Calcium, Dairy Products and Osteoporosis

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Osteoporosis is a multifactorial disorder in which nutrition plays a role but does not account for the totality of the problem. 139 papers published since 1975 and describing studies of the relationship of calcium intake and bone health are briefly analyzed. Of 52 investigator-controlled calcium intervention studies, all but two showed better bone balance at high intakes, or greater bone gain during growth, or reduced bone loss in the elderly, or reduced fracture risk. This evidence firmly establishes that high calcium intakes promote bone health. Additionally, three-fourths of 86 observational studies were also positive, indicating that the causal link established in investigator-controlled trials can be found in free-living subjects as well. The principal reason for failure to find an association in observational studies is the weakness of the methods available for estimating long-term calcium intake. While most of the investigator-controlled studies used calcium supplements, six used dairy sources of calcium; all were positive. Most of the observational studies were based on dairy calcium also, since at the time the studies were done, higher calcium intakes meant higher dairy intakes. All studies evaluating the issue reported substantial augmentation of the osteoprotective effect of estrogen by high calcium intakes. Discussion is provided in regard to the multifactorial complexity of osteoporotic response to interventions and to the perturbing effect in controlled trials of the bone remodeling transient, as well as about how inferences can validly be drawn from the various study types represented in this compilation.

Key teaching points:

- A very large body of evidence establishes that high calcium intakes augment bone gain during growth, retard age-related bone loss, and reduce osteoporotic fracture risk.
- Dairy sources of calcium are at least as efficacious in this respect as are calcium supplements.
- The protein and sodium contents of dairy foods do not adversely affect the bone benefit of the dairy package of calcium, phosphorus, protein, and vitamin D.
- Osteoporosis is a complex, multifactorial disorder, and ensuring a high calcium intake is only one of several necessary preventive strategies.
- High calcium intakes are especially important as adjunctive therapy in patients with osteoporosis receiving currently approved bone-active drugs. With estrogen, for example, high calcium intakes greatly augment the protective estrogen effect.

INTRODUCTION

Osteoporosis is a condition of skeletal fragility characterized by decreased bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in risk of fracture [1]. Fractures occur not only because of the resulting intrinsic bony weakness, but also because of external factors such as falling, defective postural reflexes and insufficient soft tissue padding over bony prominences. Nutrition plays an important role in protecting against osteoporosis both by its direct involvement in development and maintenance of bone mass and by maintaining normal postural reflexes and soft tissue mass. Because osteoporotic fractures late in life are such multifactorial affairs, our approach to skeletal fragility must be multifaceted as well. And while nutrition is a key component of that approach, it must be understood that it addresses only a portion of this multifactorial problem. This insight both allows us to exercise a certain economy of our expectations and helps us to interpret the sometimes differing results of published studies.

Dairy products are themselves complex: they are polyvalent foods containing many essential nutrients. Their effects on bone health are likely more than can be accounted for by any single constituent, and, indeed, the totality of their effects may

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be more than the sum of the parts. Nevertheless, the one mineral present in abundance in dairy products and otherwise often deficient in the diets of the industrialized nations is calcium, which is, at the same time, the major cation of bone. Thus there is a natural and intuitively evident connection between dairy foods and bone health.

Although there is a respectable and persuasive body of evidence demonstrating beneficial effects on bone health of dairy products *per se*, most of the evidence for a bony benefit of high calcium intakes involved interventions in which calcium was given as a single nutrient (sometimes with vitamin D, as well).

In what follows I shall review first the part played by nutrition in the development and maintenance of a healthy skeleton, with special emphasis on those nutrients abundant in milk and milk products. I will then summarize the recent literature relating calcium intake to bone health and will note those studies that directly demonstrated that dairy products, specifically, produced the desired effects on bone health and fracture protection. Then I will summarize the role of calcium in treatment of established osteoporosis. Finally, because there is much public and media uncertainty concerning the rules for inference from studies of various sorts, as well as considerable inherent complexity both in bone biology and in osteoporosis itself, I have included an Appendix briefly treating those issues as they relate to interpreting the results of calcium intake interventions.

NUTRITION AND BONE HEALTH

Bone is living tissue like any other, and its cells have the same kinds of nutrient needs as those of the rest of the body, not just for energy supply, but for protein and micronutrients as well. Bone growth is stunted in general malnutrition, and specific bony abnormalities develop with deficiencies of protein, ascorbic acid, vitamin D, magnesium, zinc, copper and manganese, to name only a few of the better studied instances [2,3]. Additionally, bone depends upon dietary intake to supply the bulk materials needed for synthesis of the extracellular material which composes more than 95% of the substance of bone and which is largely responsible for its structural and mechanical properties. These bulk materials are mainly calcium, phosphorus and protein. Roughly half the volume of the extracellular material of bone consists of protein and the other half of calcium phosphate crystals. It is self-evident that a growing organism cannot amass this structural material if the bulk components of bone are not present in adequate amounts in the diet.

Moreover, the need for a mineral-rich diet persists even after growth has ceased. This is because calcium (particularly) is lost daily from the body in considerable quantity, and if this loss is not offset by corresponding inputs from ingested food, the body tears down bony structural units in order to scavenge their calcium. This behavior reflects the fact that, from an evolutionary standpoint, bone functions as a large nutritional reserve for calcium and phosphorus. (The mechanical significance of the skeleton arose later in the course of evolution, as vertebrates emerged from the sea and needed internal stiffening in order to resist gravity.) Also, since the diet of most terrestrial mammals and, specifically, evolving hominids, was very calcium-rich, there was no natural selective advantage related to evolving means of conserving calcium.

Calcium is lost through shed skin, hair, nails, sweat, urine and digestive secretions, with total daily losses in adults today, by these routes combined, in the range of 4 to 8 mmol, depending upon extent of physical activity and the levels of other dietary constituents, such as sodium. When absorbed calcium input from ingested foods in an adult fails to match daily losses, blood calcium levels begin to fall, setting in motion a chain of events, beginning with increased secretion of parathyroid hormone (PTH), which resorbs bone and releases its constituents into the blood.

This background helps to define the relationship between low calcium intake and low bone mass, both in respect to failure to achieve the genetically programmed peak mass (when calcium intake is inadequate during growth), and in respect to losses of bone after maturity (when ingested calcium is not sufficient to offset daily loss from the body).

In a general way, the same considerations apply to the other bulk constituents of bone, phosphorus and protein. However, these nutrients are less apt to be present in limiting quantities in modern diets. One notable exception may be the group of old elderly, in many of whom total *food* intake may be suboptimal. Fractures of the upper femur are known to be concentrated in individuals with multiple evidences of nutritional deficiency [4,5], suggesting that nutritional preventive measures would be helpful. While the fraction will vary from country to country, it can be estimated from U.S. data that, in the industrialized nations, roughly one-fifth of elderly individuals regularly ingest less than 60% of the RDA for either phosphorus or protein [6] (or both) and may thus be either in direct nutritional jeopardy or at least unable to respond adequately to modern bone-building pharmacotherapy. Delmi and colleagues [7] showed that hypoproteinemia is common in elderly patients admitted with fracture of the femoral neck, that protein supplementation improved outcomes after fracture, and even favorably altered the pattern of bone loss after fracture [8]. This is an important finding, inasmuch as it shows that the observed nutritional deficiency state is not solely a marker for frailty, but is actually causal instead.

Finally, it should be noted that elderly individuals given supplemental calcium and vitamin D, either alone or as an adjuvant to anti-osteoporosis drugs, may develop relative hypophosphatemia (which arrests bone repair) if attention is not paid to ensuring an adequate phosphorus intake. This is because the bone building stimulus pulls the constituents of bone mineral out of the blood and into the bone. (Bone mineral is, after

all, ~40% calcium and ~60% phosphate.) It may not be coincidental that the most dramatic of the nutritional trials in the elderly (see below) used calcium *phosphate* as the supplement, rather than the carbonate or citrate salt [9].

It goes without saying that dairy products provide, in addition to high quality protein, both calcium *and* phosphorus, and in a ratio tuned over the millennia of evolution to be optimal for the building of tissue. Where the question has been addressed, bone status is found to be significantly better in individuals with higher intakes of potassium and magnesium, as well as calcium [10,11]. In fact, in the work of New and colleagues [11], BMD exhibited the expected dose response relationship with intake quartile for several nutrients, including potassium. Since there is no known requirement for potassium *per se* for bone building, the most plausible interpretation of these data is that potassium serves as a marker for the quality of the total diet. Thus, the higher the potassium intake, the better the diet, overall. And, the better the diet, the better the bones.

STUDIES RELATING CALCIUM INTAKE TO BONE HEALTH

In the past 25 years there have been at least 139 published reports in English exploring the relationship between calcium intake and bone status (bone mass, calcium balance, bone loss, or fractures), almost all of them published since the work of the 1989 RDA Committee was completed. These 139 studies are assembled in Table 1, sorted according to inferential type (see Appendix), together with an indication of their findings and certain other pertinent features.

Investigator-Controlled Intervention Studies. Fifty-two of these studies consisted of investigator controlled interventions (randomized controlled trials, calcium balance studies and bone metabolic studies), 37 in adults, 14 in children or adolescents and one combining both age groups. All of the metabolic and physiologic studies [12–24] showed that higher calcium intakes produced better calcium retention or reduced bone remodeling. Two of these metabolic balance studies used dairy products as the calcium source. Several of the balance studies used dose-ranging approaches to estimate the average requirement for maximal retention during adolescence and for zero balance during maturity [15,17,19,21]. Results were in the range of 35 to 40 mmol/d for growth and varied from 22 to 40 mmol/d for mature adults. Even the low ends of these ranges are substantially above both typical intakes today and the 1989 RDAs.

All but two of the randomized, controlled trials (RCTs) in adults showed that elevating calcium intake reduced or halted age-related bone loss [9,25–45,47,49,50,52–61] or reduced osteoporotic fractures [9,31–34,52,54] at one or another bony site, or both. In one of the trials failing to find a benefit of increased calcium intake, the study consisted of only 77 healthy men in whom the mean calcium intake of the control group was 29 mmol/d (1159 mg), already relatively high [48]. In the other, the subjects were early postmenopausal women [46], a group in whom bone loss is predominantly related to estrogen withdrawal, not to nutrition (see below). Six controlled trials used dairy products as the calcium source, and all were positive.

All 15 of the RCTs and balance studies in children and adolescents showed greater bone gain in calcium-supplemented subjects than in controls, despite the fact that the control group in several of the studies was already ingesting a calcium intake close to, or above, the then applicable RDA. Four of these investigator-controlled interventions employed dairy products as the source of the supplemental calcium and one a fortified snack food. All were positive.

Four of the trials, while finding a positive effect of calcium intake in either pre- or late postmenopausal women, found a much smaller effect in women studied less than five years postmenopause [25,33,39,53]. Only a few other studies specifically tested calcium supplementation in early postmenopausal women. When compared with estrogen at this life stage, the calcium effect has generally been found to be either indistinguishable from placebo or intermediate between placebo and estrogen. (Nevertheless, the Food and Nutrition Board of the National Academy of Sciences in the U.S., in its summary of calcium requirements [147], specifically evaluated the question of the requirement in the early and late postmenopausal phases and concluded that there was insufficient information to allow separate recommendations for early and late postmenopause.)

As described in detail in the Appendix, all controlled manipulations of calcium intake produce a bone remodeling transient, generally expressing itself mainly during the first year of treatment. Only after this time can the nutrient effects of extra calcium on bone balance be evaluated. Most studies have failed to discriminate adequately between these two effects; hence, it is usually not possible to determine how much of a trial's effect reflects closing of the remodeling space and how much is a change in bone balance. One exception is a study by Reid *et al.* [55,56], in which the calcium-supplemented group increased bone mass 2% at the spine in the first year, with no significant change thereafter, while the placebo group lost at a rate of about 0.5%/yr throughout. The first-year gain reflects the expected remodeling transient. The test of the nutrient effect of the extra calcium comes in the analysis of the loss rate from year two onwards, which was significantly slower in the calcium-supplemented subjects than in the placebo-treated controls. Thus, the calcium-supplemented subjects benefited both from the reduced remodeling space and from the slowed rate of bone loss.

Taken together, these controlled trials demonstrate convincingly that prevailing calcium intakes in both children and adults are not sufficient to ensure full realization of the genetic potential or full protection of acquired bone capital and that increasing calcium intake across the life span will enhance bone acquisition during growth, stabilize bone mass at maturity and minimize bone loss during involution. These trials also

Table 1. Published Reports of Studies of Calcium Intake & Skeletal Status*

Senior Author	Ref.	Year	Age Group	Calcium source	Co-therapy	Effect	Outcome Variables	Bony site	Comment
Physiological & Metabolic Studies									
Abrams	12	1994	pubertal	diet	na	+	Ca metabolism	—	
Charles	13	1989	adult	diet	na	+	Ca balance +	—	
Hasling	14	1990	adult	diet	na	+	Ca balance	—	
Hasling	14a	1992	adult	diet	na	+	Ca balance	—	
Heaney	15	1977	adults	diet	na	+	Ca balance +	—	
Horowitz	16	1988	adults	suppl	na	+	Bone remodeling	—	
Jackman	17	1997	adolescent	dairy	na	+	Ca balance +	—	
Matkovic	18	1990	adolescent	diet	na	+	Ca balance	—	
Matkovic	19	1992	1—30 yrs	diet	na	+	Ca balance	—	
McKane	20	1996	adult	suppl	na	+	PTH & Dpd	—	
Nordin	21	1997	adol & adult	diet	na	+	Ca balance +	—	
O'Brien	22	1996	adolescent	diet	na	+	Ca absorption	—	
Recker	23	1985	adult	dairy	na	+	Ca balance	—	
Riggs	24	1998	elderly	suppl	na	+	PTH & Dpd	—	
Randomized controlled trials									
Aloia	25	1994	adult	suppl	na	+	bone mass	h,s,b	+ for hip & total body; 0 for spine
Baran	26	1989	adult	dairy	na	+	bone mass	s	
Bonjour	27	1997	children	Ca-fort foods	na	+	bone mass	b	
Cadogan	28	1997	adolescent	dairy	na	+	bone mass	b	
Cepollaro	29	1996	adult	min. H_2O	na	+	bone mass	r	
Chan, G	30	1987	adolescent	suppl	na	+	bone mass	r	prev. lactational bone loss
Chan, G	31	1995	children	dairy	na	+	bone mass	h,s,r,b	+ at spine & total body
Chapuy	9	1992	elderly	suppl	Vit D	+	fractures/bone mass	h	+ for both fractures & hip BMD
Chapuy	32	1994	adult	suppl	Vit D	+	fractures/bone mass	h	followup to Ref 9
Chevalley	33	1994	elderly	suppl	na	+	fractures/bone mass	h,s	+ for vert fx & hip bone loss
Dawson-Hughes	34	1990	adult	suppl	na	+	bone mass	h,s,r	+ for >5 yr postmenopausal
Dawson-Hughes	35	1997	elderly	suppl	Vit D	+	fractures/bone mass	h,s,b	+ at all bony sites; fewer fractures
Devine	36	1995	adult	suppl	na	+	bone mass	h	
Devine	37	1997	elderly	suppl	na	+	bone mass	h	extension of Ref 35
Dibba	38	2000	children	suppl	na	+	bone mass		
Elders	39	1991	adult	suppl	na	+	bone mass	s	
Elders	40	1994	adult	suppl	na	+	bone mass	s,m	0 in early postmeno; + premeno
Haines	41	1995	adult	suppl	ERT	+	bone mass	h,s	+ at hip; 0 at spine
Johnston	42	1992	child & adol	suppl	na	+	bone mass	h,s,r	
Lee	43	1995	children	suppl	na	+	bone mass	h,s,r	+ at spine & radius; 0 at hip
Lloyd	44	1993	child & adol	suppl	na	+	bone mass	s,b	
Nieves	45	1998	adult	suppl	na	+	bone mass	h,s,r	meta-anal; ERT-Ca interact
Nilas	46	1984	adult	suppl	na	0	bone mass	r	early postmeno only
Nowson	47	1997	adolescent	suppl	na	+	bone mass	h,s,b	
Orwoll	48	1990	adult	suppl	na	0	bone mass	s,r	control grp: 1159 mg Ca
Peacock	49	1997	elderly	suppl	na	+	bone mass	h	
Polley	50	1987	adult	suppl	na	+	bone mass	r	
Prestwood	51	1999	elderly	suppl	vit D	+	bone resorption	—	
Prince	52	1995	adult	dairy/suppl	na	+	bone mass	h,s	
Recker	53	1977	adult	suppl	na	+	bone mass	m,r	
Recker	54	1996	adult	suppl	na	+	fractures/bone mass	r	+ in prevalent fx group

* a report may appear in more than one category.

Year: the emphasis is mostly on studies published since 1980; see *AJCN* 36:986—1013 (1982) for earlier studies.

Effect: "+": significantly greater bone gain, reduced bone loss, reduced fracture, more positive Ca balance, reduced bone resorption.

"0": no significant change in the above.

"−": significantly greater fracture risk or significantly greater bone loss.

Co-therapy: any agent given as part of a trial that might affect response to Ca.

Calcium source: "dairy" indicated only when explicitly queried or manipulated by investigators; however, most of the high diet Ca sources would inevitably have been of dairy origin also.

Bony site: "b" = total body; "h" = hip; "r" = radius; "s" = lumbar spine; "o" = os calcis; "m" = metacarpals or phalanges.

Comment: special features singled out; for fracture end-point in observational studies, study type identified.

Table 1. Continued

Senior Author	Ref.	Year	Age Group	Calcium source	Co-therapy	Effect	Outcome Variables	Bony site	Comment
Reid	55	1993	adult	suppl	na	+	bone mass	s,b	
Reid	56	1995	adult	suppl	na	+	bone mass	s,b,h	extension of Ref 55
Renner	57	1998	adolescent	dairy	na	+	bone mass	r	
Riggs	24	1998	elderly	suppl	na	+	bone mass	h,s,b	
Riis	58	1987	adult	suppl	na	+	bone mass	s,b,r	3-way trial with ERT
Specker	59	1996	adult	diet/suppl	na	+	bone mass	s,r	meta-anal; exercise-Ca interact
Storm	60	1998	elderly	dairy/suppl	na	+	bone resorption/ mass	h,s	+ for both resorption & BMD
Strause	61	1994	adult	suppl	na	+	bone mass	s	4-way trial with tr. minerals
Observational studies									
Andon	62	1991	adult	diet	na	+	bone mass	s	
Aptel	63	1999	elderly	min H_2O	na	+	bone mass	h	EPIDOS study
Barr	64	1998	adult	diet	na	+	bone mass	s	vegetarians/omnivores
Barrett-Connor	65	1994	elderly	diet	na	+	bone mass	h,s	milk offset neg caffeine effect
Bauer	66	1993	adult	suppl	na	0	bone mass	r,o	
Black-Sandler	67	1985	adult	dairy	na	+	bone mass	r	
Chan, G	68	1991	child & adol	diet	na	+	bone mass	r	
Chan, H	69	1996	adult	diet	na	+	vert fractures	—	case-control study
Chiu	70	1997	adult	diet	na	+	bone mass	h,s	late vegetarian effects
Cumming	71	1994	elderly	diet/dairy	na	−	hip fractures	—	recalled dairy 60 yrs earlier
Cumming	72	1997	elderly	diet	na	−	fractures	—	cohort study (SOF)
Cumming	73	1997	elderly	diet	na	+	fractures	—	meta-analysis
Cummings	74	1995	elderly	diet	na	0	hip fracture	—	cohort study (SOF)
Davis	75	1995	adult	suppl	na	+	bone mass	o,r	Ca augments ERT
Davis	76	1996	adult	dairy	na	+	bone mass	r,s,o	
Farmer	77	1989	elderly	diet	na	0	hip fractures	—	NHANES-I cohort followup study
Feskanich	78	1997	adult	diet	na	0	fractures	—	cohort study
Finkenstedt	147	1986	adult	dairy	na	+	osteoporosis	—	case control study
Fujiwara	79	1997	elderly	dairy	na	+	hip fractures	—	cohort study
Fuss	80	1990	adult	diet	na	+	bone mass	r	male stone formers
Gunnes	81	1996	child & adol	diet	na	+	bone mass	r	
Halioua	82	1989	adult	diet	na	+	bone mass	r	
Henderson	83	1994	child & adol	diet	na	+	bone mass	h,s	
Hirota	84	1992	adult	diet/dairy	na	+	bone mass	r	
Holbrook	85	1988	elderly	diet	na	+	hip fracture	—	cohort study
Honkanen	86	1996	adult	diet	na	+	bone mass	h,s	± lactase nonpersistence
Honkanen	87	1997	adult	diet	na	+	fractures	—	± lactase nonpersistence
Hoover	88	1996	adult	diet	na	+	bone mass	h,s	
Hu	89	1993	adult	diet	na	+	bone mass	r	
Ilich	90	1998	children	diet	na	+	bone mass	b,r	
Johnell	91	1995	elderly	diet/dairy	na	+	hip fracture	—	case control study (MEDOS)
Kanis	92	1992	adult	diet	na	+	hip fracture	—	case control study
Kanis	93	1999	adult	dairy	na	+	hip fracture	—	case control study (MEDOS)
Kardinaal	94	1999	adolescent	diet	na	+	bone mass	r	strongest assoc pre-menarche
Kelly	95	1990	adult	diet	na	+	bone mass	h,s	males
Kelsey	96	1992	elderly	diet	na	0	upper extr. fractures	—	0 wrist; + humeral
Kiel	97	1997	adult	diet	na	+	bone mass	b	calcium effect in VDR(bb) genotype
Kleerekoper	98	1989	adult	diet	na	0	vert. fractures	—	case control study
Kristinsson	99	1994	adolescent	diet	na	+	bone mass	r	
Lau	100	1988	elderly	diet	na	+	hip fracture	—	case control study
Lau	101	1990	elderly	diet	na	+	hip fracture	—	case control study
Lau	102	1998	elderly	diet	na	+	bone mass	h,s	vegans vs omnivores
Lee	103	1993	children	diet	na	+	bone mass	r	
Looker	104	1993	adult	diet	na	0	hip fracture	—	cohort study
Matkovic	105	1979	adult	diet	na	+	bone mass/fractures	m	0 wrist fx; + bone mass & hip fx
Michaelsson	106	1997	adult	diet	na	+	bone mass	h,s,b	

Table 1. Continued

Senior Author	Ref.	Year	Age Group	Calcium source	Co-therapy	Effect	Outcome Variables	Bony site	Comment
Moro	107	1996	adolescent	diet	na	0	bone mass	b,h	
Murphy	108	1994	elderly	dairy	na	+	bone mass	h,s	
New	11	1997	adult	diet	na	+	bone mass	h,s	
Nieves	109	1992	adult	diet	na	0	hip fracture	—	case-control study
Nieves	110	1995	adult	diet	na	+	bone mass	h,s,r	
Nordin	111	1987	adult	diet	na	+	bone mass	r	
Ooms	112	1993	elderly	diet	na	0	bone mass	h,r	mean Ca intake high all groups
Orwoll	113	1996	elderly	diet	na	+	bone mass	h,s	
Owusu	114	1997	adult	diet	na	0	fractures	—	cohort study
Parsons	115	1997	adolescent	diet	na	+	bone mass	h,s,b,r	vegan diet effects on growth
Pettifor	116	1997	children	diet	na	+	bone mass	r	
Pollitzer	117	1989	adult	diet	na	+	bone mass	h,s,b,m	
Ramsdale	118	1994	adult	diet	na	+	bone mass	h,s,r	
Recker	119	1992	young adult	diet	na	+	bone mass	r,s,b	
Reid	120	1994	adult	diet	na	+	bone mass	h,s	
Rubin	121	1999	adult	diet	na	+	bone mass	h,s	+ hip; 0 spine
Ruiz	122	1995	child & adol	diet	na	+	bone mass	h,s	
Salamone	123	1996	adult	diet	na	+	bone mass	h,s	
Shaw	124	1993	adult	diet/dairy	na	+	bone mass	s	
Slemenda	125	1992	adult	diet	na	+	bone mass	r	males
Smart	126	1997	adolescent	diet	na	+	bone mass	h,s,b	+ hip & spine; 0 total body
Sone	127	1996	adult	dairy	na	+	bone mass	h,s	
Soroko	128	1994	adult	dairy	na	+	bone mass	h,s,r	
Specker	129	1999	infant	diet	na	+	bone mass	b	
Stracke	130	1993	adult	dairy	na	+	bone mass	r	
Suleiman	131	1997	adult	diet	na	+	bone mass	h,s,o	
Tavani	132	1995	adult	diet	na	0	hip fracture	—	case-control study
Teegarden	133	1999	young adult	dairy	na	+	bone mass	h,s,r	
Tsukahara	134	1997	adolescent	diet	na	+	bone mass	m	
Turner	135	1998	elderly	dairy	na	0	hip fracture	—	case control (NHANES-I)
Tylavsky	136	1988	elderly	dairy	na	0	bone mass	r	
Ulrich	137	1996	adult	dairy/suppl	na	+	bone mass	b	
Uusi-Rasi	138	1997	child & adol	diet	na	0	bone mass	h,s,r	Ca Int high all groups
van Beresteijn	139	1990	adult	diet	na	0	bone mass	r	
VandenBergh	140	1995	children	dairy	na	0	bone mass	m	mean Ca intake v. high all groups
Welten	141	1994	adolescent	dairy	na	0	bone mass	s	
Wickham	142	1989	adult	diet	na	+	hip fracture	—	cohort study; + men; 0 women
Wittich	143	1998	young adult	dairy	na	0	bone mass	b	
Wolman	144	1992	adult	diet	na	+	bone mass	s	female athletes
Wyshak	145	1989	adult	dairy	na	+	fractures	—	cohort study
Yano	146	1985	adult	dairy	na	+	bone mass	r,o	men & women

show that previous RDAs were not adequate to ensure optimal bone status in individuals consuming Western diets.

Observational Studies. Of the 86 observational studies, 69 were in adults and 17 in children or adolescents. Sixty-four found a significant positive association between calcium intake and bone mass, bone loss or fracture risk [11,62–65,67–70, 73,75,76,79–95,97,99–103,105,106,108,110,111,113,115–131, 133,134,137,142,144–147]; one found a positive effect in men only [141]; 19 found no effect [66,74,77,78,96,98,104,107, 109,112,114,132,135,136,138–141,143] and two found a negative effect [71,72]. In one of these negative trials [72] the authors state explicitly that they interpreted their findings not as a true negative effect of calcium but as a reflection of limited ability to control for confounding variables. Four of the 16 observational studies in children and adolescents found no effect [107,138,140,141], while 12 were positive.[1]

Thus a clear majority (approximately three-fourths) of the observational studies also support the hypothesis that increased calcium intake protects the skeleton. Given the problem of accurately assessing lifetime integrated calcium intake from

[1]Another study, not directly assessing calcium intake, showed that fracture risk in adolescents was a function of bone mass, just as in the elderly [149]. This latter finding

current self reports, it is remarkable that so many of the observational studies were positive. That fact itself speaks to the strength of the association.

For reasons discussed in more detail in the Appendix, the overwhelmingly positive data from the stronger, controlled trials renders these observational studies, in a certain sense, superfluous. Nevertheless, it is distinctly helpful to know that the effects achievable in the artificial context of a controlled trial, often using non-food sources of calcium, can be seen also in a more natural situation, in which the principal calcium source is food (and high calcium intakes almost always mainly from dairy sources). Also, since the observational studies generally involve no alteration of customary calcium intakes, there is no study-induced change in bone remodeling, and hence most observational studies avoid the confounding problem of the remodeling transient. An example of the kind of support an observational study can provide is seen in the study of Recker *et al.* [119] of third decade women. In a four-year prospective study the authors showed that bone mass was still increasing in these fully grown young women and that gain was greater in those with higher self-selected calcium intakes.

The general congruence of the data from the two study types reinforces the conclusion that a higher calcium intake confers a bone benefit. The fact that the proportion of positive studies is somewhat smaller for observational studies than for controlled trials (and the effect size seemingly smaller [73]) can be explained, as already noted, in part by the much weaker ability to quantify calcium intake in observational studies [150] and in part by the fact that the effect seen in the RCTs is inflated by being a compound of the remodeling transient and an improvement in bone balance.

Consistent with, and supportive of the foregoing conclusions has been the virtually universal finding in epidemiological studies that thiazide use is associated with decreased hip fracture risk [e.g., 151,152]. Thiazides decrease obligatory urinary calcium loss. Because net intestinal absorption efficiency for calcium is only about 10%, a decrease in urine calcium of as little as 1 mmol/d produces effectively the same result as an increase in dietary calcium of 10 mmol/d. Thus, while not strictly reflective of calcium *intake*, thiazide use is in one sense equivalent to dietary supplementation.

Meta-analyses and Study Syntheses. The foregoing compilations have cited individual, peer-reviewed publications, without fitting them into any *a priori* scheme beyond their study type. However, during the past 10 years there have been several formal meta-analyses of calcium trials published [59,73,153,154] and one compilation [19] of studies measuring calcium balance during growth. The studies included in the meta-analyses were, up to the dates of their publication, much the same as those listed in the foregoing summary, and the conclusions that all reached are concordant with the results of this summary compilation, i.e., a higher calcium intake protects the skeleton and reduces fracture risk. In one [59], the author was able to show, from published trials, that the beneficial skeletal effect of increased physical activity was achievable only at calcium intakes above 25 mmol/d (1000 mg).

Matkovic and Heaney assembled over 500 published metabolic balances for calcium obtained during growth [19] and demonstrated, for food calcium sources (mainly dairy), that calcium retention in humans follows a threshold pattern of behavior comparable to that previously shown for laboratory animals [155]. This pattern of behavior allowed estimation of minimal requirements by growth stage, which the authors calculated as approximately 35 mmol/d in children, 2 to 8 years, 37 mmol/d in adolescents, 9 to 17 years, and 27 mmol/d in young adults, 18 to 30 years.

Estimated Average Requirements. Only a few of the individual clinical studies were explicitly dose ranging, so, aside from the few balance-based estimates such as those of Matkovic and Heaney [19], the precise quantity of calcium required to produce the full benefit at each life stage cannot be unambiguously determined. Nevertheless, total calcium intakes in the treatment arms of most of the controlled trials ranged between 37.5 and 60 mmol (1500–2400 mg/d), while control group calcium intakes were generally in the range of 12–20 mmol/d (480–800 mg/d). In the study of Jackman *et al.* [17], each girl was studied on two intakes so as to allow estimation of the response plateau. The authors' estimate of the mean requirement from the aggregate of all of their studies in peripubertal girls was 32.5–37.5 mmol/d (1300–1500 mg/d), essentially the same as the estimate Matkovic and Heaney [19] derived from pooling published balance data.

Although cross-sectional in nature, the study of calcium balance in middle-aged women by Heaney *et al.* [15] indicated a mean requirement of approximately 25 mmol/d for estrogen-replete women and approximately 40 mmol/d for estrogen-deprived. Hasling *et al.* [14a] using similar methods found a mean requirement in women with osteoporosis of slightly more than 30 mmol/d. The balance studies of Nordin [e.g., 21] result in a somewhat lower estimate (~22 mmol/d), but are otherwise consistent with the foregoing in that lower intakes cause excessive bone loss and weaken the skeleton. In this same connection, the physiological studies of McKane *et al.* [20] showed that the elevated parathyroid function and high bone remodeling typically found in elderly women could be restored to young adult normal levels by a calcium intake averaging ~60 mmol/d. Whether the same benefit could have been achieved at a somewhat lower intake is uncertain; however, the control group in the McKane study had an average intake of ~20 mmol/d, and their PTH function and bone remodeling were

established that strong bones confer a *current*, and not just a delayed, benefit, even in children.

clearly higher than young adult normal. It seems likely, therefore, that the Nordin estimate, which was virtually the same as the control group intake in the McKane study, may be low, at least for older women.

Comment. It would not have been possible, within the space available here, to touch upon most of the foregoing studies individually. Manifestly not all are of equal strength, nor are they all intercomparable. Some had sample sizes insufficient to find likely effects; others combined calcium with other nutritional interventions (indeed, this is inevitable whenever dairy foods, for example, are used as the calcium source). Others tested calcium effects in groups who already had relatively high calcium intakes. (Predictably, they found little effect.) Nevertheless, the aggregate impact of them all and the congruence and internal consistency of the findings from various study types establish firmly the conclusions reached at the 1994 Consensus Development Conference on Optimal Calcium Intake [156], namely: 1) high calcium intakes are important throughout life, 2) the American people are not getting enough today, and 3) the need is greater than had once been thought.

CALCIUM TREATMENT IN OSTEOPOROSIS

The foregoing section has dealt primarily with calcium *nutrition*; to some extent it presumed underlying health in individuals exposed to differing levels of calcium intake and focused on prevention of skeletal problems attributable to nutritionally-induced reduction in bone mass. In doing so, it summarized the evidence indicating the importance of a high calcium intake throughout life and showed how low intakes predispose to development of osteoporosis by reducing achieved peak bone mass during growth and by causing or aggravating age-related bone loss later in life. In brief, it summarized the evidence with respect to why high calcium intakes are recognized as protective against osteoporosis [157].

But there is an additional question: What role does a high calcium intake play for individuals who already have depleted skeletons? As noted above, the calcium-induced reduction in remodeling produces a modest increase in strength of the bony structures present at the time supplementation is started. But, with the stimulus of growth long past, and with some of the bony scaffolding already destroyed by prior bone loss, supplemental calcium alone does not usually restore lost bone. However, high calcium intakes play a crucial and often little appreciated role as an adjuvant to formal therapeutic regimens. For example, high calcium intake augments the bone protective effect of standard estrogen replacement therapy in postmenopausal women [45,75,158], allowing a doubling or even tripling of the estrogen effect. Moreover, very high calcium intakes are clearly essential to support an osteogenic regimen such as fluoride therapy [159].

These latter findings should not be surprising: while hormonal and pharmacotherapy may provide the stimulus for bone building, such agents do not themselves provide the raw materials of bone, which must come from the diet. Most of the therapeutic trials of bone-active agents have used, at most, very modest levels of calcium supplementation, and virtually none has used currently recommended maintenance intakes. It is likely, therefore, that we do not yet know the full therapeutic efficacy of the several agents now approved for treatment or prevention of osteoporosis, simply because none has been formally tested in the presence of full calcium and vitamin D sufficiency. From the fragmentary, but consistent, evidence now available, it seems prudent to accompany most of the current regimens directed at increasing bone mass with a calcium intake in the range of 40–60 mmol/d.

DAIRY PRODUCTS AS A SOURCE OF NEEDED NUTRIENTS

Six of the randomized controlled trials in adults and children used dairy products as the principal source of calcium. All showed significantly positive effects that were at least as strong as the effects of calcium supplements. This should come as no surprise. It is long established and well understood that milk supports growth; thus, it is evident that milk and milk products are good sources of the nutrients needed for bone development and maintenance.

One sometimes encounters arguments that the protein and sodium of milk somehow negate the potential benefit of its calcium. These speculations are based on the established fact that both protein and sodium lead to increased urinary calcium excretion [160,161]. However, the negative effects of protein and sodium are observed mainly at low calcium intakes, when, with absorption already operating at an individual's maximum, there is no possibility of increasing calcium extraction from the diet so as to offset an increment in excretory loss. By contrast, at high calcium intakes and correspondingly lower absorption efficiencies, the body has room to adapt to altered loads. Moreover, even at low calcium intakes, the ratio of the calcium in milk to its sodium and protein content is so high as to offset directly any calciuric effects; that is, even without physiological adjustment, the calcium absorbed exceeds the calcium eliminated by virtue of sodium and protein. Finally, the argument is curious on its face. Had it any cogency, milk could never support growth, nor could it sustain health in adults, yet it manifestly does both, as for example, in infants and children of all races and in adults of nomadic, pastoralist peoples.

The total nutrient content of milk is also well understood, and it is almost unnecessary to state here that milk products are richer sources of calcium, phosphorus, magnesium, potassium, zinc and protein, per unit energy, than the average of other typical foods in an adult diet. As a consequence, a diet devoid of dairy products will often be a poor diet, not just in respect to

calcium, but for many other nutrients as well. Devine *et al.* [10], in their study of milk supplementation in postmenopausal women, described a substantial improvement in intake of 10 key nutrients in individuals randomized to receive a milk supplement, and when Barger-Lux and Heaney [162] analyzed the diets of premenopausal female volunteers, they noted that women getting less than 60% of the recommended calcium intake had intakes formally deficient with respect to at least four other key nutrients as well. Analysis of their data reveals that one or two servings of dairy products would have corrected virtually all of those shortfalls.

Thus, while it is possible to arrange an adequate diet using available Western foods, it is usually difficult to do so without including dairy products. Few individuals succeed, and, in general, a diet low in dairy foods means a diet that is poor in several respects beyond insufficiency of calcium. Additionally, in the industrialized nations with a dairy industry, milk is almost always less expensive per calorie than the average of all foods in the diet. Thus a high dairy-food intake is cost-efficient as well as cost-effective.

APPENDIX: INTERPRETATION OF THE EVIDENCE

Clinical studies of the relationship to bone health of dairy products and of the nutrients they contain present special difficulties related both to bone biology and to study design. The evidence produced by such studies can easily be misinterpreted unless there is understanding of these issues. These matters are therefore discussed briefly here.

Bone Remodeling and the Remodeling Transient

Bony tissue is continually remodeling itself, for several reasons: 1) to adapt bone structure to new loads, 2) to repair incurred fatigue damage and 3) to regulate extracellular fluid [Ca^{++}]. Typical bone remodeling follows a stereotyped sequence: first, a microscopic site is activated; then, osteoclastic resorption erodes into the bony surface; then, later, osteoblastic formation fills in the cavity. The total quantity of skeletal remodeling is regulated by circulating levels of parathyroid hormone (PTH), which operates mainly by controlling the activation threshold for new remodeling loci. (A reduction today of PTH leads to fewer new remodeling loci's being activated today, while an increase in PTH leads to more loci being activated.) Because of the temporal sequence of the remodeling phases, any acute reduction in remodeling suppresses bone resorption first. However, mineralizing bone at previously activated remodeling sites continues to come back into service at the rate at which it was earlier remodeled, i.e., faster than new units are being taken out of service. This temporary imbalance increases measurable bone mass for a time. This phenomenon is known as "filling in the remodeling space" and produces a change in bone mass and/or calcium balance termed a "remodeling transient" [163]. In children and adolescents the transient lasts from three to six months after starting on a PTH suppressive regimen, in mature adults, from six to 12 months, and in the elderly, it may continue to evolve for as long as 18 months. This means that first-year effects of any intervention that alters bone remodeling can be dominated, at least in adults, by changes that represent principally the remodeling transient. As much as anything else, the presence of such first year effects indicates mainly that the subjects took the prescribed supplement and that the remodeling apparatus is responding normally. In brief, response over the first six to twelve months of treatment with supplemental calcium tells us relatively little about what may occur later.

PTH is secreted in response to both systemic, i.e., *non-skeletal*, calcium demand and to the demands to mineralize bone undergoing the formation phase of the remodeling cycle. PTH secretion is reduced to low levels on high calcium intakes and rises to high levels on low intakes. As a direct consequence, the quantity of bone being remodeled at any given time is an inverse function of effective calcium intake. Thus, whenever calcium intake is raised experimentally in a group of adults, bone remodeling falls, first resorption, then, later, formation, as well. That response is an inescapable consequence of the way the system is controlled and does not necessarily have nutritional significance, particularly since it will happen even at calcium intakes well above the nutritional requirement.

At the same time, and despite the self-limited character of the transient, it must also be said that this one-time increase in bone mass does result in a small increase in bone strength in its own right (which becomes relatively more important in individuals with depleted skeletons). This increase in strength is partly because there is more usable bone available to the subject to resist the forces experienced in daily living. Also, since remodeling sites are themselves foci of weakness until fully repaired, a lowering of remodeling strengthens bone by reducing the number of these points of local weakness. Thus, in this sense, a high calcium intake can be said to be good for bone, even if it did nothing more than slow remodeling. This conclusion might seem strange, since remodeling has as one of its purposes the repair of micro-damage in bone. In other words, remodeling should, ultimately, lead to stronger bone. However, the calcium intake of evolving hominids was regularly far higher than what, for modern humans, would seem to be "high," and it is likely that much of the remodeling in skeletons of individuals consuming contemporary calcium intakes serves *homeostatic* rather than *structural repair* purposes, i.e., it is a consequence of contemporary low intakes and is driven by extraskeletal calcium needs rather than by skeletal microdamage. By contrast the remodeling rates of our hominid ancestors would have been substantially below ours, and it may be presumed that such lower rates are sufficient to repair fatigue damage. Higher calcium intakes can therefore be seen

as suppressing mainly the homeostatic component of remodeling and as restoring a more natural remodeling context for the skeleton.

While an understanding of the remodeling transient is necessary to interpret interventional studies, there is, of course, more to the matter of calcium intake than simply slowing remodeling. Calcium intake influences bone balance, i.e., the difference between the quantity of bone removed in the resorptive phase of the remodeling process and the quantity ultimately returned in the reparative phase. If absorbed calcium is less than excretory and dermal losses, then the body will break down bone to scavenge its calcium, i.e., low calcium intakes contribute to or, in some individuals, may be wholly responsible for the negative bone balance that produces age-related bone loss and the fragility and fractures that it causes. For this reason, individuals on higher calcium intakes will, in general, be losing bone less rapidly than individuals on low intakes. When calcium supplementation is studied in a controlled trial, the remodeling transient can make it difficult to ascertain steady-state rate of change since, if measurement is made from the start of an intervention, *any* remodeling suppressive regimen will appear to halt or even reverse bone loss. To determine whether or not it actually does, it is necessary to begin the measurement of rate of bone loss after the transient has fully expressed itself [163], not from start of treatment. Few studies have reported their data in this way. One that did, discussed above, was the study in postmenopausal women of Reid *et al.* from New Zealand [55,56]. At the end of three years of intervention with a 25 mmol calcium supplement, bone mass was significantly greater in the treated subjects than in the controls, as would be expected from simple remodeling suppression. More importantly, while bone loss continued in both groups after the transient, the rates of loss in years two and three were significantly slower in the calcium-supplemented group than in the controls, thus establishing, at least for this group, that low calcium intake was a part of the cause of their age-related loss and that raising the calcium intake reduced this drain.

The Heterogeneity of Osteoporosis

Osteoporotic fractures are multifactorial in nature. Among the many identified pathogenetic factors may be listed low bone mass, altered bone architecture, reduced inherent bone material strength, age-related changes in postural reflexes and in falling patterns, and varying soft tissue distribution over bony prominences. Each of these factors has its own determinants; for example, bone mass is dependent upon gonadal hormones, nutrition, exercise and various life-style factors, as well as upon medical diseases and their treatments. These many interacting factors have been explored in greater detail elsewhere [164].

The importance of discussing this complexity here is to underscore the fact that no single intervention, whether pharmacologic, hormonal or nutritional, can be expected to solve the whole osteoporosis problem. Even within the same individual, fractures at different bony sites probably have different pathogeneses. For example, in the study by Matkovic *et al.* from Croatia [105], individuals with high life-time calcium intakes had far fewer hip fractures than those with low intakes, but there was no significant difference in wrist fracture incidence in the two groups. Ignoring the effects of differences in calcium intake, it remains very clear that the two populations had different fracture *patterns*. Another example is the frequent observation that Japanese (and Asians generally) have somewhat more vertebral osteoporosis than Caucasians (by a factor of $\sim$1.2–1.5$\times$); nevertheless, they have only one-half the hip fracture rate of Caucasians [165]. Possible protective factors for Asians include shorter hip-axis length, smaller hip-axis angle and the trophic effect on hip structures of squatting (as contrasted with life-long chair-sitting in Caucasians).

Yet another example is found in the report of Ettinger *et al.* [166] of fracture prevention with estrogen in postmenopausal women. The authors report a $\sim$70% reduction in vertebral fractures in estrogen-treated women, no effect on tibial or humeral fractures and an actual increase in risk of rib fractures. While the latter is probably a chance occurrence, it is clear from the pattern of responses in this study that bony response, even to an agent universally recognized as efficacious, is not constant across the skeleton.

Given both this heterogeneity and the associated multiplicity of factors influencing bone at each skeletal site, it should not be surprising that a particular intervention reduces fractures at some sites in some populations, but not in others. The questions with regard to calcium are not whether it will influence fractures at all sites in all individuals of all races, but whether it will reduce some fractures in some individuals and whether the size of the effect is large enough to warrant public policy changes or public health interventions.

Controlled Trials and Observational Studies

It is generally recognized that investigator-controlled, prospective, interventional studies are the only certain way to establish causal relationships in clinical investigations. Commonly these will take the form of randomized, controlled trials, preferably double-blind. Metabolic balance studies, although not randomized or blinded, also fall into this category, principally because the independent variable can be well controlled and other interfering variables eliminated or otherwise controlled. By contrast, in observational studies, whether cohort or case-control in type, the investigator controls exposure to neither the independent variable nor any of the many potential confounding variables. Such studies are able only to note associations between a presumed causal factor (e.g., calcium intake) and some outcome variable (e.g., bone mass and/or bone loss and/or fracture rate). Generally, such studies are useful for generating hypotheses for subsequent testing in stronger designs, as well as for identifying potentially harmful

factors that could never ethically be directly tested in humans. In brief, since observational studies cannot adequately control for other factors—known and unknown—that may obscure or exaggerate the sought for relationship, they can never establish causal relationships, no matter how large the population or cohort studied, nor can they negate evidence produced from studies with stronger designs, e.g., randomized, controlled trials.

Egregious examples of uncontrolled variables in observational studies which appear to alter the underlying relationship are found in the several ecologic studies that have described the relationship between national hip fracture rates and national calcium (or protein) intakes [167,168]. In these reports, nations with the highest hip fracture rates are sometimes characterized as having higher calcium and/or protein intakes, suggesting to their authors that high calcium intakes might even be harmful or, at least, certainly not helpful. No fewer than two factors are known which resolve this seeming paradox (and there may be others as well). Both are related to the predominance of Black and Asian populations in the group of nations that have both low hip fracture rates and lower calcium intakes. As it turns out, these associations are coincidental (see below).

In Blacks the skeleton is *genetically* heavier than in Caucasians. Blacks utilize dietary calcium more efficiently than Caucasians [169] and, despite often poor calcium intakes, manage to have a denser skeleton than Caucasians. As a group, therefore, they have lower fracture rates. In Asians the hip is shaped differently, with a shorter, less sharply angled upper femoral segment ("hip axis") than is typical of Caucasians; engineering analysis shows that, holding density constant, a long hip axis or a large hip axis angle is structurally weaker than the contrary arrangement [170]. Thus, and altogether unrelated to nutrition, Caucasians have higher hip fracture rates than both Asians, because the upper femur is shaped differently, and Blacks, because Blacks have greater bone mass. The correct way of evaluating the role of putative causative factors in an observational study design must be *within* a population, not across cultural and ethnic groups. When this is done, for example in studies of Blacks or Asians, it is seen that bone mass rises with calcium intake for both mainland Chinese [89] and US Blacks [117], just as it does for Caucasians, and one of the two principal determinants of hip fracture risk among Hong Kong Chinese is low calcium intake [101]. The system operates around different fracture equilibrium points in each group; nevertheless, all races so far studied exhibit the same basic relationship between calcium intake and bone mass.

In brief, racial factors influence absorption and conservation of calcium and, hence, how much bone can be accumulated for any given intake, while other cultural and genetic factors influence inherent structural fragility.

Perhaps the most serious weakness of observational studies of nutrient relationships lies in their inability accurately to assess the independent variable, i.e., calcium intake. Most studies derive their values for calcium intake by asking people what they eat and estimate calcium intake from these self reports. Even those few which estimate intake from weighed duplicate diets, rarely *analyze* the foods consumed, relying instead on published food databases. Furthermore, most such studies estimate intake at only one point in time, whereas bone mass is the integral of many years of varying intakes and diets. The weakness of relying on subject-based recall methods has been explored in depth elsewhere [150]. Large studies such as the Nurses' Study (cohort size: ~77,800), the Study of Fractures (cohort size: ~10,000) or the Framingham Osteoporosis Study (cohort size: ~1150) [72,78,97] depend upon food frequency questionnaires or diet diaries to estimate calcium intake in their subjects. And, although such studies are valuable in many other ways, they usually can tell us very little about how much calcium their individual subjects consumed and, thus, very little about the relationship of calcium intake to bone mass and fracture.

Only when the intake difference in observational studies can be independently validated is it possible to know for certain that one group's intake is higher than another's. Occasionally circumstances provide such objectively verifiable differences in long-term intake between groups. One such was the original observation of Matkovic *et al.*, reporting differences in fracture rate and bone mass between two rural districts of Croatia [105]. Without a nationwide food distribution system, the diets of the two populations were made up of foods produced locally. The people of one district, with dairy animals, had higher calcium intakes than the other which, without access to dairy foods, had estimated calcium intakes only about half as large. The people of the low calcium (i.e., non-dairy) district had lower bone mass and higher hip fracture rates. (Interestingly, the fracture rate for the distal forearm was the same for both groups, a point emphasizing the heterogeneity and complexity of osteoporotic fragility [164]).

More recently, a large population-based study from Finland contrasted bone mass and fracture rates in individuals with symptomatic, medically diagnosed lactose intolerance with the rest of the district population. Bone mass was lower and fracture rates higher in the lactose intolerant group [86,87]. Since symptomatic lactose intolerance does not cause malabsorption in calcium, but leads to reduced dairy intake and, since Finland has a high dairy calcium intake at a population level, there was a large difference in calcium intake between groups, not in any sense dependent upon, or determinable by, asking the individuals in either group what they ate.

NOTE ADDED IN PROOF:

Since submission of this manuscript, 13 additional reports have been published, one metabolic study, four randomized controlled trials, and eight observational studies. Two of the 13 studies explicitly evaluated dairy calcium sources. All 13 found a benefit from extra calcium. A revised version of Table 1 with its references is available from the author at rheaney@creighton.edu.

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