Original Research

Magnesium Intake and Risk of Coronary Heart Disease among Men

Wael K. Al-Delaimy, MD, PhD, Eric B. Rimm, ScD, Walter C. Willett, MD, DrPH, Meir J. Stampfer, MD, DrPH, Frank B. Hu, MD, PhD

Department of Nutrition (W.K.A.-D., E.B.R., W.C.W., M.J.S., F.B.H.), Department of Epidemiology (E.B.R., W.C.W., M.J.S.), Harvard School of Public Health, Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital (E.B.R., W.C.W., M.J.S., F.B.H.), Boston, Massachusetts

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Objective: Our aim in this study was to assess the relationship between magnesium intake and risk of coronary heart disease (CHD) among men.

Methods: A total of 39,633 men in the Health Professionals Follow-up Study who returned a dietary questionnaire in 1986 were followed up for 12 years. Intakes of magnesium, zinc and potassium and other nutrients were assessed in 1986, 1990 and 1994. Total CHD incidence (nonfatal myocardial infarction (MI) and fatal CHD) was ascertained by biennial questionnaire and mortality surveillance confirmed by medical record review. Standard CHD risk factors were recorded biennially.

Results: During 12 years of follow-up (414,285 person-years), we documented 1,449 cases of total CHD (1,021 non-fatal MI cases, and 428 fatal CHD). The age-adjusted relative risk (RR) of developing CHD in the highest quintile (median intake = 457 mg/day) compared with the lowest quintile (median intake = 269 mg/day) was 0.73 (95% CI 0.62–0.87, p for trend <0.0001). After controlling for standard CHD risk factors and dietary factors, the RR for developing CHD among men in the highest total magnesium intake quintile compared with those in the lowest was 0.82 (95% CI 0.65–1.05, p for trend = 0.08). For supplemental magnesium intake, the RR comparing the highest quintile to non-supplement users was 0.77 (95% CI 0.56–1.06, p for trend = 0.14).

Conclusions: These results suggest that intake of magnesium may have a modest inverse association with risk of CHD among men.

INTRODUCTION

Inadequate magnesium intake in the US population may be a risk factor for cardiovascular diseases [1]. There is still controversy on the use of magnesium to prevent CHD because most of the published data on the protective effects of magnesium involve CHD patients [2–5] and there are limited studies on prevention among healthy adults. Higher magnesium intake through water supplies rich in this and other minerals (hard water) has been associated with decreased prevalence of cardiac mortality in several ecological studies [6–8], but these studies did not adjust for possible confounders and the inverse association was not seen in other studies [9–10]. Magnesium deficiency has been related to coronary spasm and various arrhythmias through the loss of cellular potassium [11]. In a controlled clinical trial, higher magnesium intake was associated with a significant antiarrhythmic effect [12]. In the Caerphilly cohort no association was seen between magnesium intake and CHD, but the number of cases was relatively small [13].

The primary aim of this analysis was to investigate the association between intake of magnesium and risk of CHD (fatal CHD and non-fatal myocardial infarction (MI)) among men participating in the Health Professionals Follow-up Study (HPFS). We also assessed the associations between intakes of the other minerals, potassium and zinc, and incidence of CHD because potassium is metabolically related to magnesium [14,15] and zinc deficiency is a suspected CHD risk factor [16].

MATERIALS AND METHODS

The Health Professionals Follow-up Study (HPFS) is a prospective cohort initiated in 1986, when 51,529 predominantly white men 40 to 75 years of age answered a detailed

Address correspondence to: Wael K Al-Delaimy, MD, PhD, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115. E-mail: wael@hsph.harvard.edu.

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questionnaire by mail on diet and medical history. This cohort consists of dentists (57.6%), veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%), osteopathic physicians (4.3%), and podiatrists (3.1%). All 50 states of the United States were represented, and no exclusions were made by race. Every two years, follow-up questionnaires were mailed to all surviving cohort members, up to six times per follow-up cycle for nonrespondents, to update data on medical conditions and exposures.

For this analysis, we excluded men with implausibly high or low scores for total food intake (outside the range of 800–4200 kcal/day) or with 70 items or more left blank on the baseline dietary questionnaire in 1986 [17]. In addition, men with cancers (excluding nonmelanoma skin cancer) diagnosed at baseline, or before the development of CHD (during follow up) were excluded because these men may have changed their diets as a result of their cancer. Men with myocardial infarction or other cardiovascular diseases at baseline were also excluded. The remaining 39,633 men were eligible for follow-up. The follow-up rate for the cohort averaged 94% per follow-up cycle during the five biennial cycles from 1986 through 1996. The National Death Index was used to determine vital status for nonrespondents, and the remaining nonrespondents were assumed to be alive and at risk for CHD.

Dietary Intake

To assess dietary intake, we used a 131-item semiquantitative food-frequency questionnaire (FFQ) [17], which is an expanded version of a previously validated questionnaire [18]. The baseline dietary questionnaire was administered in 1986, and dietary information was updated in 1990 and 1994. The questionnaire assesses average frequency of intake over the previous year. For each man, we calculated caloric and nutrient intakes by multiplying the frequency that each food item was reported by the caloric or nutrient content for the specified portion size. We asked about use of multivitamins in addition to the use of specific supplements of magnesium and zinc. Total magnesium and zinc intakes were calculated as the sum of dietary and supplemented intake. Nutrient intake was adjusted for total energy intake using the residual approach [19]. The food composition database used to calculate nutrient values is based primarily on U.S. Department of Agriculture publications [20] supplemented with other published data in the literature and manufacturers' data.

The validity of the food-frequency questionnaire was evaluated in a random sample of 127 men from the HPFS living in the Boston area. In that study, nutrient intakes as computed from the questionnaire were compared (unadjusted for energy) with nutrients from two one-week diet records spaced six months apart [17]. A correlation coefficient of 0.69 between questionnaires and diet records was observed for total magnesium intake, and a correlation of 0.65 was observed for both zinc and potassium.

Ascertainment of End Points

On each questionnaire, participants indicated whether they had been diagnosed with any major cancer (e.g., prostate or colon cancer), heart disease, or other medical conditions. As described elsewhere in detail [21], the end-points in our analyses were fatal CHD (including sudden death) and nonfatal myocardial infarction; for the present study, we included events that occurred between the return of the 1986 questionnaire and January 31, 1998. Participants who reported an incident myocardial infarction on a follow-up questionnaire were asked for permission to review medical records. We only used confirmed nonfatal myocardial infarction for the analyses by using the World Health Organization criteria [22]: symptoms plus either typical ECG changes or elevated cardiac enzymes.

Deaths were reported by next-of-kin, coworkers or postal authorities or in the National Death Index [23]. Fatal CHD was confirmed with medical records, autopsy reports or the death certificate if CHD was the underlying cause, and a diagnosis of coronary disease was confirmed by other sources. Deaths due to sudden death within one hour of the onset of symptoms in men with no other apparent cause of death (other than CHD) were also included.

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the 1986 questionnaire to the date of CHD diagnosis, to the day of death from any cause, or January 31, 1998, whichever came first. In the main analysis, exposure categories were updated every two years in all analyses. The incidence rate for each category of magnesium, zinc and potassium was calculated as the number of cases with CHD divided by the person-time of follow-up. These nutrients were all energy-adjusted [19]. Energy adjustment is based on the *a priori* biologic consideration that a larger, more physically active person will require a higher caloric intake, which will also be associated with a higher absolute intake of all nutrients. Cut points for the different groupings of magnesium, zinc and potassium intakes were obtained by dividing each into quintiles. To adjust for age (five-year categories) and other covariates, we employed pooled logistic regression [24] using SAS statistical software Version 6.12 [25]. This approach is asymptotically equivalent to the Cox regression model with time-dependent covariates, given short time intervals and low probability of the outcome within the interval, as in this study.

Total caloric intake was also included in multivariate models to minimize extraneous variation introduced by underreporting or over-reporting in the FFQ. In multivariate analyses, in addition to age, we included time period (two-year intervals), smoking (never smoker, past smoker, current 1–14 cigarettes/day smoker, current 15–24 cigarettes/day smoker and current 25 or more cigarettes/day smoker), alcohol consumption (0, 1 to 4.9, 5 to 29, and $\geq$30 g/day), history of diabetes, history of hypercholesterolemia, parental history of myocardial infarction

before age 65 years, body mass index (body mass index was calculated as weight in kilograms divided by the square of height in meters and included as an updated variable in the analyses in categories: <21, 21–22.9, 23–24.9, 25–26.9, 27–28.9, 29–31, >31 kg/m^2), aspirin intake (yes, no), vitamin E intake quintiles and total energy intake quintiles. Physical activity was measured by the time per week engaged in ten specified physical activities and four sedentary activities during the previous year [26]. Using these activities, we calculated a weekly metabolic equivalent task (MET) score for total physical activities. The validity of the questionnaire in assessing physical activity has been described elsewhere [26]. We conducted further analysis to adjust for dietary variables that are related to risk of CHD: quintiles of dietary trans fatty acids, protein, omega-3 fatty acids, folate, cereal fiber and potassium.

We examined intakes of magnesium, zinc and potassium in relation to incidence of CHD by updating the baseline dietary data with information from subsequent questionnaires (in 1990 and 1994). In these analyses, dietary data from the 1986 questionnaire were used to predict outcomes during the period from 1986 to 1990; the average of 1986 and 1990 dietary intakes was used to predict outcomes during the period from 1990 to 1994, and the average of 1986, 1990, and 1994 was used for subsequent cases (i.e., 1994 to 1998). Cumulative averaging reduces within-person variation and thus can better represent long-term intake [27].

Mantel extension tests for trend [28] were obtained by assigning the median value for each category and modeling this variable as a continuous variable, using pooled logistic regression for multivariate analyses at two-year intervals. All *p* values are two-sided. Analyses stratified by history of diabetes were carried out for the association between magnesium intake and total CHD because lower magnesium intake is related to poor diabetes control [29,30], and diabetic patients may have magnesium depletion as a result of glycosurea [31].

RESULTS

During 414,285 person-years of follow up of 39,633 men over 12 years (1986–1998), we documented 1,449 cases of total CHD (1,021 non-fatal MI cases, and 428 fatal CHD). Table 1 shows the characteristics of the study population according to magnesium intake in 1986. Men in the highest quintile for total magnesium intake were much more likely to have increased intake of vitamin E, potassium, folate and cereal fiber, to be more physically active and to have diabetes and high cholesterol levels than those in the lower quintiles, but they were less likely to smoke.

The association between total magnesium intake and total CHD (fatal CHD and nonfatal MI) is shown in Table 2. In age-adjusted analyses, with increasing quintiles of total magnesium intake there was a highly inverse significant trend in the risk of CHD. The relative risk (RR) for the highest quintile of magnesium intake (median = 457 mg/day) compared with the lowest quintile (median = 269 mg/day) was 0.73 (95% CI

Table 1. Age-adjusted characteristics of men according to energy adjusted magnesium intake quintiles in 1986

	Magnesium				
	1	2	3	4	5
N	7919	8098	7969	7871	8003
Median intake/day (mg)	261	306	341	381	453
Mean values					
Age (year)	50	51	53	54	54
BMI (kg/m^2)	25.8	25.7	25.6	25.4	25.0
Saturated fatty acid (g/day)	28	27	25	23	21
Trans fatty acid (g/day)	3.5	3.2	2.9	2.5	2.1
Polyunsaturated fatty acid (g/day)	13	13	13	13	13
3-omega fatty acid (g/day)	1.3	1.4	1.4	1.4	1.5
Animal protein (g/day)	65	68	68	69	68
Cereal fiber (g/day)	4.1	4.8	5.5	6.3	8.5
Physical activity (METS)*	16	18	21	23	27
Vitamin E (mg)	53	64	80	103	169
Potassium (mg)	2749	3160	3422	3670	4074
Folate (mcg)	351	407	454	511	674
Calories (kcal/day)	1956	1996	2030	2011	1968
Alcohol (g/day)	12	11	12	12	11
Prevalence					
History of diabetes (%)	1.5	1.9	2.4	2.8	3.1
History of high blood pressure (%)	21	20	18	19	19
History of high cholesterol (%)	8	9	9	11	13
Current Smokers (%)	13	12	10	9	8
Parental history of MI (%)	12	12	12	11	12

* METS = Metabolic equivalent task.

Table 2. Age- and multivariate*-adjusted relative risks of developing CHD according to the quintiles of total magnesium, dietary magnesium, and supplement magnesium intake among men in the HPFS

	Quintiles						
Total magnesium	1	2	3	4	5		
No of cases	316	301	292	270	270		
Median (mg/day)	269	312	347	387	457		
Age-adjusted RR	1.00	0.95 (0.81–1.11)	0.87 (0.74–1.02)	0.77 (0.65–0.90)	0.73 (0.62–0.87)	$p < 0.0001$	
Multivariate RR	1.00	0.98 (0.83–1.15)	0.93 (0.79–1.10)	0.85 (0.72–1.01)	0.86 (0.72–1.02)	$p = 0.04$	
^Multi-Nutrient RR	1.00	0.96 (0.80–1.14)	0.90 (0.74–1.10)	0.82 (0.66–1.01)	0.82 (0.65–1.05)	$p = 0.08$	
Dietary magnesium (exc supp users)	1	2	3	4	5		
No of cases	255	249	240	232	227		
Median (mg/day)	264	305	336	371	427		
Age-adjusted RR	1.00	0.98 (0.82–1.17)	0.90 (0.75–1.08)	0.85 (0.71–1.01)	0.77 (0.65–0.93)	$p = 0.001$	
Multivariate RR	1.00	1.01 (0.85–1.21)	0.95 (0.79–1.14)	0.93 (0.77–1.12)	0.88 (0.73–1.06)	$p = 0.11$	
^Multi-Nutrient RR	1.00	1.01 (0.83–1.23)	0.93 (0.75–1.16)	0.91 (0.71–1.15)	0.86 (0.65–1.13)	$p = 0.19$	
Magnesium supplement	0**	1	2	3	4	5	
No of cases	1260	57	40	33	15	44	
Median (mg/day)	0	9	50	57	79	100	
Age-adjusted RR	1.00	1.23 (0.94–1.61)	0.76 (0.56–1.05)	0.75 (0.53–1.06)	0.80 (0.48–1.33)	0.70 (0.52–0.95)	$p = 0.74$
Multivariate RR	1.00	1.26 (0.96–1.66)	0.84 (0.61–1.17)	0.77 (0.54–1.10)	0.89 (0.53–1.50)	0.75 (0.55–1.02)	$p = 0.33$
^Multi-Nutrient RR	1.00	1.24 (0.94–1.63)	0.85 (0.62–1.19)	0.76 (0.53–1.08)	0.90 (0.54–1.51)	0.77 (0.56–1.06)	$p = 0.14$

* Covariates: age, time period, energy intake, history of diabetes, history of high cholesterol, family history of MI, smoking history, aspirin intake, BMI, alcohol intake, physical activity, vitamin E intake.

^ The above covariates plus nutrient variables (trans fatty acid, total protein intake, cereal fiber, folate, omega 3 fatty acid, potassium).

** The reference group are the non-supplement users.

0.62–0.87, p for trend <0.0001). The association did not change after adding calorie intake to the model. The association was attenuated after including standard CHD risk factors (diabetes history, high cholesterol history, smoking history, family history of myocardial infarction, aspirin intake, BMI, alcohol intake, physical activity, vitamin E intake, and total energy intake) in multivariate analyses (RR = 0.86; 95% CI 0.72–1.02, p for trend = 0.04). After further adjustment for nutrient variables (trans fatty acids, protein intake, omega-3 fatty acids, folate, potassium, and cereal fiber) there was still an inverse trend in the association between magnesium intake and risk of CHD: RR for the highest quintile of magnesium intake compared with the lowest quintile was 0.82 (95% CI 0.65–1.05, p for trend = 0.08). In the latter model, potassium intake had the strongest confounding effect among other nutrients. Excluding potassium from the model attenuated the results towards the null. There was no evidence of serious collinearity for energy-adjusted magnesium and potassium intake in 1986 (r = 0.32). These results were similar when further adjusting for the poly-unsaturated fatty acids to saturated fatty acids ratio (p/s ratio).

In age-adjusted analyses for dietary magnesium (after exclusion of magnesium supplement users), there was a similar significant trend to that for total magnesium intake, but this became nonsignificant in the multivariate analyses models. Similarly, for supplemental magnesium, there was an inverse association with the risk of CHD, but it was not significant (Table 2). The associations between magnesium intake and risk of CHD was slightly stronger among diabetes than among nondiabetics, but the test for interaction was not significant (p = 0.3) (Fig. 1). When fatal CHD and non-fatal MI were separately examined, the relative risks for total and dietary magnesium intake showed a nonsignificant inverse association for both fatal CHD and nonfatal MI (data not shown). For supplemental magnesium intake, there was a stronger inverse association in relation to nonfatal CHD (the highest quintile of magnesium supplement intake compared with the lowest quintile was 0.73 [95% CI 0.49–1.10, p for trend = 0.09]).

There was no appreciable association between total and supplement zinc intake and incidence of CHD (Table 3). This lack of association was also observed when total and supplement zinc intake were separately examined in relation to fatal CHD and non-fatal CHD (data not shown). For potassium intake, the age-adjusted and multivariate analyses showed no association with risk of CHD, although including magnesium intake in the multivariate model made the association weakly positive (Table 3).

DISCUSSION

In this prospective cohort study, we found a modest inverse association between magnesium intake and risk of CHD that did not reach statistical significance. The inverse association was seen for both dietary magnesium and supplemental magnesium intake.

An advantage of this study is the relatively long follow up

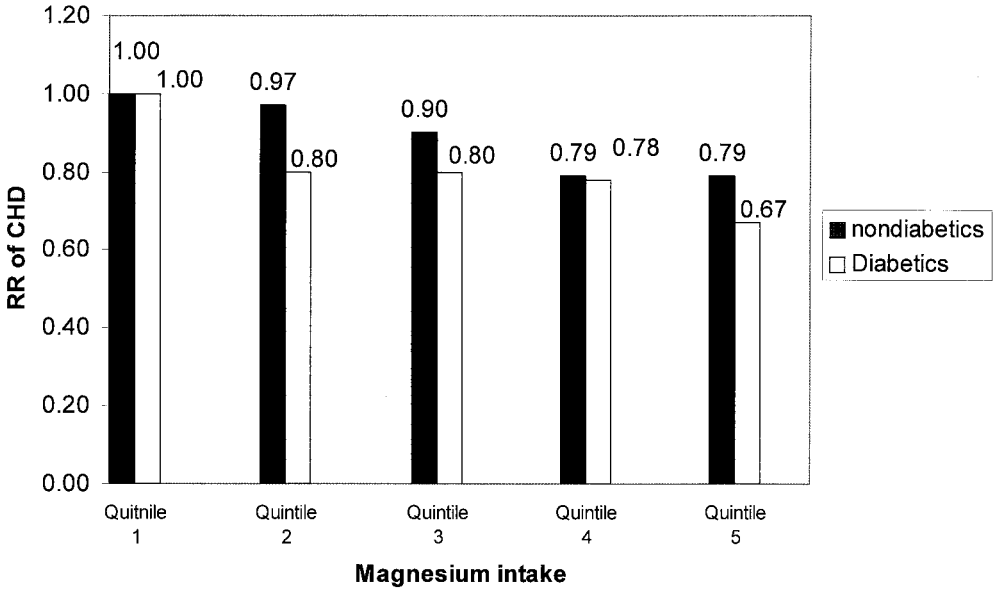

Fig. 1. Magnesium levels and multivariate adjusted* relative risk of coronary heart disease among men according to diabetes status. *(Covariates: age, time period, energy intake, history of diabetes, history of high cholesterol, family history of MI, smoking history, aspirin intake, BMI, alcohol intake, physical activity, vitamin E intake, trans fatty acids, total protein intake, cereal fiber, folate, omega 3 fatty acid, potassium.)

Table 3. Age- and multivariate*-adjusted relative risks of developing CHD according to the quintiles of zinc, potassium, and supplement zinc intake among men in the HPFS

	Quintiles						
Total Zinc	1	2	3	4	5		
No of cases	273	274	311	314	277		
Median (mg/day)	10	12	14	17	37		
Age-adjusted RR	1.00	1.12 (0.95–1.33)	1.22 (1.04–1.44)	1.23 (1.04–1.45)	0.96 (0.81–1.14)	$p = 0.06$	
Multivariate RR	1.00	1.09 (0.92–1.29)	1.14 (0.97–1.35)	1.14 (0.97–1.36)	1.05 (0.87–1.28)	$p = 0.93$	
^Multi-Nutrient RR	1.00	1.08 (0.91–1.28)	1.12 (0.94–1.34)	1.12 (0.93–1.34)	1.07 (0.87–1.30)	$p = 0.93$	
Zinc supplement	0**	1	2	3	4	5	
No of cases	1162	65	60	49	60	53	
Median (mg/day)	0	1.5	10	19	42	80	
Age-adjusted RR	1.00	0.96 (0.74–1.23)	0.89 (0.69–1.16)	0.75 (0.56–1.00)	0.70 (0.54–0.91)	0.91 (0.69–1.20)	$p = 0.82$
Multivariate RR	1.00	0.98 (0.76–1.27)	1.02 (0.78–1.34)	0.82 (0.61–1.11)	0.81 (0.61–1.07)	1.03 (0.77–1.39)	$p = 0.53$
^Multi-Nutrient RR	1.00	0.96 (0.73–1.25)	1.02 (0.78–1.34)	0.84 (0.62–1.14)	0.83 (0.63–1.10)	1.06 (0.79–1.43)	$p = 0.44$
Potassium	1	2	3	4	5		
No of cases	268	248	296	283	354		
Median (mg/day)	2632	3042	3341	3672	4250		
Age-adjusted RR	1.00	0.87 (0.74–1.04)	1.01 (0.86–1.20)	0.89 (0.75–1.05)	0.99 (0.84–1.16)	$p = 0.99$	
Multivariate RR	1.00	0.92 (0.77–1.10)	1.06 (0.90–1.26)	0.95 (0.80–1.12)	1.01 (0.86–1.20)	$p = 0.83$	
^^Multi-Nutrient RR	1.00	0.99 (0.82–1.19)	1.18 (0.97–1.43)	1.10 (0.89–1.35)	1.27 (1.01–1.58)	$p = 0.03$	

* Covariates: age, time period, energy intake, history of diabetes, history of high cholesterol, family history of MI, smoking history, aspirin intake, BMI, alcohol intake, physical activity, vitamin E intake.

^ The above covariates plus nutrient variables (trans fatty acid, total protein intake, cereal fiber, folate, omega 3 fatty acid).

^^ The above plus magnesium.

** The reference group are the non-supplement users.

(12 years) and the large number of incident CHD cases. Recall bias would not have influenced our results as all the dietary data were collected prospectively. Food frequency questionnaires are subject to inaccuracies in self-reporting of food intakes. However, our questionnaire has been validated, and the measure of magnesium intake by food frequency questionnaires as compared with diet records is reasonably accurate [17]. Although we adjusted for possible confounders in the analyses, there is still the possibility of confounding due to unmeasured variables. Magnesium intake could be a marker of

healthier diet and life-style, and adjusting for possible confounders might not isolate the independent effect of magnesium. Other possible sources of exposure measurement error may be related to water sources of magnesium because we did not have any data collected on the mineral content of water in our cohort.

There are limited data from cohort studies on the association between magnesium intake and risk of CHD. In the Caerphilly cohort [13] where 2,172 men were followed up for ten years and 269 CHD cases recorded, magnesium intake was not related to the risk of CHD after adjustment for possible confounders (RR = 1.01). On the other hand, another cohort of 13,922 men and women followed up for four to seven years reported protective effects [32]. For 223 men who developed CHD, the RR for highest quintile of magnesium intake compared to the lowest magnesium intake was 0.69 (95% CI 0.45 to 1.05). The RR for 96 women who developed CHD was 1.32 (95% CI 0.68 to 2.55). The Framingham heart study [33] followed up 3,123 eligible subjects to assess magnesium and potassium serum levels in relation to the risk of ventricular arrhythmias. Lower magnesium or potassium levels were associated with higher incidence of ventricular arrhythmias, even after adjusting for possible confounders in logistic regression models (OR = 1.20 (95% CI 1.03–1.41) for magnesium and 1.27 (95% CI 1.06–1.51) for potassium intake). However, serum magnesium levels are homeostatically controlled [30] and are not well correlated with magnesium intake, and therefore the results from the Framingham heart study are not applicable to magnesium intake. A randomized clinical trial of magnesium intake found after ten years of follow up a significantly low incidence of CHD complications among the intervention group (29% *vs.* 60%); however, other dietary variables also changed and were not adjusted for [34]. Other studies have found that higher magnesium intake was associated with lower blood pressure [35,36] and lower risk of type 2 diabetes [37], both of which are known risk factors for CHD.

Magnesium is needed for the electrical stability of the myocardium and prevention of irregular arrhythmias [38] by regulating the flux of cellular potassium levels across cell membrane and trans-membrane potentials [39] by activating adenosinetriphosphatase (ATPase) enzyme [40,41]. Magnesium has also been known for its calcium channel blocking ability by preventing entrance of calcium into the cells [41,42] and minimizing the potential of increased contractility and nerve conduction of the heart. In addition, magnesium may reduce CHD risk as a result of inhibiting platelet function [4,43], smooth muscle contraction [2,44–46] and by reducing free fatty acids [5,47]. Low intracellular magnesium content can increase membrane microviscosity, which may impair the interaction of insulin with its receptor on the plasma membrane, and this may explain the mechanism of insulin resistance caused by low magnesium intake [29,36,48].

We did not find a material association between zinc intake and risk of CHD, although other studies have suggested low serum levels of this mineral are related to increased risk of CHD [49]. Others have reported that increased dietary zinc increases cholesterol levels and atherosclerosis and decreases HDL levels [50–52]. For potassium, although there was a modest increase in risk of CHD with increased intake, this was not consistent, and no clear trend of intake in relation to CHD risk was found in the other models. There is sparse data in the literature on the association between potassium and CHD; some animal studies show increased arrhythmias and atherosclerotic lesions when hypokaliemia is induced [53,54], and there are also suggestions that potassium deficiency may cause increased risk of CHD in humans through increased arrhythmias or indirectly through its relation to increased risk of hypertension [12,55].

CONCLUSION

In conclusion, we found that increased magnesium intake was possibly associated with a modestly lower risk of CHD among men. Whether this represents a causal effect of magnesium is not certain. Nevertheless, there is sufficient reason to encourage a balanced diet rich in magnesium sources, such as whole grains, fruits and vegetables to lower the risk of CHD.

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