

Magnesium intake and risk of type 2 diabetes: a meta-analysis

■ S. C. Larsson & A. Wolk

From the Division of Nutritional Epidemiology, National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Abstract. Larsson SC, Wolk A (National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden). Magnesium intake and risk of type 2 diabetes: a meta-analysis. *J Intern Med* 2007; **262**: 208–214.

Objective. To assess the association between magnesium intake and risk of type 2 diabetes.

Design. Meta-analysis of prospective cohort studies.

Data Sources. We retrieved studies published in any language by systematically searching MEDLINE from 1966 to February 2007 and by manually examining the references of the original articles.

Study Selection. We included prospective cohort studies reporting relative risks with 95% confidence intervals for the association between magnesium intake and incidence of type 2 diabetes.

Results. The seven identified cohort studies of magnesium intake [from foods only ($n = 4$) or from foods

and supplements combined ($n = 3$)] and incidence of type 2 diabetes included 286 668 participants and 10 912 cases. All but one study found an inverse relation between magnesium intake and risk of type 2 diabetes, and in four studies the association was statistically significant. The overall relative risk for a 100 mg day⁻¹ increase in magnesium intake was 0.85 (95% CI, 0.79–0.92). Results were similar for intake of dietary magnesium (RR, 0.86; 95% CI, 0.77–0.95) and total magnesium (RR, 0.83; 95% CI, 0.77–0.89). There was no evidence of publication bias ($P = 0.99$).

Conclusions. Magnesium intake was inversely associated with incidence of type 2 diabetes. This finding suggests that increased consumption of magnesium-rich foods such as whole grains, beans, nuts, and green leafy vegetables may reduce the risk of type 2 diabetes.

Keywords: cohort studies, diabetes, magnesium, meta-analysis.

Introduction

Over the last decades, there has been a rapid increase in the prevalence of type 2 diabetes in parallel with the obesity epidemic [1]. Although obesity is the strongest risk factor for type 2 diabetes, evidence is mounting that certain foods and dietary factors may be associated with this disease [2]. In particular, high consumption of whole grains, beans, nuts, fruits and vegetables has been related to a reduced risk of type 2 diabetes [2]. These foods are rich sources of

magnesium, a trace mineral involved in over 300 enzymatic reactions in the body [3]. Magnesium is an essential cofactor for multiple enzymes involved in glucose metabolism and is hypothesized to play a role in glucose homeostasis, insulin action and in the development of type 2 diabetes [4–6]. Studies in animals have shown that a diet low in magnesium leads to impaired insulin secretion and action [7] and that magnesium supplementation lowers the incidence of type 2 diabetes [8]. In humans, several experimental

studies [9–13], but not all [14, 15], have suggested that magnesium supplementation has beneficial effects on glucose metabolism, insulin action and/or insulin sensitivity. In addition, cross-sectional studies have found an inverse association between magnesium intake and fasting insulin concentrations [16–19], a good marker of insulin resistance. In the Atherosclerosis Risk in Communities (ARIC) Study, a dose-response inverse relation between serum magnesium concentrations and the incidence of type 2 diabetes was observed amongst white participants [20]. The ARIC Study [20] did not find an association with dietary magnesium intake. However, several subsequent large prospective cohort studies have reported a statistically significant reduction in risk of type 2 diabetes associated with increased magnesium intake [21–23].

The purpose of this study was to summarize the evidence from cohort studies of the association between magnesium intake and risk of type 2 diabetes following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analyses of observational studies [24].

Methods

Study selection

We conducted a literature search of MEDLINE (from 1966 to February 2007) using the search term *magnesium* combined with *diabetes*. We also examined the reference lists of the retrieved articles. No language restrictions were imposed.

Studies were included if they met the following criteria: (i) presented original data from prospective cohort studies; (ii) the exposure of interest was intake of magnesium from foods (dietary) or foods and supplements combined (total); (iii) the outcome of interest was incidence of type 2 diabetes; and (iv) they provided relative risks (RR) with 95% confidence intervals (CI). We identified seven cohort studies [19–23, 25] (one article presented results from two separate cohorts [22]), which all provided the necessary data to be used in the meta-analysis.

Data extraction

Information on study location, participant characteristics, sample size, assessment of type 2 diabetes, adjustment for potential confounders and RR estimates with 95% CIs was abstracted independently by two investigators. We used the most fully adjusted RRs for all studies except for the study by Kao *et al.* [20]; for that study, we used the reported RRs without adjustment for fasting glucose and insulin levels to avoid overadjustment.

Statistical analysis

We examined the dose-response relationship between magnesium intake and risk of type 2 diabetes. Only one study had analysed the magnesium intake as a continuous variable [25]. For the other studies (where categories were used), we estimated a RR for a 100 mg d⁻¹ increase in magnesium intake by regressing the natural log RRs according to magnesium intake categories on the median intake in each category. This was performed using the method described by Greenland and Longnecker [26, 27] which takes into account that the level-specific RRs are correlated. Overall RR estimates were obtained from the DerSimonian and Laird random-effects model [28] applied to the study-specific linear trends.

We used the Q and I^2 statistics [29] to examine statistical heterogeneity amongst the studies included in this meta-analysis. I^2 is the proportion of total variation contributed by between-study variation [29]. Publication bias was evaluated with the Egger's regression asymmetry test [30]. All statistical analyses were performed using STATA, version 9.0 (StataCorp, College Station, TX, USA).

Results

The seven cohort studies of magnesium intake and type 2 diabetes [19–23, 25] (one article presented results from two separate cohorts [22]), involved a total of 286 668 participants and 10 912 incident cases. Six studies were conducted in the United States and one in Australia (Table 1). Two studies included

Table 1 Characteristics of cohort studies of magnesium intake and type 2 diabetes

| Study [Ref.] | Country; study name | Participants; mean follow-up | No. of cases | Type 2 diabetes assessment | Adjusted RR (95% CI) ^a | Adjustments |
|---|--|--|--------------|---|---|---|
| Kao <i>et al.</i> , 1999 [20] | United States; Atherosclerosis Risk in Communities Study | 11 896 men and women aged 45–64 years; 6 years | 1106 | Glucose levels, use of diabetic medication, and self-report | Dietary magnesium 0.98 (0.57–1.72) (black participants) 1.08 (0.78–1.49) (white participants) | Age, sex, education, family history, BMI, WHR, sports index, diuretic use, intakes of alcohol, calcium, and potassium |
| Meyer <i>et al.</i> , 2000 [21] | United States; Iowa Women's Health Study | 35 988 women aged 55–69 years; 6 years | 1141 | Self-report | Dietary magnesium 0.67 (0.55–0.82) | Age, education, smoking, BMI, WHR, physical activity, intakes of total energy, alcohol, whole grains and cereal fibre |
| Lopez-Ridaura <i>et al.</i> , 2004 [22] | United States; Health Professionals' Follow-up Study | 42 872 men aged 40–75 years; 11 years | 1333 | Confirmed self-report | Total magnesium 0.72 (0.58–0.89) | Age, family history, hypertension, hypercholesterolemia, smoking, BMI, physical activity, intakes of total energy, alcohol, glycemic load, polyunsaturated fats, trans fatty acid, processed meat and cereal fibre |
| Lopez-Ridaura <i>et al.</i> , 2004 [22] | United States; Nurses' Health Study | 85 060 women aged 30–55 years; 17 years | 4085 | Confirmed self-report | Total magnesium 0.73 (0.65–0.82) | Age, family history, hypertension, hypercholesterolemia, smoking, BMI, physical activity, intakes of total energy, alcohol, glycemic load, polyunsaturated fats, trans fatty acid, processed meat, and cereal fibre |
| Song <i>et al.</i> , 2004 [19] | United States; Women's Health Study | 38 025 women aged ≥ 45 years; 6 years | 918 | Confirmed self-report | Dietary magnesium 0.88 (0.71–1.10) Total magnesium 0.89 (0.71–1.10) | Age, family history, smoking, BMI, physical activity, intakes of total energy and alcohol |
| Hodge <i>et al.</i> , 2004 [25] | Australia; Melbourne Collaborative Cohort Study | 31 641 men and women aged 40–69 years; 4 years | 365 | Confirmed self-report | Dietary magnesium 0.73 (0.51–1.04) ^b | Age, sex, education, country of birth, family history, BMI, WHR, weight change, physical activity, intakes of total energy and alcohol |
| van Dam <i>et al.</i> , 2006 [23] | United States; Black Women's Health Study | 41 186 women aged 21–69 years; 6 years | 1964 | Confirmed self-report | Dietary magnesium 0.65 (0.54–0.78) | Age, education, family history, smoking, BMI, physical activity, intakes of total energy, alcohol, coffee, sugar-sweetened drinks, red meat, processed meat, and calcium |

BMI, body mass index; CI, confidence interval; RR, relative risk; WHR, waist-to-hip ratio.

^aRelative risk for the highest versus the lowest category of magnesium intake; relative risks were incidence rate ratios from Cox proportional hazards models, except for the studies by Kao *et al.* [20] and Hodge *et al.* [25], which used odds ratios obtained by logistic regression to estimate relative risks. ^bRelative risk for a 500 mg d⁻¹ increment.

both men and women, one study consisted entirely of men, and four studies consisted of women only. All studies used food-frequency questionnaires to collect dietary data. Four studies presented results for the dietary magnesium intake [20, 21, 23, 25], two for total magnesium intake [22], and one for both dietary and total magnesium intake [19]; for that study, we used the results for total magnesium intake in the overall analysis. The estimated median magnesium intake in the studied populations ranged from 168 mg d⁻¹ (US black women) [23] to 348 mg d⁻¹ (male health professionals) [19]. The mean range of magnesium intake between the highest and the lowest category across studies was about 150 mg d⁻¹. In all studies, age, sex, body mass index, physical activity and alcohol consumption were considered as potential confounders.

The estimated RRs of type 2 diabetes for a 100 mg d⁻¹ increase in magnesium intake for each of the seven studies are shown in Fig. 1. A statistically significant inverse association between magnesium intake and type 2 diabetes was observed in four studies [21–23], and a nonsignificant inverse association was found in two studies [19, 25]. In analysis of all studies, the overall RR of type 2 diabetes for a 100 mg d⁻¹ increase in magnesium intake was 0.85 (95% CI, 0.79–0.92). There was statistically signifi-

cant heterogeneity amongst studies ($Q = 22.09$, $P = 0.002$, $I^2 = 68.3\%$). In a sensitivity analysis in which one study at a time was removed and the rest analysed, the RR ranged from 0.84 (95% CI, 0.77–0.91) when the study by Kao *et al.* [20] was excluded to 0.87 (95% CI, 0.82–0.93) when the study by van Dam *et al.* [23] was excluded. Restricting the analysis to the three studies that controlled for cereal fibre intake [21, 22] yielded a RR of 0.81 (95% CI, 0.77–0.86), without heterogeneity amongst studies ($Q = 1.00$, $P = 0.60$, $I^2 = 0\%$). The results were similar for intake of dietary magnesium (RR, 0.86; 95% CI, 0.77–0.95; $n = 5$) and total magnesium (RR, 0.83; 95% CI, 0.77–0.89; $n = 3$). There was statistically significant heterogeneity amongst the studies of dietary magnesium ($Q = 18.04$, $P = 0.003$, $I^2 = 72.3\%$) but not amongst studies of total magnesium intake ($Q = 3.48$, $P = 0.18$, $I^2 = 42.5\%$). The Egger's test provided no evidence of publication bias ($P = 0.99$).

Discussion

Findings from this meta-analysis of cohort studies support a statistically significant inverse association between magnesium intake and the risk of type 2 diabetes. The overall estimate indicated a 15% reduction in risk of type 2 diabetes for a 100-mg d⁻¹ increase in magnesium intake, which is approximately equivalent

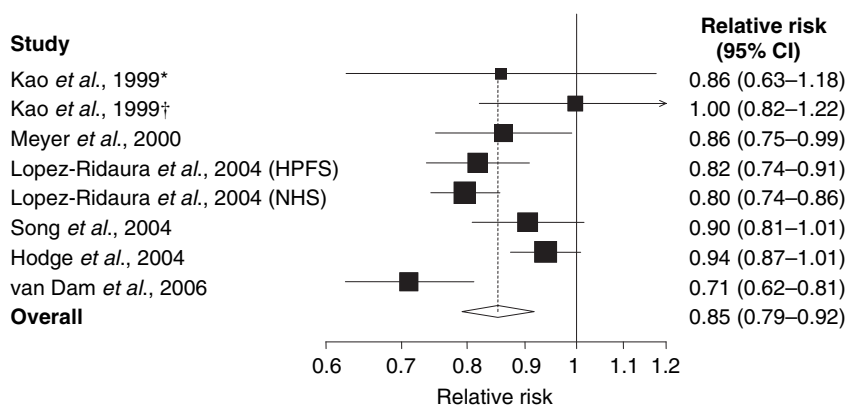


Fig. 1 Relative risks for the association between magnesium intake (for a 100 mg d⁻¹ increase) and incidence of type 2 diabetes. Squares represent study-specific relative risks (the square sizes are proportional to the weight of each study in the overall estimate); horizontal lines represent 95% confidence intervals (CIs); diamond represent the overall relative risk estimate with its 95% CI. *Black participants. †White participants. HPFS, Health Professionals' Follow-up Study; NHS, Nurses' Health Study.

to the magnesium content in four slices of whole grain bread, four cups of cooked oatmeal, one cup of beans, ¼ cup of nuts, four tablespoons peanut butter, ½ cup of cooked spinach, or three bananas per day.

Our study has several strengths. First, our quantitative assessment was based on data from prospective cohort studies, which eliminated recall and selection biases. In addition, the included studies had large numbers of incident cases of type 2 diabetes. Hence, meta-analysis of these studies provides high statistical power for estimating the relationship between magnesium intake and type 2 diabetes.

There are also some limitations that should be considered when interpreting the results from this meta-analysis. First, as a meta-analysis of observational studies, the possibility of confounding as a potential explanation for the observed inverse association between magnesium intake and type 2 diabetes cannot be excluded. For example, individuals with high consumption of magnesium-rich foods may be leaner, more physically active, and more likely to be non-smokers than those with low intake of magnesium [19, 22, 23]. Such characteristics have been associated with a reduced risk of type 2 diabetes [2]. Although all studies included in this meta-analysis adjusted for body mass index and physical activity and all but two studies [20, 25] adjusted for smoking, there remains the potential for residual confounding by inadequately measured covariates. Moreover, it cannot be ruled out that other nutrients or dietary factors that are correlated with magnesium intake may be responsible for the observed association. For instance, cereal fibre intake tends to be correlated with the magnesium intake and has been inversely associated with risk of type 2 diabetes [2]. Nevertheless, the inverse relationship between magnesium intake and type 2 diabetes remained in the studies that controlled for intake of cereal fibre [21, 22] and/or whole grains [21, 23].

A second limitation is that all studies assessed diet with a self-administered food-frequency questionnaire and in all but two studies [22], dietary intake was based on responses to a single questionnaire administered only at baseline. Hence, some misclassification of exposure is

inevitable and this misclassification would tend to weaken any true relationship between magnesium intake and type 2 diabetes. The heterogeneity amongst study results may, in part, be related to different accuracy in the assessment of the magnesium intake as well as differences in baseline magnesium intake across studies.

A third limitation is that cases of type 2 diabetes were ascertained by self-report in all but one study [20]. Although positive self-report may be reasonably accurate, some incident cases would have been missed. Underascertainment of diabetes could have affected the results if diabetes detection was associated with the magnesium intake.

Fourth, there was heterogeneity amongst the results of individual studies in the overall analysis. However, the association between magnesium intake and incidence of type 2 diabetes was markedly consistent, and differences in risk estimates were largely in the magnitude rather than the direction of the association.

Finally, because our meta-analysis was based on published studies, publication bias could be of concern. Nevertheless, we found no evidence of such bias in this meta-analysis.

The potential protective role of magnesium intake against type 2 diabetes may be due to improvement of insulin sensitivity. Studies in animals have demonstrated an adverse effect of magnesium deficiency on glucose-induced insulin secretion and insulin-mediated glucose uptake [7, 31]. In contrast, magnesium supplementation was shown to prevent fructose-induced insulin resistance [32] and reduce the development of diabetes in a rat model of spontaneous type 2 diabetes [8].

A recent cross-sectional study showed that magnesium intake was associated with insulin sensitivity in a threshold fashion [33]. It was found that magnesium intake of more than 325 mg d⁻¹, which is close to the recommended dietary allowance (420 mg d⁻¹ for men and 320 mg d⁻¹ for women) [34], might not provide further benefit with respect to insulin sensitivity [33]. Hence, increased intake of magnesium may be more beneficial amongst individuals with some degree of

magnesium deficiency. Of note, the strongest inverse relation between magnesium intake and risk of type 2 diabetes was found in the study population with the lowest estimated magnesium intake [23].

The relation between magnesium intake and the incidence of type 2 diabetes could potentially be modified by other factors affecting insulin resistance, such as excess body weight and physical inactivity. In one study [19], a significant inverse association between magnesium intake and type 2 diabetes was observed only in overweight (BMI ≥ 25 kg m⁻²) women. The relationship between magnesium intake and type 2 diabetes was not modified by BMI or physical activity in two other cohorts [22].

In conclusion, findings from this meta-analysis of cohort studies indicate that increased intake of magnesium may reduce the incidence of type 2 diabetes. This observational evidence should be treated as compelling but not definitive. Additional large cohort studies that comprehensively control for potential dietary confounders are warranted. Whether long-term magnesium supplementation reduces the risk of type 2 diabetes needs to be addressed in intervention studies. Whilst it is premature to recommend magnesium supplementation to prevent type 2 diabetes, increased consumption of magnesium-rich foods such as whole grains, beans, nuts and green leafy vegetables seems prudent.

Conflict of interest statement

None of the authors had any conflict of interest.

Acknowledgement

The study was supported by grants from the Swedish Council for Working Life and Social Research.

References

- Larsson SC, Wolk A. Epidemiology of Obesity and Diabetes. In: Mantzoros C, ed *Obesity and Diabetes*. Boston: Humana Press, 2006; 429–43.
- Hu F. Diet and lifestyle in prevention and management of type 2 diabetes. In: Mantzoros C, ed *Obesity and Diabetes*. Boston: Humana Press, 2006; 429–43.
- Shils ME. Magnesium. In: Shils M, Olson J, Shike M, Ross AC, ed *Modern Nutrition in Health and Disease*. Baltimore: Williams & Wilkins, 1999; 169–92.
- Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta* 2000; 294: 1–26.
- Paolisso G, Scheen A, D'Onofrio F, Lefebvre P. Magnesium and glucose homeostasis. *Diabetologia* 1990; 33: 511–4.
- Barbagallo M, Dominguez LJ, Galioto A *et al*. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. *Mol Aspects Med* 2003; 24: 39–52.
- Suarez A, Pulido N, Casla A, Casanova B, Arrieta FJ, Rovira A. Impaired tyrosine-kinase activity of muscle insulin receptors from hypomagnesaemic rats. *Diabetologia* 1995; 38: 1262–70.
- Balon TW, Gu JL, Tokuyama Y, Jasman AP, Nadler JL. Magnesium supplementation reduces development of diabetes in a rat model of spontaneous NIDDM. *Am J Physiol* 1995; 269 (4 Pt 1): E745–52.
- Sjögren A, Floren CH, Nilsson A. Oral administration of magnesium hydroxide to subjects with insulin-dependent diabetes mellitus: effects on magnesium and potassium levels and on insulin requirements. *Magnesium* 1988; 7: 117–22.
- Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. *Diabetes Care* 1989; 12: 265–9.
- Paolisso G, Sgambato S, Gambardella A *et al*. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 1992; 55: 1161–7.
- Paolisso G, Scheen A, Cozzolino D *et al*. Changes in glucose turnover parameters and improvement of glucose oxidation after 4-week magnesium administration in elderly noninsulin-dependent (type II) diabetic patients. *J Clin Endocrinol Metab* 1994; 78: 1510–4.
- Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care* 2003; 26: 1147–52.
- de Lordes Lima M, Cruz T, Pousada JC, Rodrigues LE, Barbosa K, Cangucu V. The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care* 1998; 21: 682–6.
- de Valk HW, Verkaaik R, Van Rijn HJ, Geerdink RA, Struyvenberg A. Oral magnesium supplementation in insulin-requiring Type 2 diabetic patients. *Diabet Med* 1998; 15: 503–7.
- Fung TT, Manson JE, Solomon CG, Liu S, Willett WC, Hu FB. The association between magnesium intake and fasting insulin concentration in healthy middle-aged women. *J Am Coll Nutr* 2003; 22: 533–8.
- Ma J, Folsom AR, Melnick SL *et al*. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. *J Clin Epidemiol* 1995; 48: 927–40.

- 18 He K, Liu K, Daviglius ML *et al.* Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006; 113: 1675–82.
- 19 Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27: 59–65.
- 20 Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med* 1999; 159: 2151–9.
- 21 Meyer KA, Kushi LH, Jacobs DR Jr., Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 2000; 71: 921–30.
- 22 Lopez-Ridaura R, Willett WC, Rimm EB *et al.* Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 2004; 27: 134–40.
- 23 van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in U.S black women. *Diabetes Care* 2006; 29: 2238–43.
- 24 Stroup DF, Berlin JA, Morton SC *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–12.
- 25 Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diabetes Care* 2004; 27: 2701–6.
- 26 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; 135: 1301–9.
- 27 Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J* 2006; 6: 40–57.
- 28 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–88.
- 29 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–58.
- 30 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–34.
- 31 Kandeel FR, Balon E, Scott S, Nadler JL. Magnesium deficiency and glucose metabolism in rat adipocytes. *Metabolism* 1996; 45: 838–43.
- 32 Balon TW, Jasman A, Scott S, Meehan WP, Rude RK, Nadler JL. Dietary magnesium prevents fructose-induced insulin insensitivity in rats. *Hypertension* 1994; 23 (6 Pt 2): 1036–9.
- 33 Ma B, Lawson AB, Liese AD, Bell RA, Mayer-Davis EJ. Dairy, magnesium, and calcium intake in relation to insulin sensitivity: approaches to modeling a dose-dependent association. *Am J Epidemiol* 2006; 164: 449–58.
- 34 Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board. Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington, DC: National Academy Press; 1997.

Correspondence: Susanna C Larsson, Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institutet, P.O. Box 210, SE-171 77 Stockholm, Sweden. (fax: +46 (0)8 304571; e-mail: susanna.larsson@ki.se) ■