

The Magnesium Hypothesis of Cardiovascular Disease

The Missing Mineral—Magnesium

(The Strong Link of Low Nutritional Magnesium and High Calcium-to-Magnesium Ratio in the Genesis of Cardiovascular Disease)

A Review of the Peer-Reviewed Science

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Mid-1950s, USA: Middle-aged people start dying of heart attacks. The new “epidemic” is so sudden and so forceful that doctors ask researchers for help: “How do we treat and prevent this onslaught of sudden death?” Many also wonder, “What is causing this phenomenon?” [[See Fig. 1](#) and [Appendix I](#)]

Early Heart Disease Research Turns Away from Strong Evidence for Magnesium Hypothesis

Something in our lifestyle was allowing many otherwise healthy people to drop dead from heart attacks. The search was on for the cause. With no pathogen and no toxin, researchers began to look for things that “correlated” with heart attacks or strokes. Factors associated with an elevated risk of heart disease became the way to study this increasing problem. High blood pressure, smoking, obesity and high serum cholesterol came to be the best known of a growing list of cardiovascular risk factors—things to avoid or clinical measurements to correct.

However, populations from all over the world showed high rates of sudden cardiac death in areas with low soil and/or water magnesium levels; and animal research as early as 1936 implicated low nutritional magnesium in atherosclerosis—the hardening of arteries. **By 1957 low magnesium was shown to be, strongly, convincingly, a cause of atherogenesis and the calcification of soft tissues.** But this research was widely and immediately ignored as cholesterol and the high saturated-fat diet became the culprits to fight [[see Appendices I and II](#)].

Common Cardiovascular Disease (CVD) Risk Factors Are Linked to Low Mg Status

Ever since this early “wrong turn,” **more and more peer-reviewed research has shown that low Mg is associated with all known cardiovascular risk factors, such as cholesterol and high blood pressure** [[see Appendix III](#)].

Serum Magnesium Levels and Risk of CVD Death

A study as early as 1995 showed that serum Mg below 0.85 mmol/L was a risk factor for heart disease in a national study (NHANES) that ran from the first half of the 1970s through the early 1980s (see Gartside & Glueck, 1995). In 1999, Ford expanded this original 10-year NHANES study out to 19 years follow-up and found the same association: **serum Mg below 0.85 mmol/L was associated with a higher risk of heart disease, both incidence and death.** As with previous studies generating and supporting the Mg Hypothesis of CVD, these studies were pretty much ignored, and NHANES even stopped measuring urinary and serum Mg values, leaving researchers with only dietary Mg to study the world’s largest population with a high rate of CVD. Recent studies have confirmed this early work from NHANES data ([see Appendix IV for list of studies validating this early NHANES work](#)). Unfortunately, in the meantime

(and presently in many areas) **serum Mg levels of 0.75 mmol/L, and even as low as 0.60 mmol/L, were seen as “normal” range for most clinical laboratories.** Thus, when doctors test a patient with early signs of possible CVD for serum Mg, many values **below** the “safe” range—i.e., below 0.85 mmol/L—are deemed “normal” range Mg by the labs; so low Mg is often eliminated as a potential cause of the symptoms [[see Appendix IV](#)].

Importance of Calcium–Magnesium Balance and Danger of the Rising Ca:Mg Ratio

Calcium supplement recommendations have become common in medicine, however, without the necessary balancing with magnesium. As a result, recent studies are showing what the Magnesium Hypothesis of CVD long ago predicted: **a rise in Ca intake from foods and/or supplements, without a concomitant balancing rise in Mg intake, can bring on heart disease.** Why is this? The earliest animal studies of the Mg Hypothesis showed how low Mg status in animals caused calcification of soft tissues (see Appendix I). In the 1990s, Resnick and colleagues showed how high cellular Ca:Mg ratios manifest in tissues as the “fight or flight” response, bringing on clinical symptoms of CVD ([see Fig. 4, Appendix V](#)). After decades of rising dietary calcium intakes **not balanced with rising dietary magnesium intakes** and a population where **a majority of US adults are not getting their daily Mg requirement**, [[See Fig. 5a, 5b](#) and Appendix V], dietary Ca:Mg ratios are on the rise [[See Fig. 6](#) and [Appendix V](#)] and studies are showing that Ca supplements not balanced with magnesium increase the risk of heart disease ([see Appendix V](#)).

Why Is This Happening?

The modern processed food diet, so widespread for decades in the United States, is made from food commodities that are low in magnesium (and some other essential nutrients), mainly due to processing losses but also due to decreasing Mg levels in wheat [[See Fig. 8](#) and [Appendix VI](#)], vegetables [[See Fig. 9](#) and [Appendix VI](#)], and perhaps other food crops over the past 30+ years (see Appendix VI). Thus it is not surprising that most US adults are not getting their daily Mg requirement from the foods they eat ([Fig. 7](#)). Nuts and legumes, foods generally high in magnesium, are not a large part of the modern processed-food diet; trying to avoid calories and fats to prevent heart disease, people tend to avoid the fat in nuts even though it's healthy fat, and in so doing they miss one of our highest food sources of Mg. Chocolate is quite high in magnesium but so often comes with sugar, a commodity that can tend to elevate the excretion of Mg in the urine. Leafy green vegetables are frequently seen as a good source of Mg; however, there is evidence that these sources may be providing less Mg than in the past ([Appendix VI](#))—and certainly very few people in the general US population consume 7–9 fruit and vegetable servings every single day of their lives. Now that we are a few generations into this new, modern low-Mg diet, young mothers who are themselves low or deficient in Mg are having babies that start out life on a marginal Mg basis—a condition largely unrecognized by the medical community. At the same time, the stressful modern lifestyle, so widespread in the United States, can increase Mg need. Therefore, as a whole, our population certainly does not have the high body stores of Mg experienced by our ancestors or by peoples on traditional diets. **As the modern processed-food diet and the stressful high-Mg--requiring lifestyle that goes with it expand throughout the world, more and more of the growing human population will experience the marginal Mg status our society has been living with for decades [[Fig. 2 & 3](#) and [Appendix I](#)], and we can expect (and we now see) increasing levels of CVD as a result. ([See Appendices II](#) and [VI](#).)**

What Can Medicine Do?

Given the facts that modern diets are low in Mg and rising in Ca and that the modern stressful lifestyle can raise Mg requirements, it can be expected that many will need to use Mg supplements regularly to prevent developing cardiovascular disease and its risk factors. When you as a physician see a patient with a CVD risk factor, measure the serum Mg. If it is below 0.85 mmol/L, start that patient on Mg therapy (see Appendix VII). If their serum Mg is at or above this level and they still have risk factors, consider doing a Mg retention test before eliminating “low Mg” as a possible causative factor. If CVD risk factors are not yet severe, consider doing this before prescribing statins,

antihypertension medications and glucose-lowering medications. It is hoped that raising Mg status to a healthy, replete level will make it safe to gradually lower (and hopefully eliminate) the levels of medications ([see Appendix VII](#)).

How Much Mg? What Form of Mg? For How Long?

There are many forms of supplemental magnesium available for oral Mg therapy ([see Appendix VII](#)). It is common to prescribe 500 mg/day or more if it can be tolerated, less if not. Research subjects with low serum Mg have shown dips in serum Mg for the first 1–3 months of Mg therapy, followed by a rise in serum Mg to normal by 4–6 months ([see Fig. 10a,10b](#) and [Appendix VII](#)). If you monitor the Mg therapy by measuring urinary Mg, be aware that some research subjects low in Mg status show low urinary Mg during initial oral Mg therapy while their stores presumably replenish. It is a good idea to try oral Mg therapy as high as can be tolerated (given GI and bowel comfort) for 6 months at least. Powdered Mg supplements allow for easily altered Mg dose for personal tolerance, for daily Mg prescriptions to be easily broken into two or more doses, and for persons who don't like pills to take their Mg supplement as a liquid.

When nutritional Mg is low, it is quite possible that other essential nutrients are either low or out of balance. Adequate and balanced intake of all essential nutrients is necessary for optimal health.

Figures:

- [1. As Mg intakes have gone down in the USA, heart disease has risen.](#)
- [2. 1968 USA: The peak in US Coronary Heart Disease mortality coincides with the nadir of Mg availability in the US food supply.](#)
- [3. Global heart disease death rates are rising as the modern food diet \(low in Mg\) expands.](#)
- [4. Some cellular effects of high Ca:Mg that can manifest as aspects of heart disease.](#)
- [5a. and 5b. For the past 30 years in the USA, calcium intakes from food have risen sharply compared to Mg intakes from food.](#)
- [6. The Ca:Mg ratio from food intake in the USA is rising to an unhealthy level.](#)
- [7. Many people in the USA do not get their required daily Mg from food.](#)
- [8a.and 8b. Mg has declined in wheat crops since 1968.](#)
- [9. Mg has declined in both wheat and vegetable crops over the past 35+ years.](#)
- [10a. and 10b. Oral Mg therapy can take up to 8 to 10+ weeks to normalize a low serum Mg level.](#)

Appendices & Associated References:

[Appendix I. A brief history of the beginnings of the Mg Hypothesis of Cardiovascular Disease](#)

[Vitale et al abstract from the 1957 Fed Proc.](#)

[Appendix II. Rise in cardiovascular disease occurs with declining Mg intakes](#)

[Rosanoff A. Changing crop magnesium concentrations: impact on human health. Plant and Soil. 2012. DOI 10.1007/s11104-012-1471-5.](#)

[Appendix III. Both old and new peer-reviewed studies show that cardiovascular disease risk factors are related to Mg status](#)

[Appendix IV. New and old studies showing low Mg status \(hypomagnesemia\) is associated with stroke and sudden cardiac death](#)

[Highlighted Abstracts for Appendix IV. Studies showing Low Mg status \(hypomagnesemia\) is associated with stroke and sudden cardiac death](#)

[Appendix V: The importance of balancing Ca with Mg and dangers of the rising Ca:Mg dietary intake ratio](#)

[Highlighted Abstracts for Appendix V – Importance of Balancing Ca with Mg...](#)

[Rosanoff A. 2010. Rising Ca:Mg intake ratio from food in USA adults: a concern - Magnes Res 23\(4\): 181–93.](#)

[Rosanoff A, et al. 2012. Suboptimal magnesium status in the United States: Are the health consequences underestimated? Nutr Rev 70\(3\): 153–64.](#)

[Appendix VI: Declining food Mg concentrations over time have resulted in low Mg intakes for many](#)

[Rosanoff A. Changing crop magnesium concentrations: impact on human health. Plant and Soil. 2012. DOI 10.1007/s11104-012-1471-5.](#)

[Rosanoff A, et al. 2012. Suboptimal magnesium status in the United States: Are the health consequences underestimated? Nutr Rev 70\(3\): 153–64.](#)

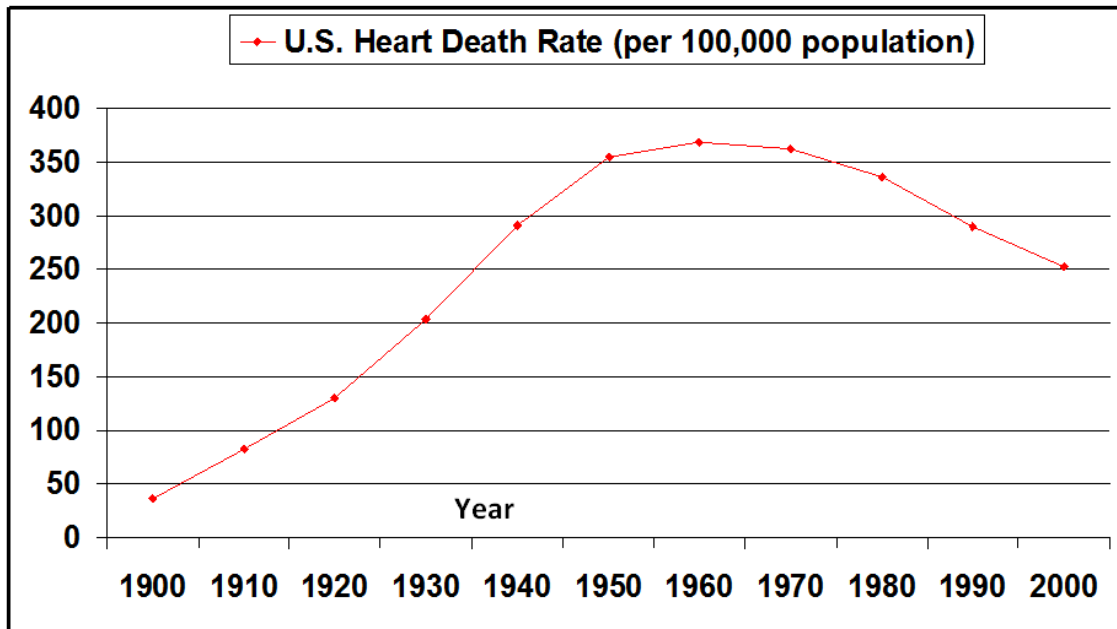
[Appendix VII: Mg therapy—things to consider](#)

[Highlighted Abstracts for Appendix VII - References](#)

[Rosanoff A, et al. 2012. Suboptimal magnesium status in the United States: Are the health consequences underestimated? Nutr Rev 70\(3\): 153–64.](#)

For more information go to www.MagnesiumEducation.com

Fig. 1 As Mg intakes have gone down in USA, heart disease has risen.



Calculated w/ data from: AHA, U.S. Census – not adjusted for age

From Marier, 1982: **Estimated Mg intakes in USA:** 1910 – 410 mg/day per person
1980 – 300 mg/day per person

See also Fig. 2

Fig. 2 1968 USA - The Peak in USA Coronary Heart Disease mortality coincides with the Nadir of Mg availability in the USA food supply

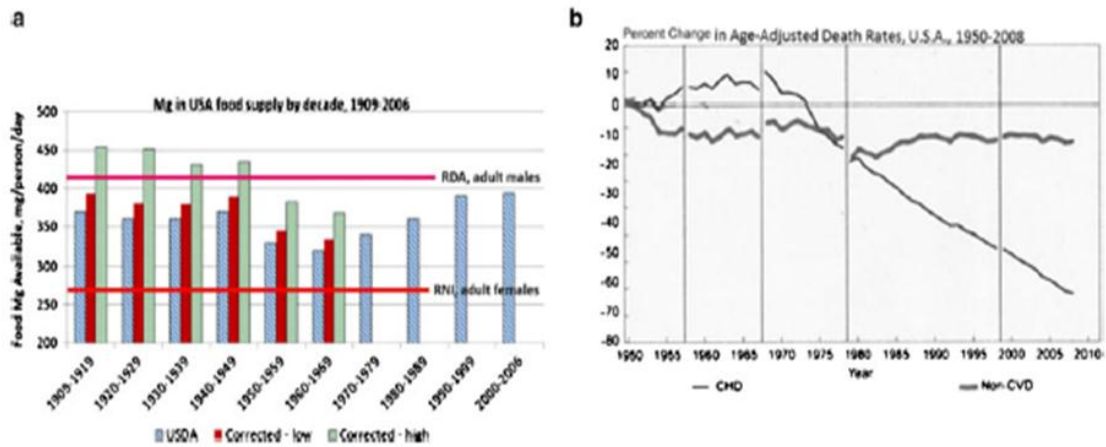
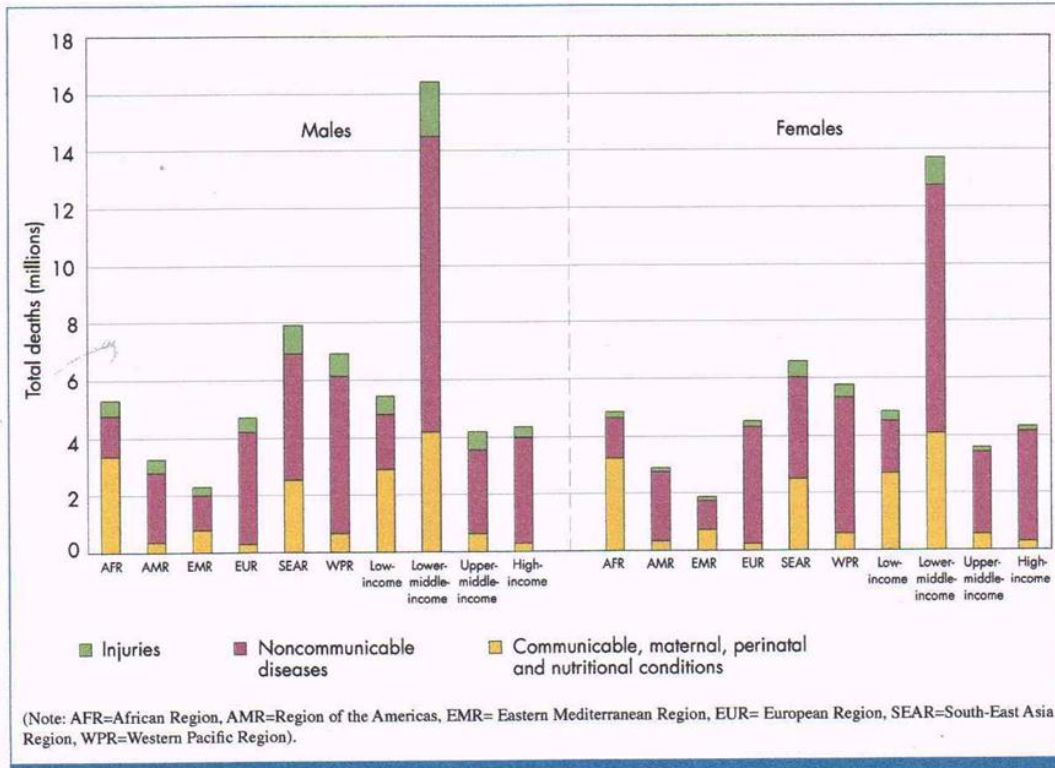


Fig. 4 Coronary Heart Disease (CHD) mortality peak in USA coincides with nadir of USA Mg in food supply. **a** Mg in USA food supply per capita per day by decade, 1909-2006, with recalculation using crop %Mg declines summarized in Tables 2 and 3. USDA data from Genior et al. 2004 and Hiza and Bente 2011:

Data recalculated with data from Fan et al. 2008; Ficco et al. 2009; Murphy et al. 2008; White and Broadley 2005; Davis 2009; Rosanoff 2012 (unpublished). **b** Change in age adjusted death rates for cardiovascular (CHD) and non-cardiovascular diseases, USA, 1950-2008. Adapted, with permission (NIH 2012)

Fig. 3 Global Heart Disease Death Rates are Rising as Modern Food Diet (low in Mg) Spreads

Total Deaths by Cause, WHO Regions & World Bank income groups



WHO Global Status report on non-communicable diseases, 2010

Fig. 4 Some Cellular Effects of High Ca:Mg that can Manifest as Aspects of Heart Disease

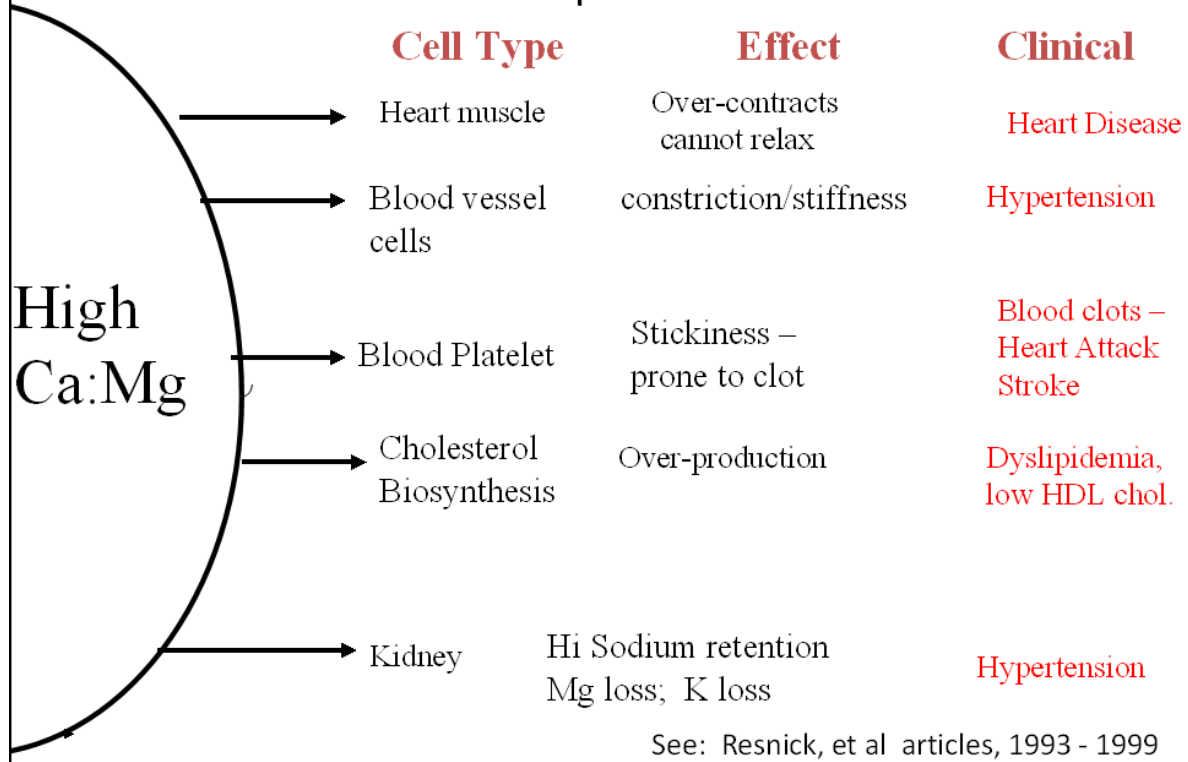
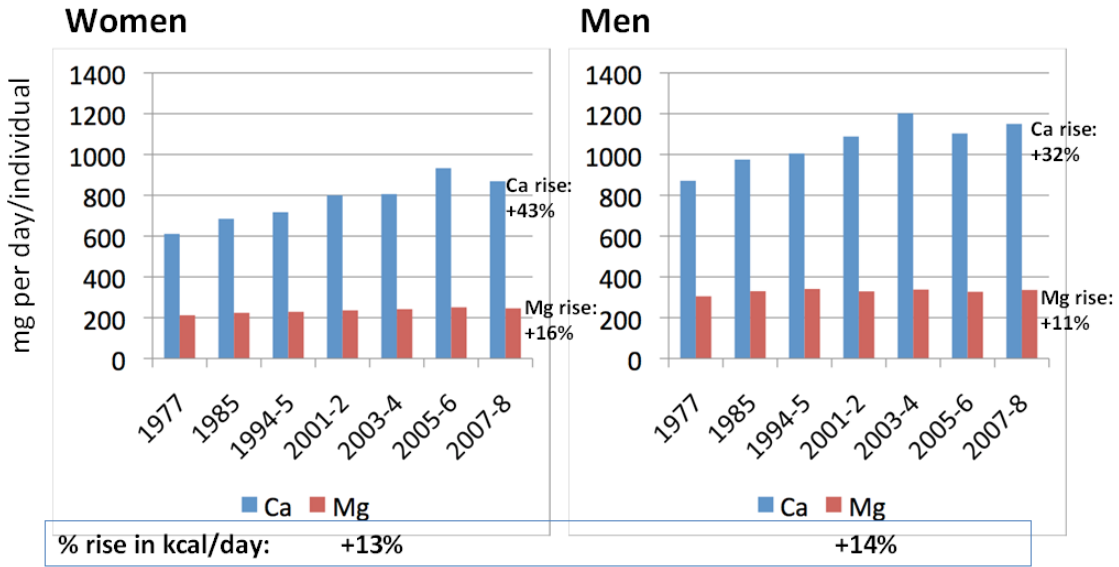


Fig. 5 For the past 30 years, Calcium Intakes from food have risen sharply compared to Mg Intakes from food in USA

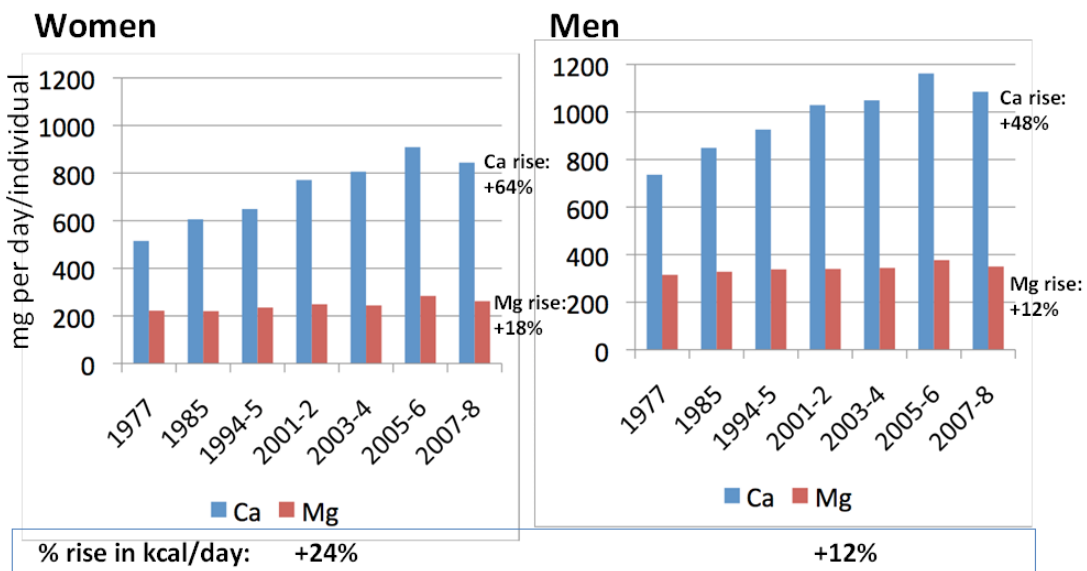
Fig. 5a Mean Ca & Mg intakes from food over time
USA Young Adults 19/20 – 29/34 yrs



Source: Rosanoff, A., 2010

Fig. 5 For the past 30 years, Calcium Intakes from food have risen sharply compared to Mg Intakes from food in USA

Fig. 5b Mean Ca & Mg intakes from food over time
USA Adults 30/35 to 49/50 yrs



Source: Rosanoff, A. 2010

Fig. 6 The Ca:Mg Ratio from Food Intake in the USA is rising to an unhealthy level

Rising Ca:Mg Intake from Food over time in USA

Men and Women age 19 – 50 yrs

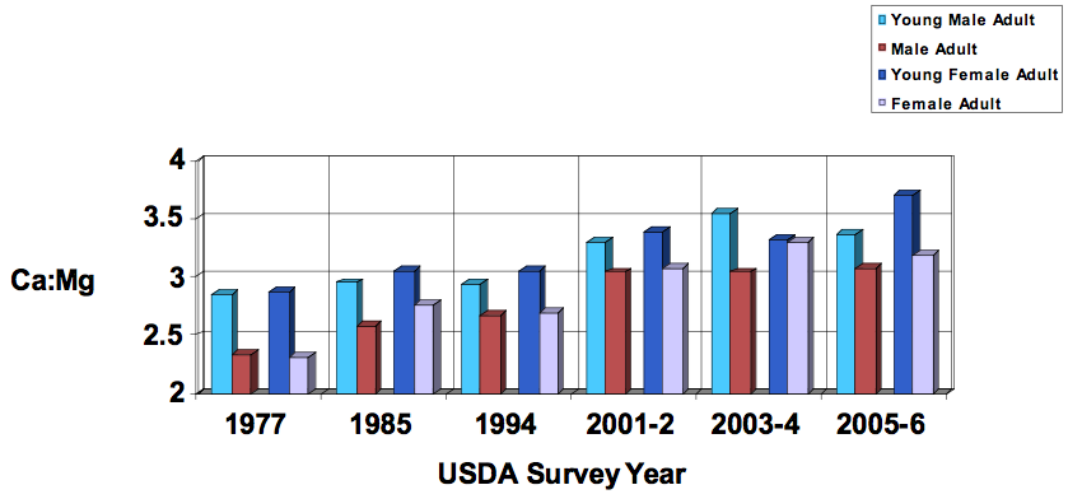
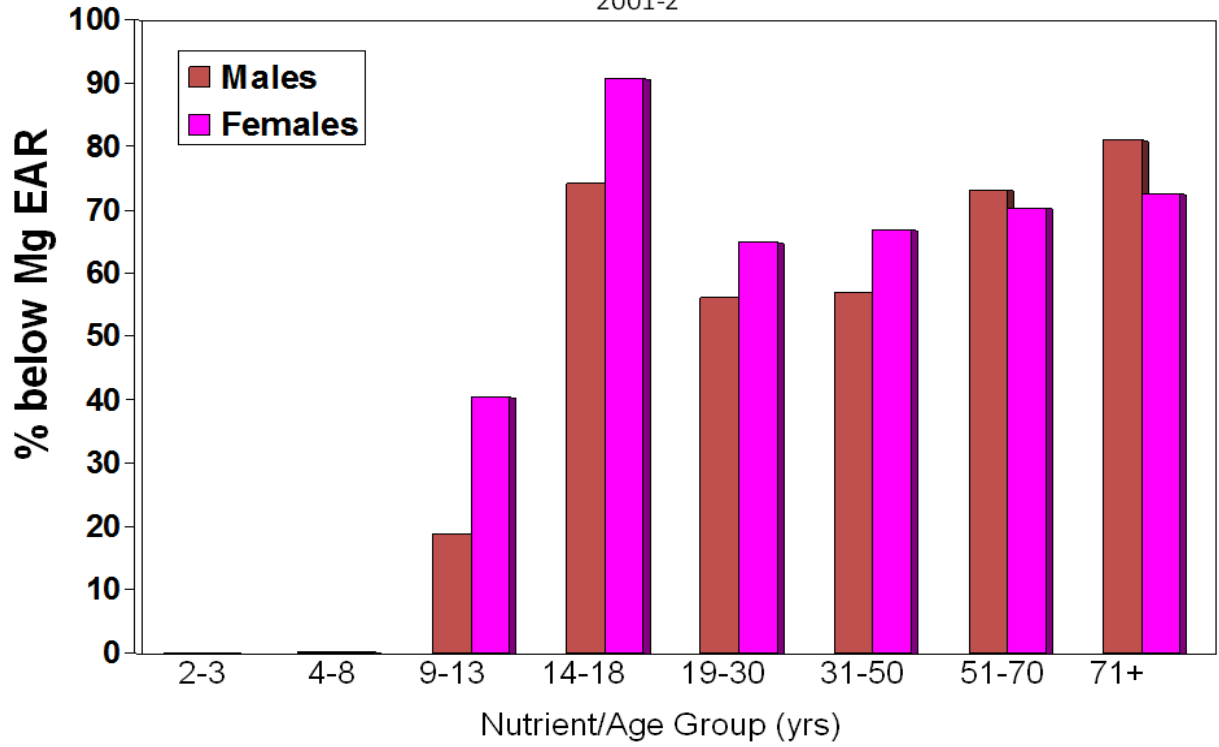


Fig. 7 Many People in the USA do NOT get their Required Daily Mg from Food

Proportion of the USA Population Below the Estimated Average Requirement (EAR) for Magnesium in 2001-2



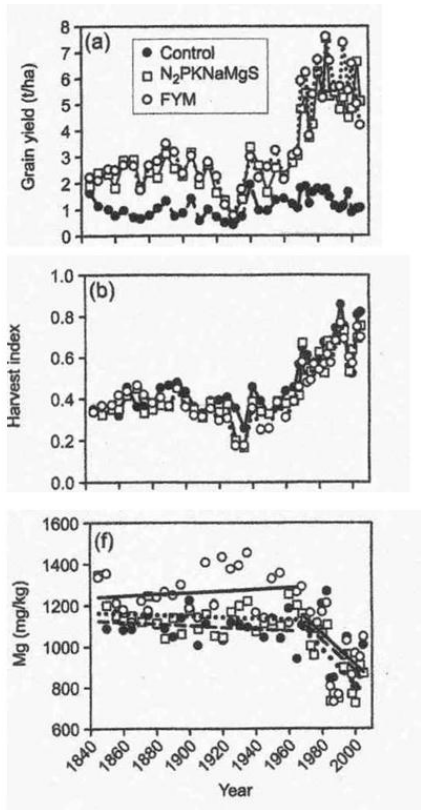


Fig. 8 Mg Has Declined in Wheat Crops Since 1968

Mg Declines with rises in wheat grain yield over 160 years (at 85% dry matter) at Rothamsted, England

Sources: Fan et al. 2008; and Rosanoff, 2012

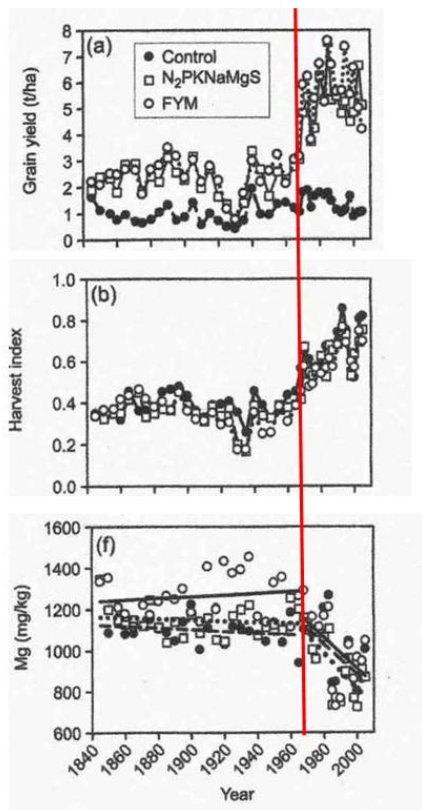


Fig. 8 Mg Has Declined in Wheat Crops Since 1968

Mg Declines with rises in wheat grain yield over 160 years (at 85% dry matter) at Rothamsted, England

1968 – Short-straw cultivars first introduced

Sources: Fan et al. 2008; and Rosanoff, 2012

Fig. 9 Mg Has Declined in Wheat & Vegetable Crops Over the Past 35+ Years

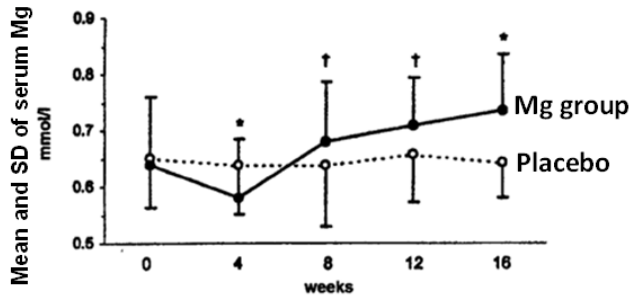
Decline in Food Crop Mg Contents

References	Crop	% decline
Fan et al. 2008	Wheat - pre-1965 to post-1968	19.6%
Ficco et al. 2009	Wheat – pre-1974 to post-1974	12.4%
Murphy et al. 2008	Wheat – pre-1965 to post 2004	7%
USDA tables	Wheat grain – 1930's to 1989	23% - 29%
UK Tables	Wheat Flours – 1942 to 1978	7 to 16%
White & Broadley 2005	English Vegetables – 1930s to 1980s	18 - 19%
Mayer 1997	English Vegetables	23 – 35%
Rosanoff 2012	USA Vegetables 1940s to 2011	15%

Source: Rosanoff, A. 2012 Changing crop magnesium concentrations: impact on human health

Fig. 10 Oral Mg Therapy Can Take up to 8 to 10+ weeks to normalize a low serum Mg level

Fig. 10a from Rodriguez-Moran & Guerrero-Romero, 2003

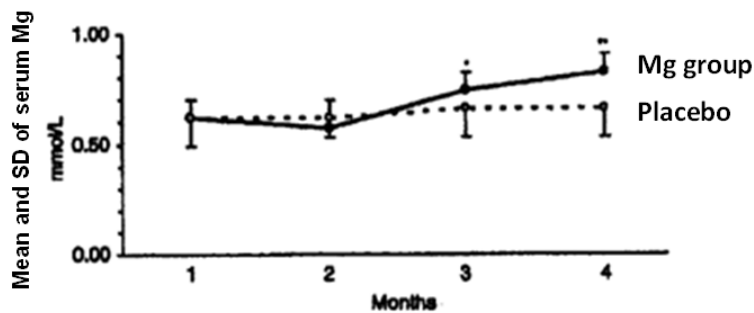


Note: length of Mg therapy is important when Mg def is being corrected rather than prevented.

Original Figure Caption: Mean and SD of serum Mg in all participants evaluated (dark circles, 32 MgCl₂ recipients; open circles, 31 placebo recipients). Mg levels in the subjects who received MgCl₂ showed a significant reduction for the first month, followed by a sustained and significant increase.

Fig. 10 Oral Mg Therapy Can Take up to 8 to 10+ weeks to normalize a low serum Mg level

Fig. 10b from Guerrero-Romero & Rodriguez-Moran, 2009



Note: length of Mg therapy is important when Mg def is being corrected rather than prevented.

Original Figure Caption: serum Mg levels, in the subjects who received Mg supplementation, showed a gradual increase that reached significance at the 3rd month of treatment.

Appendix I: A brief history of the beginnings of the Mg Hypothesis of Cardiovascular Disease

In 1936, Greenberg and colleagues showed that Mg deficiency in animals caused myocardial degeneration with fibrosis. In 1938, L. A. Moore and colleagues reported that Mg deficient calves displayed atherosclerotic lesions with **calcification** in aortas and some hearts. In 1957, researchers at Harvard reported that male rats fed an atherogenic diet for only 24–26 days (Vitale et al., 1957; Hellerstein et al., 1957; Vitale et al., 1959) developed a low serum Mg (Mg deficiency) along with **calcium deposition** in kidney tubular lesions that could be wholly prevented by feeding the animals 8 to 16 times their normal requirement of Mg. These animals also developed early atherosclerotic lesions in the heart valves and aortas, which could be diminished but not totally abolished with exceedingly high dietary levels of Mg if dietary protein was normal (10%), but not in cases where dietary protein was high (20%). This atherosclerotic diet was high in cholesterol and fat. Such atherosclerotic lesions had previously been seen in animals fed a severely Mg deficient diet (see review of Bajusz, 1965).

In addition to the above findings, early studies from 1957 through the 1990s also showed low water/soil Mg correlating with high rates of sudden cardiac death rates and ischemic heart disease in several countries. (Kobayashi, J., 1957; Seelig & Rosanoff, 2003, pp. 303–7). In confirmation, recent epidemiological studies have inversely related both serum magnesium levels (Leone et al., 2006) and magnesium levels in drinking water to cardiovascular death rates (Catling et al., 2008; Monarca et al., 2003, 2006).

References

Greenberg DM, Anderson CE, Tufts EV. 1936. *J Biol Chem* 114:xlili.
Moore LA, Hallman ET, Sholl LB. 1938. *Arch Path* 26:820.

Vitale JJ, White PL, Nakamura M, Hegsted DM, Zamcheck N, Hellerstein EE. 1957. Interrelationships between experimental hypercholesteremia, magnesium requirement, and experimental atherosclerosis. *J Exp Med* 106(5) (Nov 1): 757–66. PubMed PMID: 13475629; PubMed Central PMCID: PMC2136817.
For full text of article: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2136817/>.

Hellerstein EE, Vitale JJ, White PL, Hegsted DM, Zamcheck N, Nakamura M. 1957. Influence of dietary magnesium on cardiac and renal lesions of young rats fed an atherogenic diet. *J Exp Med* 106(5) (Nov 1): 767–76. PubMed PMID: 13475630; PubMed Central PMCID: PMC2136825. **For full text of article:** <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2136825/>.

Vitale JJ, Hellerstein EE, Hegsted DM, Nakamura M, Farbman A. Studies on the interrelationships between dietary magnesium and calcium in atherogenesis and renal lesions. 1959. *Am J Clin Nutr* 7(1) (Jan–Feb): 13–22. PubMed PMID: 13626881. **For full text of article:** <http://ajcn.nutrition.org/content/7/1/13.long>.

Bajusz E. *Nutritional Aspects of Cardiovascular Diseases*. 1965. See p. 69 of this monograph, available for purchase at <http://www.cabdirect.org/abstracts/19661403690.html;jsessionid=399828FCEBB2DBC55D488E61EEADA00C>.

Early articles reporting higher rates of cardiovascular mortality in areas of low Mg soil/water:

Koyayashi J. 1957. On geographical relationship between the chemical nature of river water and death rate from apoplexy. *Berichte des Ohara Instituts fur Landwirtschaftliche Biologie* 11:12–21.
Seelig MS, Rosanoff A. 2003. *The Magnesium Factor*. New York: Avery Penguin Putnam. See pp. 302–7 For bibliography of hard---soft water and heart disease mortality studies (1957–1998).

Confirming recent articles on cardiovascular mortality rates with low Mg water:

Catling LA, Abubakar I, Lake IR, Swift L, Hunter PR. 2008. A systematic review of analytical observational studies investigating the association between cardiovascular disease and drinking water hardness. *J Water Health* 6(4): 433–42. <http://www.ncbi.nlm.nih.gov/pubmed/18401109>.

Monarca S, Donato F, Zerbini I, Calderon RL, Craun GF. 2006. Review of epidemiological studies on drinking water hardness and cardiovascular diseases. *Eur J Cardiovasc Prev Rehabil* 13(4):495–506. <http://www.ncbi.nlm.nih.gov/pubmed/16874137>.

Monarca S, Zerbini I, Simonati C, Gelatti U. 2003. [Drinking water hardness and chronic degenerative diseases. II. Cardiovascular diseases.] *Ann Ig* 15(1): 41–56. <http://www.ncbi.nlm.nih.gov/pubmed/12666324>.

See next page or [Click here for the Vitale et al abstract from the 1957 Fed Proc.](#)

Federation Proceedings 1957

vol 16: 400-401

1718. EFFECT OF FEEDING AN ATHEROGENIC DIET ON MAGNESIUM REQUIREMENT. Joseph J. Vitale,* P. L. White,* M. Nakamura* and D. M. Hegsted. Dept. of Nutrition, Harvard School of Public Health, Boston, Mass.

The addition of thyroxine to the diet of rats results in an inhibition of growth and a decrease in the serum magnesium levels, both of which are partially overcome by feeding excess magnesium. These observations together with the known effect of thyroxine on the level of serum cholesterol led us to investigate the effect of feeding an atherogenic diet on Mg metabolism. A 10% protein and 20% fat diet, with and without cholesterol (1%) and cholate (.3%) and containing various levels of Mg (12, 24, 48, 96 and 192 mg %) was fed to weanling rats for 24 days at which time blood samples were drawn and the animals killed for histological study. The control animals fed the diets containing no cholesterol and cholate grew maximally when fed 24 mg % Mg, had an average serum Mg level of 1.9 mg %, had no morphological changes in any of the organs examined and had serum cholesterol concentrations ranging from 90 to 110 mg %. Animals fed the diets with cholesterol and cholate did not grow maximally, had low levels of serum Mg, high levels of serum cholesterol (639-808 mg %), and had an extensive heart score (Sudanophilia of heart and aorta). Increasing the Mg content of the diet to 192 mg % largely overcame all of these effects except the level of serum cholesterol which remained high. It is concluded that the atherogenic diet used in these studies produces a magnesium deficiency accompanied by hypercholesteremia and an extensive Sudanophilia of the heart and aorta. (Extensive kidney lesions were also produced in these rats, see abstract by E. Hellerstein and N. Zamcheck.)

Appendix II. Rise in Cardiovascular Disease occurs with declining Mg intakes

The rise in cardiovascular disease in 20th Century USA occurred while Mg intakes declined in that country. The current rise of CVD in other areas of the world occurs as dietary Mg intakes decrease.

Heart disease has risen steadily in the USA throughout the 20th century while Mg intakes in that country, during that time, have diminished.

[[Figure 1](#): As Mg intakes have gone down in USA, heart disease has risen.

American Heart Association deaths from heart disease, 1900 – 2000 with concurrent decrease in Mg intake as estimated by J. Marier (full paper available on request). Also, see pg. 5 of “The Magnesium Factor.”]

The steep rise in heart disease deaths in the American Heart Association [Figure 1](#) is not age adjusted. A more accurate visual is found in [Figure 2](#) which shows how the peak in USA coronary heart disease death rates (1968) coincided with that country’s nadir in available food Mg.

[[Figure 2](#). 1968 USA – The Peak in USA Coronary Heart Disease mortality coincides with the Nadir of Mg availability in the USA food supply

USA dietary Mg availability, 1900 – 2006 with age-adjusted coronary heart disease death mortality rates. The peak in coronary heart disease death rate (1968) coincides with the nadir of food Mg availability in this country. From: Rosanoff, A., 2012 Plant & Soil paper ([see full paper](#))

As the modern processed food diet, lower in Mg than traditional diets, spreads around the globe, we see rising death rates from cardiovascular diseases.

[[Figure 3](#). Global Heart Disease Death Rates are Rising as Modern Food Diet (low in Mg) Spreads

World Health Organization chart showing changing pattern of death in world: (non-communicable diseases, which are roughly 50% CVD, are becoming the main cause of death worldwide)].

Full paper of following available upon request:

Marier J R 1982 Quantitative Factors Regarding Magnesium Status in the Modern-Day World. Magnesium 1, 3-15.

Abstract: A large-scale US survey has shown that the dietary magnesium intake tends to be lower than recommended. The suboptimal intake prevalent among US adults is consistent with the pattern observed in other North American and European surveys. Several factors are discussed, including the waterborne magnesium factor, the loss of magnesium during food refining and the magnesium content of vegetarian diets, as well as various metabolic situations, e.g., hypertension, pregnancy, osteoporosis, drug therapy, alcoholism, stress and cardiac trauma. The benefits of magnesium supplementation among those with sub-RDA intakes are illustrated.

([See full paper of the following](#))

Rosanoff, A. 2012 Changing crop magnesium concentrations: impact on human health, Plant and Soil, DOI 10.1007/s11104-012-1471-5.

Abstract: Aims: Decreasing mineral concentrations in high-yield grains of the Green Revolution have coincided in time with rising global cardiovascular disease (CVD) mortality rates. Given the Magnesium

(Mg) Hypothesis of CVD, it's important to assess any changes in food crop Mg concentrations over the past 50+ years.

Methods: Using current and historical published sources, Mg concentrations in “old” and “new” wheats, fruits and vegetables were listed/calculated (dry weight basis) and applied to reports of USA's historic Mg supply, 1900–2006. Resulting trend in USA Mg supply was compared with USA trend in CVD mortality. Human Mg intake studies, old and new, were compared with the range of reported human Mg requirements.

Results: Acknowledging assessment difficulties, since the 1850s, wheats have declined in Mg concentration 7–29%; USA and English vegetables' Mg declined 15–23%, 1930s to 1980s. The nadir of USA food Mg supply in 1968 coincides with the USA peak in CVD mortality. As humans transition from “traditional” to modern processed food diets, Mg intake declines. [See Tables 4 & 5 of full text paper](#)

Conclusions: Rising global CVD mortality may be linked to lower Mg intakes as world populations transition from traditional high Mg foods to those low in Mg due to declining crop Mg and processing losses.

Changing Crop Magnesium Concentrations: Impact on Human Health

Plant and Soil - October 2012 – Andrea Rosanoff, Ph.D

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Plant Soil - DOI 10.1007/s11104-012-1471-5

Abstract

Aims

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Methods

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Conclusions

Rising global CVD mortality may be linked to lower Mg intakes as world populations transition from traditional high Mg foods to those low in Mg due to declining crop Mg and processing losses.

[Complete Document](#)

Appendix III: Both old and new peer-reviewed studies show that CVD risk factors are related to Mg status

Discussed below are a few of the most commonly known CVD risk factors with some of the peer-reviewed science that relates them to Mg status.

See references of *The Magnesium Factor* by Mildred Seelig and Andrea Rosanoff.

See also “The Mg Hypothesis of Cardiovascular Disease: A Bibliography”

<http://www.magnesiumeducaGon.com/the---mg---hypothesis---of---cardiovascular---disease---a---bibliography>

High Blood Pressure — Mg normalizes blood pressure, perhaps the most predictive and certainly the oldest cardiovascular risk factor. Mg supplementation also enhances the action of anti-hypertension medications (Rosanoff, 2010; Houston, 2011). Three meta-analyses on Mg therapy for blood pressure (Dickinson et al., 2006; Jee et al., 2001; Kass et al., 2012) have all reported that Mg supplements do have a small but significant effect on blood pressure, which appears so small as to be clinically insignificant. However, a recent study shows how these meta-analyses failed to include high-responder studies that demonstrate Mg therapy has a highly significant and profound effect on high blood pressure in **some** subjects—that Mg therapy in some hypertensive individuals can consistently lower SBP by 19 mm Hg and DBP by about 8 mm Hg; but other hypertensive subjects as well as normotensive subjects show a much lower or even zero response to Mg therapy. When meta-analyses and studies “average” all these various subjects together, they get the erroneous conclusion that Mg therapy has only a small albeit significant effect on human blood pressure. Not having reliable methods to ascertain Mg status hinders these studies and the interpretation of their results.

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Cholesterol — Several studies have shown that adequate Mg or Mg therapy will lower LDL (bad) cholesterol and raise HDL (good) cholesterol (see Seelig & Rosanoff,2003: 330–42). Mg is an essential cofactor for the rate limiting enzyme in the cholesterol biosynthesis sequence, HMG-CoA-Reductase, the enzyme targeted by the statins (Rosanoff & Seelig, 2004). High cholesterol in rats was an early aspect of atherosclerotic disease that was tightly tied to Mg status ([see appendix I](#)). There is ample evidence to consider a high-LDL and/or low-HDL cholesterol as an aspect of Mg deficit warranting Mg therapy.

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Diabetes —More and more medical science is accepting the strong link between Mg status and the onset of type 2 diabetes (Barbagallo et al., 2007). Diabetes is a risk factor for CVD, and the low Mg status of both is part of the Mg Hypothesis of CVD. Type 1 diabetics have long been known to be at high risk for CVD. These people need insulin to keep their blood glucose from becoming too high; a high blood glucose enhances Mg excretion by the kidneys—open leading to a low magnesium status and its risk of CVD.

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Olatunji LA and Soladoye AO. 2007. Effect of increased magnesium intake on plasma cholesterol, triglyceride and oxidative stress in alloxan-diabetic rats. *Afr J Med Med Sci* 36:155–61.

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Mg and Insulin Resistance

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Smoking — This habit has long been associated with a higher risk of CVD than for nonsmokers. Smoking a tobacco cigarette raises the basal metabolic rate, undoubtedly raising the Mg requirement in smokers. With a higher requirement than the general nonsmoking population, the Mg Hypothesis predicts that smokers will show a higher degree of CVD than nonsmokers, taken as a whole.

C---Reactive Protein and Inflammation — A high C---reactive protein in the serum is a newer predictor of CVD (Albert & Ridker, 1999) and is highly inversely related to Mg status (Almonznino- - Sarafian et al., 2007). The first symptom of Mg deficiency in mice is biochemical inflammation reactions (Weglicki et al., 2010).

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Djurhuus MS, Henriksen JE, Klitgaard NA, Blaabjerg O, Thye---Ronn P, Altura BM, Altura BT, and Beck---Nielsen H. 1999. Effect of moderate improvement in metabolic control on magnesium and lipid concentrations in patients With type 1 diabetes. *Diabetes Care* 22:546–54.

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Other CVD Risk Factors Linked to Mg status — depression, microalbuminuria, polycystic ovary syndrome, hemodynamic changes, renal sodium retention, prothrombic factors, fibrinogen and other inflammation markers, C---Reactive Protein, endothelial---dependent vasodilation.

References available upon request.

Appendix IV. New and Old Studies showing Low Mg status (hypomagnesemia) is associated with stroke and sudden cardiac death

Low serum Mg is a risk factor for sudden cardiac death, and low Mg intake is a risk factor for stroke.

[For Highlighted Abstracts for the following references click here "Abstracts document" for Appendix IV.](#)

Earlier work of the 1990s:

Gartside P S and Glueck C J 1995 The important role of modifiable dietary and behavioral characteristics in the causation and prevention of coronary heart disease hospitalization and mortality: the prospective NHANES I follow-up study. *J Am Coll Nutr* 14, 71-79. **Hanes I study with 10 yr follow-up**

Ford E S 1999 Serum magnesium and ischaemic heart disease: findings from a national sample of US adults. *Int J Epidemiol* 28, 645-651. **Hanes I with 19-yr follow-up**

Liao F, Folsom A R and Brancati F L 1998 Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 136, 480-490.

Recent studies that confirm the earlier work:

Leone N, Courbon D, Ducimetiere P and Zureik M 2006 Zinc, copper, and magnesium and risks for all-cause, cancer, and cardiovascular mortality. *Epidemiology* 17, 308-314.

Peacock J M, Ohira T, Post W, Sotoodehnia N, Rosamond W and Folsom A R 2010 Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 160, 464-470.

Chiuvè S E, Korngold E C, Januzzi J L, Jr., Gantzer M L and Albert C M 2011 Plasma and dietary magnesium and risk of sudden cardiac death in women. *Am J Clin Nutr* 93, 253-260.

Khan A M, Sullivan L, McCabe E, Levy D, Vasan R S and Wang T J 2010 Lack of association between serum magnesium and the risks of hypertension and cardiovascular disease. *Am Heart J* 160, 715-720.

[See abstract for comment on these "negative" results that appear contrary to other studies' results.](#)

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May Khan A, Lubitz S A, Sullivan L M, Sun J X, Levy D, Vasan R S, Magnani J W, Ellinor P T, Benjamin E J and Wang T J 2012 Low Serum Magnesium and the Development of Atrial Fibrillation in the Community: The Framingham Heart Study. *Circulation*. [See abstract for comment on degree of association concluded in this paper.](#)

And for stroke:

Nie Z L, Wang Z M, Zhou B, Tang Z P and Wang S K 2012 Magnesium intake and incidence of stroke: Meta-analysis of cohort studies. *Nutr Metab Cardiovasc Dis*.

Larsson S C, Orsini N and Wolk A 2012 Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. *Am J Clin Nutr* 95, 362-366.

Singh, H., et al. (2012). "Role of magnesium sulfate in neuroprotection in acute ischemic stroke." *Ann Indian Acad Neuro* 15(3): 177-180. [See abstract for comment on these "negative" results that appear contrary to other studies' results.](#)

Highlighted Abstracts for Appendix IV. Studies showing Low Mg status (hypomagnesemia) is associated with stroke and sudden cardiac death

Low serum Mg is a risk factor for sudden cardiac death, and low Mg intake is a risk factor for stroke.

Earlier Work of the 1990s:

Gartside PS, Glueck CJ.

J Am Coll Nutr. 1995 Feb;14(1):71-9.

The important role of modifiable dietary and behavioral characteristics in the causation and prevention of coronary heart disease hospitalization and mortality: the prospective NHANES I follow-up study.

Source: University of Cincinnati College of Medicine, Biostatistics Division, Ohio, USA.

Abstract

OBJECTIVE: Our specific aim in the prospective, longitudinal assessment of 8,251 subjects in the National Health and Nutrition Examination Survey, NHANES I, followup study was to assess the important roles of modifiable dietary and behavioral characteristics in the causation and prevention of coronary heart disease (CHD).

METHODS: Using NHANES I prospective 10 year followup data, we studied 8,251 subjects; 492 with cardiovascular events and 7,759 without events during the followup period (1971-75 to 1982-84). Using general linear models and logistic regression, we assessed the relationships of CHD risk factors to CHD morbidity and mortality.

RESULTS: By logistic regression, the following factors were independently, significantly, and inversely associated with coronary heart and vascular disease deaths and hospitalizations: alcohol intake, dietary riboflavin, dietary iron, serum magnesium, leisure time exercise, habitual physical activity, and female gender. Positive significant independent determinants of CHD events included cigarette smoking, sedimentation rate, Quetelet index, maximum body weight, and age.

CONCLUSIONS: These associations emphasize the important role of modifiable dietary and behavioral characteristics in the causation and prevention of CHD.

Ford ES.

Int J Epidemiol. 1999 Aug;28(4):645-51.

Serum magnesium and ischaemic heart disease: findings from a national sample of US adults.

Source: Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA.

Abstract

BACKGROUND: Animal and human data suggest that magnesium may play an important role in ischaemic heart disease. Few prospective epidemiological studies have related serum magnesium concentrations to mortality from ischaemic heart disease (IHD) or all-causes.

METHODS: Data from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study were used to examine the association between serum magnesium concentration, measured

between, 1971-1975, and mortality from IHD or all-causes in a national sample of 25-74-year-old participants followed for about 19 years.

RESULTS: The analytical samples for IHD and all-cause-mortality included 12 340 and 12 952 participants, respectively (1005 IHD deaths, 2637 IHD deaths or hospitalizations, 4282 total deaths). Hazard ratios for IHD mortality from proportional hazards analysis comparing the second (1.59- <1.68 mEq/l), third (1.68-<1.77 mEq/l), and fourth (> or =1.77 mEq/l) quartiles of serum magnesium concentration with the lowest quartile were 0.79 (95% CI: 0.58-1.08), 0.66 (95% CI: 0.47-0.93), 0.69 (95% CI: 0.52-0.90), respectively. For all-cause mortality, hazards ratios were 0.82 (95% CI: 0.72-0.93), 0.84 (95% CI: 0.73-0.96), 0.85 (95% CI: 0.75-0.95). No significant interactions between serum magnesium concentration and age, sex, race, and education were observed.

CONCLUSION: Serum magnesium concentrations were inversely associated with mortality from IHD and all-cause mortality.

Liao F, Folsom AR, Brancati FL.

Am Heart J. 1998 Sep;136(3):480-90.

Is low magnesium concentration a risk factor for coronary heart disease?
The Atherosclerosis Risk in Communities (ARIC) Study.

Source: Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis 55454-1015, USA.

Abstract

BACKGROUND: Hypomagnesemia has been hypothesized to play a role in coronary heart disease (CHD), but few prospective epidemiologic studies have been conducted.

METHODS AND RESULTS: We examined the relation of serum and dietary magnesium with CHD incidence in a sample of middle-aged adults (n=13,922 free of baseline CHD) from 4 US communities. Over 4 to 7 years of follow-up, 223 men and 96 women had CHD develop. After adjustment for sociodemographic characteristics, waist/hip ratio, smoking, alcohol consumption, sports participation, use of diuretics, fibrinogen, total and high-density lipoprotein cholesterol levels, triglyceride levels, and hormone replacement therapy, the relative risk of CHD across quartiles of serum magnesium was 1.00, 0.92, 0.48, and 0.44 (P for trend=0.009) among women and 1.00, 1.32, 0.95, and 0.73 (P for trend=0.07) among men. The adjusted relative risk of CHD for the highest versus the lowest quartile of dietary magnesium was 0.69 in men (95% confidence interval 0.45 to 1.05) and 1.32 in women (0.68 to 2.55).

CONCLUSIONS: These findings suggest that low magnesium concentration may contribute to the pathogenesis of coronary atherosclerosis or acute thrombosis.

Recent Work Confirming Earlier Work Cited Above:

Leone N, Courbon D, Ducimetiere P, Zureik M.

Epidemiology. 2006 May;17(3):308---14.

Zinc, copper, and magnesium and risks for all---cause, cancer, and cardiovascular mortality.

Source: Unit 744 National Institute of Health and Medical Research (INSERM), Lille Pasteur Institute, Lille, France.

BACKGROUND: Experimental data suggest that zinc, copper, and magnesium are involved in carcinogenesis and atherogenesis. Few longitudinal studies have related these minerals to cancer or cardiovascular disease mortality in a population.

METHODS: Data from the Paris Prospective Study 2, a cohort of 4035 men age 30---60 years at baseline, were used to assess the association between serum zinc, copper, and magnesium and all---cause, cancer, and cardiovascular disease mortality. Serum mineral values measured at baseline were divided into quartiles and classified into low (1st quartile, referent group), medium (2nd---3rd quartiles), and high (4th quartile) values. During 18---year follow up, 339 deaths occurred, 176 as a result of cancer and 56 of cardiovascular origin. Relative risks (RRs) for each element were inferred using Cox's proportional hazard model after controlling for various potential confounders.

RESULTS: High copper values (4th quartile) were associated with a 50% increase in RRs for all---cause deaths (RR = 1.5; 95% confidence interval = 1.1---2.1), a 40% increase for cancer mortality (1.4; 0.9---2.2), and a 30% increase for cardiovascular mortality (1.3; 0.6---2.8) compared with low values (1st quartile). High magnesium values were negatively related to mortality with a 40% decrease in RR for all---cause (0.6; 0.4---0.8) and cardiovascular deaths (0.6; 0.2---1.2) and by 50% for cancer deaths (0.5; 0.3---0.8). Additionally, subjects with a combination of low zinc and high copper values had synergistically increased all---cause (2.6; 1.4---5.0) and cancer (2.7; 1.0---7.3) mortality risks. Similarly, combined low zinc and high magnesium values were associated with decreased all---cause (0.2; 0.1---0.5) and cancer (0.2; 0.1---0.8) mortality risks.

CONCLUSIONS: High serum copper, low serum magnesium, and concomitance of low serum zinc with high serum copper or low serum magnesium contribute to an increased mortality risk in middle---aged men.

Peacock JM, Ohira T, Post W, Sotoodehnia N, Rosamond W, Folsom AR.

Am Heart J. 2010 Sep;160(3):464-70.

Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study.

Source: University of Minnesota, Minneapolis, 55454, USA.

Abstract

BACKGROUND: We hypothesized that serum magnesium (Mg) is associated with increased risk of sudden cardiac death (SCD).

METHODS: The Atherosclerosis Risk in Communities Study assessed risk factors and levels of serum Mg in a cohort of 45- to 64-year-old subjects in 1987-1989 (n = 14,232). After an average of 12 years of follow-up, we observed 264 cases of SCD, as determined by physician review of all suspected cases. We used proportional hazards regression to evaluate the association of serum Mg with risk of SCD.

RESULTS: Individuals in the highest quartile of serum Mg were at significantly lower risk of SCD in all models. This association persisted after adjustment for potential confounding variables, with an almost 40% reduced risk of SCD (hazard ratio 0.62, 95% CI 0.42-0.93) in quartile 4 versus 1 of serum Mg observed in the fully adjusted model.

CONCLUSIONS: This study suggests that low levels of serum Mg may be an important predictor of SCD. Further research into the effectiveness of Mg supplementation for those considered to be at high risk for SCD is warranted.

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Chiuvè SE, Korngold EC, Januzzi JL Jr, Gantzer ML, Albert CM.
Am J Clin Nutr. 2011 Feb;93(2):253-60. Epub 2010 Nov 24.

Plasma and dietary magnesium and risk of sudden cardiac death in women.

Source: Center for Arrhythmia Prevention, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. Schiuvè(at)hsph.harvard.edu

Abstract

BACKGROUND: Magnesium has antiarrhythmic properties in cellular and experimental models; however, its relation to sudden cardiac death (SCD) risk is unclear.

OBJECTIVE: We prospectively examined the association between magnesium, as measured in diet and plasma, and risk of SCD.

DESIGN: The analysis was conducted within the Nurses' Health Study. The association for magnesium intake was examined prospectively in 88,375 women who were free of disease in 1980. Information on magnesium intake, other nutrients, and lifestyle factors was updated every 2-4 y through questionnaires, and 505 cases of sudden or arrhythmic death were documented over 26 y of follow-up. For plasma magnesium, a nested case control analysis including 99 SCD cases and 291 controls matched for age, ethnicity, smoking, and presence of cardiovascular disease was performed.

RESULTS: After multivariable adjustment for confounders and potential intermediaries, the relative risk of SCD was significantly lower in women in the highest quartile compared with those in the lowest quartile of dietary (relative risk: 0.63; 95% CI: 0.44, 0.91) and plasma (relative risk: 0.23; 95% CI: 0.09, 0.60) magnesium. The linear inverse relation with SCD was strongest for plasma magnesium (P for trend = 0.003), in which each 0.25-mg/dL (1 SD) increment in plasma magnesium was associated with a 41% (95% CI: 15%, 58%) lower risk of SCD.

CONCLUSIONS: In this prospective cohort of women, higher plasma concentrations and dietary magnesium intakes were associated with lower risks of SCD. If the observed association is causal, interventions directed at increasing dietary or plasma magnesium might lower the risk of SCD.

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Khan AM, Sullivan L, McCabe E, Levy D, Vasan RS, Wang TJ.
Am Heart J. 2010 Oct;160(4):715-20.

Lack of association between serum magnesium and the risks of hypertension and cardiovascular disease.

Source: Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.

Abstract

BACKGROUND: Experimental studies have linked hypomagnesemia with the development of vascular dysfunction, hypertension, and atherosclerosis. Prior clinical studies have yielded conflicting results but were limited by the use of self-reported magnesium intake or short follow-up periods.

METHODS: We examined the relationship between serum magnesium concentration and incident hypertension, cardiovascular disease (CVD), and mortality in 3,531 middle-aged adult participants in the Framingham Heart Study offspring cohort. Analyses were performed using Cox proportional hazards regressions, adjusted for traditional CVD risk factors.

RESULTS: Follow-up was 8 years for new-onset hypertension (551 events) and 20 years for CVD (554 events). There was no association between baseline serum magnesium and the development of hypertension (multivariable-adjusted hazards ratio per 0.15 mg/dL 1.03, 95% CI 0.92-1.15, $P = .61$), CVD (0.83, 95% CI 0.49-1.40, $P = .49$), or all-cause mortality (0.77, 95% CI 0.41-1.45, $P = .42$). Similar findings were observed in categorical analyses, in which serum magnesium was modeled in categories (<1.5, 1.5-2.2, >2.2 mg/dL) or in quartiles.

CONCLUSIONS: In conclusion, data from this large, community-based cohort do not support the hypothesis that low serum magnesium is a risk factor for developing hypertension or CVD.

COMMENT: This Khan article found apparently opposite results from other studies listed above, reporting no significant differences in multivariable-adjusted hazards ratio for baseline serum Mg and the development of hypertension, CVD or all-cause mortality. However, their data shows the hazard ratio was significant ($P=0.04$) for the development of CVD and for death when adjusted for age and sex only, with Mg as a categorical variable. This was not reported or discussed in the article text. (see Rosanoff et al., 2012)

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Curiel-García JA, Rodríguez-Morán M, Guerrero-Romero F.
Magnes Res. 2008 Sep;21(3):163-6.

Hypomagnesemia and mortality in patients with type 2 diabetes.

Source: General Hospital of the Mexican Social Security Institute at Durango, Av. Normal y Predio Canoas S/N; 34067, Durango, Dgo., Mexico.

Abstract

To evaluate if hypomagnesemia, at the time of admission in the Intensive care Unit (ICU), is associated with a higher mortality in critically ill patients with type 2 diabetes. Fourteen consecutive critically ill patients with type 2 diabetes admitted in the ICU of a teaching General Hospital serving an inner city population were enrolled in a follow-up study. Parenteral or enteral nutritional support, surgical procedures, malignancy, traumatism or physical injury, pulmonary and/or cardiovascular diseases,

chronic renal failure, hepatic cirrhosis, cerebrovascular disease, and disorders of the thyroid gland, were exclusion criteria. Hypomagnesemia was defined by serum magnesium levels < 0.66 mmol/L (1.6 mg/dL). At the time of admission in the ICU, 10 (71.4%) individuals had hypomagnesemia. Mortality rates in the hypomagnesemic and normomagnesemic individuals were 80 and 25%, respectively. Serum magnesium levels were significantly lower in the subjects who died (0.51 [0.41, 0.62] mmol/L) compared with those who survived (0.85 [0.65, 1.11], mmol/L), $p = 0.01$. The logistic regression model adjusted by APACHE II score and hsCRP levels showed that hypomagnesemia is independently associated with mortality (OR 1.9, CI95% 1.2-14.7). Hypomagnesemia at the time of admission in the ICU seems to be associated with high mortality in critically ill patients with type 2 diabetes.

May Khan A, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS, Magnani JW, Ellinor PT, Benjamin EJ, Wang TJ. - see note below abstract

Circulation. 2012 Nov 21. [Epub ahead of print]

Low Serum Magnesium and the Development of Atrial Fibrillation in the Community: The Framingham Heart Study.

1 University of Pennsylvania, Philadelphia, PA;

BACKGROUND: Low serum magnesium has been linked to increased risk of atrial fibrillation (AF) following cardiac surgery. It is unknown whether hypomagnesemia predisposes to AF in the community. **METHODS AND RESULTS:** We studied 3,530 participants (mean age, 44 years; 52% women) from the Framingham Offspring Study who attended a routine examination, and were free of AF and cardiovascular disease. We used Cox proportional hazard regression analysis to examine the association between serum magnesium at baseline and risk of incident AF. Analyses were adjusted for conventional AF risk factors, use of antihypertensive medications, and serum potassium. During up to 20 years of follow-up, 228 participants developed AF. Mean serum magnesium was 1.88 mg/dl. The age- and sex-adjusted incidence rate of AF was 9.4 per 1,000 person-years (95% confidence interval, 6.7 to 11.9) in the lowest quartile of serum magnesium (≤ 1.77 mg/dl), compared with 6.3 per 1,000 person-years (95% confidence interval, 4.1 to 8.4) in the highest quartile (≥ 1.99 mg/dl). In multivariable-adjusted models, individuals in the lowest quartile of serum magnesium were approximately 50% more likely to develop AF (adjusted hazard ratio, 1.52, 1.00 to 2.31; $P=0.05$), compared with those in the upper quartiles. Results were similar after excluding individuals on diuretics. **CONCLUSIONS:** Low serum magnesium is moderately associated with the development of AF in individuals without cardiovascular disease. Because hypomagnesemia is common in the general population, a link with AF may have potential clinical implications. Further studies are warranted to confirm our findings and elucidate the underlying mechanisms.

Comment on May Khan et al., 2012: Authors report a moderate association between low serum Mg And occurrence of atrial fibrillation. However, the quartiles for serum Mg values they use are all below the Recommended level of 2.07 mg/dL (i.e. 0.85 mmol/l, see Elin R J 2011 Re-evaluation of the concept of chronic, latent, magnesium deficiency. Magnes Res 24, 225-227). If they had compared those with serum Mg below 2.07 mg/dL with those above that level, the association could be stronger than moderate. A. Rosanoff.

For Stroke:

Nie ZL, Wang ZM, Zhou B, Tang ZP, Wang SK.

Nutr Metab Cardiovasc Dis. 2012 Jul 10. [Epub ahead of print]

Magnesium intake and incidence of stroke: Meta-analysis of cohort studies.

Source: Central Laboratory, Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing, China.

Abstract

BACKGROUND AND AIMS: Prospective cohort studies are inconsistent regarding the association between magnesium intake and the risk of stroke. The objective was to perform a meta-analysis to summarize the relationship between magnesium intake and risk of stroke in observational studies.

METHODS AND RESULTS: We searched the PubMed and EMBASE databases for studies conducted from 1966 through August 2011. Prospective studies that provided relative risk (RR) estimates with 95% confidence intervals (CIs) for the association between magnesium intake and the risk of total stroke incidence or mortality were included. Data were independently abstracted by two investigators using a standardized protocol. Study-specific risk estimates were combined by using a random effects model. A total of eight studies, with 8367 stroke cases among 304,551 participants, were included in the meta-analysis. The summary RR indicated a significant association between the highest magnesium intake and reduced risk of total stroke (summary RR: 0.89; 95% CI: 0.82, 0.97); our dose-response analysis showed a borderline inverse association between magnesium intake and total stroke risk (an increment of 100 mg day⁻¹; summary RR: 0.98; 95% CI: 0.95, 1.00). Subgroup analyses suggested a significant inverse association between highest magnesium intake and the risk of ischaemic stroke (summary RR: 0.88; 95% CI: 0.80, 0.98).

CONCLUSION: The present meta-analysis of prospective cohorts suggests that higher magnesium intake is associated with reduced risk of total and ischaemic stroke. However, well-designed randomized controlled trials are needed to draw a definitive conclusion.

Larsson SC, Orsini N, Wolk A.

Am J Clin Nutr. 2012 Feb;95(2):362-6. Epub 2011 Dec 28.

Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies.

Division of Nutritional Epidemiology, National Institute of Environmental Medicine, Stockholm, Sweden. [susanna.larsson\(at\)ki.se](mailto:susanna.larsson@ki.se)

Comment in Am J Clin Nutr. 2012 Feb;95(2):269-70.

BACKGROUND: Prospective studies of dietary magnesium intake in relation to risk of stroke have yielded inconsistent results.

OBJECTIVE: We conducted a dose-response meta-analysis to summarize the evidence regarding the association between magnesium intake and stroke risk.

DESIGN: Relevant studies were identified by searching PubMed and EMBASE from January 1966 through September 2011 and reviewing reference lists of retrieved articles. We included prospective studies that reported RRs with 95% CIs of stroke for ≥ 3 categories of magnesium intake. Results from individual studies were combined by using a random-effects model.

RESULTS: Seven prospective studies, with 6477 cases of stroke and 241,378 participants, were eligible for inclusion in the meta-analysis. We observed a modest but statistically significant inverse association

between magnesium intake and risk of stroke. An intake increment of 100 mg Mg/d was associated with an 8% reduction in risk of total stroke (combined RR: 0.92; 95% CI: 0.88, 0.97), without heterogeneity among studies ($P = 0.66$, $I(2) = 0\%$). Magnesium intake was inversely associated with risk of ischemic stroke (RR: 0.91; 95% CI: 0.87, 0.96) but not intracerebral hemorrhage (RR: 0.96; 95% CI: 0.84, 1.10) or subarachnoid hemorrhage (RR: 1.01; 95% CI: 0.90, 1.14).

CONCLUSION: Dietary magnesium intake is inversely associated with risk of stroke, specifically ischemic stroke.

Singh, H., et al. (2012). "Role of magnesium sulfate in neuroprotection in acute ischemic stroke." *Ann Indian Acad Neurol* **15**(3): 177---180. **AIMS:** To study the effect of intravenous magnesium sulfate infusion on clinical outcome of patients of acute stroke.

MATERIALS AND METHODS: Sixty consecutive cases of acute ischemic stroke hospitalized within 24 h of an episode of stroke were taken as subjects. All subjects underwent a computed tomography head, and those found to have evidence of bleed/space---occupying lesions were excluded from the study. The subjects taken up for the study were divided into two groups of 30 subjects each. Both the groups received the standard protocol management for acute ischemic stroke. Subjects of Group 1 additionally received intravenous magnesium sulfate as initial 4 g bolus dose over 15 min followed by 16 g as slow infusion over the next 24 h. In all the subjects of the two study groups, serum magnesium levels were estimated at the time of admission (Day 0), Day 1 and Day 2 of hospitalization using an atomic absorption spectrometer.

STATISTICAL ANALYSIS USED: Scandinavian stroke scores were calculated on Day 3, day of discharge and Day 28. Paired t ---test was employed for comparison of stroke scores on Day 3, day of discharge and Day 28 within the same group and the unpaired t ---test was used for the intergroup comparison, i.e. comparison of stroke scores of control group with corresponding stroke scores of magnesium group.

RESULTS: Comparison of stroke scores on Day 3 and day of discharge, on the day of discharge and Day 28 and on Day 3 and Day 28 in the magnesium group produced a t ---value of 5.000 and $P < 0.001$, which was highly significant. However, the comparison of the mean stroke scores between the magnesium and the control groups on Day 3, day of discharge and Day 28 yielded a P ---value of > 0.05 , which was not significant.

CONCLUSIONS: The study failed to document a statistical significant stroke recovery in spite of achieving a significant rise in serum magnesium level, more than that necessary for neuroprotection, with an intravenous magnesium sulfate regime. **Comment:** The Singh et al study seems to be contrary to the other studies showing Mg status is associated with stroke. However, this study's control subjects' mean serum Mg was 2.2 mg/dL, i.e. in the normal, replete range of serum Mg. See discussion on serum Mg levels in Appendix VII and Main Heart Project paper, paragraph 5.

Appendix V: Importance of Balancing Ca with Mg and Dangers of the Rising Ca:Mg Dietary Intake Ratio

1. Magnesium balances Calcium: Importance of the Ca:Mg Ratio – see Fig. 4

Of Central importance to the Mg Hypothesis of CVD is the intracellular Calcium to Magnesium Ratio (Ca:Mg). In the 1990s, Resnick and co-workers discovered that the intracellular calcium to magnesium ratio (Ca:Mg) was totally predictive of tissue responses that, taken together, manifest as cardiovascular disease. For example, when Mg becomes low in the cell, calcium rises in the cell, raising the cell's Ca:Mg ratio which causes a firing off a cascade of reactions particular to that cell's "fight or flight" response. If it's a nerve cell, it rapidly and continuously fires. If a muscle cell, it will contract and not relax until the Ca:Mg ratio is brought to normal resting state. These various tissue manifestations of the high Ca:Mg intracellular ratio are illustrated in [Figure 4](#).

A marginal Mg status or Mg deficit state will often manifest these abnormal Ca:Mg responses as clinical symptoms so often seen in our society on the low Mg diet. Modern medicine, not yet accepting the Mg Hypothesis of CVD, treats these symptoms with medications rather than nutrient therapy that could correct the high Ca:Mg ratio causing the symptoms.

Some references of Resnick and colleagues work on Ca:Mg ratio in cells with links to pubmed abstracts:

Resnick, L. (1999). "The cellular ionic basis of hypertension and allied clinical conditions." *Prog Cardiovasc Dis* 42(1): 1-22.
<http://www.ncbi.nlm.nih.gov/pubmed/10505490>

Resnick, L. M. (1992). "Cellular calcium and magnesium metabolism in the pathophysiology and treatment of hypertension and related metabolic disorders." *Am J Med* 93(2A): 11S-20S.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1387762

Resnick, L. M. (1992). "Cellular ions in hypertension, insulin resistance, obesity, and diabetes: a unifying theme." *J Am Soc Nephrol* 3(4 Suppl): S78-85.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1457764

Resnick, L. M. (1993). "Ionic basis of hypertension, insulin resistance, vascular disease, and related disorders. The mechanism of "syndrome X"." *Am J Hypertens* 6(4): 123S-134S.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8507440

2. The Ca:Mg ratio in USA diets is increasing – see [Figs. 5a, 5b & 6](#)

Since 1977 the Ca in USA diets has risen much more than the Mg in USA diets. This trend is shown in [Figures 5a and 5b](#). As a result, the food intake Ca:Mg ratio in the USA has gone from largely below 3.0 to largely above 3.0 during the last 35 years ([see Figure 6](#)). This rising ratio does not include supplements, only food sources of Ca and Mg. It has been recommended that a Ca:Mg intake ratio should not exceed 2.0 for both foods and supplements.

References on rising Ca:Mg food intake ratios in USA with links to Full Texts and to Pubmed abstracts:

[\(for highlighted abstracts of the following references, click here "Abstract" document for Appendix V\)](#)

(See Full Texts of the following papers)

Rosanoff, A. (2010). "Rising Ca:Mg intake ratio from food in USA Adults: a concern?" *Magnes Res* **23**(4): 181-193. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21233058

Rosanoff, A., et al. (2012). "Suboptimal magnesium status in the United States: are the health consequences underestimated?" *Nutr Rev* **70**(3): 153-164. <http://www.ncbi.nlm.nih.gov/pubmed/22364157>

3. Recent studies show Ca supplementation puts people more at risk of CVD.

For the past decade, Ca supplements have been widely recommended to prevent osteoporosis. This has widely been assumed "safe" as USA Calcium intakes from food are often below recommended levels. However, given our society's low Mg intakes, Ca from supplements may not be balanced with Mg and can exacerbate the high Ca:Mg ratio and bring on heart disease, unexpected in *a medical paradigm that does not include the Mg Hypothesis of CVD*.

References on CVD risks with Ca supplementation:

[\(For Appendix V highlighted abstracts click\)](#)

Li, K., et al. (2012). "Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg)." *Heart* **98**(12): 920-925. <http://www.ncbi.nlm.nih.gov/pubmed/22626900>

Reid, I. R., et al. (2011). "Cardiovascular effects of calcium supplementation." *Osteoporos Int* **22**(6): 1649-1658. <http://www.ncbi.nlm.nih.gov/pubmed/21409434>

Reid, I. R., et al. (2011). "Calcium supplementation: balancing the cardiovascular risks." *Maturitas* **69**(4): 289-295. <http://www.ncbi.nlm.nih.gov/pubmed/21621353>

Bolland, M. J., et al. (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. <http://www.ncbi.nlm.nih.gov/pubmed/21505219>

Bolland, M. J., et al. (2010). "Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis." *Bmj* **341**: c3691. <http://www.ncbi.nlm.nih.gov/pubmed/20671013>

Importance of Calcium in CVD

Gopal, A. and M. J. Budoff (2006). "Coronary calcium scanning." *Am Heart Hosp J* **4**(1): 43-50. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16470104

Early References by M.S. Seelig that predicted the adverse effect of Ca supplementation on cardiovascular health, given the Mg Hypothesis of CVD:

Seelig, M. (2006). "Value of raising magnesium to calcium intake ratio for health." *New Data in Magnesium Research, John Libbey Eurotext. In Press.*: 1-16.

Seelig, M. S. (1990). "Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment." *Magnes Res* **3**(3): 197-215. (See highlighted abstract in "Abstracts" folder for Appendix V)

Seelig, M. S. (2001). Epidemiologic data on magnesium deficiency-associated cardiovascular disease and osteoporosis; consideration of risks of current recommendations for high calcium intake. *Advances in magnesium Research: Nutrition and Health*. Y. Rayssiguier, A. Mazur and J. Durlach. London, John Libby & Co.: 177-190.

What About Vitamin D?

Many recent reports show low serum vitamin D values being related to several health issues including bone health and heart health (Gotsman et al, 2012). Magnesium is required for the biological activation of Vitamin D. When Magnesium status is low, Serum Vitamin D levels remain low (Rude, 1985) as do serum Calcium and serum Potassium. It remains to be shown whether recent reports on Vitamin D and health issues are truly due to low levels of vitamin D, low levels of magnesium or both.

Gotsman, I., et al. (2012). "Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome." *Eur J Heart Fail* **14**(4): 357-366.

<http://www.ncbi.nlm.nih.gov/pubmed/22308011>

Rude, R. K., J. S. Adams, et al. (1985). "Low serum concentrations of 1,25-dihydroxyvitamin D in human magnesium deficiency." *J Clin Endocrinol Metab* **61**(5): 933-40.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3840173

To read on other research aspects of the calcium to magnesium ratio, see:

Dai, Q., M. J. Shrubsole, et al. (2007). "The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk." *Am J Clin Nutr* **86**(3): 743-51.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17823441

Highlighted Abstracts for Appendix V – Importance of Balancing Ca with Mg . . .

The Ca:Mg ratio in US diets is increasing – see [Figs. 5a, 5b & 6](#)

Rosanoff, A. (2010). "Rising Ca:Mg intake ratio from food in USA Adults: a concern?" *Magnes Res* **23**(4): 181-193. ([See Full Paper](#))

USDA food surveys from 1977 through 2007-8 show a rising food Ca:Mg ratio for all USA adult age-gender groups. **Food Ca:Mg intake ratios rose from 2.3-2.9 in 1977 to 2.9-3.5 in 2007-8.** The % rise in mean Mg intakes compared closely with % rise in mean energy intakes while % rise in mean Ca intakes were substantially higher in all groups, suggesting **the rising Ca:Mg comes from higher Ca intakes via food selections, rising food Ca contents or both.** Original intake data from these surveys need to be accessed to calculate each individual's Ca:Mg for statistical assessment of this ratio rise. Ca:Mg rose from largely below 3.0 in 1994-5 to generally above or approaching 3.0 after 2000, coinciding with a sharp **2% rise in type 2 diabetes incidence and prevalence in the USA** population and a 1994-2005 rise in **colorectal cancer incidence** among young white, non-Hispanic adult men and women in the USA. The intracellular Ca activation response to low Mg is discussed as a possible mechanism linking metabolic

and inflammatory syndromes with low dietary Mg and rising dietary Ca:Mg ratio. Adequacy of both Ca and Mg as well as the Ca:Mg ratio are important in assessing study outcomes. Health consequences should be considered for the USA's 64-67% adults not meeting their Mg requirement from foods, many also consuming below their Ca requirements, and their increasing Ca:Mg ratio from foods.

Rosanoff, A., et al. (2012). "Suboptimal magnesium status in the United States: are the health consequences underestimated?" *Nutr Rev* **70**(3): 153-164. ([See Full Paper](#))

In comparison with calcium, magnesium is an "orphan nutrient" that has been studied considerably less heavily. Low magnesium intakes and blood levels have been associated with type 2 diabetes, metabolic syndrome, elevated C-reactive protein, hypertension, atherosclerotic vascular disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer. Almost half (48%) of the US population consumed less than the required amount of magnesium from food in 2005-2006, and the figure was down from 56% in 2001-2002. Surveys conducted over 30 years indicate rising calcium-to-magnesium food-intake ratios among adults and the elderly in the United States, excluding intake from supplements, which favor calcium over magnesium. The prevalence and incidence of type 2 diabetes in the United States increased sharply between 1994 and 2001 as the ratio of calcium-to-magnesium intake from food rose from <3.0 to >3.0. Dietary Reference Intakes determined by balance studies may be misleading if subjects have chronic latent magnesium deficiency but are assumed to be healthy. Cellular magnesium deficit, perhaps involving TRPM6/7 channels, elicits calcium-activated inflammatory cascades independent of injury or pathogens. Refining the magnesium requirements and understanding how low magnesium status and rising calcium-to-magnesium ratios influence the incidence of type 2 diabetes, metabolic syndrome, osteoporosis, and other inflammation-related disorders are research priorities.

Recent studies show Ca supplementation puts people more at risk of CVD.

Li, K., et al. (2012). "Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg)." *Heart* **98**(12): 920-925.

BACKGROUND: It has been suggested that a higher calcium intake might favourably modify cardiovascular risk factors. However, findings of an ultimately decreased risk of cardiovascular disease (CVD) are limited. Instead, recent evidence warns that taking calcium supplements might increase myocardial infarction (MI) risk. **OBJECTIVE:** To prospectively evaluate the associations of dietary calcium intake and calcium supplementation with MI and stroke risk and overall CVD mortality. **METHODS:** Data from 23 980 Heidelberg cohort participants of the European Prospective Investigation into Cancer and Nutrition study, aged 35-64 years and free of major CVD events at recruitment, were analysed. Multivariate Cox regression models were used to estimate HRs and 95% CIs. **RESULTS:** After an average follow-up time of 11 years, 354 MI and 260 stroke cases and 267 CVD deaths were documented. Compared with the lowest quartile, the third quartile of total dietary and dairy calcium intake had a significantly reduced MI risk, with a HR of 0.69 (95% CI 0.50 to 0.94) and 0.68 (95% CI 0.50 to 0.93),

respectively. Associations for stroke risk and CVD mortality were overall null. **In comparison with non-users of any supplements, users of calcium supplements had a statistically significantly increased MI risk (HR=1.86; 95% CI 1.17 to 2.96), which was more pronounced for calcium supplement only users (HR=2.39; 95% CI 1.12 to 5.12).** CONCLUSIONS: Increasing calcium intake from diet might not confer significant cardiovascular benefits, while calcium supplements, which might raise MI risk, should be taken with caution.

Reid, I. R., et al. (2011). "Cardiovascular effects of calcium supplementation." *Osteoporos Int* **22**(6): 1649-1658.

Trials in normal older women and in patients with renal impairment suggest that **calcium supplements increase the risk of cardiovascular disease.** To further assess their safety, we recently **conducted a meta-analysis of trials of calcium supplements, and found a 27-31% increase in risk of myocardial infarction and a 12-20% increase in risk of stroke.** These findings are robust because they are based on pre-specified analyses of randomized, placebo-controlled trials and show consistent risk across the trials. The fact that cardiovascular events were not primary endpoints of any of these studies will introduce noise but not bias into the data. A **recent re-analysis of the Women's Health Initiative suggests that co-administration of vitamin D with calcium does not lessen these adverse effects.** The increased cardiovascular risk with calcium supplements **is consistent with epidemiological data relating higher circulating calcium concentrations to cardiovascular disease in normal populations.** There are several possible pathophysiological mechanisms for these effects, including effects on vascular calcification, on the function of vascular cells, and on blood coagulation. Calcium-sensing receptors might mediate some of these effects. Because calcium supplements produce small reductions in fracture risk and a small increase in cardiovascular risk, there may be no net benefit from their use. Food sources of calcium appear to produce similar benefits on bone density, although their effects on fracture are unclear. Since food sources have not been associated with adverse cardiovascular effects, they may be preferable. Available evidence suggests that other osteoporosis treatments are still effective without calcium co-administration.

Reid, I. R., et al. (2011). "Calcium supplementation: balancing the cardiovascular risks." *Maturitas* **69**(4): 289-295.

Calcium supplementation has been widely accepted as a key strategy in the prevention and treatment of osteoporosis. Its role has been undermined, to some extent, by its disappointing effects on fracture in randomised controlled trials, but its use has continued to be encouraged on the grounds that it is physiologically appealing, and is **[assumed] unlikely to cause harm.** **The latter assumption is now under threat from accumulating evidence that calcium supplement use is associated with an increased risk of myocardial infarction and, possibly, stroke.** The latest data, based **on meta-analysis of trials involving 29,000 participants, indicate that this risk is not mitigated by co-administration of vitamin D, and that the number of cardiovascular events caused is likely to be greater than the number of fractures prevented.** These findings indicate that calcium supplementation probably does not have a role as a

routine preventative agent and that dietary advice is the appropriate way to attain an adequate calcium intake in most situations. Patients at high risk of fracture need to take interventions of proven anti-fracture efficacy. Available evidence suggests that this efficacy is not dependent on the co-administration of calcium supplements.

Bolland, M. J., et al. (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.

OBJECTIVES: To investigate the effects of personal calcium supplement use on cardiovascular risk in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), using the WHI dataset, and to update the recent meta-analysis of calcium supplements and cardiovascular risk.

DESIGN: Reanalysis of WHI CaD Study limited access dataset and incorporation in meta-analysis with eight other studies. Data source WHI CaD Study, a seven year, randomised, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36 282 community dwelling postmenopausal women. Main outcome measures Incidence of four cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data. **RESULTS:** In the WHI CaD Study there was an interaction between personal use of calcium supplements and allocated calcium and vitamin D for cardiovascular events. In the 16 718 women (46%) who were not taking personal calcium supplements at randomisation the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 (P=0.05 for clinical myocardial infarction or stroke, P=0.04 for clinical myocardial infarction or revascularisation), whereas in the women taking personal calcium supplements cardiovascular risk did not alter with allocation to calcium and vitamin D. In meta-analyses of three placebo controlled trials, calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21 (95% confidence interval 1.01 to 1.44), P=0.04), stroke (1.20 (1.00 to 1.43), P=0.05), and the composite of myocardial infarction or stroke (1.16 (1.02 to 1.32), P=0.02). In meta-analyses of placebo controlled trials of calcium or calcium and vitamin D, complete trial-level data were available for 28 072 participants from eight trials of calcium supplements and the WHI CaD participants not taking personal calcium supplements. In total 1384 individuals had an incident myocardial infarction or stroke. **Calcium or calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.24 (1.07 to 1.45), P=0.004) and the composite of myocardial infarction or stroke (1.15 (1.03 to 1.27), P=0.009).**

Conclusions Calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction, a finding obscured in the WHI CaD Study by the widespread use of personal calcium supplements. A reassessment of the role of calcium supplements in osteoporosis management is warranted.

Bolland, M. J., et al. (2010). "Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis." *Bmj* **341**: c3691.

OBJECTIVE: To investigate whether calcium supplements increase the risk of cardiovascular events.

DESIGN: Patient level and trial level meta-analyses. DATA SOURCES: Medline, Embase, and Cochrane Central Register of Controlled Trials (1966-March 2010), reference lists of meta-analyses of calcium supplements, and two clinical trial registries. Initial searches were carried out in November 2007, with electronic database searches repeated in March 2010. STUDY SELECTION: Eligible studies were randomised, placebo controlled trials of calcium supplements (≥ 500 mg/day), with 100 or more participants of mean age more than 40 years and study duration more than one year. The lead authors of eligible trials supplied data. Cardiovascular outcomes were obtained from self reports, hospital admissions, and death certificates. RESULTS: 15 trials were eligible for inclusion, five with patient level data (8151 participants, median follow-up 3.6 years, interquartile range 2.7-4.3 years) and 11 with trial level data (11 921 participants, mean duration 4.0 years). In the five studies contributing patient level data, 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, $P=0.035$). Non-significant increases occurred in the incidence of stroke (1.20, 0.96 to 1.50, $P=0.11$), the composite end point of myocardial infarction, stroke, or sudden death (1.18, 1.00 to 1.39, $P=0.057$), and death (1.09, 0.96 to 1.23, $P=0.18$). The meta-analysis of trial level data showed similar results: 296 people had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (pooled relative risk 1.27, 95% confidence interval 1.01 to 1.59, $P=0.038$).

CONCLUSIONS: Calcium supplements (without coadministered vitamin D) are associated with an increased risk of myocardial infarction. As calcium supplements are widely used these modest increases in risk of cardiovascular disease might translate into a large burden of disease in the population. A reassessment of the role of calcium supplements in the management of osteoporosis is warranted.

Gopal, A. and M. J. Budoff (2006). "Coronary calcium scanning." *Am Heart Hosp J* 4(1): 43-50.

While there is no doubt that high-risk patients (those with more than a 20% 10-year risk of a future cardiovascular event) need more aggressive preventive therapy, a majority of cardiovascular events occur in individuals at intermediate risk (10%-20% 10-year risk). Data suggest that it will be most cost-effective to concentrate screening efforts on this group of patients. Coronary artery calcium has been shown to be highly specific for atherosclerosis, occurring only in the intima of the coronary arteries. There is evidence to show that elevated coronary calcium scores are predictive of cardiovascular events, both independently of and incrementally to conventional cardiovascular risk factors. Based on current available data, patients with increased plaque burdens (increased coronary calcium scores) are approximately 10 times more likely to suffer a cardiac event over the next 3-5 years. Coronary calcium scores have outperformed conventional risk factors, high sensitivity C-reactive protein, and carotid intima-media thickness as a predictor of cardiovascular events. Both electron beam tomography and multidetector computed tomography can accurately detect and quantify the coronary calcium scores. In summary, coronary calcium detection significantly improves the accuracy of global cardiovascular risk prevention, the noninvasive tracking of the atherosclerotic burden, and the prediction of cardiovascular events.

Seelig, M. S. (1990). "Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment." Magnes Res 3(3): 197-215.

Prophylactic treatment of postmenopausal osteoporosis with oestrogen and calcium, often in combination, disregards the likelihood that an excess of each agent may increase magnesium requirements and decrease serum Mg levels. Relative or absolute Mg deficiency, which is likely in the Occident where the Mg intake is commonly marginal, can militate against optimal therapeutic bone response, Mg being important for normal bone structure, and can increase the risk of adverse effects. Although oestrogen has cardiovascular protective effects (expressed by the lower incidence of heart disease in premenopausal women than in men, and also in postmenopausal women given low dosage oestrogen replacement treatment), high dosage oestrogen oral contraceptives have caused increased intravascular blood clotting with resultant thromboembolic cardio- and cerebrovascular accidents. This might be contributed to by the oestrogen-mediated shift of circulating Mg to soft and hard tissues, which in persons with marginal Mg intakes may lead to suboptimal serum levels. If the commonly recommended dietary Ca/Mg ratio of 2/1 is exceeded (and it can reach as much as 4/1 in countries with low to marginal Mg intakes), relative or absolute Mg deficiency may result, and this may increase the risk of intravascular coagulation, since blood clotting is enhanced by high Ca/Mg ratios. Mechanisms by which Ca activates the various steps in blood coagulation that are also stimulated by oestrogen are considered here, as are the multifaceted roles of Mg that favourably affect blood coagulation and fibrinolysis, through its activities in lipoprotein and prostanoid metabolism.

Rising Ca:Mg intake ratio from food in USA Adults: a concern?

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Abstract. USDA food surveys from 1977 through 2007-8 show a rising food Ca:Mg ratio for all USA adult age-gender groups. Food Ca:Mg intake ratios rose from 2.3-2.9 in 1977 to 2.9-3.5 in 2007-8. The % rise in mean Mg intakes compared closely with % rise in mean energy intakes while % rise in mean Ca intakes were substantially higher in all groups, suggesting the rising Ca:Mg comes from higher Ca intakes via food selections, rising food Ca contents or both. Original intake data from these surveys need to be accessed to calculate each individual's Ca:Mg for statistical assessment of this ratio rise. Ca:Mg rose from largely below 3.0 in 1994-5 to generally above or approaching 3.0 after 2000, coinciding with a sharp 2% rise in type 2 diabetes incidence and prevalence in the USA population and a 1994-2005 rise in colorectal cancer incidence among young white, non-Hispanic adult men and women in the USA. The intracellular Ca activation response to low Mg is discussed as a possible mechanism linking metabolic and inflammatory syndromes with low dietary Mg and rising dietary Ca:Mg ratio. Adequacy of both Ca and Mg as well as the Ca:Mg ratio are important in assessing study outcomes. Health consequences should be considered for the USA's 64-67% adults not meeting their Mg requirement from foods, many also consuming below their Ca requirements, and their increasing Ca:Mg ratio from foods.

Keywords: magnesium calcium Ca:Mg ratio dietary intake ratio, adults, elderly, metabolic syndrome, inflammation syndrome

The large, genetically variable population of the United State of America (USA) has spent decades consuming a modern, processed food diet. The majority of this population has recently been shown to consume, with foods, well below their daily Estimated Average Requirement (EAR) of nutritional magnesium (Mg) (table 1). Many also consume below the amount of calcium (Ca) considered to be an adequate intake with their foods [2]. The ratio between these two nutrients (Ca:Mg) is rarely calculated, monitored or reported.

As early as 1964, in a quantitative review of human balance studies, M.S. Seelig reported dietary Ca to be a factor in the retention of dietary Mg [3]. Seelig further considered the impact of high Ca with low Mg intakes on physiological Ca:Mg ratios affecting myocardium and intravascular coagulation in later reviews [4-6], and in 1978, a population's Ca:

Mg intake ratio was seen as important to ischemic heart disease death rates [7]. In 1989, Durlach warned against excessive Ca relative to Mg intakes and recommended that total dietary Ca to Mg ratios (Ca:Mg) remain close to 2.0 [8]. High cellular Ca:Mg can effect metabolic syndrome dysfunction in various tissues, bringing attention to this ratio's potential importance in the etiology of type 2 diabetes (DM2) [9]. The nutritional Ca:Mg intake ratio has recently been delineated by Dai et al. as important in a genetic-dietary interaction study impacting colon cancer [10]. These authors found "that total magnesium consumption was linked to a significantly lower risk of colorectal adenoma, particularly in those subjects with a low Ca:Mg intake, and that subjects who carried ≥ 1 1482Ile allele and who consumed diets with a high Ca:Mg intake

(i.e. Ca:Mg > 2.76) were at a higher risk of adenoma

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Table 1. Estimated Average Requirement (EAR) and Recommended Daily Allowance (RDA) for USA adults [1] and proportion of USA adults consuming less than EAR for Mg with their daily food diet according to NHANES 2001-2002 [2].

Age	EAR for Mg (mg/day)	% consuming < EAR	RDA for Mg (mg/day)
Men			
19-30 yrs	330	55%	400
31-50 yrs	350	61%	420
51-70 yrs	350	70%	420
71+ yrs	350	81%	420
All Men 19+ yrs	—	64%	—
Women			
19-30 yrs	255	64%	310
31-50 yrs	265	65%	320
51-70 yrs	265	64%	320
71+ yrs	265	82%	320
All Women 19+ yrs	—	67%	—

(odds ratio: 1.60; 95% CI: 1.12, 2.29) and hyperplastic polyps (odds ratio: 1.85; 95% CI: 1.09-3.14) than were the subjects who did not carry the polymorphism”.

It's appropriate to assess any trend of dietary Ca: Mg ratio in human populations. This study is a preliminary attempt to assess the Ca:Mg intake ratio from food over time in USA adults, a large, genetically variable population with decades on a modern, processed food diet which does not provide adequate Mg intake for many.

Methods

Seven United States Department of Agriculture (USDA) nutritional surveys, beginning in 1977 to date (table 2), have reported Mg intakes from food [11-17]. USDA surveys before 1977 reported Ca but not Mg intakes from food (table 3A). Mean Mg (mg/ day) and Ca (mg/day) intake data from these 7 USDA surveys were tabulated and used to calculate Ca:Mg intake ratios from food for the various age-gender groupings reported in the 7 surveys.

The earliest two surveys that included Mg intake (1977 and 1985) cover adults up to and including age 50 yrs; surveys starting in 1994-5 expanded to include adults aged 50+ years. Thus, this calculation of Ca:Mg intake ratio from food over the 30-year time span (from 1977 to 2007-8) only includes adults \leq 50 years of age, and the Ca:Mg intake ratio for USA adults 50+ years of age covers only a 13-year time span (from 1994-5 to 2007-8) (table 3B).

All 7 USDA surveys reported mean Ca (mg/day), Mg (mg/day) and energy (kcal/day) intake from

food per individual for several age-gender groupings (table 3B), and provided the number (N) or relative % (%N) of individuals in each group. These data were used for two age comparisons of Ca and Mg intakes: – a 30-yr comparison of adults aged 19-50 yrs using all surveys with varying age groupings that required calculation of some weighted means (see below), and a 13-yr comparison of adults 50+ yrs using the 5 surveys from 1994-5 forward which all reported means for the same age groupings. For each age-gender grouping in both comparisons, mean Ca and Mg intakes from food were used to calculate the Ca:Mg ratio for that age-gender group. Trend of mean Ca and mean Mg intake from food for each age-gender group was assessed for both the 30-yr and 13-yr comparisons by calculating the % rise over time (see below for method).

Changes in dietary assessment methods over the years of these surveys were made with progress in methodology. To help assess any impact these changing methods may have had on changes in Ca and/or Mg intakes over the survey years, mean daily energy intakes from foods (kcal/day/individual) were gathered using the same methods used to determine mean Ca and Mg intakes and their % rise over time.

These comparisons are for food intakes only and do not include Mg or Ca intake from supplements.

30-year trend (1977 through 2007-8 surveys) for adults age \leq 50 yrs

The earliest two surveys that included Mg intake (1977 and 1985) did not include adults > 50 yrs and used 15-year age-gender groupings to report mean

Table 2. USDA Surveys reporting both Ca and Mg intakes. Source data for mean dietary (Food only) Ca, Mg and energy Intakes in USA, 1977-2006; used to calculate mean Ca:Mg intake ratio from foods.

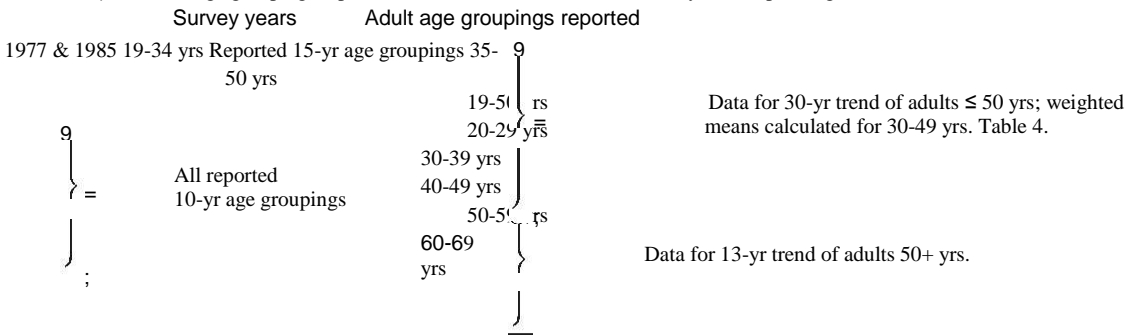
Survey year(s)	Website data source with Table/Page numbers	Citation
1977 & 1985; Men	www.ars.usda.gov/ba/bhnrc/fsrg	USDA Food Surveys, 1935-1998; 1985-86 Continuing [11]
Survey of Food Intakes by Individuals; 1985 Report: Men 19-50 yrs, 1 day; Men: Table 2.1A. – Nutrient Intakes: Mean per Individual in a Day, by Income Level, Summer 1977 and Summer 1985, Pg. 21 – Men: All Income Levels		
1977 & 1985; Women	www.ars.usda.gov/ba/bhnrc/fsrg	USDA Food Surveys, 1935-1998; 1985-86 Continuing [12]
Survey of Food Intakes by Individuals; 1985 Report: Women 19-50 yrs and Children 1-5 yrs, 1 day; Women: Table 2.1A. – Nutrient Intakes: Mean per Individual In a day, By Income Level, Spring 1977 and Spring 1985, Pg. 23 – Women: All Income Levels		
1994-1995	http://www.ars.usda.gov/Services/docs.htm?docid=14531	[13] Report 5 Food and Nutrient Intakes & Diet Knowledge by Gender and Age, 1994-95 Table 1. Nutrient Intakes: Mean amount consumed per individual, by sex and age, 1 day, 1994-5, pp. 2, 4-5
2001-2002	www.ars.usda.gov/ba/bhnrc/fsrg	What We Eat In America; Data Tables; 2001-2; Nutrient [14]
Intakes from Food, 1. Mean Amounts, by Gender and Age; Table 1. Nutrient Intakes: Mean Amount Consumed per Individual, One Day, 2001-2002		
2003-2004	www.ars.usda.gov/ba/bhnrc/fsrg	What We Eat In America; Data Tables; 2003-4; Nutrient [15]
Intakes from Food, 1 By Gender and Age; Table 1. Nutrient Intakes from Food: Mean Amounts consumed per Individual, One Day, 2003-2004		
2005-2006	www.ars.usda.gov/ba/bhnrc/fsrg	What We Eat In America; Data Tables; 2005-6; Nutrient [16]
Intakes from Food 1 by Gender and Age; Table 1. Nutrient Intakes from Food: Mean Amounts Consumed per Individual, One Day, 2005-2006		
2007-2008	www.ars.usda.gov/ba/bhnrc/fsrg	What We Eat In America; Data Tables; 2007-8; Nutrient [17]
Intakes from Food 1 by gender and age; Table 1. Nutrient Intakes from Food: Mean Amounts Consumed per Individual, by Gender and Age, in the United States, 2007-2008		

Table 3.

A) USDA Food Intake Surveys that include Ca and/or Mg.

Survey Year	Includes Ca intake	Includes Mg Intake
1936	Yes	No
1948	Yes	No
1955	Yes	No
1977	Yes	Yes
1985	Yes	Yes
1994-5	Yes	Yes
2001-2	Yes	Yes
2003-4	Yes	Yes
2005-6	Yes	Yes
2007-8	Yes	Yes

B) Different age groupings reported in the 7 USDA Food Intake Surveys that report Mg intake.



intakes (table 3B) while the 5 USDA surveys from 1994-5 through 2007-8 included all adults age 20+yrs and used 10-year age/gender groups to report mean intakes (table 3B). To provide somewhat comparable mean intakes for Mg, Ca and energy for a full 30-yr trend, four age-gender groups were designated: Young Adult Men, Young Adult Women, Adult Men and Adult Women. "Young Adult" men and women for this 30-yr trend compared age groups 19-34 years from the 1977 and 1985 surveys with the groups aged 20-29 yrs in the later 5 surveys. "Adult" men and women included age groups 35-50 yrs from the earlier surveys and a calculated weighted mean for ages 30-49 from the latter 5 surveys (table 4). Thus, for this 30-yr comparison, groups aged 50+ had to be excluded and weighted means for age-groupings 30-49 yrs had to be calculated for surveys after 1985 using 30-39 yr and 40-49 yr means plus their N or %N (table 4). Mean Ca and mean Mg intakes for these four designated age-gender groups are charted in figures 1 and 2 along with % rise for Ca, Mg and energy calculated using the following formula:

$$\% \text{ rise} = [(2007-8 \text{ survey year value} - 1977 \text{ survey year value}) / 1977 \text{ survey year value}] \times 100.$$

13-year trend (1994-5 through 2007-8 surveys) for adults age 50+ yrs

The 5 USDA surveys from 1994-5 through 2007-8 included groups aged 50+yrs, and all used the same 10-year age/gender groups (table 3B) so their reported means for Mg, Ca and energy intakes over those years are fully age-comparable, unlike the 30-yr trend. Ca and Mg mean intakes/individual are charted in figures 3 and 4 along with % rise in each (as well as % rise in kcal) calculated using the formula:

$$\% \text{ rise} = [(2007-8 \text{ survey year value} - 1994-5 \text{ survey year value}) / 1994-5 \text{ survey year value}] \times 100.$$

Ca:Mg intake ratio from foods over time

Using mean Ca and mean Mg intakes for each adult age-gender group in all 7 surveys, the Ca:Mg intake ratio for each group was calculated using the formula:

$$\text{Ca:Mg ratio} = \text{mean Ca intake (mg/day)} / \text{mean Mg intake (mg/day)}$$

and is presented in table 5. The 13-yr % rise in Ca: Mg was calculated for each age gender group using the formula

$$\% \text{ rise} = [(2007-8 \text{ Ca:Mg value} - 1994-5 \text{ Ca:Mg value}) / 1994-5 \text{ Ca:Mg value}] \times 100$$

and charted in figure 5.

The 30-yr % rise in Ca:Mg was calculated for only the 20-29 and 40-49yr age groupings (using the 1977 means for 19-34 and 35-50 yr group means, see table 4) and charted in figure 6.

Statistical analysis was not possible for Ca:Mg ratio, the focus of this investigation, as this ratio for individuals was not calculated in the original surveys. One must go back to the original data, compute individual Ca:Mg ratios in order to assess any statistical significance of these rises in mean Ca : mean Mg ratio.

Results

Adults ≤ 50 yrs, 30-yr trend

From the 1977 to the 2007-8 survey, mean Ca intakes from food rose substantially more than mean Mg intakes in all age-gender groups. Mean Ca intake rose 43% in Young Women and 32% in Young Men while mean Mg for these two groups

Table 4. Age-gender groupings used for 30-yr comparison of mean Ca, Mg and energy intakes; as presented in figures 1, 2 and 8.

Population Survey Yr	Young Adults	Adults	Source of data
1977	19-34*	35-50*	Direct from survey
1985	19-34*	35-50*	Direct from survey
1994	20-29*	30-49**	Direct and calculated weighted mean
2001-2002	20-29*	30-49**	Direct and calculated weighted mean
2003-2004	20-29*	30-49**	Direct and calculated weighted mean
2005-2006	20-29*	30-49**	Direct and calculated weighted mean
2007-2008	20-29*	30-49**	Direct and calculated weighted mean

* Values for mean intakes of Ca, Mg and Kcal taken directly from surveys; ** Values for mean intakes of Ca, Mg and Kcal calculated using reported means and N (number of individuals) or %N for 30-39 and 40-49 age groupings.

rose only 16% and 11% (figure 1, also see table 4 for age ranges from survey years used for this 30-yr comparison). Energy intake rises of 13% and 14% were comparable to the rises in mean Mg intakes (figure 1). Results are similar for adults > 30/35 and <50 yrs (figure 2): women's mean Ca intake rose 64% while their mean Mg intake rose only 18% (mean kcal/day rose 24%), and men's mean Ca intake rose 48% over the 30 years while their mean Mg and energy intakes both rose only 12% (figure 2). The % rises in mean energy intake for the 4 age-gender groups of 12% to 24% (figures 1, 2) are smaller than the % rises in mean Ca intake (32-64%) and comparable to the % rises in Mg intake (11-18%) over this 30-yr time period. Both Men and Women Adult groups plus Young Adult Women showed the trend for rising Ca intakes to level off or decrease slightly in 2007-8, while this leveling off appears to occur in Young Men with the 2005-6 survey (figures 1, 2).

Adults 50+ yrs, 13-yr trend

From the 1994-5 through the 2007-8 surveys, mean Ca intakes rose substantially more than mean Mg intakes from food. Mean Ca and Mg intakes for

3 age groups of older adult women over the 13 years of 1994-5 through 2007-8 are shown in Figure 3; those for men appear in figure 4. The 3 age groupings, 50-59 yrs, 60-69 yrs and 70+ yrs, are fully comparable over all 5 surveys (table 3B).

Ca Rise, Men: Between the 1994-5 USDA survey and that of 2007-8, mean Ca intake from foods for USA older men rose from a range of 754-792 mg/day to 837-1,005 mg/day, an 11 to 30.7% rise in the 3 age groupings of 50+ yrs (figure 4). Elderly Men > 70 yrs had the lowest mean Ca intakes of all adult men for each survey year, rising steadily from 754 mg/day in 1994-5 to 881 mg/day in the 2005/2006 survey, dropping slightly to 837 mg/day in 2007-8, an 11% rise over 13 years. Men in the 3 age groups covering 20 to 49 yrs (not shown) in these fully comparable surveys had mean Ca intakes of 890-1,005 mg/day in 1994-5 that rose 13-22.8% in 13 years to 1,077-1,150 mg/day in 2007-2008. Men aged 50-59 showed the largest % rise in Ca intake over the 13 years, from 769 mg/day to 1,005 mg/day for a 31% rise, followed by 40-49 yrs who showed a 22.8% rise in Ca intake.

Mg Rise, Men: These same older age groups experiencing an 11 to 30.7% rise in mean Ca intake

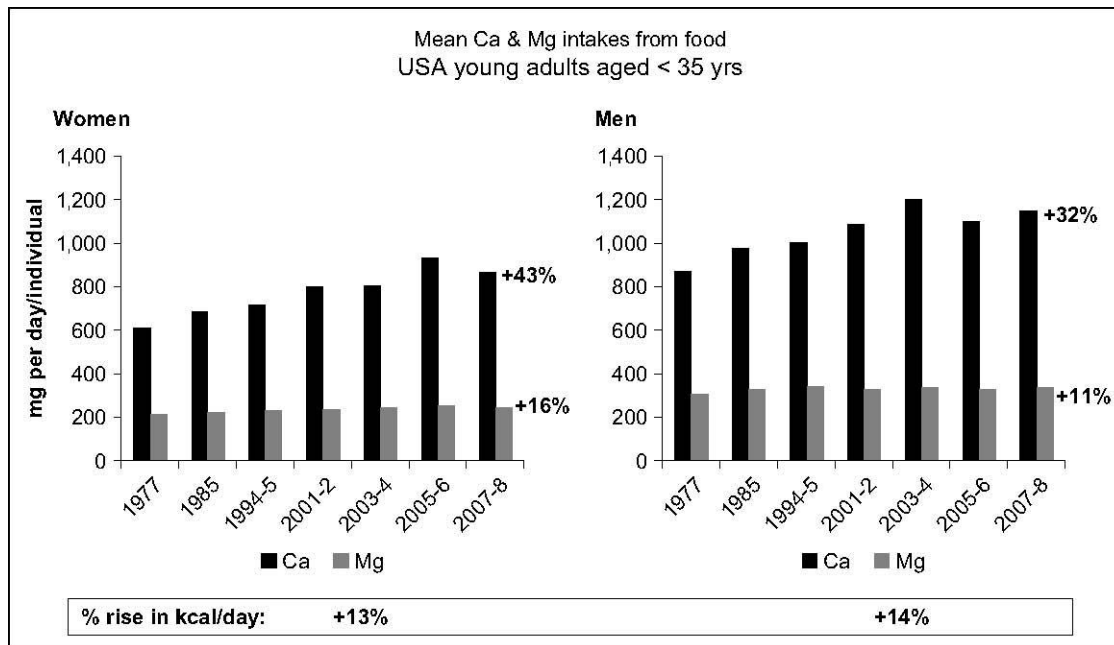


Figure 1. Mean Ca and Mg intakes from food, 1977 to 2007-8, for USA Young Adults, with % rise in mean Ca, Mg and energy (kcal) intakes. Includes ages 19-34 yrs for earliest 2 survey years and 20-29 yrs for later 5 survey years. See Table 4 for age groupings used in this chart.

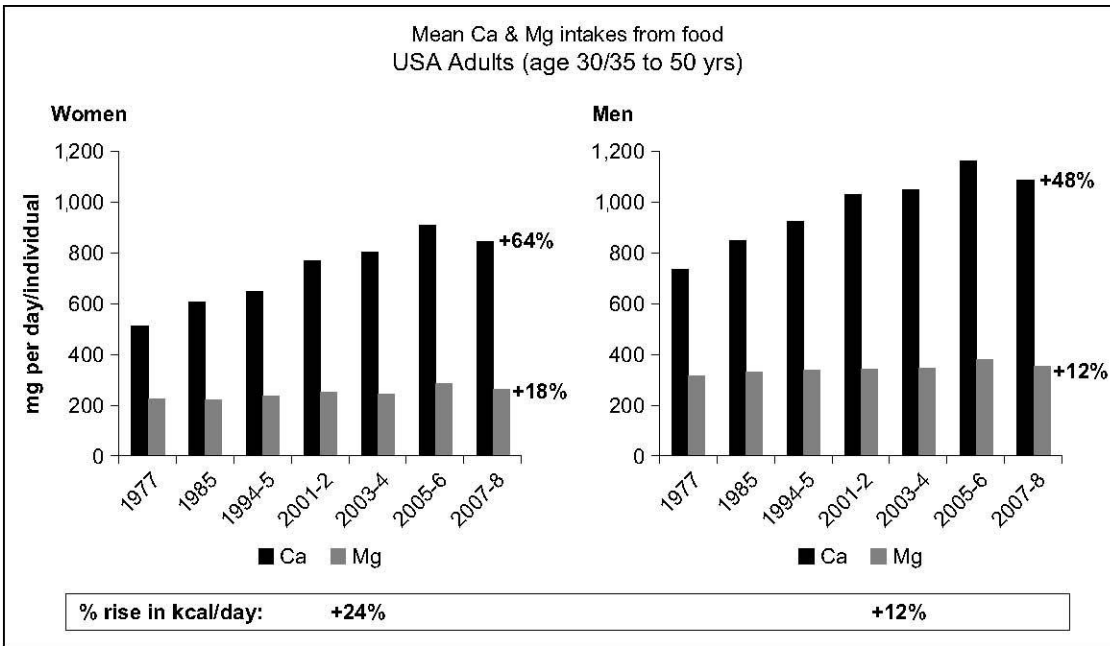


Figure 2. Mean Ca and Mg intakes from food, 1977 to 2007-8, with % rise in mean Ca, Mg and energy (kcal) intakes. Includes ages 35-50 yrs for earliest 2 survey years and 30-49 yrs in later 5 survey years. See Table 4 for age groupings used for this chart.

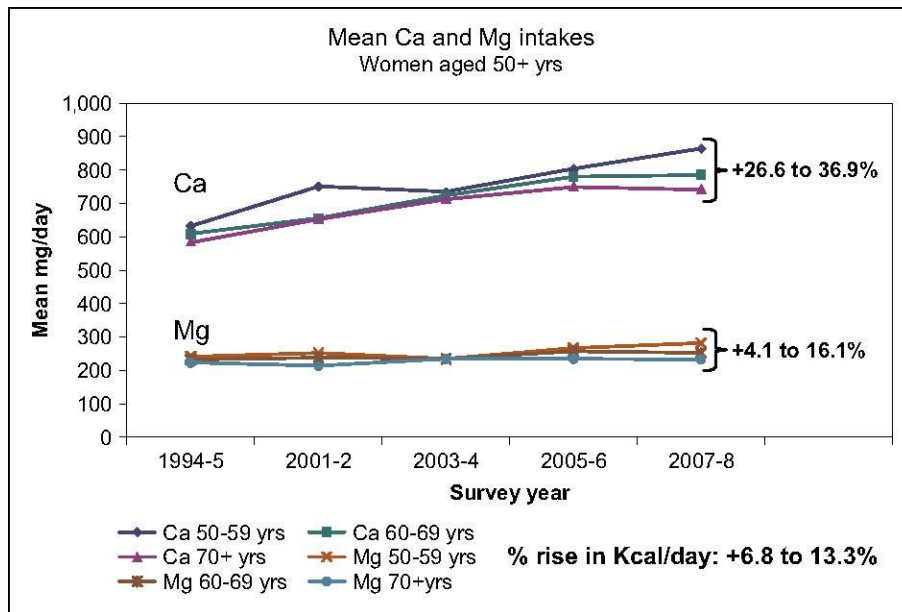


Figure 3. Mean Ca and Mg intakes from food, 1994-5 to 2007-2008, for USA Women, age 50+ yrs, with % rise in Ca, Mg and energy mean intakes.

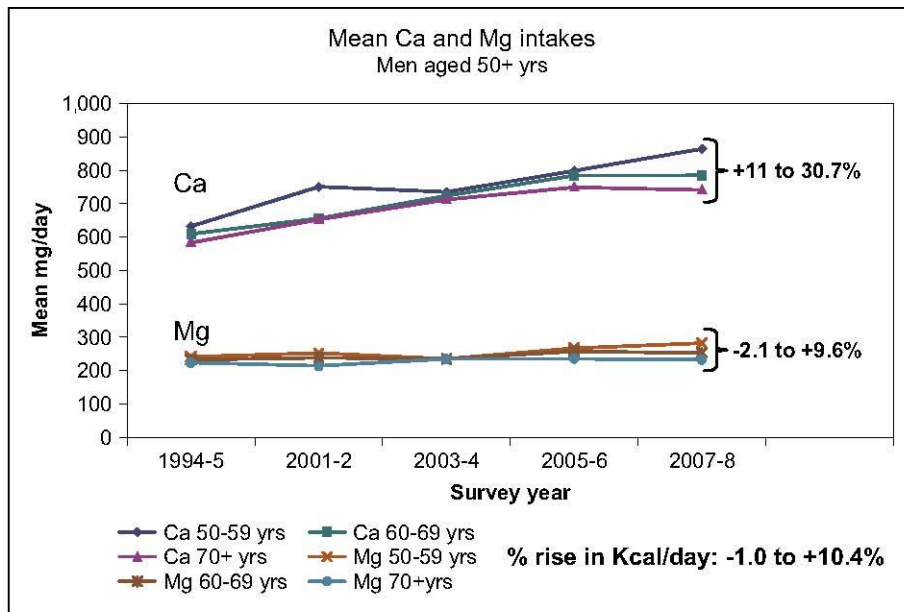


Figure 4. Mean Ca and Mg intakes from food, 1994-5 to 2007-2008, for USA Men, age 50+ yrs, with % rise in Ca, Mg and energy mean intakes.

showed a much smaller change in both mean Mg and mean energy intakes over the 13 years: 50-59 year old men showed the highest rise in mean Mg intake at + 9.6% while elderly men over age 60 experienced a slightly lower (or steady) mean Mg intake over this time period, from -2.1% to -0.7%. Mean energy intakes for these groups changed by -1.0 to + 10.4%, comparable to the %changes in mean Mg intakes. The younger men's age groups (not shown) over the 13 years of comparable surveys all showed changes in mean Mg intake of -1.5 to + 4.9%, similar to that of the change in energy for these age groups, -3.1 for 20-29 yrs, -1.8% for 30-39 yrs, and + 11.7% for 40-49 yrs.

Ca Rise, Women: Mean Ca intakes for the 3 older age groupings rose from 587-632 mg/day in the 1994-1995 survey to 743-865 mg/day in the 2007-8 survey for a 26.6 to 36.9% rise in mean Ca intake over the 13 years (figure 3). The lowest mean Ca intake from foods appeared in the elderly women > 70 yrs, and the highest mean Ca intake from foods were seen in the younger adult women, aged 20-29 and 30-39 yrs (not shown).

Mg Rise, Women: Mean Mg intake for the 3 older age groups of adult women rose from a range of 224-243 mg/day in the 1994-5 survey to 233-282 mg/day in the 2007-2008 survey, a + 4 to 16.1% rise over

the 13 years, quite comparable to the concurrent % rise in kcal/day for these age groups, i.e. + 6.8 to 13.3%.

Ca:Mg Ratio intake ratios from food over time

In each age-gender group, for both the 30-yr and 13yr comparisons, the % rise over time for mean Ca intake from food was several times larger than the % rise for Mg, resulting in a Ca:Mg intake ratio that rose 10-22% in the 13-yr comparison (table 5, figure 5) and 20 to 37% for the 30 year comparisons (table 5, figure 6). The greatest rises in Ca:Mg ratio occurred for women 40-49 yrs, 60-69 yrs and those > 70 yrs and for men aged 50-59 yrs.

Younger women were the first group to show a Ca:Mg intake ratio > 3.0, as early as 1985 for the 19-34 yr group and remaining > 3.0 for all 5 later surveys for ages 20-29 yrs. Ca:Mg for Women aged 30-39 yrs rose to > 3.0 with the 2001-2 survey, and all other women age groups showed a Ca:Mg ratio rising from < 3.0 to > 3.0 by the 2003-4 survey. For men, the Ca:Mg intake ratio rose to > 3.0 by 2001-2 for ages 20-39 yrs, by 2003-4 for men 40-49 yrs and only approached 3.0 in groups aged 50+ yrs by the 2007-8 survey.

Using the weighted age-gender groupings charted in figures 1 and 2 (table 4), the Ca:Mg intake ratio

Table 5. Ca:Mg ratios from food intake by USA adult age-gender groupings, calculated from mean Ca and Mg intakes reported in USDA surveys, 1977 through 2007-2008.

A) Females Ca:Mg							
Survey year	19-34 yrs	35-50 yrs	50 + yrs	19-50 yrs			
1977	2.88	2.32	Not reported	2.64			
1985	3.06	2.76	Not reported	2.93			
	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70+ yrs	20+ yrs
1994-1995	3.13	2.83	2.67	2.60	2.61	2.62	2.76
2001-2002	3.39	3.26	2.90	2.97	2.74	3.07	3.08
2003-2004	3.33	3.47	3.12	3.12	3.07	3.04	3.21
2005-2006	3.72	3.17	3.24	2.99	3.04	3.20	3.24
2007-2008	3.53	3.27	3.18	3.07	3.11	3.19	3.23
13-yr % rise	12.8	15.6	19.1	18.1	19.2	21.8	17.1%
30-yr % rise	22.6		37.1				22.4%
B) Males Ca:Mg	19-34 yrs	35-50 yrs	50 + yrs	19-50 yrs			
1977	2.86	2.34	Not reported	2.64			
1985	2.96	2.59	Not reported	2.79			
	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70+ yrs	20+ yrs
1994-1995	2.95	2.77	2.70	2.44	2.51	2.64	2.72
2001-2002	3.31	3.20	2.88	2.90	2.81	2.89	3.03
2003-2004	3.56	3.07	3.03	2.69	2.88	3.04	3.08
2005-2006	3.37	3.22	2.95	2.88	2.97	3.05	3.08
2007-2008	3.42	3.05	3.16	2.91	2.96	2.99	3.11
13-yr % rise	16.0	10.1	17.1	19.3	18.0	13.3	14.4%
30-yr % rise	19.6		35.1				17.8%

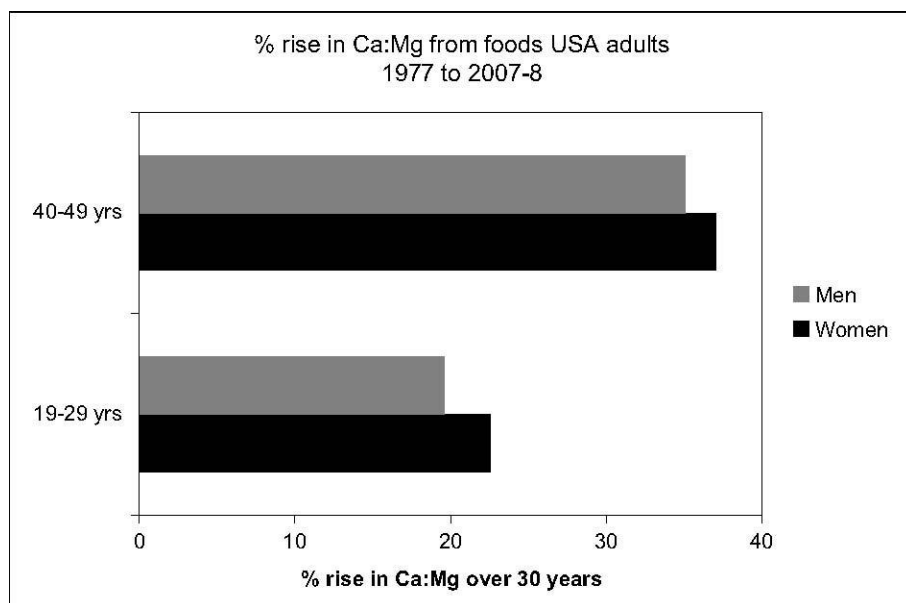


Figure 6. 30-yr % rise in Ca:Mg Ratio from foods, USA Adults, age 19-29 and 40-49 yrs, 1977 through 20078 surveys. See table 5 for source of data.

from food rose 20% in young adult males, 23% in young adult females, 33% in adult males and 40% in adult females between the 1977 and 2007-8 surveys. For “all-adults” groupings over the 30 years from 1977 to 2007-8 (which includes only ≤ 50 yrs for 1977 and 1985), the Ca:Mg intake from foods increased 22% for women and 17.8% for men (table 5), with the Ca:Mg intake ratio rising to >3.0 between the 1994-1995 and 2001-2002 surveys for both men and women.

Discussion

This assessment is not precise.

–The earliest two surveys’ age groupings do not match those of the latter 5 surveys, and are not strictly comparable in the 30-yr comparison (table 3B).

–As already mentioned, no statistical analysis is possible from these data on the possible rise in Ca:Mg ratio over time. For variance to be truly measured and statistically tested, original intake data from individuals in these surveys must be used to calculate Ca:Mg ratio for each individual and means and variance for age/gender groupings calculated for appropriate statistical testing.

–This apparently increasing Ca:Mg intake ratio calculation does not include supplements which highly favor Ca intake over Mg in this population: Ca supplements sales were 10+ times Mg supplement sales in 2007, and although 2008 Mg supplement sales increased 14% while Ca supplement sales grew by only 6%, Ca sales accounted for 54% and Mg 15% of all nutritional mineral sales for that year [18]. In addition, one study including Ca and Mg supplements [19] showed that USA adults using Ca and Mg supplements all raised their Mg intake from below their EAR to above that average daily requirement, but the data show that all, and especially adult women, increased their Ca:Mg ratio substantially via supplement use.

Nonetheless, mean Ca intake from foods rose substantially compared with changes in mean Mg and mean energy intakes between 1977 and 2007-8 in USDA surveys for all adult age-gender groupings, strongly suggesting a rising Ca:Mg intake ratio for USA adults from foods alone during this 30-yr time-frame. This rise may have leveled off by the 2007-8 survey, but rose from < 3.0 in 1977 to > 3.0 by 2003-4 for all adult age-gender groupings up to 50 yrs of age. Likewise, in the fully comparable surveys between 1994-5 and 2007-8 that include adult age groups > 50 yrs, Ca:Mg intake ratios went

from largely < 3.0 in the 1994-5 survey (all save women aged 29-29 yrs) to > 3.0 in all groups aged 20-39 yrs by 2001-2, to > 3.0 in women of all age groups and men 40-49 yrs and 70+ yrs by 2003-4, and approached 3.0 in men aged 50+ yrs by the 2007-8 survey. The Ca:Mg intake ratios for "all adults" groupings (19-50 yrs for earlier surveys and 20+ yrs for later 5 surveys) rose steadily from 2.64 in 1977 to 3.23 for women and 3.11 for men by 2007-8 (see table 5).

Is this rising Ca:Mg ratio a concern? Conflicting results between Mg, Ca intakes and mortality have been reported. For instance, dietary Ca was associated with a significantly lower rate of all causes mortality while Mg intake was not associated with all cause, CVD or cancer mortality in an informative recent Swedish Study [20].

In this study, Mg intakes were adequate in even the lowest tertile for Mg with the 5 percentile Mg intake (355 mg/day) exceeding the EAR (350 mg/day) for these adult men, leading the authors to conclude that all subjects were adequate in Mg. This was not the case for Ca, however. Ca intakes were largely less than adequate for the $n = 7,786$ men in the lowest tertile at $< 1,230$ mg

Ca/day with the 5th percentile Ca intake (798 mg/day) only 2/3 of the 1,200 mg/day Adequate Intake (AI) for Ca. This study thus found that men, all adequate in their Mg nutrition and one out of three inadequate in their Ca intake, showed lower all cause mortality as their Ca intake rose to adequacy levels. This is not a surprising result as Ca is an essential nutrient, necessary in adequate amounts for optimal health, and does not suggest Ca intake is more important than Mg intake in all cause mortality: Both are necessary, in fact, all essential nutrients in balanced adequacy are necessary for optimal health. This study does show that additional Mg above adequacy does not lower mortality for CVD, cancer or all cause, but does not tell us if the higher than adequate intakes of Mg impacted the lower, less than adequate Ca intakes, and this is where calculation of individual Ca:Mg ratios with statistical analysis could further our knowledge. This study also confirms the Seelig finding [3] that above optimal intakes of Ca (in this case $> 1,599$ mg/day) in the face of fully adequate Mg intakes will not cause a negative Mg balance and its concomitant loss of optimal health. This is probably not true in studies with less than adequate Mg intakes:

Seelig showed that at all Mg intake levels < 10 mg/kg/day, high Ca intake (> 10 mg/kg/day) decreased Mg retention; given high Ca intakes, those at or above 6 mg/kg/day Mg remained in positive Mg balance

while those at or below 5 mg/kg/day Mg were mostly forced into negative Mg balance. Thus, for studies at barely adequate Mg intakes we might expect positive Mg balance (and thus no negative health impacts due to Mg deficit) on low Ca intakes but not on high Ca intakes for both men and women [3]. Studies below adequacy for Mg intake deal with the complex situation of Mg deficit and the fact that diets low in Mg are often also low in Ca [21]. In such studies, increasing Ca and/or Mg intake can show inconsistent results, i.e. both rising and falling Mg and/or Ca balance with concomitant health outcomes. Study of Ca:Mg intake ratios with regards to the degree of Mg as well as Ca dietary adequacy might be a worthy effort and might lead to better understanding of the many studies on Ca, Mg and both intakes on health.

The importance of cellular Ca:Mg ratio on the physiological function of several tissues has been largely elucidated by Resnick and others showing a strong physiological/cellular link between a rising Ca:Mg intracellular ratio and aspects of metabolic syndrome including hypertension, hyperinsulinemia, insulin resistance and left ventricular cardiac hypertrophy [9, 22, 23]. Inflammatory syndrome can also be added to these aspects of possible cytosolic Ca activation as a result of Mg deficit [24] and its concomitant high Ca:Mg ratio. This possible common link between stress, inflammation and metabolic syndrome shows how a Mg deficiency at the cellular level can bring on Ca activation in various tissues that are not an appropriate response to an environmental injury or pathogen but rather a result of Mg deficit. It is possible that this cellular Ca activation is part of the pathology of a dietary Mg deficit caused by low dietary Mg, which can be exacerbated by a high dietary Ca:Mg ratio, and this inappropriate Ca activation at the cellular level can lead to type 2 diabetes, CVD or other manifestations of Mg deficiency if the Mg inadequacy is not corrected.

Considering this background, the following associations are intriguing, and warrant further research with measurement of Ca:Mg ratio in physiological studies as well as nutrient intake studies.

Association of rising Ca:Mg with prevalence of type 2 diabetes

Because diabetes mellitus has been considered a Mg wasting disease, the relationship between Mg status and incidence of this chronic disease is of interest [25, 26]. Many studies indicate that a diet high in Mg-rich foods is associated with a

substantially lower risk of type 2 diabetes [27-29] while other studies indicate that Ca and Mg intake may protect against the development of type 2 diabetes [30].

In addition to their rising Ca:Mg ratio from foods (and presumably supplements), over half of the USA population has been shown to be below their EAR for Mg with many low in Ca intakes as well from foods, at least since 2001 [2]. Between 1980 and 2007 the crude incidence of diagnosed diabetes in this population increased 136%, and the age-adjusted incidence rose 123% [31, 32]. The rate of change in incidence of diagnosed diabetes has not been constant; rather the incidence remained largely unchanged in the 1980's and increased sharply in the mid-1990's through 2007 – the same time frame in which the Ca:Mg intake ratio from foods for this population (with less than adequate Mg intake in 60+%) went from largely below 3.0 to largely above 3.0 (figure 7).

Association of rising Ca:Mg with incidence of colorectal cancer in young adults

All four age-gender groups < 50 yrs show mean Ca:Mg > 2.78 after the 1985 survey (table 5). Intakes below this Ca:Mg ratio have been associated with a

significantly decreased risk of colorectal cancer with increasing Mg intake [10]. Additionally, during the time frame in which we have shown the Ca:Mg intake from foods to be rising in the USA ages 19-50 yrs, Siegel et al. [33], in 2009, reported a rising colorectal cancer incidence trend among young non-Hispanic white adults, aged 20-49 years between 1992 and 2005 (figure 8).

Conclusion

A study of USDA food intake surveys from 1977 through 2007-8 show a rising Ca:Mg intake ratio from foods for all USA adult age-gender groupings. Ca:Mg intake ratio from foods ranged from 2.3 to 2.86 in the 1977 survey and rose to a range of 2.91 to 3.53 in the 2007-2008 survey. By 2001-2002, the Ca:Mg ratio from foods had risen above the 2.78 ratio found by Dai et al. [10] to be associated with an increased risk of colorectal cancer in subjects with decreasing Mg intakes in all but one age-gender group (women 60-69 yrs) and by all age-gender groups by the 2003-4 survey. This rise in Ca:Mg ratio from below 3.0 in 1977 to generally above or approaching 3.0 after 2000 coincides with the rise in incidence and prevalence of type 2 diabetes in the USA population as well as a rise in colorectal

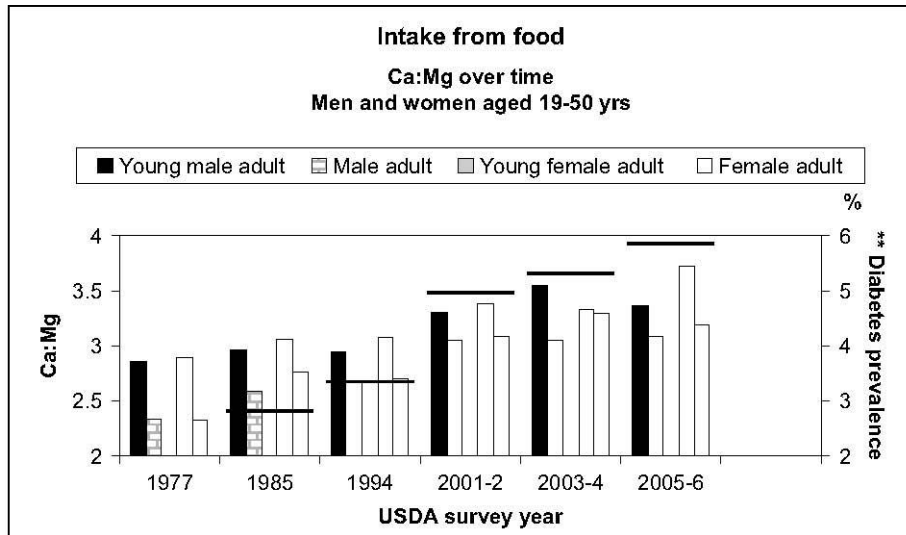


Figure 7. Ca:Mg from foods over time for USA Adults age 19-50 yrs (see table 4 for age ranges) charted with rise in Diabetes prevalence, USA, 1980-2006 (source: CDC [31, 32]).

**Diabetes Prevalence: Crude & Age-Adjusted % of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, United States, 1980-2006.

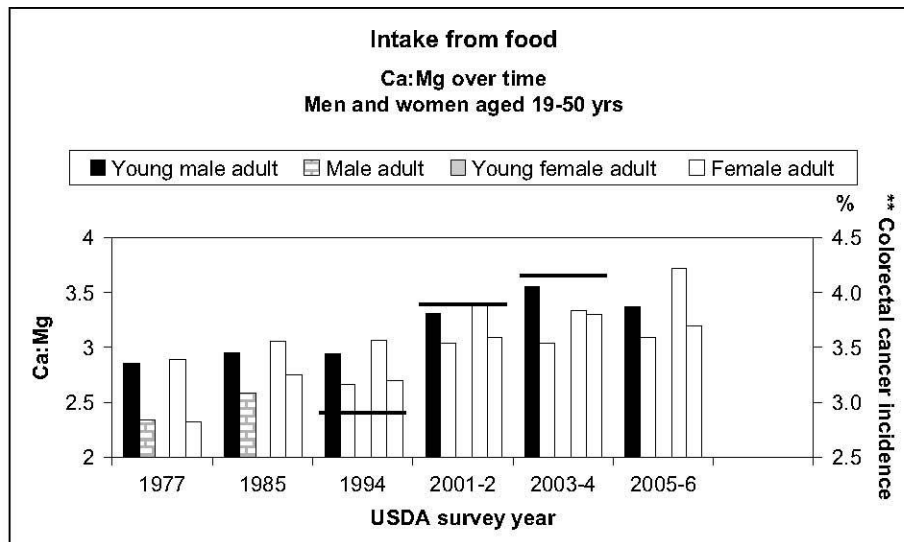


Figure 8. Ca:Mg from foods over time for USA Adults age 19-50 yrs (see *table 4* for age ranges) and rising incidence of colorectal cancer in USA non-Hispanic white adults age 20-49 yrs (source: [33]).

**Colorectal Cancer Incidence in Young Adults, USA.

cancer incidence among young white, non-hispanic adult men and women in the USA. The rise in Mg intake over these 30 years is highly comparable to the rise in mean energy intake for these men and women, while the rise in Ca intake is substantially higher, lending credence to the hypothesis that this rise in Ca:Mg over the years is a result of higher intake of Ca from foods either from changes in food selections, a rising content of food Ca or both. Original intake data for individuals from these surveys needs to be accessed, if possible, to calculate Ca:Mg ratio for each individual and do a proper statistical assessment of this ratio's rise over the years and to appropriately compare it with incidence and prevalence of colon cancer in 19-50 yr adults and type 2 diabetes in the adult population to better assess the validity of these associations. Individuals can raise their Mg adequacy plus lower their dietary Ca:Mg ratio by consuming more vegetables, legumes, whole grains and nuts. Calculation of Ca:Mg intake ratio in individual assessments might be added to medical and dietary exams as well as research studies with informative results. Health consequences need to be considered for the 64-67% [2] yr old adults in the USA not meeting their requirement for Mg from foods, many being also below their requirements for Ca, and their increasing Ca:Mg ratio from foods.

Disclosure

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Suboptimal magnesium status in the United States: are the health consequences underestimated?

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In comparison with calcium, magnesium is an “orphan nutrient” that has been studied considerably less heavily. Low magnesium intakes and blood levels have been associated with type 2 diabetes, metabolic syndrome, elevated C-reactive protein, hypertension, atherosclerotic vascular disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer. Almost half (48%) of the US population consumed less than the required amount of magnesium from food in 2005–2006, and the figure was down from 56% in 2001–2002. Surveys conducted over 30 years indicate rising calcium-to-magnesium food-intake ratios among adults and the elderly in the United States, excluding intake from supplements, which favor calcium over magnesium. The prevalence and incidence of type 2 diabetes in the United States increased sharply between 1994 and 2001 as the ratio of calcium-to-magnesium intake from food rose from <3.0 to >3.0. Dietary Reference Intakes determined by balance studies may be misleading if subjects have chronic latent magnesium deficiency but are assumed to be healthy. Cellular magnesium deficit, perhaps involving TRPM6/7 channels, elicits calcium-activated inflammatory cascades independent of injury or pathogens. Refining the magnesium requirements and understanding how low magnesium status and rising calcium-to-magnesium ratios influence the incidence of type 2 diabetes, metabolic syndrome, osteoporosis, and other inflammation-related disorders are research priorities.

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INTRODUCTION Dietary magnesium received less attention than dietary calcium by the nutrition research community in the United States during the 20th century – a time of prolific and varied research in nutrition. The US Department of Agriculture (USDA) first published the values for the calcium, phosphorus, and iron content of foods in 1945, while the values for magnesium content were not reported until preliminary findings of the magnesium content of 444 food items first appeared in 1963.¹ Magnesium first became a standard nutrient in food composition tables in the revised USDA Agriculture Handbook published in November of 1976,² but as late as 1984, values for the magnesium content of foods were not as prevalent as those for many other nutrients and they were particularly limited for commercial food products.³ The National Health and Nutrition Examination Survey (NHANES) has reported on intakes of magnesium, but beyond NHANES1 (personal communication, CDC-Info, 8-3-10) and its large study of the population’s serum magnesium levels in 1971–1974,⁴ funding has been insufficient for NHANES to include blood or urinary magnesium values among its vast array of measurements in representative samplings of the population.⁵

Almost half (48%) of the US population has been shown to consume less than the daily requirement of magnesium from foods.⁶ Magnesium is widespread in foods and is regulated physiologically by both renal and gut conservation.⁷ Overt signs of clinical magnesium deficiency have not been routinely recognized in the healthy population, but because magnesium deficiency has been associated with critical health issues, including cardiovascular disease (CVD),⁸ type 2 diabetes mellitus (DM2),^{9,10} and osteoporosis,¹¹ a review of current research and dietary trends is warranted.

DISEASE STATES ASSOCIATED WITH DIETARY MAGNESIUM

Although diets ordinarily consumed by healthy Americans often do not meet the Dietary Reference Intake (DRI) values for magnesium,¹² they are not generally recognized as leading to symptomatic magnesium depletion. However, a number of clinical disorders have been associated with a low-magnesium diet. It has been suggested that mild degrees of magnesium deficiency present over time may contribute to a number of disease states, including those outlined below.

Type 2 diabetes and metabolic syndrome

CVD risk factors are strongly associated with DM2,¹³ and both CVD and DM2 are considered as components of metabolic syndrome, a magnesium wasting disease.^{9,14,15}

Dietary magnesium intakes have been negatively associated with metabolic syndrome,^{9,16–18} as have serum magnesium levels.¹⁹ Both DM2 and metabolic syndrome have been associated with low serum magnesium,¹⁰ but the lower levels of serum magnesium in individuals with DM2 may be a consequence of the disease and its hypermagnesuria rather than a cause.²⁰

Risk of DM2 has been associated with low dietary magnesium intake,^{21,22} which may be influenced by fiber and glycemic load^{23,24} as well as other nutrients such as calcium^{25,26} and chromium.²⁷

Elevated C-reactive protein

In human studies, reports consistently link both magnesium intake and serum magnesium status with C-reactive protein (CRP), a measure of inflammation associated with CVD risk,^{28–30} metabolic syndrome,¹⁹ and DM2.^{28,31} CRP was found to be inversely proportional to magnesium intake in epidemiological studies,²⁹ children,³² the Women's Health Initiative study,³³ a cross-section of the Nurses Study,³⁴ patients with DM2 and metabolic syndrome (in whom the association was independent of fiber intake),³⁵ adults in NHANES,³⁶ and women over 45 years of age in the Women's Health Study.³⁷ In addition, serum magnesium has been consistently shown to be inversely proportional to serum or plasma CRP in overweight/obese patients,^{19,38} in hemodialysis patients,³⁹ and in patients hospitalized for both heart failure and other causes.³⁰ In one study, CRP was significantly higher (and serum magnesium significantly lower) in patients admitted for heart failure versus those admitted for other causes³⁰; this study also showed oral magnesium of 300 mg/day given to heart failure patients raised both intracellular and serum magnesium while lowering serum CRP compared with control heart failure patients who were not receiving oral magnesium and showed no change in CRP, no rise in cellular magnesium, and a lesser rise in serum magnesium.

Hypertension

A number of studies have demonstrated an inverse relationship between low dietary intake of magnesium and blood pressure.^{37,40,41} Hypomagnesemia and/or reduction of intracellular magnesium ion (Mg^{2+}) also has been inversely correlated with blood pressure. Patients with essential hypertension were found to have reduced free magnesium concentrations in erythrocytes. The magnesium levels were inversely related to both systolic and diastolic blood pressure. Intervention studies with magnesium therapy in hypertension have led to conflicting results, but a recent review of 44 studies⁴² concluded that 486 mg magnesium/day, which is 1.2 to 1.6 times the adult Recommended Dietary Allowance (RDA), is necessary to achieve significant lowering of high blood pressure, unless subjects have been taking antihypertensive medications; in such medicated subjects, the daily critical magnesium dose is lowered by half, to 243 mg magnesium/day. The review also showed that magnesium supplementation as high as 600 mg/day did not lower blood pressure in studies with a majority of subjects who were normotensive at baseline.⁴² Other dietary factors may also play a role. A diet of fruits and vegetables that increased magnesium intake from 176 mg/day to 423 mg/day (along with an increase in potassium) significantly lowered blood pressure.⁴³ The addition of nonfat dairy products that increased calcium intake lowered blood pressure even further.

The mechanism by which magnesium deficiency may affect blood pressure is not clear, but it may involve aspects of inflammation such as decreased production of prostacyclins and increased production of thromboxane A₂, as well as enhanced vasoconstrictive effect of angiotensin II and norepinephrine. Transient receptor potential melastatin 7 (TRPM7) is an ion channel and protein kinase that is highly permeable to both calcium and magnesium and has been suggested to be involved in magnesium homeostasis. Recently, it has been suggested that vascular TRPM7 channels, which transport magnesium, may be altered in hypertension.^{40,44}

Atherosclerotic vascular disease

Another potential cardiovascular complication of magnesium deficiency is the development of atheromatous disease.⁴⁵ Lipid alterations, including low HDL cholesterol, ^{38,46} have been reported in hypomagnesemic human subjects.⁴⁷ Epidemiological studies have inversely related both serum magnesium levels⁴⁸ and magnesium levels in drinking water to cardiovascular death rates.^{49–51}

Platelet hyperactivity is a recognized risk factor in the development of CVD. Magnesium has been shown to inhibit platelet aggregation against a number of aggregation agents.⁵² Diabetic patients with magnesium depletion have been shown to have increased platelet aggregation. Magnesium therapy in these subjects returned the response toward normal.⁵³ The antiplatelet effect of magnesium may be related to the finding that magnesium inhibits the synthesis of thromboxane A₂ and 12-HETE, which are inflammatory eicosanoids that are thought to be involved in platelet aggregation.⁵² Magnesium also inhibits the thrombin-induced calcium influx in platelets⁵² and stimulates the synthesis of prostacyclin (PGI₂), the potent antiaggregatory eicosanoid.⁵⁴

Sudden cardiac death

Occurrence of sudden cardiac death was reportedly reduced by almost 40% in subjects with serum magnesium levels of ≥ 1.75 mEq/L compared with subjects having serum magnesium levels of ≥ 1.5 mEq/L in 14,232 adults aged 45–64 years who were followed up for 12 years.⁵⁵ In addition, it was significantly reduced with either higher dietary or plasma magnesium levels in women who were followed up for 26 years in the Nurses Health Study.⁵⁶ Khan et al.⁵⁷ found apparently opposite results, reporting no significant differences in multivariable-adjusted hazards ratio for baseline serum magnesium and the development of hypertension, CVD, or all-cause mortality in 3,531 middle-aged subjects over an 8-year period. However, the hazard ratio was significant ($P = 0.04$) for the development of CVD and for death when adjusted for age and sex only, with magnesium as a categorical variable. Hypomagnesemia at the time of admission to an intensive care unit seems to be associated with high mortality in critically ill patients with DM2.⁵⁸

Osteoporosis

Osteoporosis accounts for approximately 2 million bone fractures per year in the United States, at a cost of over \$17 billion.⁵⁹ This condition has been associated with magnesium deficiency. Experimental dietary magnesium deficit in animals has been associated with a decrease in skeletal growth^{11,60} and a reduction in osteoblastic bone formation. Markers of bone formation have also been reduced, suggesting a decrease in osteoblastic function in these magnesium-deficient animals. An increase in the number and activity of osteoclasts in the magnesium-deficient rat and mouse has been reported. Bone from magnesium-deficient rats has been described as brittle and fragile. Biomechanical testing has directly demonstrated skeletal fragility in the magnesium deficient rat and pig. Such experimental studies have been mostly conducted using levels of severe magnesium deficiency not common in the human population; however, animals with magnesium levels at 10%, 25%, or 50% of the requirement (levels which are present in the US population) show bone loss, decreased osteoblasts, and increased osteoclasts by histomorphometry.¹¹ In humans, epidemiological studies have demonstrated a correlation between bone mass and dietary magnesium intake in the appendicular and axial skeleton.¹¹ Few studies have assessed magnesium status in patients with osteoporosis. Low concentrations of magnesium in serum and erythrocytes, as well as high retention of parenterally administered magnesium, have suggested a magnesium deficit; however, these results are not consistent from one study to another. Similarly, while low skeletal magnesium content has been observed in some studies, normal or even high magnesium content has been found in others. The effect of dietary magnesium supplementation on bone mass in patients with osteoporosis has not been studied extensively. The effect of magnesium supplements on bone mass has generally led to an increase in bone mineral density, but larger, long-term, placebo-controlled, double-blind investigations are required. There are several potential mechanisms that may account for a decrease in bone mass in magnesium deficiency; for example, magnesium is mitogenic for bone cell growth, which may directly result in a decrease in bone formation with magnesium deficit. A recent study suggested that the TRPM7 magnesium channel is critical for osteoblast function and that magnesium deficiency may thereby decrease bone formation.⁶¹ Magnesium also affects crystal formation; a lack of magnesium results in a larger, more perfect crystal, which may affect bone strength. Magnesium deficiency results in a drop in both serum parathyroid hormone and 1,25(OH)₂D; because both hormones are trophic for bone, impaired secretion or skeletal resistance may result in osteoporosis. An increased release of inflammatory cytokines may result in activation of osteoclasts and increased bone resorption in rodents.^{11,60}

Other disorders

Magnesium deficiency has been associated with migraine headache, and magnesium therapy has been reported to be effective in the treatment of migraine.^{62,63} Because magnesium deficiency results in smooth muscle spasm, it has also been implicated in asthma, and magnesium therapy has been effective for treating asthma in some studies.⁶⁴⁻⁶⁶ A decrease in intracellular magnesium ion shown during acute asthma attacks was followed by an increase as the attacks subsided.⁶⁷ However, neither diet nor serum magnesium values were associated with asthma prevalence in Taiwanese children⁶⁸; no difference in plasma magnesium was found between asthmatic and non-asthmatic children in Iran, while erythrocytic magnesium was significantly lower in the asthmatic group.⁶⁹ Lastly, high dietary magnesium intake has been associated with a reduced risk of colon cancer.⁷⁰

DIETARY MAGNESIUM STATUS IN THE GENERAL US POPULATION

Insufficient magnesium intake from food

The current RDA for magnesium, based on balance studies, is 400 mg/day for young adult males and 310 mg/day for young adult females and increases to 420 mg/day and 320 mg/day for men and women, respectively, over 30 years of age (Table 1).¹² The Estimated Average Requirement (EAR) for magnesium, i.e., the average daily amount deemed necessary for healthy individuals, is 330 mg/day for young adult males and 255 mg/day for young adult females, increasing to 350 mg/day and 265 mg/day, respectively, for men and women over 30 years of age.¹² Currently, almost half (48%) of the entire US population does not meet the EAR for magnesium from food consumed,⁶ but this does not appear to be a static situation: This estimate is down from 56% for the same calculation using NHANES 2001–2002 food intake data.⁷¹ Table 1 shows the percentage of various US age gender groups ≥ 9 years of age who consumed less than the EAR for magnesium from food, using the same calculations of NHANES data from 2001–2002,⁷¹ 2003–2004,⁷² and 2005–2006.⁶ This calculation for 2007–2008 intake data is not yet available. Only males aged 9–13 years show a possible increase in the percent inadequacy of magnesium intake from food, from 14% in 2001–2002 to 22% in 2005–2006; all other male age groups between 14 and 70 years show a possible decrease in the percent inadequacy, from 55–78% collectively in 2001–2002 down to 45–68% collectively in 2005–2006. Among elderly males ≥ 71 years, no change was observed from the high level of 80% who consumed less than the EAR for magnesium from food. These possible trends have not been tested statistically. For females, Table 1 shows a possible decrease in magnesium inadequacy for girls aged 9–13 years (from 44% in 2001–2002 to 30% in 2005–2006) and for all age groups ≥ 31 years, from 64–82% in 2001–2002 to 48–70% in 2005–2006. Females in the prime childbearing age group of 14–30 years, appear to show the same high level of inadequacy throughout the survey periods, about 90% for teens 14–18 years and 64% for women aged 19–30 years. Averaging the three surveys performed in 2001–2002, 2003–2004, and 2005–2006 (Figure 1) shows that over 50% of all adult groups of both sexes failed to meet the EAR, and for males and females aged 14–18 years, this figure rose to an average of >70% and 90%, respectively.

Table 1 Estimated average requirement (EAR) and recommended daily allowance (RDA) for US children, teens, and adults,¹² along with proportion of US children, teens, and adults consuming less than the EAR of magnesium (Mg) with their daily food diet according to NHANES 2001–2002,⁷¹ 2003–2004,⁷² and 2005–2006.⁶

Age	RDA for Mg (mg/day)	EAR for Mg (mg/day) ¹²	Percentage consuming <EAR 2001–2002	Percentage consuming <EAR 2003–2004	Percentage consuming <EAR 2005–2006
Males					
9–13 years ^a	240	200	14%	18.7%	22%
14–18 years ^b	410	340	78%	74.2%	68%
19–30 years ^b	400	330	55%	56.1%	51%
31–50 years ^b	420	350	61%	56.9%	45%
51–70 years ^b	420	350	70%	73.1%	58%
◆71 years	420	350	81%	81.0%	80%
All men ◆19 years ^b	–	–	64%	–	53%
Females					
9–13 years ^b	240	200	44%	40.4%	30%
14–18 years	360	300	91%	90.7%	89%
19–30 years	310	255	64%	64.8%	65%
31–50 years ^b	320	265	65%	67.0%	48%
51–70 years ^b	320	265	64%	70.4%	55%
◆71 years ^b	320	265	82%	72.5%	70%
All women ◆19 years ^b	–	–	67%	–	56%
All persons ◆1 year ^b	–	–	56%	56.6%	48%

^a Age-gender group may be declining in Mg adequacy.

^b Age-gender group may be gaining in Mg adequacy.

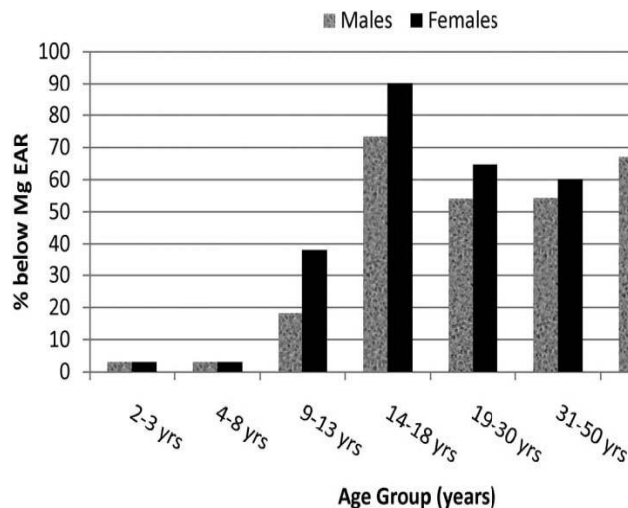


Figure 1 Proportion of the US population below the Estimated Average Requirement (EAR) for magnesium (Mg). Average of three USDA surveys, 2001–2002,⁷¹ 2003–2004,⁷² and 2005–2006,⁶ for each age-gender group.

Accuracy of current EAR and RDA for magnesium

The estimates of magnesium deficits in the US population are based on the EAR and RDA of 1997.¹² The EAR for magnesium estimates the amount of daily magnesium that provides magnesium balance in 50% of the population. The RDA uses the EAR plus twice the standard deviation (based upon an assumption that the coefficient of variation is 10%) to estimate the amount of daily magnesium necessary to provide the EAR for 97.5% of the healthy population. The balance study most relied upon to set the EAR was a year-long study performed by Lakshmanan et al.⁷³ of 34 free-living subjects on self-selected

diets; balance was measured during four 1-week-long periods. Duplicate plate composites of subjects' habitual diets were collected during balance periods for analysis of magnesium content. The level of magnesium found to supply balance in just above half of the men and just under half of the women was 4.3 mg/kg/day, an amount that was somewhat confirmed by Seelig's review⁷⁴ of 14 pre-1962 magnesium balance studies: in about half of the balance periods, males had a negative magnesium balance on intakes between 4.0 mg/kg/day and 5.9 mg/kg/day (depending upon whether a +15 mg correction for sweat losses was made), and in roughly half of the balance periods, women had a negative magnesium balance on intakes between 4.0 mg/kg/day and 4.9 mg/kg/day.⁷⁴ The studies examined in the Seelig review were not included in the DRI assessment, as they were all performed before atomic absorption spectrophotometry was available for magnesium determinations.¹² A more recent magnesium balance study performed by Hunt and Johnson⁷⁵ used data from several metabolic unit studies at the Grand Forks Human Nutrition Research Center in a model that predicted neutral magnesium balance at 2.36 mg magnesium/kg/day for healthy persons, regardless of age or sex; this is just over half (55%) the magnesium level used by the DRI Committee to achieve balance in half the population. Conducted in 2006, the study was not available to the DRI Committee, which released its report in 1997. Serum magnesium values were not reported in the Hunt and Johnson study.⁷⁵ Lakshmanan et al.³ reported serum magnesium values a bit below 0.80 mmol/L, which is considered within the normal range⁴ but is also associated with impaired glucose tolerance and high fasting glucose¹⁰ as well as chronic latent magnesium deficiency (CLMD),⁷⁶ a subtle chronic negative magnesium balance in a large number of people who appear healthy. Although in magnesium deficit, persons with CLMD show serum magnesium levels within the "normal" reference interval primarily due to magnesium contributions from bone maintaining the serum magnesium concentration. Such individuals might require a higher magnesium intake to achieve magnesium balance than do individuals who are fully magnesium replete, but this has not been measured directly. The inclusion of assumed healthy subjects with CLMD in magnesium balance studies may result in higher measures of magnesium balance and high variability.

The Hunt and Johnson⁷⁵ study predicted a magnesium EAR of 165 mg/day for healthy adults, which, using magnesium intakes from the 2005–2006 NHANES study,⁶ would result in 0% of all adult males and 7–19% of all healthy adult women having inadequate magnesium intake from food; this is remarkably less than the 53% of adult males and 56% of adult females who consume less than the current EAR for magnesium (Table 1). To evaluate how these two divergent estimates of US magnesium adequacy are to be viewed, the details below are provided.

The RDA is defined as the EAR plus two standard deviations of the EAR. Hunt and Johnson⁷⁵ reported two standard deviations or 95% of the prediction interval for a recommended magnesium RDA at 237 mg/day. Supporting this lower-than-current magnesium RDA for healthy adults is an NHANES study³⁶ that showed adults receiving less than 50% of the RDA of magnesium (i.e., <210 mg for males and <160mg for females) were likely to have normal-range-but-elevated CRP levels (1.48- to 1.75-fold). Moreover, women over the age of 43 years showed elevated CRP levels (as well as other inflammation biomarkers) within the normal range at dietary intakes of magnesium below 230 mg/day.³⁴ The Shanghai Women's Study showed a significant negative association between dietary magnesium and diabetes at magnesium intakes below 213.8 mg/day (lowest quintile median); however, these subjects were also low in calcium.²⁶ There are also studies suggesting an adult magnesium RDA of 237 mg/day could be too low. Women above the age of 45 years showed raised levels of CRP as well as significantly more components of metabolic syndrome at total magnesium intakes of \geq 250 mg/day.³⁷ Postmenopausal women in the lowest quintile of magnesium intake (low quintile median = 269.5 mg/day) showed CRP levels approaching and/or surpassing the high normal limit of 3.0 mg/L.³³ A study of middle-aged and older Chinese people reported magnesium intakes of 372 mg/day in the "normal" group and 315–332 mg/day in the "non-normal" groups associated with hypertension, impaired fasting glucose, or diabetes as well as lower erythrocytic magnesium, but no significant differences in the erythrocytic levels and dietary intakes of other minerals.⁷⁷ The Women's Health Study showed a significant negative trend for hypertension and magnesium intake when the lowest quintile median of magnesium intake was 250 mg/day,³⁷ and it has been reported that genetic variants of the magnesium channels, TRPM6 and TRPM7, increase the risk of DM2 in women whose intake of dietary magnesium is less than 250 mg/day.⁷⁸ Such studies suggest that part of the healthy adult population may have CLMD. Studies to determine the proportion of the "healthy"

adult population with CLMD are needed to further the existing knowledge of magnesium requirements and enable a true evaluation of magnesium status in the US population.

The increasing ratio of calcium-to-magnesium intake from foods

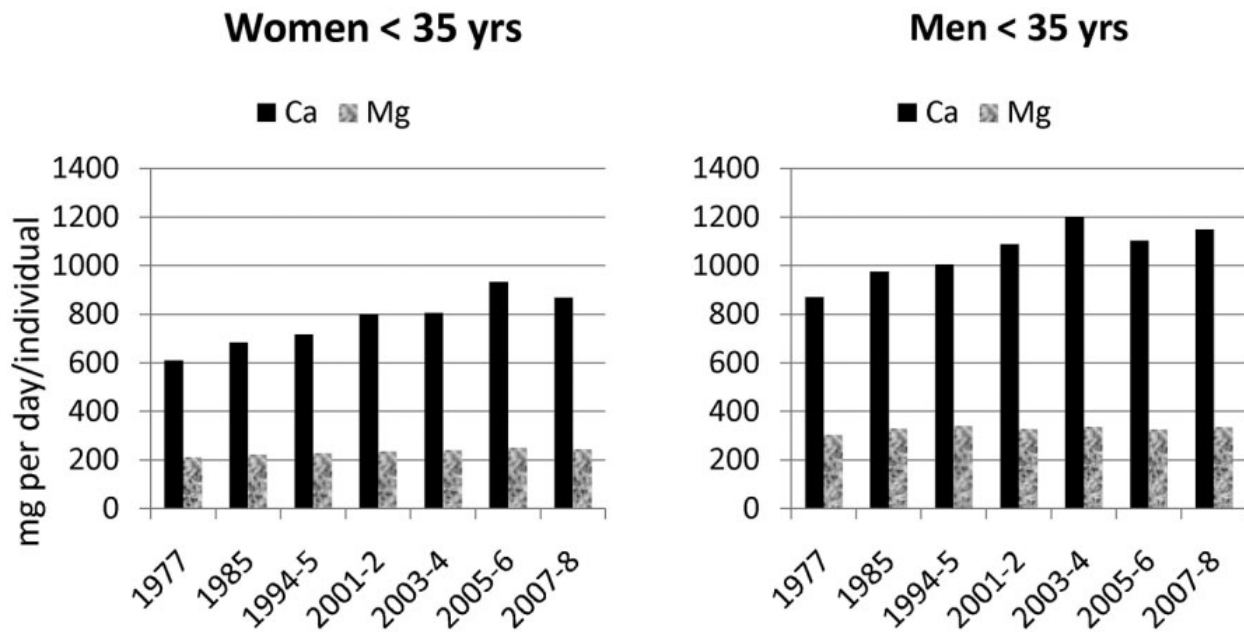
Calcium intake from food in the United States has increased over time relative to magnesium intake, according to an analysis⁷⁹ of USDA surveys since 1977.^{80–86} Between the USDA's 1977 and 2007–2008 surveys, the mean magnesium intake in young adults aged 19–34 years rose by 11–16%, while mean calcium intake in the same group rose by 32–43% (Figure 2). Similarly, the mean magnesium intake for adults aged 35–50 years rose by 12–18%, while the mean calcium intake for this group rose by 48–64% (Figure 3). Adults aged 50 years showed 11–40% increases in calcium intake from food, with increases in magnesium intake from food at -2% to +16% over the 13 years between 1994–1995 and 2007–2008 (data not shown). For all age-gender groups in this analysis, the percent increase in mean magnesium intakes compared closely with the percent increase in mean energy intakes, while the percent increase in mean calcium intakes was substantially higher (Figures 2 and 3); this suggests the increasing calcium-to-magnesium ratio comes from higher calcium intake via food selections, the rising calcium content of food, or both.

Contribution of supplement usage to magnesium and calcium-to-magnesium intake

Both food and supplement intakes of calcium and magnesium have increased in the US population over the past 15–30 years, with calcium intake increasing at a greater rate than that of magnesium. As a result, the ratio of calcium-to-magnesium intake from food appears to be increasing, a trend enhanced with mineral supplement usage. Less than 20% of the US population take magnesium supplements, mostly as MgO,⁸⁷ and in 2008, calcium sales accounted for 54% of all nutritional mineral sales, while magnesium represented only 15% of these sales.⁸⁸ While sales of magnesium supplements grew at twice the rate as sales of calcium supplements in 2008,⁸⁸ one study showed that US adults using calcium and magnesium supplements all raised their magnesium intake from below their EAR to above, yet all, and especially adult women, substantially increased their ratio of calcium-to-magnesium intake via supplement usage.⁸⁹

The increasing calcium-to-magnesium ratio and potential concerns

Recent studies have linked calcium supplementation in older women with increased risk of heart attack. In a 5-year study of 1,471 postmenopausal women (mean age 74 years), subjects randomized to calcium supplementation experienced myocardial infarction (heart attack) significantly more frequently ($P = 0.01$) than subjects receiving placebo.⁹⁰ Additional evidence comes from a meta-analysis of 11 trials representing 11,921 women aged ≥ 40 years, which showed a 27% increase ($P = 0.038$) in heart attacks in the calcium-supplemented groups (without vitamin D) compared to placebo.⁹¹ When expanded to data from 28,072 participants in the Women's Health Initiative Calcium-Vitamin D Supplementation Study, the 25% increase in heart attacks with calcium supplementation (now with or without vitamin D) was confirmed ($P = 0.004$), and the 15% higher risk of stroke/heart attack ($P = 0.009$) with calcium supplementation in the larger sample reached significance.⁹²



<u>% rise in mean intake, 1977 - 2007/8</u>		
	<u>Women</u>	<u>Men</u>
Ca, mg/day:	+43%	+32%
Mg, mg/day:	+16%	+11%
Energy, kcal/day:	+13%	+14%

Figure 2 Mean calcium (Ca) and magnesium (Mg) intakes from food, with percent increases in mean Ca, Mg, and energy intakes, 1977 through 2007–2008, US young adults aged <35 years.⁷⁹

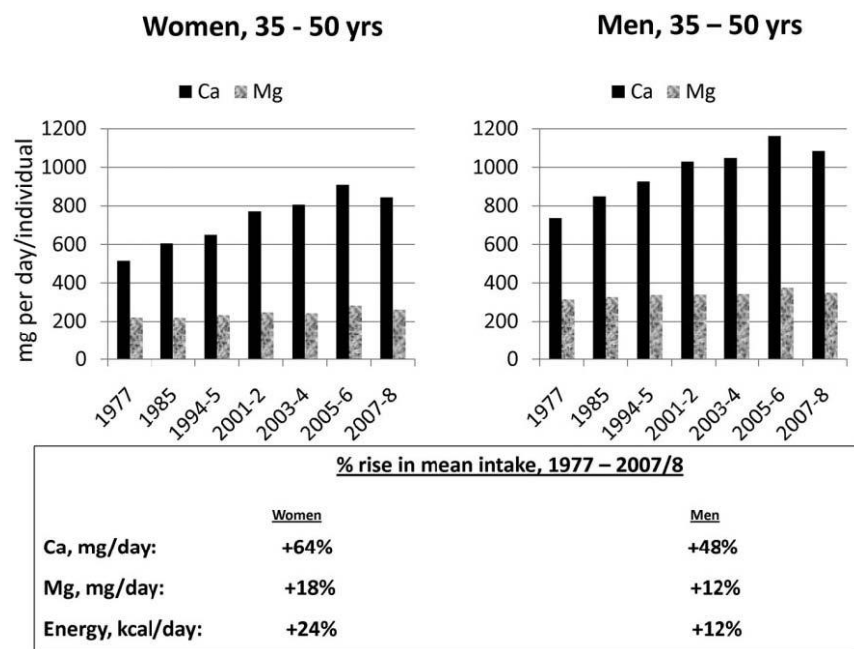


Figure 3 Mean calcium (Ca) and magnesium (Mg) intakes from food, with percent increases in mean Ca, Mg, and energy intakes, 1977 through 2007–2008, US adults aged 35–50 years.⁷⁹

Dietary magnesium was not considered in the studies performed by Bolland et al.,^{90–92} so it is not known if low magnesium status with concomitant high ratios of calcium-to-magnesium intake upon calcium supplementation may have contributed to the results. Evidence supporting the hypothesis that adequate magnesium intake may attenuate the risks associated with high calcium intakes by providing a lower calcium-to-magnesium ratio is seen in another study focusing on mortality. Kaluza et al.⁹³ found that dietary calcium intakes of 1,230 mg/day to over 1,600 mg/day were associated with a significantly lower rate of all-cause mortality than calcium intakes of less than 1,230 mg/day in a large study of men aged 45–79 years.⁹³ Calcium interaction with magnesium (and moderate ratios of calcium-to-magnesium intake, neither measured nor reported) may have been important in this recent Swedish study in which magnesium intake was not associated with all-cause, CVD, or cancer mortality.⁹³ Magnesium intakes were adequate in even the lowest tertile of magnesium intake, with subjects in the 5th percentile of magnesium intake (355 mg/day) exceeding the EAR (350 mg/day) for adult men; this led the authors to conclude that all subjects had adequate magnesium status. However, calcium intakes were slightly less than adequate (<1,230 mg calcium/day) in the 7,786 men in the lowest tertile, with the 5th-percentile of calcium intake (798 mg/day) being approximately equal to the newly established calcium EAR (800 mg/day)⁹⁴ for men under the age of 70 years and 20% below the new calcium EAR (1,000 mg/day)⁹⁴ for men ≥ 70 years. Thus, this study found that men, all with adequate magnesium status and some with inadequate calcium intake, showed lower all cause mortality as their calcium intake rose to adequate levels and beyond. This result is not surprising, as calcium is an essential nutrient necessary in adequate amounts for optimal health, nor does it suggest calcium intake is more or less important than magnesium intake in all-cause mortality. This study does show that above-adequate intake of magnesium does not lower mortality for CVD, cancer, or all cause, but it does not show whether the higher-than-adequate intakes of magnesium impacted the lower, less-than-adequate intakes of calcium or whether the ratio of calcium-to-magnesium intake was associated with mortality; this is where the calculation of individual calcium-to-magnesium ratios with statistical analysis could provide further knowledge.

Kaluza et al.⁹³ also confirm the Seelig⁷⁴ finding that above-optimal intakes of calcium (in this case >1,599 mg/day) in the face of fully adequate magnesium intakes will not cause a negative magnesium balance. This is probably not true in studies with less-than adequate magnesium intakes: Seelig⁷⁴ showed that at magnesium intake levels between 4 mg/kg/day and 10 mg/kg/day, calcium intake levels close to

800 mg/day decreased magnesium retention in men. Men with magnesium intake levels at or above 6 mg/kg/day remained in positive magnesium balance, while those with magnesium intake levels at or below 5 mg/kg/day usually moved into negative magnesium balance on calcium intakes close to current EAR levels of calcium. Thus, for studies employing close-to-adequate magnesium intakes, one might expect positive magnesium balance (and thus no negative health impacts caused by magnesium deficit) with low calcium intakes but not with calcium intakes at or higher than EAR levels.⁷⁴ However, both men and women with magnesium intakes below 4 mg/kg/day showed less negative magnesium balance with EAR levels of calcium than with lower calcium intakes.⁷⁴ These complex interactions between calcium and magnesium mean that nutrition studies measuring either magnesium or calcium without the other can produce inconsistent results due to unintended or unknown rising or falling magnesium and/or calcium balance with concomitant health outcomes. Studies can be further complicated by the fact that diets which are low in magnesium are often low in calcium as well.⁹⁵ To fully understand the relationships between magnesium and/or calcium intakes and health, study of the ratio of calcium-to-magnesium intake as well as the degrees of both magnesium and calcium adequacy are necessary.

CALCIUM-TO-MAGNESIUM RATIO IN CALCIUM ACTIVATION, INFLAMMATION, AND METABOLIC SYNDROME

The importance of the cellular calcium-to-magnesium ratio for the physiological function of several tissues has been largely elucidated by Resnick,^{96–98} who showed a strong physiological/cellular link between a rising intracellular ratio of calcium to magnesium and aspects of metabolic syndrome, including hypertension, hyperinsulinemia, insulin resistance, and left ventricular cardiac hypertrophy. Inflammatory syndrome can also be added to the effects of possible cytosolic calcium activation as a result of magnesium deficit⁹⁹ and its concomitant high calcium-to-magnesium ratio within cells.

Activation of calcium ion (Ca_{2+})-dependent signaling events occurs when intracellular levels of calcium are increased. This induces a range of downstream cascades, including the uncoupling mitochondrial electron transfer from ATP synthesis and the activation and overstimulation of enzymes such as proteases, protein kinases, and nitric oxide synthase.¹⁰⁰ In rodent studies, neuronal sources of a neuropeptide, substance P, contributed to very early pro-oxidant/pro-inflammatory changes during magnesium deficiency.¹⁰¹ Such neurogenic inflammation was systemic, affecting blood cells and cardiovascular, intestinal, and other tissues in this rat model, leading to impaired cardiac contractility similar to that seen in patients with heart failure.¹⁰¹

Mechanisms for such calcium activation occurring with magnesium depletion may be elucidated by active research of the TRPM channels. Patients with genetic primary hypomagnesemia and secondary hypocalcemia showed TRPM6 and its homologue TRPM7 to be key components of epithelial magnesium reabsorption, and TRPM7 has been characterized functionally as a constitutively active ion channel permeable for a variety of cations, including Ca_{2+} and Mg_{2+} , and regulated by intracellular concentrations of magnesium and/or magnesium nucleotide complexes.^{102,103} While TRPM6 appears to be involved mainly in regulating total body magnesium levels through the kidneys and gastrointestinal tract, TRPM7 may be more important in regulating intracellular Mg_{2+} homeostasis.⁴⁴ At physiological pH, both Ca_{2+} and Mg_{2+} bind to TRPM7, while currents for monovalent ions are inhibited.¹⁰⁴ Dysregulation of TRPM7 is associated with molecular processes that promote vascular calcification, including vascular smooth muscle cell transformation to an osteogenic phenotype. Magnesium normalized TRPM7 dysregulation and prevented calcification of vascular smooth muscle cells. Magnesium appears to negatively regulate vascular calcification and osteogenic differentiation through increased/restored TRPM7 activity and increased expression of anti-calcification proteins. These new molecular insights suggest a protective role for TRPM7/magnesium in processes associated with vascular calcification.¹⁰⁵ Additionally, it has been recently proposed via protein structural analysis that Mg_{2+} plays an active role in the Ca_{2+} -ion-dependent regulation of cellular processes by stabilizing the resting state of some calcium-binding proteins that contain the EF-hand motif, a common building block of a large family of proteins that function as intracellular Ca_{2+} receptors.¹⁰⁶

Magnesium deficiency may be a common link between stress, inflammation, and metabolic syndrome because magnesium deficiency at the cellular level can elicit calcium activation in an inappropriate response, i.e., the calcium-activated cascade is not triggered by an environmental injury or pathogen but

rather as a result of a magnesium deficit that manifests in various tissues as aspects of CVD, DM2, and other health conditions associated with low magnesium. Active research on the recently discovered TRPM channels, which regulate both calcium and magnesium ion transport and calcium binding proteins such as those with the EF-hand motif that depend upon adequate Mg_{2+} to remain “at rest,” may lead to an understanding of possible mechanisms to explain how rising calcium-to-magnesium ratios at the cellular level may be among the root causes of metabolic syndrome and its links to DM2, CVD, osteoporosis, and other diseases. Other proteins important in the cellular transport of magnesium may yet be found¹⁰⁷ in the complex dynamics of magnesium homeostasis.

It is possible that the cellular calcium activation phenomenon is part of the pathology of a dietary magnesium deficit caused by low dietary magnesium, which can be exacerbated by a high dietary calcium-to-magnesium ratio, and this inappropriate calcium activation at the cellular level can lead to DM2, CVD, or other manifestations of magnesium deficiency if the magnesium inadequacy is not corrected.

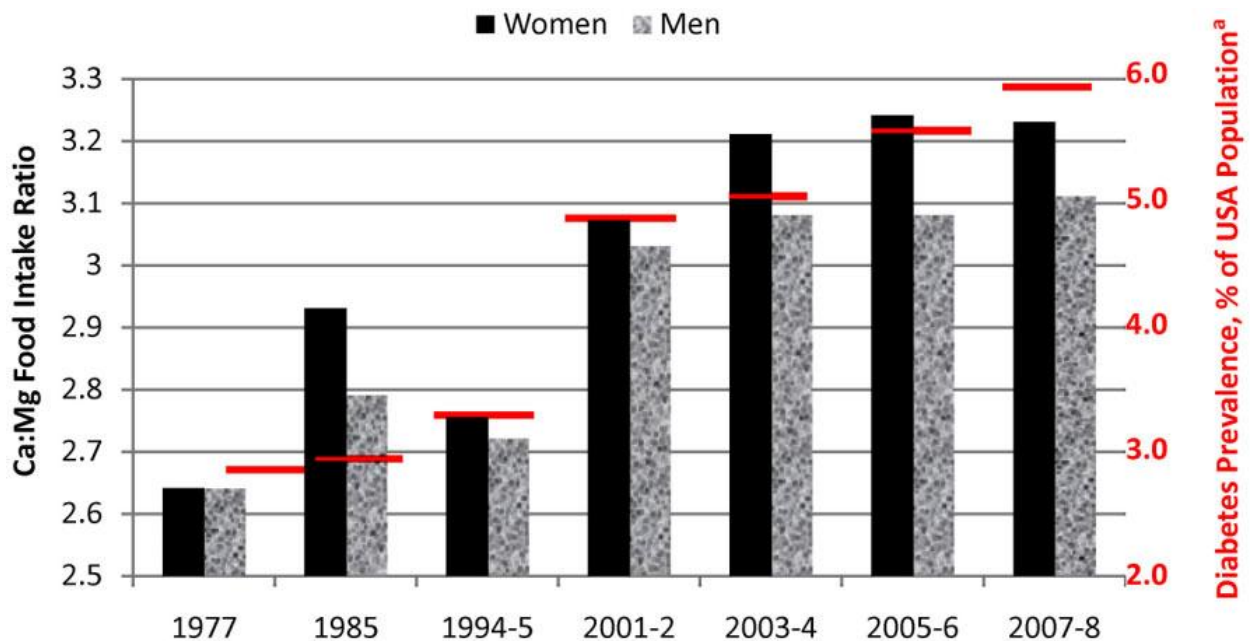


Figure 4 Dietary calcium-to-magnesium (Ca:Mg) intake ratio from foods for US adults,⁷⁹ along with prevalence of diabetes.¹⁰⁹ The 1977 and 1985 intake surveys cover adults aged 19–50 years; all other surveys cover adults aged ≥ 20 years. ^aDiabetes prevalence: Age-adjusted percentage of civilian, non-institutionalized population with diagnosed diabetes in the United States, 1980–2008, as reported by the CDC¹⁰⁹

Considering this background, the following association is intriguing and warrants further research by means of measurement of the calcium-to-magnesium ratio in physiological studies as well as in nutrient intake studies.

RELATIONSHIP BETWEEN INCREASING CALCIUM-TO-MAGNESIUM INTAKE AND PREVALENCE OF DIABETES

Because symptoms of DM2 have been associated with intracellular calcium-to-magnesium ratios,^{96–98} the relationship between the calcium-to-magnesium ratio from food intake and the incidence of DM2 is of interest. Between 1980 and 2008, the crude incidence of diagnosed DM2 in the US population increased 164%, and the age adjusted incidence rose 143%.¹⁰⁸ The rate of change in the incidence of diagnosed DM2 has not been constant; rather, the incidence remained largely unchanged in the 1980s and increased sharply in the mid-1990s through 2008, the same timeframe in which the calcium-to-

magnesium intake from foods for this population went from largely below 3.0 to largely above 3.0 (Figure 4). Proper statistical assessment of the increase in the calcium-to-magnesium ratio over the years is required to appropriately compare it with the incidence and prevalence of DM2 and to better assess the validity of this association. Informative results might also be gained by measuring and calculating the ratio of calcium-to magnesium intake as part of individual medical and dietary exams as well as research studies.

CONCLUSION

It is clear that a substantial proportion of the US population does not meet the requirement for dietary magnesium as outlined by the RDA or EAR, and the ratio of calcium-to-magnesium intake for this population is rising. The possibility that some portion of the US population, who are assumed to be healthy and fully magnesium replete, in fact have a chronic latent magnesium deficit complicates the true assessment of this population with regard to magnesium status. Health consequences need to be considered for the 48% of persons in the United States who are not meeting the EAR for dietary magnesium, many of whom are also consuming lower than optimal levels of calcium. Moreover, the health consequences of the increasing ratio of calcium-to magnesium from food should be addressed. The inclusion of serum and urinary magnesium reporting by NHANES would be beneficial. Longitudinal studies that include an assessment of initial magnesium status, prevalence of CLMD, and calcium-to-magnesium ratios in diet and/or tissues are necessary and clinical trials testing magnesium supplementation against placebo and pharmaceuticals for cardiovascular risk factors/events, DM2, and osteoporosis should be research priorities.

Acknowledgments

Declaration of interest. The authors have no relevant interests to declare.

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Appendix VI: Declining Mg concentrations in foods over time have resulted in low Mg intakes for many who consume the modern food diet

As a result of Food processing Mg losses plus declines in minerals in some high yield grains and the Mg declines in vegetables, an assumed rich source of nutritional Mg, many people consuming modern foods are not getting their daily Mg requirement from their foods ([See Figure 7](#)).

1. Mg Loss With Food Processing/Refining

The highest Mg loss in common foods is due to decreases during food processing. Refined grains, for example, lose up to 85% of whole grain Mg during processing. Seeds from which we extract oil have all their Mg removed in the process. Refining sugar from beets or cane has the same effect. These and other low Mg food components are used to formulate modern processed foods. The result: a low Mg diet termed the modern processed food diet. (See <http://www.magnesiumeducation.com/whole-vs-refined-food>)

2. Mg Declines in Modern Food Crops

In addition to losses of Mg due to processing and refining, grains of the Green Revolution (begun in the 1960s) show declining mineral contents, among them Mg in whole wheat grain ([See Figures 8 & 9](#)). In addition, analyses of modern and historic British and American food tables have shown that Mg concentration of some vegetables may have declined during the last 50+ years ([See Figure 9](#)).

3. Other Pressures that Lower Mg Intakes

Additional pressures toward inadequate Mg intake with foods is the growing trend of consuming deionized water which has all Mg removed and the possible impact of pesticides, some of which are chelators (Metal binding) of Mg and Ca (Cakmak et al., 2009).

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Rosanoff A 2012 Changing crop magnesium concentrations: impact on human health. Plant Soil. ([See full text](#))

Rosanoff A, Weaver C M and Rude R K 2012 Suboptimal magnesium status in the United States: are the health consequences underestimated? Nutr Rev 70, 153-164. ([See full text](#))

Cakmak I, Yazici A, Tutus Y and Ozturk L 2009 Glyphosate reduced seed and leaf concentrations of calcium, manganese, magnesium, and iron in non-glyphosate resistant soybean. Europ. J. Agronomy 31, 114-119. http://stopogm.net/webfm_send/54

Appendix VII: Mg Therapy – Things to Consider

1. Who needs to use Mg supplements?

Given the facts that modern food diets are low in Mg, rising in Ca, and the modern lifestyle can raise Mg requirements, it is a good idea for most (if not all) people consuming a modern processed food diet to consider using Mg supplements.

2. Things to know about using Oral Mg therapy (Mg Supplements) for CVD and/or CVD risk factors

Monitoring oral Mg therapy by assessing Mg status can be difficult. Serum Mg can be a useful tool. Some clinical laboratories erroneously consider serum Mg levels lower than 0.85 mmol/L (as recommended by Dr. Elin, which is the same as 2.07 mg/dl and 1.70= mEq/L using other “units”) to be “normal” but research shows serum Mg levels lower than these to be within the “low” Mg range and indicative of a Mg deficit status. Many physicians are not aware of research on Chronic Latent Magnesium Deficit (CLMD) – a condition in which serum Mg appears in the “normal” range but the patient actually is in a marginal Mg status (Elin, 2010; Rosanoff et al., 2012). In such cases, a Mg retention test is usually necessary and available in most clinical laboratories.

When correcting a low Mg status, serum Mg may actually decline during the first few months of oral Mg therapy. Oral Mg therapy should be given for at least 6 months in these cases. ([See Figures 10a and 10b.](#))

Hypertension medications have been shown to enhance the effect of oral Mg therapy in the treatment of high blood pressure. (Rosanoff, 2010)

3. There are many forms of Mg supplements –

Inorganic forms such as magnesium oxide and magnesium chloride as well as

Organic forms such as magnesium citrate, magnesium malate, magnesium lactate, etc.

And amino acid chelate forms such as magnesium aspartate or magnesium tartarate.

In general, the organic forms seem to absorb to a greater degree in the GI tract than do the inorganic forms. Some people can only take small doses of oral Mg therapy (Mg supplements) without GI distress while others can easily take 1,000 mg per day without any GI symptoms. Breaking up the daily dose can be helpful in maximizing Mg intake and absorption while minimizing any GI distress. Selecting a form of Mg which is easily individualized as to dose is warranted since an individual’s tolerance can change as the Mg therapy becomes effective.

4. Importance of total nutritional adequacy and balance

Is low nutritional Mg the only cause of rising CVD rates? In 1975, Dr. Leslie M. Klevay introduced the zinc/copper hypothesis of coronary heart disease, linking high zinc/copper ratios, sometimes derived

from low levels of dietary copper, as a factor in the etiology of coronary heart disease (Klevay, 1975). As has Mg, both copper and zinc have declined in wheat grain since the 1960s (Fan et al., 2008). All essential nutrients (<http://www.magnesiumeducation.com/essential-nutrients-for-humans>), in adequate and balanced amounts are necessary for optimal health.

References – ([See Appendix VII Highlighted abstracts for these reference](#))

Elin, R. J. (2010). "Assessment of magnesium status for diagnosis and therapy." *Magnes Res* **23**(4): 194-198.

Rosanoff, A., et al. (2012). "Suboptimal magnesium status in the United States: are the health consequences underestimated?" *Nutrition Reviews* **70**(3): 153-164.

Rosanoff, A. (2010). "Magnesium supplements may enhance the effect of antihypertensive medications in stage 1 hypertensive subjects." *Magnes Res* **23**(1): 27-40.

Klevay, L. M. (1975). "Coronary heart disease: the zinc/copper hypothesis." *Am J Clin Nutr* **28**(7): 764-774.

Fan, M.-S., et al. (2008). "Evidence of decreasing mineral density in wheat grain over the last 160 years." *Journal of Trace Elements in Medicine and Biology* **22**(4): 315-324.

Appendix VII – highlighted abstracts for references

Elin, R. J. (2010). "Assessment of magnesium status for diagnosis and therapy." *Magnes Res* **23**(4): 194-198.

Magnesium is an essential element needed for health. Even though only 1% of the total body magnesium is present in blood, the **serum magnesium** concentration (**SMC**) is the predominant test used by medicine to assess magnesium status in patients. The traditional method to establish a reference interval for the SMC is flawed by the large number of "normal" individuals who have a subtle chronic negative magnesium balance due to a significant decrease in magnesium intake over the past century. Evidence-based medicine should be used to establish the appropriate lower limit of the reference interval for health and I **recommend 0.85 mmol/L based on current literature**. **The decrease in magnesium in the diet has led to chronic latent magnesium deficiency in a large number of people since their SMC is still within the reference interval due to primarily the bone magnesium supplementing the SMC. These individuals need adjustment of their diet or magnesium supplementation to achieve a normal magnesium status for health.**

Rosanoff, A., et al. (2012). "Suboptimal magnesium status in the United States: are the health consequences underestimated?" *Nutr Rev* **70**(3): 153-164. ([See full text](#))

In comparison with calcium, magnesium is an "orphan nutrient" that has been studied considerably less heavily. Low magnesium intakes and blood levels have been associated with type 2 diabetes, metabolic syndrome, elevated C-reactive protein, hypertension, atherosclerotic vascular

disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer. Almost half (48%) of the US population consumed less than the required amount of magnesium from food in 2005-2006, and the figure was down from 56% in 2001-2002. Surveys conducted over 30 years indicate rising calcium-to-magnesium food-intake ratios among adults and the elderly in the United States, excluding intake from supplements, which favor calcium over magnesium. The prevalence and incidence of type 2 diabetes in the United States increased sharply between 1994 and 2001 as the ratio of calcium-to-magnesium intake from food rose from <3.0 to >3.0. **Dietary Reference Intakes determined by balance studies may be misleading if subjects have chronic latent magnesium deficiency but are assumed to be healthy.** Cellular magnesium deficit, perhaps involving TRPM6/7 channels, elicits calcium-activated inflammatory cascades independent of injury or pathogens. Refining the magnesium requirements and understanding how low magnesium status and rising calcium-to-magnesium ratios influence the incidence of type 2 diabetes, metabolic syndrome, osteoporosis, and other inflammation-related disorders are research priorities.

Rosanoff, A. (2010). "Magnesium supplements may enhance the effect of antihypertensive medications in stage 1 hypertensive subjects." *Magnes Res* **23**(1): 27-40.

Comprehensive analytical review of 44 human studies in 43 publications of oral Magnesium (Mg) therapy for hypertension (HT) shows Mg supplements may enhance the blood-pressure (BP) lowering effect of anti-hypertensive medications (medications) in Stage 1 HT subjects. 9 studies conducted on **subjects treated with medications continuously \geq 6 months (with \leq 2-wk washout) resulted in significant decreases in both SBP and DBP with oral Mg supplements as low as 230 mg (10 mmol) per day. Twice this oral Mg dose, i.e. 460 mg/day, was required to significantly lower both SBP and DBP in 18 of 22 studies conducted on Stage 1 HT subjects either treatment-naïve or with their medication use interrupted \geq 4 weeks within 6 months pre-study.** Of the 4 remaining studies showing no BP change at these high Mg doses, two had large placebo effect, a third one had significant baseline discrepancies between Mg-test and placebo groups, and the fourth showed a significant decrease in DBP but not SBP. Thirteen studies on normotensive subjects, both treated and untreated with medications, showed no significant BP lowering effect with oral Mg therapy up to 25 mmol/day (607 mg). Conclusions: Mg supplements above RDA may be necessary to significantly lower high blood pressure in Stage I HT unless subjects have been continuously treated with anti-HT medications \geq 6 months. Such medication use may lower by half the oral Mg dose needed to significantly decrease high blood pressure. Oral Mg therapy may have no effect in studies with normotensive subjects. Study of oral Mg therapy for severe or complicated hypertension has been neglected. **Often the first cardiovascular risk factor to present, high blood pressure may be an early opportunity to correct poor Mg status and its possible complications including cardiovascular disease,** respiratory diseases, and type 2 diabetes. Such preventive potential encourages quantification of these findings and testing of these hypotheses with a meta-analysis using categories elucidated by this preliminary study and finally would warrant a call for a prospective study.

Klevay, L. M. (1975). "Coronary heart disease: the zinc/copper hypothesis." Am J Clin Nutr **28**(7): 764-774.

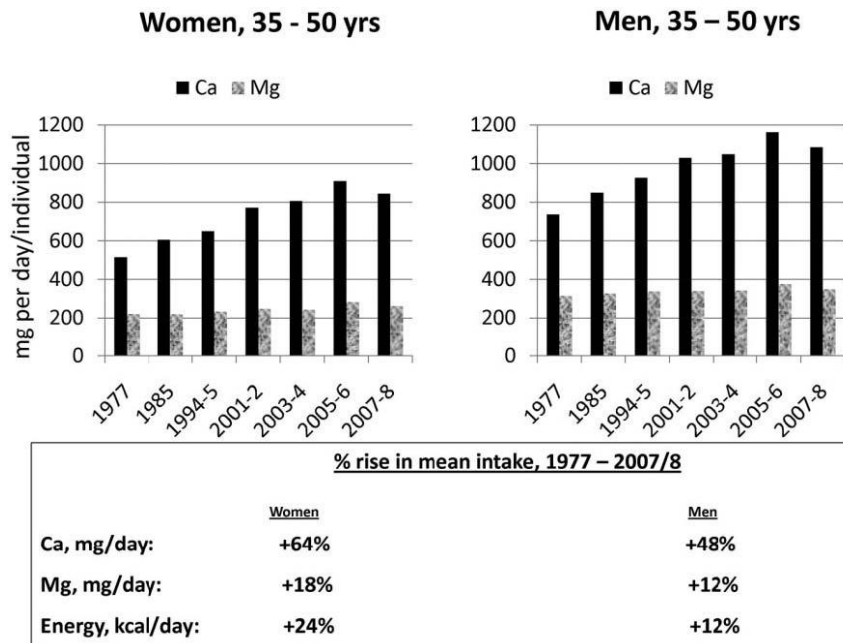
Epidemiologic and metabolic data are consonant with the hypothesis that a metabolic imbalance in regard to zinc and copper is a major factor in the etiology of coronary heart disease. This metabolic imbalance is either a relative or an absolute deficiency of copper characterized by a high ratio of zinc to copper. The imbalance results in hypercholesterolemia and increased mortality due to coronary heart disease. The imbalance can occur due to the amounts of zinc and copper in human food, to lack of protective substances in food or drinking water and to alterations in physiological status that produce adverse changes in the distribution of zinc and copper in certain important organs. Because no other agent, with the possible exception of cholesterol, has been related so closely to risk, the ratio of zinc to copper may be the preponderant factor in the etiology of coronary heart disease.

Fan, M.-S., et al. (2008). "Evidence of decreasing mineral density in wheat grain over the last 160 years " Journal of Trace Elements in Medicine and Biology **22**(4): 315-324.

Wheat is an important source of minerals such as iron, zinc, copper and magnesium in the UK diet. The dietary intake of these nutrients has fallen in recent years because of a combination of reduced energy requirements associated with sedentary lifestyles and changes in dietary patterns associated with lower micronutrient density in the diet. Recent publications using data from food composition tables indicate a downward trend in the mineral content of foods and it has been suggested that intensive farming practices may result in soil depletion of minerals. The aim of our study was to evaluate changes in the mineral concentration of wheat using a robust approach to establish whether trends are due to plant factors (e.g. cultivar, yield) or changes in soil nutrient concentration. The mineral concentration of archived wheat grain and soil samples from the Broadbalk Wheat Experiment (established in 1843 at Rothamsted, UK) was determined and trends over time examined in relation to cultivar, yield, and harvest index. The concentrations of zinc, iron, copper and magnesium remained stable between 1845 and the mid 1960s, but since then have decreased significantly, which coincided with the introduction of semi-dwarf, high-yielding cultivars. In comparison, the concentrations in soil have either increased or remained stable. Similarly decreasing trends were observed in different treatments receiving no fertilizers, inorganic fertilizers or organic manure. Multiple regression analysis showed that both increasing yield and harvest index were highly significant factors that explained the downward trend in grain mineral concentration.

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tion experienced myocardial infarction (heart attack) (without vitamin D) compared to placebo.⁹¹ When significantly more frequently ($P = 0.01$) than subjects expanded to data from 28,072 participants in the receiving placebo.⁹⁰ Additional evidence comes from a Women’s Health Initiative Calcium-Vitamin D Supplement meta-analysis of 11 trials representing 11,921 women mentation Study, the 25% increase in heart attacks with aged \diamond 40years, which showed a 27% increase ($P = 0.038$) calcium supplementation (now with or without vitamin in heart attacks in the calcium-supplemented groups D) was confirmed ($P = 0.004$), and the 15% higherriskof



Mean calcium (Ca) and magnesium (Mg) intakes from food, with percent increases in mean Ca, Mg, and energy intakes, 1977 through 2007–2008, US adults aged 35–50 years. ⁷⁹

stroke/heart attack ($P = 0.009$) with calcium supplementation in the larger sample reached significance.⁹²

Dietary magnesium was not considered in the studies performed by Bolland et al.,⁹⁰⁻⁹² so it is not known if low magnesium status with concomitant high ratios of calcium-to-magnesium intake upon calcium supplementation may have contributed to the results. Evidence supporting the hypothesis that adequate magnesium intake may attenuate the risks associated with high calcium intakes by providing a lower calcium-to-magnesium ratio is seen in another study focusing on mortality. Kaluza et al.⁹³ found that dietary calcium intakes of 1,230 mg/day to over 1,600 mg/day were associated with a significantly lower rate of all-cause mortality than calcium intakes of less than 1,230 mg/day in a large study of men aged 45–79 years.⁹³ Calcium interaction with magnesium (and moderate ratios of calcium-to-magnesium intake, neither measured nor reported) may have been important in this recent Swedish study in which magnesium intake was not associated with all-cause, CVD, or cancer mortality.⁹³ Magnesium intakes were adequate in even the lowest tertile of magnesium intake, with subjects in the 5th-percentile of magnesium intake (355 mg/day) exceeding the EAR (350 mg/day) for adult men; this led the authors to conclude that all subjects had adequate magnesium status. However, calcium intakes were slightly less than adequate (<1,230 mg calcium/day) in the 7,786 men in the lowest tertile, with the 5th-percentile of calcium intake (798 mg/day) being approximately equal to the newly established calcium EAR (800 mg/day)⁹⁴ for men under the age of 70 years and 20% below the new calcium EAR (1,000 mg/day)⁹⁴ for men \geq 70 years. Thus, this study found that men, all with adequate magnesium status and some with inadequate calcium intake, showed lower all-cause mortality as their calcium intake rose to adequate levels and beyond. This result is not surprising, as calcium is an essential nutrient necessary in adequate amounts for optimal health, nor does it suggest calcium intake is more or less important than magnesium intake in all-cause mortality. This study does show that above-adequate intake of magnesium does not lower mortality for CVD, cancer, or all cause, but it does not show whether the higher-than-adequate intakes of magnesium impacted the lower, less-than-adequate intakes of calcium or whether the ratio of calcium-to-magnesium intake was associated with mortality; this is where the calculation of individual calcium-to-magnesium ratios with statistical analysis could provide further knowledge.

Kaluza et al.⁹³ also confirm the Seelig⁷⁴ finding that above-optimal intakes of calcium (in this case >1,599 mg/day) in the face of fully adequate magnesium intakes will not cause a negative magnesium balance. This is probably not true in studies with less-than-adequate magnesium intakes:

Seelig⁷⁴ showed that at

magnesium intake levels between 4 mg/kg/day and 10 mg/kg/day, calcium intake levels close to 800 mg/day decreased magnesium retention in men. Men with magnesium intake levels at or above 6 mg/kg/day remained in positive magnesium balance, while those with magnesium intake levels at or below 5 mg/kg/day usually moved into negative magnesium balance on calcium intakes close to current EAR levels of calcium. Thus, for studies employing close-to-adequate magnesium intakes, one might expect positive magnesium balance (and thus no negative health impacts caused by magnesium deficit) with low calcium intakes but not with calcium intakes at or higher than EAR levels.⁷⁴ However, both men and women with magnesium intakes below 4 mg/kg/day showed less negative magnesium balance with EAR levels of calcium than with lower calcium intakes.⁷⁴ These complex interactions between calcium and magnesium mean that nutrition studies measuring either magnesium or calcium without the other can produce inconsistent results due to unintended or unknown rising or falling magnesium and/or calcium balance with concomitant health outcomes. Studies can be further complicated by the fact that diets which are low in magnesium are often low in calcium as well.⁹⁵ To fully understand the relationships between magnesium and/or calcium intakes and health, study of the ratio of calcium to magnesium intakes as well as the degrees of both magnesium and calcium adequacy are necessary.

CALCIUM-TO-MAGNESIUM RATIO IN CALCIUM ACTIVATION, INFLAMMATION, AND METABOLIC SYNDROME

The importance of the cellular calcium-to-magnesium ratio for the physiological function of several tissues has been largely elucidated by Resnick,⁹⁶⁻⁹⁸ who showed a strong physiological/cellular link between a rising intracellular ratio of calcium to magnesium and aspects of metabolic syndrome, including hypertension, hyperinsulinemia, insulin resistance, and left ventricular cardiac hypertrophy. Inflammatory syndrome can also be added to the effects of possible cytosolic calcium activation as a result of magnesium deficit⁹⁹ and its concomitant high calcium-to-magnesium ratio within cells.

Activation of calcium ion (Ca^{2+})-dependent signaling events occurs when intracellular levels of calcium are increased. This induces a range of downstream cascades, including the uncoupling of mitochondrial electron transfer from ATP synthesis and the activation and overstimulation of enzymes such as proteases, protein kinases, and nitric oxide synthase.¹⁰⁰ In rodent studies, neuronal sources of a neuropeptide, substance P, contributed to very early pro-oxidant/proinflammatory changes during magnesium deficiency.¹⁰¹ Such neurogenic inflammation

was systemic, affecting blood cells and cardiovascular, intestinal, and other tissues in this rat model, leading to impaired cardiac contractility similar to that seen in patients with heart failure.

Mechanisms for such calcium activation occurring with magnesium depletion may be elucidated by active research of the TRPM channels. Patients with genetic primary hypomagnesemia and secondary hypocalcemia showed TRPM6 and its homologue TRPM7 to be key components of epithelial magnesium reabsorption, and TRPM7 has been characterized functionally as a constitutively active ion channel permeable for a variety of cations, including Ca^{2+} and Mg^{2+} , and regulated by intracellular concentrations of magnesium and/or magnesium-nucleotide complexes. While TRPM6 appears to be involved mainly in regulating total body magnesium levels through the kidneys and gastrointestinal tract, TRPM7 may be more important in regulating intracellular Mg^{2+} homeostasis. At physiological pH, both Ca^{2+} and Mg^{2+} bind to TRPM7, while currents for monovalent ions are inhibited. Dysregulation of TRPM7 is associated with molecular processes that promote vascular calcification, including vascular smooth muscle cell transformation to an osteogenic phenotype. Magnesium normalized TRPM7 dysregulation and prevented calcification of vascular smooth muscle cells. Magnesium appears to negatively regulate vascular calcification and osteogenic differentiation through increased/restored TRPM7 activity and increased expression of anticalcification proteins. These new molecular insights suggest a protective role for TRPM7/magnesium in processes associated with vascular calcification. Additionally, it has been recently proposed via protein structural analysis that Mg^{2+} plays an active role

in the Ca^{2+} -ion-dependent regulation of cellular processes by stabilizing the resting state of some calcium-binding proteins that contain the EF-hand motif, a common building block of a large family of proteins that function as intracellular Ca^{2+} receptors.

Magnesium deficiency may be a common link between stress, inflammation, and metabolic syndrome because magnesium deficiency at the cellular level can elicit calcium activation in an inappropriate response, i.e., the calcium-activated cascade is not triggered by an environmental injury or pathogen but rather as a result of a magnesium deficit that manifests in various tissues as aspects of CVD, DM2, and other health conditions associated with low magnesium. Active research on the recently discovered TRPM channels, which regulate both calcium and magnesium ion transport and calcium-binding proteins such as those with the EF-hand motif that depend upon adequate Mg^{2+} to remain "at rest," may lead to an understanding of possible mechanisms to explain how rising calcium-to-magnesium ratios at the cellular level may be among the root causes of metabolic syndrome and its links to DM2, CVD, osteoporosis, and other diseases. Other proteins important in the cellular transport of magnesium may yet be found in the complex dynamics of magnesium homeostasis.

It is possible that the cellular calcium activation phenomenon is part of the pathology of a dietary magnesium deficit caused by low dietary magnesium, which can be exacerbated by a high dietary calcium-to-magnesium ratio, and this inappropriate calcium activation at the cellular level can lead to DM2, CVD, or other manifestations of magnesium deficiency if the magnesium inadequacy is not corrected.

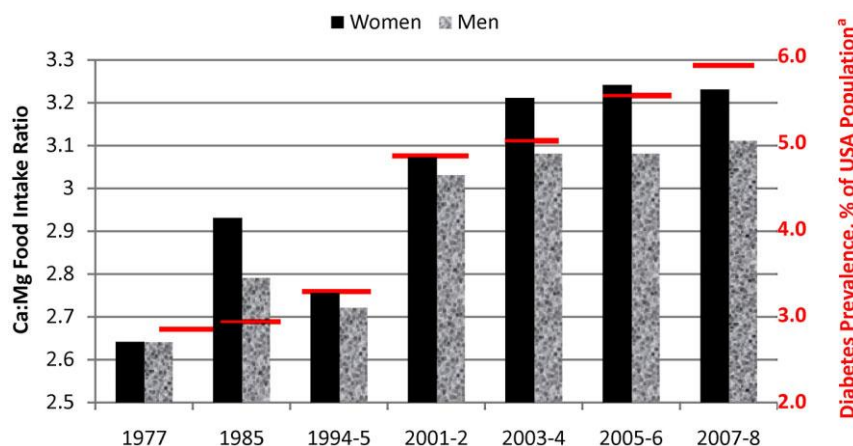


Figure 4 Dietary calcium-to-magnesium (Ca:Mg) intake ratio from foods for US adults, along with prevalence of diabetes. The 1977 and 1985 intake surveys cover adults aged 19–50 years; all other surveys cover adults aged ≥20 years. Diabetes prevalence: Age-adjusted percentage of civilian, noninstitutionalized population with diagnosed diabetes in the United States, 1980–2008, as reported by the CDC.

Considering this background, the following association is intriguing and warrants further research by means of measurement of the calcium-to-magnesium ratio in physiological studies as well as in nutrient intake studies.

RELATIONSHIP BETWEEN INCREASING CALCIUM-TO-MAGNESIUM INTAKE AND PREVALENCE OF DIABETES

Because symptoms of DM2 have been associated with intracellular calcium-to-magnesium ratios,⁹⁶⁻⁹⁸ the relationship between the calcium-to-magnesium ratio from food intake and the incidence of DM2 is of interest. Between 1980 and 2008, the crude incidence of diagnosed DM2 in the US population increased 164%, and the age-adjusted incidence rose 143%.¹⁰⁸ The rate of change in the incidence of diagnosed DM2 has not been constant; rather, the incidence remained largely unchanged in the 1980s and increased sharply in the mid-1990s through 2008, the same timeframe in which the calcium-to-magnesium intake from foods for this population went from largely below 3.0 to largely above 3.0 (Figure 4). Proper statistical assessment of the increase in the calcium-to-magnesium ratio over the years is required to appropriately compare it with the incidence and prevalence of DM2 and to better assess the validity of this association. Informative results might also be gained by measuring and calculating the ratio of calcium-to-magnesium intake as part of individual medical and dietary exams as well as research studies.

CONCLUSION

It is clear that a substantial proportion of the US population does not meet the requirement for dietary magnesium as outlined by the RDA or EAR, and the ratio of calcium-to-magnesium intake for this population is rising. The possibility that some portion of the US population, who are assumed to be healthy and fully magnesium replete, in fact have a chronic latent magnesium deficit complicates the true assessment of this population with regard to magnesium status. Health consequences need to be considered for the 48% of persons in the United States who are not meeting the EAR for dietary magnesium, many of whom are also consuming lower than optimal levels of calcium. Moreover, the health consequences of the increasing ratio of calcium-to-magnesium from food should be addressed. The inclusion of serum and urinary magnesium reporting by NHANES would be beneficial. Longitudinal studies that include an assessment of initial magnesium status, prevalence of CLMD, and calcium-to-magnesium ratios in diet and/or tissues are necessary and clinical trials testing magnesium supplementation against placebo and phar-

maceuticals for cardiovascular risk factors/events, DM2, and osteoporosis should be research priorities.

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Declaration of interest. The authors have no relevant interests to declare.

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Requirement (EAR) for magnesium, i.e., the average daily amount deemed necessary for healthy individuals, is 330mg/day for young adult males and 255mg/day for young adult females, increasing to 350mg/day and 265mg/day, respectively, for men and women over 30 years of age.¹² Currently, almost half (48%) of the entire US population does not meet the EAR for

magnesium from food consumed,⁶ but this does not appear to be a static situation: This estimate is down from 56% for the same calculation using NHANES 2001–2002 food intake data.⁷¹

Table 1 shows the percentage of various US age-gender groups \diamond 9 years of age who consumed less than the EAR for magnesium from food, using the same calculations of NHANES data from 2001–2002,⁷¹ 2003–2004,⁷² and 2005–2006.⁶ This calculation for 2007–2008 intake data is not yet available. Only males aged 9–13 years show a possible increase in the percent inadequacy of magnesium intake from food, from 14% in 2001–2002 to 22% in 2005–2006; all other male age groups between 14 and 70 years show a possible decrease in the percent inadequacy, from 55–78% collectively in 2001–2002 down to 45–68% collectively in 2005–2006. Among elderly males \diamond 71 years, no change was observed from the high level of 80% who consumed less than the EAR for magnesium from food. These possible trends have not been tested statistically. For females, Table 1 shows a possible decrease in magnesium inadequacy for girls aged 9–13 years (from 44% in 2001–2002 to 30% in 2005–2006) and for all age groups \diamond 31 years, from 64–82% in 2001–2002 to 48–70% in 2005–2006. Females in the