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Calcium, Is It Better to Have Less?—Global Health Perspectives

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ABSTRACT

Appropriate calcium intake is necessary for the accrual and maintenance of bone mass. A significant proportion of the world's population does not have adequate calcium intake, and thus, supplementation plays a key role in maintaining bone homeostasis and other aspects of health. Since a series of reports from the Auckland calcium study and meta-analysis indicated that calcium supplementation was associated with an increased risk for adverse cardiovascular events, concern over the safety of calcium supplementation has grown; however, considerable inconsistencies in the reproducibility were found and questions regarding the study methodologies have been raised. In addition, since the increased adverse cardiovascular events by calcium supplementation were observed in calcium-replete subjects, it should be clarified whether the same risk profile would be observed in countries with low calcium intake. Dietary calcium intake varies widely across the world; cardiovascular event risk factors and outcomes also vary and appear to be the opposite of calcium intake levels. Furthermore, the effects of calcium supplementation were shown to depend on dietary calcium intake, with a better bone mineral density response for low calcium intake subjects compared to that in calcium-replete subjects. Based on these evidences, the risk-benefit ratio of calcium supplement is likely to be different in different region of the world. Therefore, accumulation of evidence to establish population-specific guidelines for calcium supplementation is warranted before extrapolating the results obtained from a limited number of studies to the other people with different age, gender, ethnicity and risk profile across the world. J. Cell. Biochem. 116: 1513–1521, 2015.

KEY WORDS: CALCIUM SUPPLEMENTATION; CARDIOVASCULAR EVENTS; DIETARY INTAKE; GLOBAL HEALTH

Calcium is a crucial component of bone mineral. It has been well established that appropriate calcium intake is necessary for the development and accrual of bone mass in growing phase [Krall and Dawson-Hughes, 1993; Food and Nutrition Board, 2011] as well as the maintenance of bone mineral density (BMD) in elderly people [Health, 1994; Shea et al., 2004]. Unfortunately, a significant proportion of the world population does not meet the recommended calcium intake level [Cashman, 2002]. Therefore, for this segment, calcium supplementation is critical not only for maintaining adequate bone homeostasis but also for regulating other aspects of health status. In addition, supplement of calcium and vitamin D along with the therapeutic medication is an essential element of osteoporosis management. Indeed, in almost all the randomized trials of new osteoporosis drugs, calcium and vitamin D have been administered to both the placebo and the active drug groups [Liberman et al., 1995; Delmas et al., 1997; McClung et al., 2001; Neer et al., 2001; Cummings et al., 2009].

Recently, a secondary analysis of a large trial examining the effects of calcium supplementation on fracture and bone loss in New Zealand reveled an increased incidence of cardiovascular events [Bolland et al., 2008] in contrast to the generally held belief and the results of several observational studies [Bostick et al., 1999; Paik et al., 2014]. This controversial report has instigated a considerable debate over the safety of calcium supplementation for the past few years in the medical field. This review discusses the relevance of this controversy from the perspective of the global health.

GENERAL BELIEF AND RATIONALE FOR CALCIUM SUPPLEMENTATION

Calcium is the most abundant cation in human body and 99% of calcium is retained in skeletal tissue, while the other 1% circulates in the plasma and other soft tissues. Thousands of milligrams of calcium are exchanged daily through gastrointestinal absorption, renal

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filtration and resorption. In addition, hundreds of milligrams of calcium are actively moved into and out of the skeleton during the process of bone remodeling [Weaver, 2007; Bockman et al., 2012].

The recommended dietary allowance of calcium in the United States is 1,200 mg for adults and 1,500 mg for the elderly [Food and Nutrition Board, 2011]. According to the NHANES study 2003, however, less than 60% of the U.S. adult population meets this requirement, while 85–92% of elderly falls below the adequate intake level from diet alone [Bailey et al., 2010; Fulgoni et al., 2011]. Additionally, ~43% of the U.S. population and 70% of older women use calcium supplements [Bailey et al., 2010].

Serum calcium levels are tightly regulated by hormones, such as parathyroid hormone, vitamin D and calcitonin, although the active role of the latter is not well established. Under conditions of low serum calcium levels, the parathyroid hormone level is rapidly upregulated by a compensatory mechanism, which should be obviously deleterious to bone mass maintenance as the upregulated hormone levels increase osteoclast-mediated bone resorption [Parfitt et al., 1982; Allain and Dhesi, 2003].

Based on these facts, calcium supplementation has been routinely employed in the management of osteoporosis patients as well as in clinical trials of anti-osteoporosis medications. However, the role of calcium supplementation specifically in fracture prevention has not been well documented. Although an observational study [Chevalley et al., 1994] and a meta-analysis of randomized controlled trials (RCTs) [Tang et al., 2007] showed that calcium supplementation is effective for preventing hip fracture, subsequent data from the Auckland calcium study [Reid et al., 2008] as well as another meta-analysis of cohort studies and RCTs [Bischoff-Ferrari et al., 2007] did not find consistent effects on fracture prevention. Besides bone health, calcium supplementation has been associated with non-skeletal benefits including reduction of adenomatous polyps in the colon [Baron et al., 1999], cancers [Lappe et al., 2007] and pre-eclampsia [Hofmeyr et al., 2007].

CONTROVERSIES OVER CALCIUM SUPPLEMENT AND CARDIOVASCULAR EVENTS

Along with other health benefits delineated above, calcium supplementation has been also associated with a reduced risk of mortality from cardiovascular disease. An observational study, namely the Iowa Women's Health study, which included a prospective cohort of more than 30,000 postmenopausal women, showed that high dietary or supplemental calcium intake was associated with lower mortality from ischemic heart disease [Bostick et al., 1999]. In addition, the risk of total mortality was also inversely related to the use of calcium supplements in this cohort in more than 20 years of follow-up [Mursu et al., 2011]. Regarding the underlying mechanism for this beneficial effect, improvement of plasma lipid profile and reduction of blood pressure have been suggested [Reid et al., 2002, 2005].

Controversy over calcium supplements arose after Bolland et al. reported that calcium supplementation resulted in a significant increase of adverse cardiovascular events in a secondary analysis of a large trial that studied the effects of calcium on fracture and bone loss in New Zealand [Bolland et al., 2008]. This report provoked a series of critiques that mentioned a lack of reproducibility in other cohorts [Lappe and Heaney, 2008], unbalanced or ignored confounders [Puccetti, 2008; Ramlackhansingh, 2008], and misinterpretation of the data [Biggs, 2008]. The same authors then published the results of their post-hoc analysis of the Women's Health Initiative (WHI) study as well as a meta-analysis of trials examining calcium supplementation with or without vitamin D, which also revealed a similar increase in adverse cardiovascular events in subjects who received calcium supplementation [Bolland et al., 2010, 2011].

Again this report evoked the following concerns: (1) the meta-analysis relied heavily upon unpublished data from the "Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD)" trial; (2) myocardial infarctions were not the end point of the trial and thus were not verified; (3) low compliance (54.5%), especially in the calcium arms of the trial; (4) calcium alone is no longer recommended to prevent or treat osteoporosis; (5) most of the data are unpublished and impossible to investigate independently [Dawson-Hughes, 2010]; (6) inappropriate analysis of the WHI study result [Heiss et al., 2010]; (7) the study is dominated by one trial accounting for 66% of all the subjects (5292 out of 8033); (8) no known physiological pathway could lead from a transient 5% rise in serum calcium levels to cardiovascular damage [Nordin et al., 2010]; and (9) only 3.5% of the prescriptions were for calcium supplements not containing vitamin D [Grove and Cook, 2010].

In addition, subsequent study by Prentice et al., which was conducted on the same WHI subjects receiving 1,000 mg supplements of calcium and 400 IU of vitamin D, failed to demonstrate an increased incidence of adverse cardiovascular events after 7 years of follow up [Prentice et al., 2013]. Another meta-analysis of RCTs also showed that the risks for myocardial infarction, angina pectoris and acute coronary syndrome were not significantly increased by calcium supplements [Lewis et al., 2015]. There is, however, another study that demonstrated increased risk of cardiovascular death by calcium supplementation from a prospective cohort of men and women aged 50–71 after an average of 12 years of follow up. The result of this study indicates that supplemental calcium raised the risk of cardiovascular death by 20% among men but not women, and the there was a statistically significant interaction between smoking status and supplemental calcium intake in men [Xiao et al., 2013].

Conversely, Lewis et al. who investigated the effects of 3 years of calcium supplements on carotid artery intimal medial thickness and the presence or absence of atherosclerotic carotid plaque, showed that supplementation of calcium carbonate (1,200 mg/day of elemental calcium) to 1,500 older women with a mean baseline calcium intake of 970 mg/day did not increase carotid atherosclerosis both in intention to treat and per protocol analysis, strongly suggesting that extended daily calcium supplementation in older women does not have an adverse effect on carotid atherosclerosis [Lewis et al., 2014b].

In 2010, the Institute of Medicine (IOM) released its recommendations for the dietary intake of calcium and vitamin D, emphasizing that available scientific evidence supports a key role of calcium and vitamin D in skeletal health while extraskeletal outcomes, including cardiovascular disease is inconsistent, inconclusive as to causality. The new report has set the Recommended Dietary Allowances (covering requirements of >97.5% of the population) for calcium for

men 51–70 years of age is 1,000 mg and that for men >70 years of age and women ≥51 years of age is 1,200 mg [Food and Nutrition Board, 2011]. However, in early 2013, the U.S. Preventive Services Task Force (USPSTF) released a new statement that advised against daily supplementation with 400 IU or less of vitamin D3 and 1,000 mg or less of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women based on insufficient evidence to support the supplement although they did not express explicit concern over calcium supplementation posing a risk for adverse cardiovascular events [Moyer and USPSTF, 2013]. In response to this statement, however, the American Society of Bone and Mineral Research (ASBMR) issued a statement indicating that although calcium supplementation in healthy adults may not be needed, those at high risk for fractures in assisted living and nursing home should be receiving supplements [American Society of Bone and Mineral Research, 2013].

IMPLICATIONS IN GLOBAL HEALTH PERSPECTIVES — DIETARY CALCIUM INTAKE

As has been reviewed here, it is quite confusing in everyday clinical practice whether to recommend calcium supplements in the general public or to prescribe them to patients with osteoporosis. Even the experts do not seem to fully agree on this issue and the debate is ongoing via numerous new publications and throughout conferences.

The recent publication by Lewis et al. [2015], which described a meta-analysis of RCTs on the effects of calcium supplementation on coronary heart disease, revealed the contrasting opinions on this critical subject, as illustrated by the letter to the editor by Bolland et al. [2014] and the subsequent reply by Lewis et al. [2014a]. Although the debate centered mainly around the statistical and study design issues, whether calcium supplementation is casually related to adverse cardiovascular events is currently inconsistent and inconclusive. It would be interesting to note that the inclusion or exclusion of a couple of papers in the meta-analysis could result in quite different conclusion [Bolland et al., 2014; Lewis et al., 2014a], implying that the difference may not be huge.

Furthermore, it is yet to be determined whether such a risk does exist in low calcium intake regions, such as the countries in East Asia. The average dietary calcium intake in South Korea, Japan, Hong Kong and Thailand is 300–500 mg/day as in other countries in this region [Lau et al., 2001; Piaseu et al., 2001; Ho et al., 2005; Pongchaiyakul et al., 2008; Higashiguchi et al., 2010; Kim et al., 2014], while in New Zealand and United States, where the Auckland calcium and WHI studies were conducted, those values are 800 and 850 mg, respectively (Fig. 1). Furthermore, none of the nine studies analyzed in Bolland's meta-analysis [Bolland et al., 2011] and only one (Thailand) of the 18 studies in Lewis's meta-analysis [Lewis et al., 2015] included data from Asian countries or other ethnicities. Indeed, almost all the studies included in the meta-analysis were performed with Caucasians in United States, United Kingdom, France, Denmark, Australia and New Zealand. As shown in Fig. 1, the average dietary calcium intake in this region ranges from 800 to 1,200 mg daily, which is almost twice the amount observed in other parts of the world.

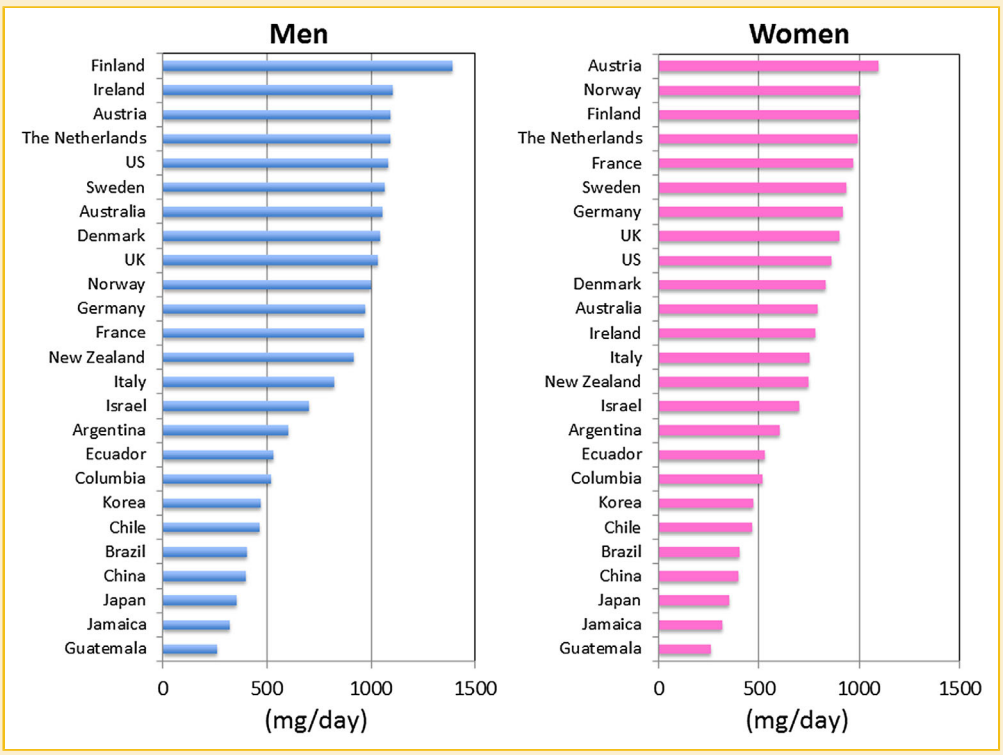

Fig. 1. World-wide distribution of dietary calcium intake. Data obtained from EFSA Panel on Dietetic Products [2012], Looker [2006], Wang and Li [2008] and Pinheiro et al. [2009].

Even in the United States, fewer than 10% of women up to the age of 70 and fewer than 1% after 70 years, along with fewer than 25% of adult men met the guideline of the U.S. National Academy of Sciences, i.e., 1200 mg of elemental calcium per day [Bailey et al., 2010; Fulgoni et al., 2011].

Whether supplemental calcium ~1,000 mg/day would elicit a similar increase in adverse cardiovascular events in people with insufficient calcium intake is questionable.

In this regard, the result of an observational cohort study from Sweden is noteworthy. In this Swedish Mammography Study consisting of a population-based cohort of 61,433 women, dietary calcium intakes above 1,400 mg/day were associated with higher all-cause and cardiovascular mortality compared to intake between 600 and 1,000 mg/day. In addition, the use of calcium tablets was associated with all cause mortality only in those with a dietary calcium intake above 1,400 mg/day. Interestingly, the mortality rates also rose among women with an intake below 600 mg/day, giving a J-shaped relationship between calcium intake and mortality [Michaelsson et al., 2013]. Similar tendency of higher mortality in subjects with low calcium intake (<700 mg/day) was observed in Iowa Womens' Health Study [Bostick et al., 1999].

The result of the Swedish Mammography Study strongly suggest that the risk for adverse cardiovascular events, if exists, may be related to the total calcium intake (dietary plus supplemental) rather than the problem of supplementation. According to the J-shaped curve shown by Michaelsson et al., in subjects who are already consuming 1,000 mg/day of dietary calcium, such as the people in United States, New Zealand or other Western countries, supplementation of 1,000 mg of elemental calcium may have led to increased mortality from cardiovascular disease [Michaelsson et al., 2013] (red arrow in Fig. 2). However, it could be argued that those with low calcium intake (less than 500 mg/day) including people in East Asian countries, the risk for cardiovascular mortality would be decreased by additional calcium intake by supplementation (blue arrow in Fig. 2). Prospective study investigating the separate effects of dietary versus supplemental calcium on adverse cardiovascular events should be the subject of future research.

IMPLICATIONS IN GLOBAL HEALTH PERSPECTIVES – FRACTURE AND CARDIOVASCULAR DISEASES

Besides the dietary calcium intake level, the epidemiological characteristics of heart disease and osteoporotic fracture also vary widely across the world. According to the annual "OECD health statistics", the consumption of anti-hypertensives or anti-cholesterols ranged from 148 to 555 defined daily dose per 1,000 people/day or 10 to 137 defined daily dose per 1,000 people/day, respectively, in OECD nations in 2011 [OECD, 2013] (Fig. 3). For example, compared to Denmark, Korea use less than 1/2 and less than 1/3 of the anti-hypertensive and anti-cholesterol medication, respectively. In addition, clinical characteristics and long-term outcomes of major cardiovascular diseases have been shown to differ among countries. Indeed, in an analysis of long-term data from the Coronary Revascularization Demonstrating Outcome registry (Kyoto, Japan)

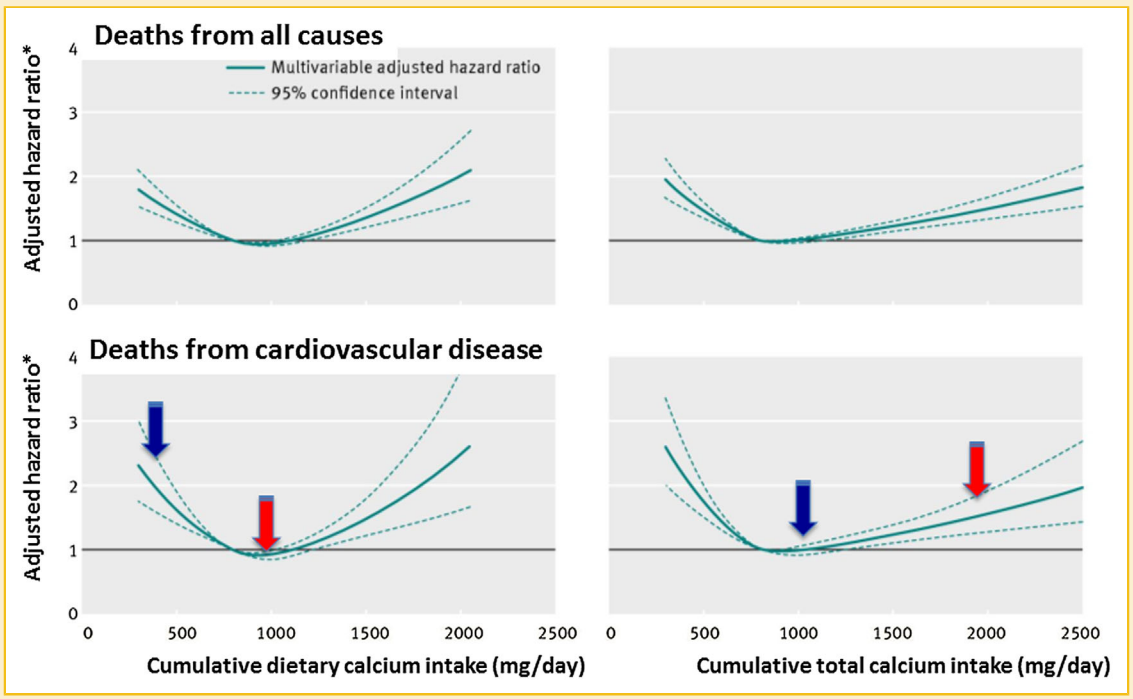

Fig. 2. Multivariable adjusted spline curves for relation between cumulative average of dietary and total calcium intake with time to death from all causes and cardiovascular disease. *Adjusted for age, total energy and vitamin D intake, healthy dietary pattern, body mass index, height, living alone, educational level, physical activity level, smoking status, use of calcium containing supplements, and score on Charlson comorbidity index. Reference value for estimation was set at 800 mg, which corresponds to the Swedish recommended level of calcium intake for women older than 50 years (adapted from Michaelsson et al. [2013] with permission).

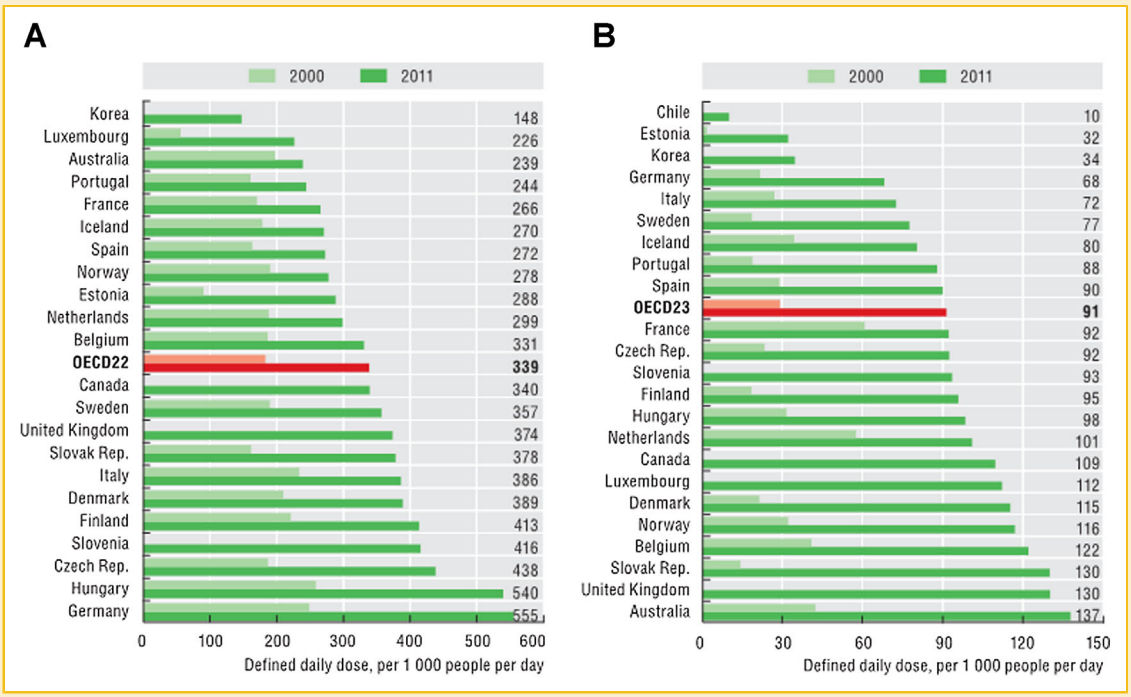

Fig. 3. (A) Hypertension drugs consumption, 2000 and 2011 (or nearest year) (B) Anti-cholesterols consumption, 2000 and 2011 (or nearest year) in OECD countries (Source: OECD Health Statistics 2013, http://dx.doi.org/10.1787/health-data-en).

and the Texas Heart Institute Research Database (Houston, Texas) including 16,100 patients who had undergone elective, initial percutaneous coronary intervention or coronary artery bypass grafting, greater long-term mortality was found in the U.S. group compared with the Japanese group after adjustment for known predictors (hazard ratio 1.71, 95% confidence interval 1.50–1.95; $P < 0.001$) [Kohsaka et al., 2010]. Consistent with this evidence, mortality from ischemic heart disease is also the lower in East Asian countries compared to the United States, Oceanian and East European countries [OECD, 2013] (Fig. 4).

Conversely, although the annual incidence of hip fracture in East Asia is lower than in Western countries, this incidence is projected to increase sharply due to the rapid ageing of the population, thereby yielding a great socio-economical burden. It has been estimated that more than half of all hip fracture will occur in Asia in year 2050 [Cooper et al., 1992].

As in the case of the relation between calcium supplements and adverse cardiovascular events, it is likely that the effects of calcium supplementation on skeletal benefits may be different depending on the region or ethnicity. However, it is still not clear whether calcium supplementation can prevent fracture. Although calcium (1,000 mg) monotherapy for 5 years was shown to prevent forearm and vertebral fracture over a 10-year period in the Auckland calcium study, the supplementation was unable to prevent hip fracture [Radford et al., 2014]. Another study from Australia showed that supplementation of calcium carbonate (elemental calcium 480 mg) for 5 years did not result in fracture prevention, although a positive effect was observed in drug-compliant subgroup [Prince et al., 2006]. In addition, calcium and vitamin D supplementation did not significantly reduce hip fracture in the WHI study, while an increased risk of kidney stones was identified [Jackson et al., 2006].

In contrast to the questionable role in fracture prevention, however, beneficial effects of calcium supplementation on bone mineral density have been observed in many studies.

Supplementation of as low as 500 mg of calcium could effectively slow lumbar spine bone loss in Japanese perimenopausal women with low calcium intake [Nakamura et al., 2012]. Similar beneficial effects have been observed in postmenopausal women from Hong Kong [Lau et al., 1992; Haines et al., 1995; Lee et al., 1995; Lau et al., 2001; Ho et al., 2005], China [Gui et al., 2012], Chile [Rodriguez and Novik, 1998], Argentina [Malpeli et al., 2012] and Nigeria [Umaretiya et al., 2013]. Interestingly, however, calcium supplementation failed to produce consistent effects on BMD in studies from calcium sufficient areas [Aloia et al., 1994; Chevalley et al., 1994; Barger-Lux et al., 2005]. This differential effect was clearly demonstrated in a study of Caucasian women aged 40–70 years old by Dawson-Hughes et al., who showed that 500 mg of calcium supplementation prevented bone loss only in those whose dietary calcium intake was less than 400 mg/day, while the effects were not evident in those with dietary intakes of 400–650 mg/day [Dawson-Hughes et al., 1990]. Another study on prepubertal girls in Switzerland also showed that 850 mg of calcium supplementation had the greatest in girls with dietary calcium intake below the median of 880 mg/day [Bonjour et al., 1997].

The differential effects of calcium depending on dietary calcium intake level were also found in cross-sectional studies that investigated the association between dietary calcium intake level

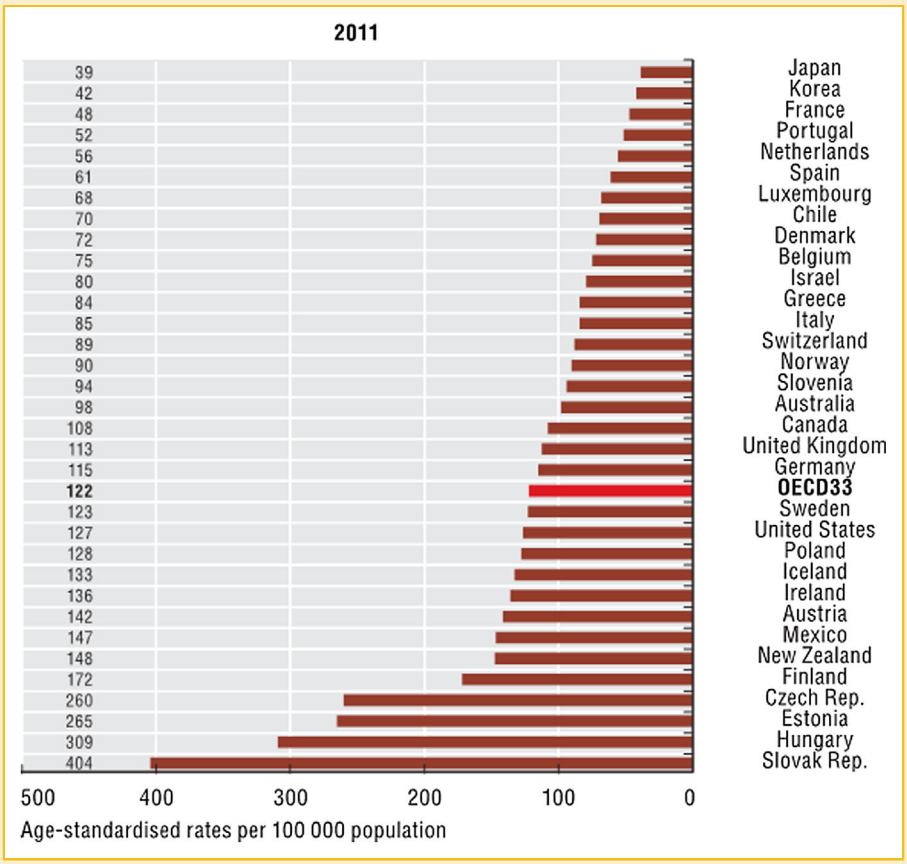

Fig. 4. Ischemic heart disease mortality 2011 in OECD countries (Source: OECD Health Statistics 2013, http://dx.doi.org/10.1787/health-data-en).

and BMD. In a study of Chinese women aged 21–30 years, dietary calcium intake of at least 600 mg/day was associated with a 4–7% higher mean BMD at the spine and femur compared to a mean intake of less than 300 mg/day [Ho et al., 1994]. A similar association was found in studies conducted in Japan [Ito et al., 2011] and Thailand [Piaseu et al., 2001; Pongchaiyakul et al., 2008], where the dietary calcium intake level is less than 500 mg/day. Recently, we have also demonstrated that dietary calcium intake is positively associated with BMD in Koreans whose average daily calcium intake is around 470 mg, particularly in subjects with very low serum 25(OH) vitamin D_3 levels [Kim et al., 2014]. Interestingly, such a positive association was not readily observed in studies from calcium-replete countries. Indeed, in NHANES 2005–2006 cohorts, representing U.S. men and women of aged 50 years and older (daily calcium intake, 890–975 mg in men; 1,003–1,009 mg in women), high calcium intake beyond the recommended dietary allowance did not provide any benefit for hip or lumbar BMD [Anderson et al., 2012]. Another study of European girls aged 11–15 years also showed that dietary calcium was not a determinant of peak BMD, although the low calcium intake group (<600 mg) exhibited an association, albeit insignificant, between calcium intake and peak BMD [Kardinaal et al., 1999]. These results support the notion that calcium is a threshold nutrient, i.e., the effect of calcium intake is observed only up to some threshold level but above which no further effect can be produced by further increase in intake [Food and Nutrition Board, 1997; Barger-Lux et al., 2005].

Altogether, these results suggest that the beneficial effects of dietary or supplemental calcium may vary depending on the dietary calcium intake level across the geographical area or ethnic background and; therefore, for people living in low calcium intake area, the benefit from calcium supplement in bone health aspects may outweigh the questionable risks associated with extraskeletal problems.

CONCLUSION

To summarize, although concern over the possible adverse cardiovascular events by calcium supplementation is emerging, there is not enough evidence to support it consistently. Furthermore, most of the data have been obtained from calcium-replete countries, where the question is whether supplementation of 1,000 mg of elemental calcium to subjects already taking ~1,000 mg of dietary calcium is safe.

Although dietary calcium is preferable to supplemental calcium, the tissues do not directly perceive the source (i.e., food vs. supplement) [Heaney et al., 2012]; therefore, it would be more reasonable to take into account the dietary calcium intake level when analyzing the risk/benefit profile of the calcium supplement in a

particular population. Reid et al. has also acknowledged the presence of interaction between the adverse cardiovascular events and dietary calcium intake in their Auckland Calcium study, albeit it is complex [Reid et al., 2014]. As dietary calcium intake level varies widely across the world, the impact of calcium supplementation is also likely to vary. Moreover, cardiovascular risk factors and outcomes tend to be better in low calcium intake countries, while the beneficial effects of calcium supplementation have shown to be greater than those in calcium-replete areas.

Based on the calculation from the Auckland calcium study, the number needed to treat one fracture by calcium supplements is 302 while the number needed to produce cardiovascular event is 178 [Bolland et al., 2011]. Although sufficient data is currently unavailable for the calculation of these values in other areas, it is quite possible that the risk/benefit ratio will be different depending on the cardiovascular disease profiles and degree of skeletal benefit from calcium supplementation. For those people living in low calcium intake areas, appropriate calcium supplementation may be beneficial for fracture prevention and even for reduction of all cause mortality. Therefore, the number needed to harm (cardiovascular disease) versus the number needed to treat (osteoporotic fracture) by calcium supplementation should be different from that in calcium-replete regions. We fully understand that this notion is presently circumstantial and unsupported. Accumulation of evidence to make population-specific guideline for calcium supplement is warranted before extrapolating the results obtained from a limited number of studies to the other people with different age, gender, ethnicity and risk profile across the world.

REFERENCES

Allain TJ, Dhesi J. 2003. Hypovitaminosis D in older adults. Gerontology 49:273–278.

Aloia JF, Vaswani A, Yeh JK, Ross PL, Flaster E, Dilmanian FA. 1994. Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. Ann Intern Med 120:97–103.

American Society of Bone and Mineral Research. 2013. New recommendations for taking calcium and vitamin D. http://www.asbmr.org/about/pressreleases/detail.aspx?cid=e03036f7-5e78-40ae-a3ad-2749b64a8b50.

Anderson JJ, Roggenkamp KJ, Suchindran CM. 2012. Calcium intakes and femoral and lumbar bone density of elderly U.S. men and women: National Health and Nutrition Examination Survey2005–2006 analysis. J Clin Endocrinol Metab 97:4531–4539.

Bailey RL, Dodd KW, Goldman JA, Gahche JJ, Dwyer JT, Moshfegh AJ, Sempos CT, Picciano MF. 2010. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr 140:817–822.

Barger-Lux MJ, Davies KM, Heaney RP. 2005. Calcium supplementation does not augment bone gain in young women consuming diets moderately low in calcium. J Nutr 135:2362–2366.

Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Bond JH, Greenberg ER. 1999. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med 340:101–107.

Biggs WS. 2008. Calcium supplementation: Data were misrepresented. BMJ 336:404.

Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, Specker B, Orav JE, Wong JB, Staehelin HB, O′Reilly E, Kiel DP, Willett WC. 2007. Calcium intake and hip fracture risk in men and women: A meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr 86:1780–1790.

Bockman RS, Zapalowski C, Kiel DP, Adler RA. 2012. Commentary on calcium supplements and cardiovascular events. J Clin Densitom 15:130–134.

Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, Gamble GD, Grey A, Reid IR. 2008. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 336:262–266.

Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. 2010. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: Meta-analysis. BMJ 341:c3691.

Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. 2011. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women′s Health Initiative limited access dataset and meta-analysis. BMJ 342:d2040.

Bolland MJ, Grey A, Avenell A, Reid IR. 2014. Calcium supplements increase risk of myocardial infarction. J Bone Miner Res 30:389–390.

Bonjour JP, Carrie AL, Ferrari S, Clavien H, Slosman D, Theintz G, Rizzoli R. 1997. Calcium-enriched foods and bone mass growth in prepubertal girls: A randomized, double-blind, placebo-controlled trial. J Clin Invest 99: 1287–1294.

Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. 1999. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 149: 151–161.

Cashman KD. 2002. Calcium intake, calcium bioavailability and bone health. Br J Nutr 87(Suppl2):S169–S177.

Chevalley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, Vasey H, Bonjour JP. 1994. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int 4:245–252.

Cooper C, Campion G, Melton LJ III. 1992. Hip fractures in the elderly: A world-wide projection Osteoporos Int 2:285–289.

Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C, Trial F. 2009. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361: 756–765.

Dawson-Hughes B. 2010. Calcium and heart attacks. The heart of the matter. BMJ 341:c4993.

Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. 1990. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. N Engl J Med 323:878–883.

Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, Draper M, Christiansen C. 1997. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 337:1641–1647.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). 2012. Scientific opinion on the tolerable upper intake level of calcium. EFSA J 10:2814.

Food and Nutrition Board, IOM. 1997. Dietary reference intakes for calcium, magnesium, phosphorus, vitamin D, and fluoride. Washington, DC: National Academies Press.

Food and Nutrition Board, IOM. 2011. Dietary reference intakes: Calcium and vitamin D. Washington, DC: The National Academies Press.

Fulgoni VL III, Keast DR, Bailey RL, Dwyer J. 2011. Foods, fortificants, and supplements: Where do Americans get their nutrients? J Nutr 141:1847–1854.

Grove ML, Cook D. 2010. Calcium and heart attacks. Doesn′t apply to most calcium prescriptions. BMJ 341:c5003.

Gui JC, Brasic JR, Liu XD, Gong GY, Zhang GM, Liu CJ, Gao GQ. 2012. Bone mineral density in postmenopausal Chinese women treated with calcium fortification in soymilk and cow′s milk. Osteoporos Int 23:1563–1570.

Haines CJ, Chung TK, Leung PC, Hsu SY, Leung DH. 1995. Calcium supplementation and bone mineral density in postmenopausal women using estrogen replacement therapy. Bone 16:529–531.

Heaney RP, Kopecky S, Maki KC, Hathcock J, Mackay D, Wallace TC. 2012. A review of calcium supplements and cardiovascular disease risk. Adv Nutr 3:763–771.

Heiss G, Hsia J, Pettinger M, Howard BV, Anderson G. 2010. Calcium and heart attacks. No evidence for increased risk. BMJ 341:c4995.

Higashiguchi M, Onoda T, Turin TC, Sakata K, Group NDR. 2010. Calcium intake and associated factors in a general Japanese population: Baseline data of NIPPON DATA80/90 and the National Nutrition Survey. J Epidemiol 20 (Suppl3):S549–S556.

Ho SC, Leung PC, Swaminathan R, Chan C, Chan SS, Fan YK, Lindsay R. 1994. Determinants of bone mass in Chinese women aged 21–40 years. II. Pattern of dietary calcium intake and association with bone mineral density. Osteoporos Int 4:167–175.

Ho SC, Guldan GS, Woo J, Yu R, Tse MM, Sham A, Cheng J. 2005. A prospective study of the effects of 1-year calcium-fortified soy milk supplementation on dietary calcium intake and bone health in Chinese adolescent girls aged 14 to 16. Osteoporos Int 16:1907–1916.

Hofmeyr GJ, Duley L, Atallah A. 2007. Dietary calcium supplementation for prevention of pre-eclampsia and related problems: A systematic review and commentary. BJOG 114:933–943.

Ito S, Ishida H, Uenishi K, Murakami K, Sasaki S. 2011. The relationship between habitual dietary phosphorus and calcium intake, and bone mineral density in young Japanese women: a cross-sectional study. Asia Pac J Clin Nutr 20:411–417.

Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D, Women's Health Initiative I. 2006. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 354:669–683.

Kardinaal AF, Ando S, Charles P, Charzewska J, Rotily M, Vaananen K, Van Erp-Baart AM, Heikkinen J, Thomsen J, Maggiolini M, Deloraine A, Chabros E, Juvin R, Schaafsma G. 1999. Dietary calcium and bone density in adolescent girls and young women in Europe. J Bone Miner Res 14:583–592.

Kim KM, Choi SH, Lim S, Moon JH, Kim JH, Kim SW, Jang HC, Shin CS. 2014. Interactions between dietary calcium intake and bone mineral density or bone geometry in a low calcium intake population (KNHANES IV 2008–2010). J Clin Endocrinol Metab 99:2409–2417.

Kohsaka S, Kimura T, Goto M, Lee VV, Elayda M, Furukawa Y, Fukushima M, Komeda M, Sakata R, Willerson JT, Wilson JM, Kita T. 2010. Difference in patient profiles and outcomes in Japanese versus American patients undergoing coronary revascularization (collaborative study by CREDO-Kyoto and the Texas Heart Institute Research Database). Am J Cardiol 105:1698–1704.

Krall EA, Dawson-Hughes B. 1993. Heritable and life-style determinants of bone mineral density. J Bone Miner Res 8:1–9.

Lappe JM, Heaney RP. 2008. Calcium supplementation: Results may not be generalisable. BMJ 336:403(author reply 404).

Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. 2007. Vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial. Am J Clin Nutr 85:1586–1591.

Lau EM, Woo J, Leung PC, Swaminathan R, Leung D. 1992. The effects of calcium supplementation and exercise on bone density in elderly Chinese women. Osteoporos Int 2:168–173.

Lau EM, Woo J, Lam V, Hong A. 2001. Milk supplementation of the diet of postmenopausal Chinese women on a low calcium intake retards bone loss. J Bone Miner Res 16:1704–1709.

Lee WT, Leung SS, Leung DM, Tsang HS, Lau J, Cheng JC. 1995. A randomized double-blind controlled calcium supplementation trial, and bone and height acquisition in children. Br J Nutr 74:125–139.

Lewis JR, Radavelli-Bagatini S, Rejnmark L, Chen JS, Simpson JM, Lappe JM, Mosekilde L, Prentice RL, Prince RL. 2014a. Response to "Calcium supplements increase risk of myocardial infarction". J Bone Miner Res 30:391–392.

Lewis JR, Zhu K, Thompson PL, Prince RL. 2014b. The effects of 3 years of calcium supplementation on common carotid artery intimal medial thickness and carotid atherosclerosis in older women: An ancillary study of the CAIFOS randomized controlled trial. J Bone Miner Res 29:534–541.

Lewis JR, Radavelli-Bagatini S, Rejnmark L, Chen JS, Simpson JM, Lappe JM, Mosekilde L, Prentice RL, Prince RL. 2015. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: A collaborative meta-analysis of randomized controlled trials. J Bone Miner Res 30:165–175.

Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M. 1995. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 333:1437–1443.

Looker AC. 2006. Dietary calcium. InWeaver CM, Heaney RP, editors. Calcium in human health. Totowa, New Jersey: Humana Press.

Malpeli A, Apezteguia M, Mansur JL, Armanini A, Macias Couret M, Villalobos R, Kuzminczuk M, Gonzalez HF. 2012. Calcium supplementation, bone mineral density and bone mineral content. Predictors of bone mass changes in adolescent mothers during the 6-month postpartum period. Arch Latinoam Nutr 62:30–36.

McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY, Hip Intervention Program Study G. 2001. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 344:333–340.

Michaelsson K, Melhus H, Warensjo Lemming E, Wolk A, Byberg L. 2013. Long term calcium intake and rates of all cause and cardiovascular mortality: Community based prospective longitudinal cohort study. BMJ 346:f228.

Moyer VA, U.S. Preventive Services Task Force. 2013. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 158:691–696.

Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. 2011. Dietary supplements and mortality rate in older women: The Iowa Women's Health Study. Arch Intern Med 171:1625–1633.

Nakamura K, Saito T, Kobayashi R, Oshiki R, Kitamura K, Oyama M, Narisawa S, Nashimoto M, Takahashi S, Takachi R. 2012. Effect of low-dose calcium supplements on bone loss in perimenopausal and postmenopausal Asian women: A randomized controlled trial. J Bone Miner Res 27:2264–2270.

National Institute of Health. 1994. Optimal calcium intake. NIH Consens Statement 12:1–31.

Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. 2001. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344: 1434–1441.

Nordin BE, Daly RM, Horowitz J, Metcalfe AV. 2010. Calcium and heart attacks. Making too much of a weak case. BMJ 341:c4997.

OECD. 2013. Health at a Glance 2013: OECD Indicators. Paris, France: OECD Publishing.

Paik JM, Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, Taylor EN. 2014. Calcium supplement intake and risk of cardiovascular disease in women. Osteoporos Int 25:2047–2056.

Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD. 1982. Vitamin D and bone health in the elderly. Am J Clin Nutr 36:1014–1031.

Piaseu N, Komindr S, Chailurkit LO, Ongphiphadhanakul B, Chansirikarn S, Rajatanavin R. 2001. Differences in bone mineral density and lifestyle factors of postmenopausal women living in Bangkok and other provinces. J Med Assoc Thai 84:772–781.

Pinheiro MM, Schuch NJ, Genaro PS, Ciconelli RM, Ferraz MB, Martini LA. 2009. Nutrient intakes related to osteoporotic fractures in men and women—The Brazilian Osteoporosis Study (BRAZOS). Nutr J 8:6.

Pongchaiyakul C, Kosulwat V, Charoenkiatkul S, Chailurkit LO, Rojroongwasinkul N, Rajatanavin R. 2008. The association of dietary calcium, bone mineral density and biochemical bone turnover markers in rural Thai women. J Med Assoc Thai 91:295–302.

Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, Chlebowski RT, Manson JE, Van Horn L, Vitolins MZ, Datta M, LeBlanc ES, Cauley JA, Rossouw JE. 2013. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int 24:567–580.

Prince RL, Devine A, Dhaliwal SS, Dick IM. 2006. Effects of calcium supplementation on clinical fracture and bone structure: Results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med 166:869–875.

Puccetti L. 2008. Calcium supplementation: Confounders were ignored. BMJ 336:403–404(author reply 404).

Radford LT, Bolland MJ, Mason B, Horne A, Gamble GD, Grey A, Reid IR. 2014. The Auckland calcium study: 5-year post-trial follow-up. Osteoporos Int 25:297–304.

Ramlackhansingh JN. 2008. Calcium supplementation: Some issues on outcomes. BMJ 336:403(author reply 404).

Reid IR, Mason B, Horne A, Ames R, Clearwater J, Bava U, Orr-Walker B, Wu F, Evans MC, Gamble GD. 2002. Effects of calcium supplementation on serum lipid concentrations in normal older women: A randomized controlled trial. Am J Med 112:343–347.

Reid IR, Horne A, Mason B, Ames R, Bava U, Gamble GD. 2005. Effects of calcium supplementation on body weight and blood pressure in normal older women: A randomized controlled trial. J Clin Endocrinol Metab 90:3824–3829.

Reid IR, Bolland MJ, Grey A. 2008. Effect of calcium supplementation on hip fractures. Osteoporos Int 19:1119–1123.

Reid IR, Bristow SM, Bolland MJ. 2014. Cardiovascular complications of calcium supplements. J Cell Biochem 116:494–501.

Rodriguez JA, Novik V. 1998. [Calcium intake and bone density in menopause. Data of a sample of Chilean women followed-up for 5 years with calcium supplementation]. Rev Med Chil 126:145–150.

Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, Hamel C, Ortiz Z, Peterson J, Adachi J, Tugwell P, Guyatt G. Osteoporosis Methodology G, Osteoporosis Research Advisory G. 2004. Calcium supplementation on bone loss in postmenopausal women. Cochrane Database Syst Rev 1:CD004526.

Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. 2007. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. Lancet 370:657–666.

Umaretiya PJ, Thacher TD, Fischer PR, Cha SS, Pettifor JM. 2013. Bone mineral density in Nigerian children after discontinuation of calcium supplementation. Bone 55:64–68.

Wang Y, Li S. 2008. Worldwide trends in dairy production and consumption and calcium intake: Is promoting consumption of dairy products a sustainable solution for inadequate calcium intake? Food Nutr Bull 29:172–185.

Weaver CM. 2007. Vitamin D, calcium homeostasis, and skeleton accretion in children. J Bone Miner Res 22(Suppl.2):V45–V49.

Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. 2013. Dietary and supplemental calcium intake and cardiovascular disease mortality: The National Institutes of Health-AARP diet and health study. JAMA Intern Med 173:639–646.