg/d. In a cohort study Cumming *et al.* (1997) did not find any protective effect with a high Ca intake. Only Cumming *et al.* (1997) took Ca supplements into account in separate analyses.

Relationships between dietary calcium intake and hip fractures

Summaries of the characteristics and results of the eleven observational studies addressing hip fractures are shown in Tables 3 and 4 (Cooper *et al.* 1988; Lau *et al.* 1988; Wickham *et al.* 1989; Paganini *et al.* 1991; Krieger *et al.* 1992; Nieves *et al.* 1992; Looker *et al.* 1993; Michaelsson *et al.* 1995; Tavani *et al.* 1995; Cumming *et al.* 1997; Meyer *et al.* 1997). Four were prospective studies, two were nested case–control studies and five were case–control studies.

The mean follow-up period in cohort studies ranged from 5·2 to 14·6 years. The loss to follow-up ranged from 1 to 41 %. Response rates in case–control studies ranged from 61 to 97 % in cases and 56 to 97 % in controls. The methods used for dietary Ca intake were food-frequency questionnaire (nine studies), 7 d record (one study) and 24 h recall (one study). The quality score for case–control studies ranged from 9 to 13 out of a possible 18 with average of 11 (SD 1·5); for cohort studies it ranged from 11 to 17 out of 20, with an average of 14 (SD 2·6).

Table 2. Methodological quality assessment criteria for case–control study

Criteria	Score*
1. Is case definition adequate?	
Fracture with independent validation, ie. Reference to primary record source, e.g. X-ray or hospital record	2
Fracture with record linkage (derived from ICD codes in database file) or self-report without reference to any primary record	1
No description about the diagnosis of fracture	0
2. Representativeness of the cases	
Consecutive or randomly selected from representative group (e.g. community) or hospitalised patients in orthopaedic ward for hip fracture, and response rate $\leq 70\,\%$ of whole original population	2
Selected group (such as volunteers, nurses, hospital patients) or cases were consecutive or randomly selected but debatable whether the group is representative of elder women (e.g. extensive eligibility criteria and no description of non-responders)	1
No method of selection described or response rate $<70\,\%$	0
3. Selection of controls	
Controls were consecutive or randomly selected from the same community as the fractured group (have the same eligibility criteria unless no fracture) and response rate $\geq 70\,\%$ of whole original population	2
Control group was matched at onset with fracture group for baseline characteristics, or subjects drawn from a different source to the fracture group but low degree of mismatch or selected group (such as volunteers, nurses, hospital controls)	1
No mention of selection described or controls drawn from a different source to the fractured group and high degree of mismatch, or response rate $<70\,\%$	0
4. Definition of controls	
If cases are first fracture, then must explicitly state that controls have no history of hip, forearm or vertebral fracture. If cases were new hip, forearm and vertebral fracture (not necessarily first fracture), then controls should not exclude those with previous hip, forearm and vertebral fracture	1
No description of history of fracture in controls or have different fracture history from cases (e.g. cases were first fracture, while controls had previous history of fracture, or cases were new fracture while controls excluded those with previous fracture)	0
5. Comparability of cases and controls	
Odds ratios for Ca intake were adjusted or groups closely matched for age (± 2 years), activity, and weight (± 3 kg) (or BMI $\pm$ $<5\,\%$ or ± 1–$2\,kg/m^2$), smoking, alcohol. Results must be shown for both cases and controls to ensure these criteria are met. Statements of no difference between groups or that differences were not statistically significant or not sufficient for establishing comparability.	4
Groups matched or adjusted on age and three other variables	3
Groups matched or adjusted on age and two other variables	2
Groups matched or adjusted on age and one other variable	1
Groups not matched or adjusted on variables, or no description, or age >2 years difference between groups, activity level not comparable or weight >3 kg, or BMI $>5\,\%$ (or 1–$2\,kg/m^2$) difference or not adjusted.	0
6. Ascertainment of exposure	
Objective measure, e.g. multiple 24 h prospective records (at least three) or weighted food intake (at least 4 d)	4
Structured interview (interviewed FFQ) where blind to case or control status	3
Interview not blinded to case or control status	2
Written self-report or medical record only (self-administered FFQ or one single 24 h food record)	1
No description	0
7. Same method of ascertainment of previous Ca intake in cases and controls? Or blinded assessment of calcium intake	
Yes	1
No	0
8. Non-response rate	
Same rate for both groups or difference between groups $\leq 5\,\%$	2
Non-respondents described, or response rate difference between groups 5–10 %	1
Rate difference between groups $>10\,\%$ or no information	0

ICD, International Classification of Diseases; FFQ, food-frequency questionnaire.
*Total score 18.

There was evidence of heterogeneity across the eleven studies (Q 21·342, $P=0{\cdot}019$) addressing the association of hip fracture with dietary Ca intake. Regression analysis of the mean effect *v.* each of the following factors: age, ethnicity, study design, method of Ca measurement, mean dietary Ca intake level, year of data collection, response rate and/or follow-up rate, follow-up time (years), continent (Europe or North America) where the study was performed and quality score, showed that only ethnicity (Western or East Asian) had a clear relationship with mean effect; this was because of one study in Chinese women in Hong Kong who had very low Ca intake (median value 128 (interquartile range 75–176) mg/d; Lau *et al.* 1988) and high soyabean intake, with phyto-oestrogens providing protection from bone loss in ageing noted in East Asian populations (Potter *et al.* 1998; Messina, 1999). After removing this study, the pooled estimate among studies of white subjects showed no heterogeneity (Q 11·402, $P=0{\cdot}249$). The funnel plot showed no evidence of publication bias (Egger's test t 0·540, $P=0{\cdot}604$; see Fig. 1). It was not possible to show that dietary Ca was associated with hip fractures (risk ratio 1·01, 95 % CI 0·96, 1·07) (Fig. 2).

When the three study designs (prospective, nested case–control and case–control) were analysed separately, the pooled estimate of each study design showed no

Table 3. Observational studies of the effect of dietary calcium on risk of hip fractures in women aged ≥35 years*

Study reference	Country	Study type	Age (years)	Type of control	Response rate and/or follow-up rate (%)	Sample size (*n*)		Method of assessing Ca	Length of follow-up (years)	Quality score†
						Case	Control			
Paganini Hill *et al.* (1991)	USA	Pro	73	Population-based cohort	59	330	8560	FFQ (not validated)	5·2	11
Looker *et al.* (1993)	USA	Pro	50–74	White only, population-based cohort	97	122	2226	24 h recall	14·6	17
Cumming *et al.* (1997)	USA	Pro	≥65	White only, population-based cohort	99	306	9704	FFQ (validated)	6·6	13
Meyer *et al.* (1997)	Norway	Pro	35–49	Population-based cohort	83	150	19 290	Semi-quantitative FFQ (not clear)	11	15
Holbrook *et al.* (1988)‡	USA	Pro	50–79	White only, upper middle-class population-based cohort	100	33	924	24 h recall	14	9
Wickham *et al.* (1989)	UK	Nested CC	≥65	Practitioner committee lists	Case 95, control 100	42	144	7 d record		13
Michaelsson *et al.* (1995)	Sweden	Nested CC	40–75	Community-based	Case 87, control 84	247	893	FFQ (not validated)		13
Cooper *et al.* (1988)	UK	CC	≥50	Community, from GP register	Case 63, control 71	240	480	FFQ (validated)		11
Lau *et al.* (1988)	Hong Kong	CC	77	First: hospital; Second: community and GP unit	Case 96, control 90	280	560	FFQ (not validated)		10
Kreiger *et al.* (1992)	Canada	CC	50–84	Hospital-based orthopaedic or surgical patients	66 of case and control	102	227	FFQ (not validated)		10
Nieves *et al.* (1992)	USA	CC	≥45	Hospital-based general or orthopaedic patients, frequency-matched to age	Case 61, control 56	161	168	FFQ (validated)		9
Tavani *et al.* (1995)	Italy	CC	45–74	Hospital-based, surgical, eye, ENT, gynaecology, dental, skin, patients	97 in cases and controls	241	719	FFQ (not validated)		11
Jaglal *et al.* (1993)‡	Canada	CC	55–84	Population-based	Case 53, control 60	381	1138	FFQ (validated)		13
Cumming & Klineberg (1994)‡	Australia	CC	≥65	Community-based	Case 96, Control 83	209	207	FFQ (reproducible, no validity test)		9
Meyer *et al.* (1995)‡	Norway	CC	≥50	Community-based	Case 87, Control 55	246	246	FFQ (not valid)		8
Johnell *et al.* (1995)‡	Southern Europe	CC	≥50	Neighbours or population-based	Case 80, Control 84	2086	3532	Milk consumption semi-quantitatively		6

Pro, prospective study; FFQ, food-frequency questionnaire; CC, case–control study; GP, general practioner; ENT, ear, nose and throat.
*For details of procedures, see pp. 625–626.
†Score out of 18 for case–control studies; score out of 20 for cohort studies.
‡Study excluded.

Table 4. Quantitative results from eleven observational studies of the effect of dietary calcium on risk of hip fractures in women aged >35 years*

Reference	Study design	Ca intake (mg/d)	Total subjects (*n*)	Subjects with fracture (*n*)	Subjects without fracture (*n*)	RR	95 % CI
Paganini Hill *et al.* (1991)	Pro	≤280	2949	102	2847	1·00	
		281–500	2878	106	2772	1·02	0·77, 1·33
		≥501	2733	122	2611	1·11	0·85, 1·44
Looker *et al.* (1993)	Pro	<300	526	30	496	1·00	
		301–501	526	32	494	0·86	0·50, 1·50
		502–776	526	35	491	1·03	0·60, 1·70
		≥777	526	25	501	0·72	0·40, 1·30
Cumming *et al.* (1997)†	Pro	<400	1451	Total 306		1·00	
		400–799	2395			1·00	0·70, 1·30
		800–1199	1244			0·80	0·50, 1·20
		≥1200	733			0·90	0·50, 1·60
Meyer *et al.* (1997)	Pro	<435	4822	40	4782	1·00	
		435–568	4823	38	4785	0·86	0·55, 1·35
		569–717	4823	40	4783	0·87	0·56, 1·35
		≥718	4822	32	4790	0·67	0·42, 1·08
Holbrook *et al.* (1988)‡	Pro	391 (SD 199)	957	33	924	0·60	$P<0·01$§
Wickham *et al.* (1989)	Nested-CC	<588	62	14	48	0·70	0·10, 3·90
		588–801	62	14	48	0·90	0·20, 4·30
		≥802	62	14	48	1·00	
Michaelsson *et al.* (1995)	Nested-CC	<585	285	62	223	1·00	
		585–786	285	62	223	1·12	0·69, 1·80
		787–1000	285	62	223	1·13	0·68, 1·89
		>1000	285	62	223	1·54	0·86, 2·76
Cooper *et al.* (1988)	CC	<433	144	47	97	1·20	0·70, 2·20
		433–566	144	51	93	1·40	0·80, 2·50
		567–683	144	48	96	1·10	0·60, 2·00
		684–837	144	47	97	1·20	0·70, 2·10
		≥838	144	47	97	1·00	
Lau *et al.* (1988)	CC	<75	230	93	137	1·90	1·20, 2·90
		75–82	119	47	72	1·90	1·10, 3·10
		83–128	147	42	105	1·10	0·70, 1·90
		129–243	183	57	126	1·20	0·80, 2·00
		≥244	161	41	120	1·00	
Kreiger *et al.* (1992)	CC	<800	331	83	248	1·00	
		800–999	[48]	[19]	[29]	2·51	0·83, 7·60
		≥1000				1·89	0·75, 4·74
Nieves *et al.* (1992)	CC	<400	77	37	40	1·00	
		400–599	70	35	35	1·43	0·68, 3·00
		600–799	65	33	32	1·19	0·55, 2·54
		800–999	38	16	22	1·09	0·45, 2·63
		≥1000	79	40	39	1·24	0·59, 2·63
Tavani *et al.* (1995)	CC	≤443	192	49	143	1·00	
		443–685	192	51	141	1·20	0·70, 2·00
		685–895	192	45	147	1·10	0·60, 1·70
		895–1026	192	50	142	1·10	0·60, 1·70
		>1026	192	46	146	1·20	0·80, 2·00
Jaglal *et al.* (1993)‡	CC	0–799	793	169	624	1·00	
		800–1499	371	72	299	0·86	0·61, 1·20
		≥1500	90	17	73	0·85	0·41, 1·39
Cumming & Klineberg (1994)‡	CC	≤300	84			1·00	
		301–600	83			1·50	0·5, 4·7

Table 4. *Continued*

Reference	Study design	Ca intake (mg/d)	Total subjects (*n*)	Subjects with fracture (*n*)	Subjects without fracture (*n*)	RR	95 % CI
		601–1170	83			1·30	0·4, 3·8
		1171–1800	83	209	207	2·70	0·8, 8·5
		1801–3450	83			1·70	0·5, 5·4
Meyer *et al.* (1995)‡	CC	1SD	492	246	246	1·04	0·83, 1·31
Johnell *et al.* (1995)‡	CC	0–234	1524	645	879	1·00	
		240–299	712	253	459	0·75	0·61, 0·93
		300–359	850	274	576	0·65	0·53, 0·80
		≥360	2532	914	1618	0·77	0·66, 0·89

RR, risk ratio; pro, prospective study; CC, case–control study.
* For details of procedures, see pp. 625–626.
† The number of subjects in each group was not provided (total only given) but the author reported that only those without history of hip fracture were included for analysis. Therefore these numbers were estimated by excluding 40 % from each group who had a history of fracture before enrolment in the study (38 % in <400 mg/d group and 42 % in ≥1200 mg/d group).
‡ Excluded study.
§ 95 % CI not provided; *p* value provided.

Fig. 1. Funnel plot for ten observational studies of the effect of dietary calcium on hip fracture in women aged ≥35 years. For details of procedures, see pp. 625–626. The effect size was the slope of the line relating calcium quartile to hip fractures.

heterogeneity. In addition, the separate pooled risk ratios did not show any association between dietary Ca and hip fractures for each of the three study designs (Table 5).

The study conducted in East Asia (Lau *et al.* 1988) was the only one to show a very strong protective effect of increased Ca intake on hip fractures; the odds ratio was 0·48 (95 % CI 0·30, 0·76).

Discussion

The present review of observational studies failed to show that dietary Ca intake was related to risk of hip fracture in adult white women aged >35 years, except when Ca intakes were very low. This is different from the meta-analysis of Cumming & Nevitt (1997). There are multiple reasons for this discrepancy, as follows.

Some studies were not included even though they had been included previously in the other meta-analyses, because the present study used relatively strict inclusion and exclusion criteria. Five observational studies included in meta-analysis of Cumming & Nevitt (1997) were excluded. One was excluded because of lack of objective diagnosis of fracture (Holbrook *et al.* 1988), one due to very low follow-up rate (36·1 %; Jaglal *et al.* 1993), two due to lack of quantitative data (we contacted the authors, but received no reply; Cumming & Klineberg, 1994; Meyer *et al.* 1995) and one due to the fact that Ca intake was derived only from milk (Johnell *et al.* 1995). Among these studies, two showed Ca (Holbrook *et al.* 1988) or milk (Johnell *et al.* 1995) consumption had a protective effect; the other three did not show this effect. The two studies that showed protective effects had relatively large sample sizes (2086 cases and 3532 controls in the study of Johnell *et al.* (1995) and 957 in the cohort of Holbrook *et al.* (1988), while the other three studies had 837 cases and 1591 controls in total). Sensitivity analysis, including the results by Cumming & Klineberg (1994), did not change the results.

We did not pool the results when there was significant heterogeneity, while the other meta-analyses pooled results using the fixed-effects model despite heterogeneity (*P* for heterogeneity 0·02; Cumming & Nevitt, 1997).

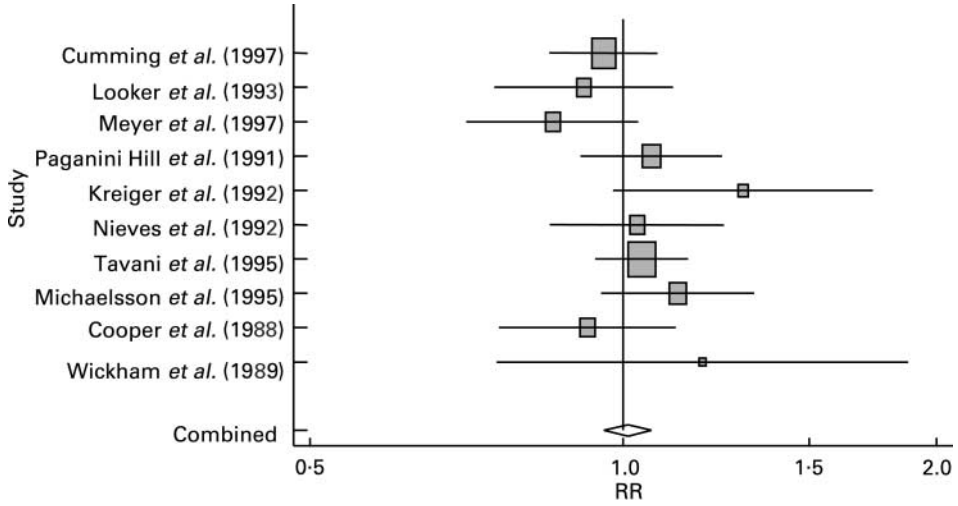

Fig. 2. Pooled risk ratio (RR) and 95% confidence intervals for dietary calcium on hip fracture in ten observational studies in women aged ≥35 years (excluding study in Hong Kong). For details of procedures, see pp. 625–626.

In the present study, we excluded studies if Ca intake was estimated from less than three sources; this was done to ensure that Ca intakes were not underestimated, since subjects derive Ca from multiple sources. The three major sources of Ca intake in western countries are whole milk, cheese and skimmed milk, which account for about 40% Ca intake (Block *et al.* 1985; Krogh *et al.* 1993; Favero *et al.* 1997). Studies using one source of Ca intake account for about one-fifth and using two sources about one-third of Ca intake at most, even when the most Ca-rich foods such as milk and/or cheese were included (Block *et al.* 1985; Krogh *et al.* 1993; Favero *et al.* 1997); using these methods would severely underestimate Ca.

One of the reasons that dietary Ca intake was not related to risk of hip fracture in adult white women aged >35 years might be that the baseline dietary Ca intakes in the included studies were relatively high: from >300 mg/d (Holbrook *et al.* 1988: cases 320, controls 401 mg/d) or median value 371 mg/d (Paganini Hill *et al.* 1991) to median value 730 (interquartile range 537–882) mg/d (Wickham *et al.* 1989). The relatively higher level of baseline dietary Ca intake might be enough to maintain blood levels, basic physiological functions and bone health. Thus, the increases in Ca intake offer no more protective effect for fractures. When the baseline intake of Ca is very low, as in the Hong Kong study (Ca intake: cases 128 (range 75–176), controls 168 (range 76–214) mg/d; Lau *et al.* 1988), the increased Ca intake may only maintain blood levels and basic physiological functions, but not be sufficient to strengthen bones and provide a protective effect for fractures. When the Ca intake increases further, increased intake not only maintains blood Ca levels, but can also be deposited in bone tissues to strengthen bone and prevent fractures. However, it is not clear if the protective effect of Ca intake has an upper limit beyond which the bone needs for Ca are saturated; this needs exploration.

There are many reasons why East Asian women differ from white women in this regard. They might include not only dietary habits such as low dietary Ca intake, low milk intake, high soyabean intake (Lau *et al.* 1988; Fujita & Fukase, 1992) and accompanying low protein intake (Nordin, 2000), but also other lifestyle factors such as types and levels of activity (Fujita & Fukase, 1992; Anderson, 2000), bone structure (Fujita & Fukase, 1992) and vitamin D receptor polymorphisms (Young *et al.* 1996). Further studies of specific East Asian populations are warranted to test the hypotheses.

Limitations of the present study

In any meta-analysis certain methodological points must be addressed.

(1) The present analysis only included studies published in English and retrieved on MEDLINE. Thus 'grey literature' (e.g. unpublished studies and company reports) or

Table 5. Separate estimates for each study design using fixed models*

Study design	No. of studies	Heterogeneity		Pooled RR	95% CI	
		Q	*P*			
All studies	10	11·402	0·249	1·01	0·96	1·07
Prospective	4	3·287	0·349	0·96	0·89	1·04
Nested case–control	2	0·049	0·824	1·14	0·97	1·33
Case–control	4	3·776	0·287	1·04	0·96	1·12

RR, risk ratio.
* For details of procedures, see pp. 625–626.

abstracts were not included. Exclusion of this literature has been shown to increase the estimate of the intervention effect by 10–15 % (Egger *et al.* 2002), and exclusion of abstracts to further increase the effect size by about 30 % (McAuley *et al.* 2000). However, there are problems with the practice of including grey literature: poor study quality due to lack of peer review (Angell, 1989), incomplete inclusion, and limitation of time, effort and cost involved in identifying, locating and retrieving grey literature (McAuley *et al.* 2000). Abstracts may not escape publication bias, since they also need to be peer reviewed before acceptance and presentation; positive abstracts are also easier to publish than negative abstracts (McAuley *et al.* 2000).

(2) Additional results also indicate that restricting searches to MEDLINE misses many controlled trials, which will overestimate effects by about 5 % (Egger *et al.* 2002), although the quality of studies identified through searching by hand or using other databases, e.g. EMBASE, does not differ from those on MEDLINE (Suarez-Almazor *et al.* 2000) and would not be expected to bias the summary effect size.

(3) The present meta-analysis was restricted to studies pubished in the English language. Some researchers have found that language restriction may affect results (Gregroire *et al.* 1995), causing a 10 % overestimation (Egger *et al.* 2002); other work has not borne this out (Moher *et al.* 2000).

All these factors would lead to an overestimate in the pooled effect and may be detected by the tests for publication bias. Since the Egger test was not significant and the pooled estimate showed no effect, we believe that these are not active issues in our present study.

Even though relatively strict inclusion and exclusion criteria were established, the quality of included studies was still not satisfactory. Most of the instruments of Ca-intake measurement were not validated. The representativeness of some studies was not clear. The duration of Ca intake measured was not clear for some studies. The difference of response rate in cases and controls were large in some studies. The review of subjects was unblinded in some studies. The recall bias between cases and controls was not mentioned in some studies. All of these issues might bias the combined results towards increasing the effect of dietary Ca on bone fractures, as seen in the previous meta-analyses.

Conclusions

Our conclusions are as follows.

(1) The data are very sparse and it is hard to draw any firm conclusion. However, the fact that several studies showed major differences in relationships (albeit not significant within study) does make one pessimistic that an effect is present. Our interpretation is that as long as Ca intake is within a reasonable range, there is no effect on hip fractures. Increasing dietary Ca, short of supplementation, is probably not an effective preventative measure for hip fractures in white women aged >35 years.

(2) At very low Ca intakes, the risk of fractures may increase. The only significant effect of dietary Ca on hip fractures was seen in the one study that included patients with very low dietary Ca intake. Because this study was also carried out in East Asian subjects, it is unclear whether it is the very low dietary Ca intake, soyabean intake in East Asian people or ethnicity that led to this effect. If further studies in East Asian countries confirm this, it would mean that East Asian subjects might be more sensitive to Ca compared with white subjects and lead to the identification of genetic factors in bone response to Ca.

(3) There are insufficient data to make any conclusions about the effect of dietary Ca on spine and forearm fractures.

A need exists for additional well-designed studies explicitly exploring the effects of increasing lengths of follow-up, age group and ethnicity on dietary Ca in postmenopausal women. The data suggested that Ca intake might have greater effects in East Asian populations than white. However, the evidence from East Asian countries was from a very small number of studies (only one from Hong Kong). More studies (both observational and experimental) from East Asian countries are needed to address this issue.

The discrepancies between our present results and previous meta-analyses also send a cautionary note about the potential bias introduced into meta-analytical results by the inclusion of lower quality trials and failure to address heterogeneity.

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