

## 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 Followup 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 ( $\geq 1.77$  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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[Chiuve 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. schiuve@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 ( $\leq 1.77$  mg/dl), compared with 6.3 per 1,000 person-years (95% confidence interval, 4.1 to 8.4) in the highest quartile ( $\geq 1.99$  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 summarise 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 standardised 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<sup>-1</sup>; 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 randomised 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@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  $\geq 3$  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 hospitalised 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.