

Magnesium's Role in the Prevention of Cardiovascular Disease

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DIE 4564 Research Methods

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September 21, 2015

### **Abstract**

This systematic literature review examines research on the relationship and effect of dietary and circulating magnesium and cardiovascular disease (CVD). The abstract databases of MedLine, CINAHL, Cochrane, and PubMed searched using keywords of magnesium, CVD, and related terms. By limiting to the search to past 5 years emphasis was placed on identifying how the evidence for an association has recently progressed. Thirteen full text articles were included in the systematic review. Low serum levels of magnesium have been clearly correlated to cardiovascular disease and mortality however causality has not been established. More robust research focused on determining the temporal relationship of magnesium deficit and CVD would be beneficial in developing the case for the impact of magnesium on CVD.

**Suggested citation:** Tas, J., Strickland, C. & Longstreet, D. (2015) Magnesium's Role in the Prevention of Cardiovascular Disease. *Center for Magnesium Education and Research.*

**Keywords:** magnesium, cardiovascular disease, hypomagnesaemia

### Magnesium's Role in the Prevention of Cardiovascular Disease

Globally, cardiovascular diseases (CVD) are the main cause of death (World Health Organization (WHO), 2015). CVD has its foundation in a slow progressive chronic alteration in heart function and blood flow. Magnesium (Mg) is the second most abundant mineral in the body and the body depends on Mg to act as a cofactor for over 300 enzymes, most importantly, Na<sup>+</sup>/K<sup>+</sup> ATPase (Chiuve et al., 2013). Mg is associated with inflammation, blood pressure, the regulation of nerve and muscle cell permeability, vasoconstriction, and electrocardiogram abnormalities (Lutsey et al., 2014). Mg acts as a calcium channel blocker and helps decrease sodium and calcium within the cell (Houston, 2011). A reduced intracellular sodium/calcium concentration with an increased intracellular Mg/potassium concentration positively affects blood pressure (Houston, 2011). The process of developing atherosclerotic plaque appears to be enhanced in the presence of a magnesium deficit (Chiuve, et al, 2013). Clearly Mg has a role in the health and functioning of the cardiovascular system.

According to the National Institute of Health (2013), the daily requirements for Mg intake for males are 400-410 mg and females 310-320 mg per day (National Institutes of Health (NIH), 2013). However, low levels of serum Mg has been identified in the general population. Normal levels of serum magnesium range from 1.7 to 2.5 mg/dl (Chiuve et al., 2013) with hypomagnesaemia being diagnosed at less than 1.6 mg/dl (Annapurna, Sujatha, & Sudha, 2015). Even though there are other risk factors, low magnesium seems to be more prevalent within the population that has CVD. A deficiency or low serum concentrations in Mg has been identified as negatively altering the cardiovascular system (Misialek et al., 2013). Alternatively, a high serum Mg level has been linked to an improvement in cardiovascular health (Misialek et al., 2013).

The purpose of this study was to identify recent evidence regarding whether increased Mg intake improves CVD health or symptoms associated with CVD.

### Methods

This was a systemic literature review completed in September 2015. A systematic search for all potential studies used the electronic databases of EBSCOhost which included MedLine, CINHALL, Cochrane, and PubMed. Key search terms involved Mg, CVD, heart disease, and coronary heart disease. Inclusion criteria were past five years, adults, English language, and peer-reviewed. Exclusion criteria included pregnancy, children, patients on beta blockers, and multiple-nutrient supplementation. Two independent reviewers (J. Tas and C. Strickland) completed the title review, abstract review, and full text article review based on the above inclusion and exclusion criteria.

### Results

Twelve studies met the criteria for full text review. All full-text articles were able to be retrieved. See Figure 1 for details on the search. Most studies examined used cohort study designs along with one randomized double-blind study, one case-control study, and two meta-analyses. Participants included individuals over the age of 18, both male and female, and all races. Circulating, dietary, and urinary Mg were measured to determine Mg status in individuals.

There was a high level of heterogeneous results evident in this review. When using the keywords of CVD there is a multitude of aspects of CVD such as heart function, blood flow, capillary bed function, and vasoconstriction/ vasodilatation. The ubiquitous nature of Mg functions was reflected in the variety of CVD-related studies identified.

A review of large cohort study over the span of approximately 14 years, reported an association with lower risk of mortality and dietary Mg (Zhang, et al 2012). In a similar prospective study, an inverse association was hardly noticeable with dietary Mg and ischemic stroke in men but, portrayed consistent findings between higher dietary Mg and lower risks of ischemic stroke, coronary heart disease, heart failure, and CVD in women (Zhang, et al, 2012). A meta-analysis found that Mg supplementation lowers blood pressure and contributes to the beneficial effects of cardiovascular health (Zhang, et al, 2012). One of the difficulties with studies on dietary Mg is the necessity to depend on self-reported intake.

Studies reflecting actual measures of Mg status were more supportive of the role of Mg in CVD. Seven of the twelve studies indicated evidence that there is a lower level of serum Mg when CVD is present. One meta-analysis found Mg within the body decreased the risk of CVD by 30% (Del Gobbo et al, 2013). The prevalence of hypomagnesaemia, low Mg in the blood, was higher in individuals with high blood pressure and heart disease (Annapurna, Sujatha, & Sudha, 2015). Hypomagnesaemia was also linked to an increased risk of left ventricular hypertrophy which may lead to cardiovascular mortality (Reffelmann et al., 2011). Additionally, people that had myocardial infarcts were identified as having lower serum Mg (Chakraborty, et al, 2014). Urinary Mg was also researched in a cohort study and low urinary Mg was correlated with a higher risk of ischemic heart disease (Joosten et al., 2013).

Mg has been demonstrated as useful adjunct in the clinical setting in the management of CVD. One study showed a reduction of premature ventricular and supraventricular complexes with Mg supplementation (Falco et al., 2012). Mg has also been shown to decrease the risk of atrial fibrillation in healthy people and postoperative atrial fibrillation, POAF (Gu, et al, 2012). After coronary artery bypass grafting, patients are at a high risk of POAF. Furthermore, Gu et

al. (2012) demonstrated through a double-blind placebo controlled randomized clinical trial that 76 of 511 developed POAF with intravenous Mg but 116 of 517 developed POAF with the control, showing an incidence reduction of 36%. The controlled clinical trials of intravenous Mg supplementation were shown to decrease the risk when given repeatedly for two days after surgery (Gu, et al, 2012). Mg may have other beneficial effects such as reducing arterial inflammation and preventing vasoconstriction by improving endothelial function. (Zhang, et al, 2012).

Limitations were noted in all the studies. Many authors reported a limitation to be Mg intake was assessed through a 24-hour recall which may not capture the complete intake of Mg. Other limitations included some studies having a modest population size, subjects lost due to long-term studies, and possible missed cases due to ICD codes. See Table 1 for more details.

## Discussion

This systematic literature review evaluated the relationship between Mg and CVD. Physical inactivity, poor diet, alcohol and tobacco are behavioral determinants for heart disease (WHO, 2015). Most but not all of the studies reviewed are suggestive that Mg deficit may have a role in potentiating the problems of various aspects of CVD.

In seeking to identify if the case for causality had progressed, temporality, that cause precedes effect, was specifically examined. The study by Gu, et al (2012) is suggestive in that introducing intravenous Mg reduced atrial fibrillation postoperatively for those that had coronary bypass. Chiuve et al's (2013) large prospective cohort study, which was derived from a secondary analysis of the Nurses' Health Study, was also suggestive. Conceivably a pre-existing low level of Mg may be associated with CVD but the evidence remains insufficient.

The limitations of this review included the time constraints for completion. Given more time, this review would have benefited from expanding the search to greater depth on each area of CVD.

### Conclusion

Overall, most but not all studies showed an association between low levels of Mg and CVD morbidity and mortality. Research indicates that application of Mg in a clinical setting may have a positive impact. However, more studies of Mg supplementation on improving heart health need to be implemented in order to advance the understanding of Mg impact on CVD to include the temporality of effect. The case for the impact of Mg on CVD is not yet been proven and further investigation is needed.

Figure 1. Details of Systematic Literature Search

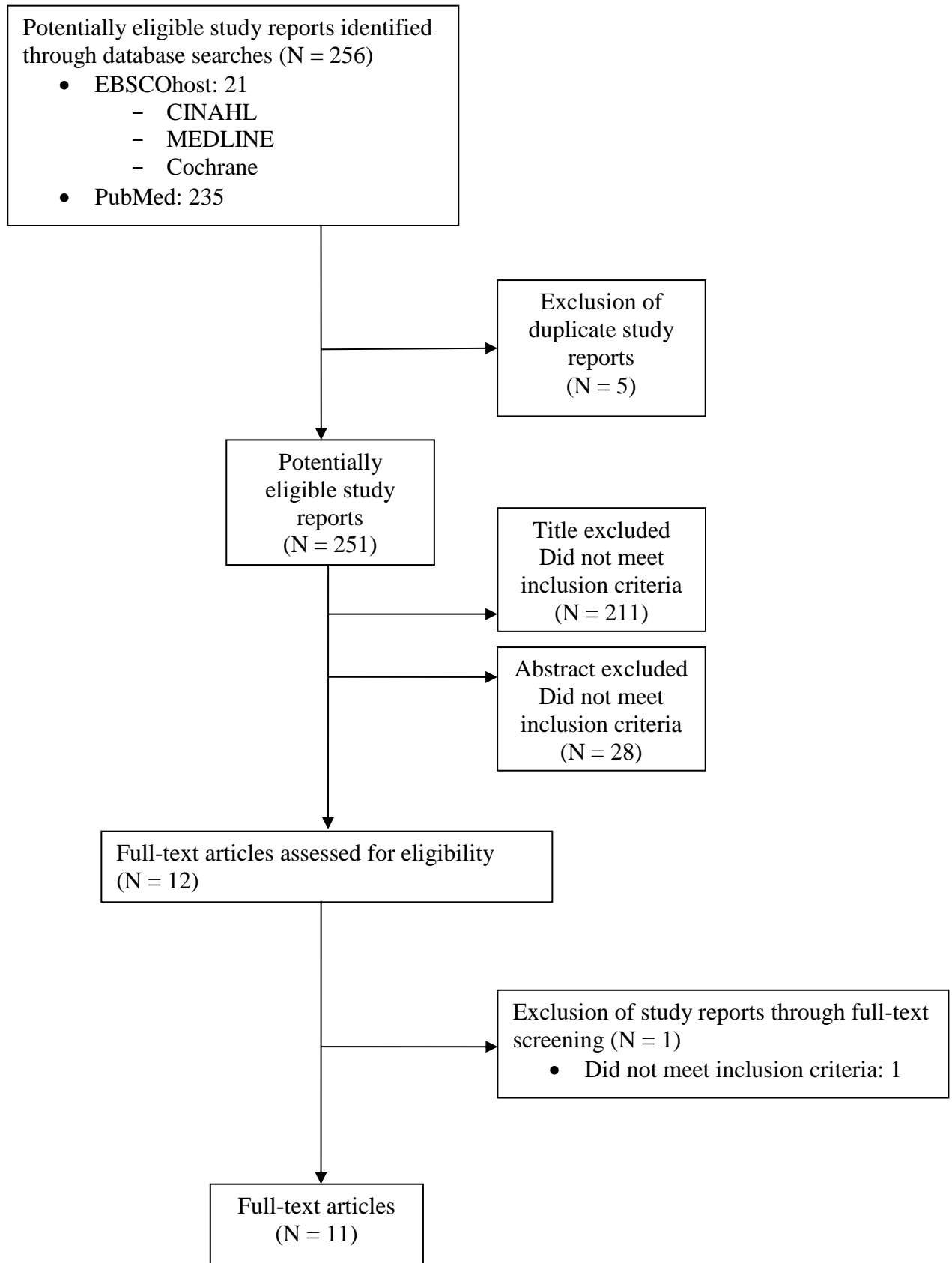




Table 1. Search Results on Magnesium's Role in Cardiovascular Disease

Authors	Types of Study	Number of subjects	Outcomes/Results	Findings/Conclusions	Limitations
Annapurna, D., Sujatha, P., & Sudha	Case-control study	80 subjects	Mg significantly lower in hypertensive patients compared to controls; hypomagnesaemia prevalent among 60% of hypertensive group compared to 0% of control group	Hypomagnesaemia is more prevalent in hypertensive patients and Mg supplementation is beneficial in these patients	Small scale trial, needed improved sensitive measures of extra cellular Mg estimation
Chakraborty, P. K., Hoque, M. R., Islam, M. R., Paul, U. K., & Husain, F.	Case-control study	100 male subjects	Group with acute myocardial infarction (AMI) had lower serum Mg ( $1.71 \pm 0.17$ mg/dl) compared to healthy group ( $2.16 \pm 0.25$ mg/dl)	Serum Mg significantly lower in patients with AMI	Small number of subjects per group
Chiuve, S., Sun, Q., Curhan, G., Taylor, E., Spiegelman, D., Willett, W., ... Albert, C.	Cohort study	121,700 female subjects	Mg intake was not associated with the risk of nonfatal CHD but inversely related to risk of fatal CHD; Mg associated with 29% of HTN and 23% of fatal CHD	Higher Mg intake associated with lower risk of fatal CHD independent of known CHD risk factors	Limited ability to explore the association between serum Mg and fatal CHD; multivitamins and Mg food sources contain other nutrients that may lower CHD risk; used self reported measures
Del Gobbo, L., Imamura, F., Wu, J., Otto, M., Chiuve, S., &	Systematic review & meta analysis	16 studies	Circulating Mg associated with 30% lower risk of CVD, not associate with IHD, a trend	Circulating Mg and CVD, an inverse relationship; circulating Mg	Dietary Mg assessed by 24-hr recall, poor availability of

Mozaffarian, D.			of lower risk of fatal IHD Dietary Mg not significantly associated with lower risk of CV and not with fatal IHD	may influence fatal IHD Dietary Mg not associated with CVD	published and unpublished data
Falco, C., Grupi, C., Sosa, E., Scanavacca, M., Hachul, D., Lara, S., ... Darrieux, F.	Randomized double-blind study	60 subjects	For subjects given Mg Pidolate 76.6% had a premature complex density (PCD) reduction >70%, 10% of them >50% and 13.4% <50%, 93.3% of subjects experienced symptom improvement compared to 16.7% of the placebo subjects	Mg replacement reduced the density of premature ventricular and supraventricular complexes; improves PCD symptoms	No long-term follow-up; intracellular Mg not measured
Gu, W., Wu, Z., Wang, P., Aung, L., & Yin, R.	Meta-analysis	7 double-blind, placebo-controlled, randomized clinical trials 1,028 individuals included	76 of 511 developed POAF with intravenous Mg, 116 of 517 developed POAF with control, reduced incidence by 36%	Intravenous Mg reduced POAF after CABG	Moderate publication bias, some clinical studies had modest sample size, exclusion may lead to bias, dose of intravenous Mg was different per study
Joosten, M., Gansevoort, R., Mukmal, K., Van de Harst, P., Geleijnse, J., Feskens, E., ... Baker, S.	Cohort study	7,664 subjects	Urinary Mg excretion associated with reduced risk of IHD, subjects in lower quintile had a higher risk of IHD and IHD-related mortality	Low urinary Mg excretion associated with risk of IHD; no association between plasma Mg and risk of IHD	24-hr urinary collections had no information about dietary origin of excreted Mg; urinary and plasma

			No association between plasma Mg and all-cause of mortality from IHD		measured at baseline only; residual confounding could explain results
Lutsey, P., Alonso, A., Michos, E., Loehr, L., Astor, B., Coresh, J., & Folsom, A.	Cohort study	14,709 biracial population	Subjects in lowest category were 2.58 times at a greater risk of incident HF	Low serum Mg was independently associated with greater risk of incident HF	Concentrations may not have been representative; biomarker concentrations; missed cases due to ICD codes
Misialek, J., Lopex, F., Lusey, P., Huxley, R., Peacock, J. Chen, L., ...Alonso, A.	Cohort study	14,290 men and female subjects	Individuals with the lowest levels of serum Mg had ~60% higher risk of atrial fibrillation (AF) compared to those with average or higher Mg levels; no association between dietary Mg and sex/race	Association between serum Mg and AF but no association with dietary Mg and AF	Serum Mg accounts for less than 1% of all Mg in the body; hypertension may be a potential cofounder between serum Mg and AF; serum Mg only measured during early follow-up
Reffelmann, T., Ittermann, T., Dorr, M., Volzke, H., Reinthaler, M., Petersmann, A., & Felix, S.	Cohort study (prospective)	3,910 subjects	Left ventricular mass (LVM) increased in subjects with lower Mg levels when compared to baseline, association between Mg and cardiovascular mortality	Low serum Mg associated with cardiovascular mortality; low Mg associated with higher LVM	Study over 10 years, subjects were lost during the process
Zang, W., Iso, H., Ohira, T., Date, C., &	Cohort study	58,615 male and female subjects	Higher dietary Mg intake associated with lower risks of stroke in men and	Dietary Mg associated with lower risk of mortality from	53% of population that responded to food

Tamakoshi, A.			ischemic stroke, CHD, heart failure and CVD in women	coronary heart disease, heart failure and total CVD	questionnaire were more educated and 3 years younger; classified by ICD codes and may be misclassified; examined Mg intake by food frequency questionnaire only
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