2017

Magnesium Intake and Depression in U.S. Adults

Emily Tarleton
University of Vermont

MAGNESIUM INTAKE AND DEPRESSION IN U.S. ADULTS

A Dissertation Presented

by

Emily Tarleton

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Clinical and Translational Science

October, 2017

Defense Date: August 16, 2017
Dissertation Examination Committee:

Benjamin Littenberg, M.D., Advisor
Gail L. Rose, Ph.D., Chairperson
Alan S. Rubin, M.D.
Amanda G. Kennedy, Pharm.D.
Cynthia J. Forehand, Ph.D., Dean of the Graduate College

ABSTRACT

Research has focused extensively on the negative health effects of inadequate Mg intake, but the extent of the problem of deficiency deserves further exploration. The notion that U.S. adults consume an inadequate amount of magnesium, leading to increased risk for chronic diseases such as depression, is plausible. National Health and Nutrition Examination Surveys (NHANES), which are large, cross-sectional, population-based data sets that assess the health and nutritional status of U.S. adults and children, indicate over half the adult population does not consume adequate amounts of magnesium based on the estimated average requirement (EAR) established by the Institute of Medicine. Using 2007 to 2010 NHANES data we found 54% of adults do not meet the EAR, confirming results from earlier surveys. As a result of this finding, a review exploring the factors impacting magnesium consumption over time and the adequacy of current intake in U.S. adults was conducted. Changes in agricultural processes that reduce magnesium levels in crops combined with the increasing consumption of processed foods containing little to no magnesium have led to a decrease in mean daily intake by 200-300 mg per day over the past century. However, population-based studies show a steady and consistent recovery in magnesium intake in U.S. adults over the past several decades. A simple, rapid, accurate test for whole body Mg status is lacking and, although population-based studies have limitations, continued monitoring of Mg consumption is essential to determine whether this positive trend continues. In the meantime, since the health consequences of inadequate magnesium are well established, there are no reported cases of hypermagnesemia from food alone, and magnesium is found in healthy foods adults should consume more often, there are few reasons not to encourage increased magnesium intake.

Cross-sectional and prospective trials in other countries report an association between magnesium intake and symptoms of depression. Depression is a chronic disease affecting a significant portion of the U.S. population. Magnesium plays a role in many of the pathways involved in the pathophysiology of depression and is found in several enzymes, hormones, and neurotransmitters. Depression and magnesium are both associated with systemic inflammation. Current treatment options for depression are limited by efficacy, cost, availability, side effects, and acceptability to patients. As a result of the need for additional treatment options, interest in the role of magnesium in modulating depressive symptoms has grown. We used the NHANES 2007-2010 data to examine this relationship in U.S. adults and found a significant association between very low magnesium intake and symptoms of depression (RR=1.16; 95% confidence interval (CI) 1.06, 1.30; P=0.03). Whether inadequate magnesium leads to increased risk for depression or depression results in poor dietary intake is not known.

To test whether supplementation with over-the-counter magnesium chloride improves symptoms of depression, an open-label, blocked, randomized, cross-over trial was carried out in outpatient primary care clinics on 126 adults (mean age 52; 38% male) diagnosed with, and currently experiencing, mild-to-moderate symptoms. Consumption of magnesium chloride tablets for 6 weeks resulted in a clinically significant net improvement in depression (Patient Health Questionnaire-9) scores of -6.0 points (95% CI -7.9, -4.2; P<0.001) and net improvement in anxiety (Generalized Anxiety Disorders-7) scores of -4.5 points (95% CI -6.6, -2.4; P<0.001). Effects were observed regardless of age, gender, baseline magnesium levels, baseline severity of depression, or use of antidepressant treatments. It worked quickly, was well tolerated, and is much safer and less expensive than conventional treatments with medication. Magnesium supplements are effective for mild-to-moderate depression and are an additional treatment option for patients suffering from depression.

CITATIONS

Material from this dissertation has been published in the following form:

Tarleton E.K., Littenberg B.. (2015). Magnesium intake and depression in adults. Journal of the American Board of Family Medicine, 28(2):249-256.

Tarleton E.K., Littenberg B., MacLean C.D, Kennedy A.G., Daley C.. (2017). Role of magnesium supplementation in the treatment of depression: a randomized clinical trial. PloS ONE,12(6):e0180067.

Material from this dissertation has been submitted for publication to *Nutrition Reviews* on August 21, 2017 in the following form:

Tarleton, E.K.. (2017). Factors influencing magnesium consumption in U.S. adults.

DEDICATION

This dissertation work is dedicated to my mother, Kathleen Tarleton. She encouraged me to start this journey and her guidance was greatly missed along the way.

ACKNOWLEDGEMENTS

I am very fortunate to have performed my graduate work at the University of Vermont. I have benefited greatly from the knowledge and guidance provided by my mentor and advisor Dr. Benjamin Littenberg. Dr. Littenberg not only offered endless support and ensured my success at every step, he was also my biggest cheerleader. Thank you to Dr. Amanda Kennedy for always knowing the right questions to ask and for the consistently excellent advice. I am thankful for the financial support provided in the form of scholarships and awards from the Honor Society of Phi Kappa Phi, Academy of Nutrition and Dietetics Foundation, Vermont Academy of Nutrition and Dietetics, and the Henry and Carleen Tufo Fund of the University of Vermont. Thank you to the participants of the magnesium and depression randomized clinical trial and the primary care providers that helped with recruitment, without whom I could not have completed my research. Many others have contributed to this research including my co-authors Dr. Charles MacLean and Dr. Christopher Daley and dissertation committee members Dr. Alan Rubin and Dr. Gail Rose. Thank you to the faculty, staff, and graduate students at the Center for Clinical and Translational Science, especially Sylvie Frisbie, Kat Cheung, Ross Colgate, Peter Durda, and Carole McBride, as well as the staff at the Clinical Research Center who offered support while I juggled work and school commitments. I am fortunate to have such caring and knowledgeable peers. Lastly, I am thankful for the support and understanding of my family especially Wylie Shipman, Libby Tarleton, John Tarleton, and Molly Tarleton. Thank you for always boosting my spirits and celebrating my successes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: Factors Influencing Magnesium Consumption in U.S. Adults

Emily Tarleton, MS, RD

Center for Clinical and Translational Science, University of Vermont

Abstract

Research has focused extensively on the negative health effects of inadequate magnesium (Mg) intake, but the extent of the problem of deficiency deserves further exploration. The notion that U.S. adults consume an inadequate amount of magnesium, leading to increased risk for chronic diseases, is plausible. Large, cross-sectional, population-based data sets indicate over half the adult population does not consume adequate amounts of magnesium. Changes in agricultural processes that reduce magnesium levels in crops combined with the increasing consumption of processed foods containing little to no magnesium have led to a decrease in mean daily intake over the past century. However, recent population-based studies show a steady and consistent recovery in magnesium consumption over the last several decades. A simple, rapid, accurate test for whole body Mg status is lacking and, although population-based studies have limitations, continued monitoring of Mg consumption is essential to determine whether this positive trend continues. In the meantime, since the health consequences of inadequate magnesium are well established, there are no reported cases of hypermagnesemia from food alone, and magnesium is found in healthy foods adults should consume more often, there are few reasons not to encourage increased magnesium intake.

Introduction

The effect of inadequate magnesium (Mg) intake on health is well established and includes electrolyte, neuromuscular, neurologic, and cardiovascular abnormalities.[1-4] Adequate intake of Mg is essential due to the mineral's role in energy production, prevention of dysrhythmias, blood pressure regulation, insulin resistance, and bone homeostasis.[2,5,6] A simple, rapid, accurate test for whole body Mg status is lacking and, as a result, monitoring Mg status in U.S. adults is difficult,[7] butMg consumption has reportedly decreased over the past century by 200-300 mg per day.[8-10] The possible reasons for this decrease are multifaceted and include changes in agricultural processes and food consumption patterns. Mg homeostasis in humans is influenced not only by dietary intake but also by absorption in the gastrointestinal (GI) tract and excretion by the kidneys.[11] However, further research is needed to draw any conclusions as to the extent of these factors on net Mg levels. If population-based studies, which use 24-hour recall data to track intake over time, support the idea of an increasingly Mg deficient population, the negative health effects are a public health concern.[4,7] The aim of this paper is to explore the factors impacting Mg consumption over time and the current adequacy of intake in U.S. adults.

Magnesium Basics

Mg, as the fourth most abundant mineral and second most abundant cation in the human body, has numerous essential roles.[12] In addition to being a cofactor for over 300 enzymes, it is essential for anaerobic and aerobic energy generation, glycolysis,

mitochondrial oxidative phosphorylation, regulating movement of potassium, and acts as nature's physiological calcium channel blocker.[13] Mg is an essential mineral that plays a role in the physiological function of the heart, brain, and skeletal muscles. The human body contains ~25 grams of Mg with 50-60% found in bone, which is responsible for maintaining normal extracellular magnesium concentrations, while the rest is found mostly in skeletal muscle and soft tissue.[6] The GI tract and kidneys are the organs primarily responsible for Mg homeostasis. When dietary intake of Mg is low the percent absorbed from the diet by the GI tract increases and the amount excreted by the kidneys decreases to replenish stores.[6] After consumption, around 30% is absorbed by the intestine, 5% is eliminated in feces, approximately 30% is used to replenish stores in bone, muscle, and other parts of the body, 30% is excreted via urine, and small amounts are lost via sweat.[13]

Assessing Magnesium Status

Bone and muscle are the two main compartments for storage and, because they are not easily or painlessly accessible, an accurate test for whole body Mg status is lacking.[7] Clinical lab tests for assessing Mg include total serum Mg concentration (SMC) and 24 hour urine excretion. Normal serum levels are 0.75-0.95 mmol/L (1.8-2.3mg/dl).[6] Only 1% of total body magnesium is present in extracellular fluids and only 0.3% is found in serum.[11] While SMC is the most convenient and economical way to measure magnesium, it is not reflective of intracellular magnesium levels[14] and does not reflect bone stores, which might be dangerously low as the body uses them to preserve serum levels.[6,15] SMC can also be low while total body stores are adequate as when a person is

taking a drug that acutely increases excretion of Mg.[16] Twenty-four hour urine excretion is readily available, but it is a better assessment of magnesium wasting by the kidneys and not necessarily a test to assess Mg status.[16] Mg in urine most likely shows the current snapshot of intake and a single 24 hour urinary Mg is not adequate for assessing Mg status due to the rapidity of change in urinary Mg excretion in response to dietary intake.[7,15]

Other potential tests of Mg status are not widely available. Serum concentration of ionized Mg, the biologically active form, may be the most reflective of current status.[7] However, very few clinical laboratories offer this service.[16] A Mg retention test, which assesses the amount of Mg excreted in urine after a parentally administered load test, is probably the best assessment of Mg deficiency since intracellular levels are physiologically representative.[16] But it is a more invasive technique, is usually limited to use in research studies, and it is only appropriate for adults with adequate kidney and intestinal function.[6,17] Also of interest, but requiring additional research, are phosphorous nuclear magnetic resonance (NMR) spectroscopy to measure brain magnesium and total and free red blood cell Mg concentrations.[16,18]

Daily Requirements

The response by the body to ensure Mg homeostasis makes it difficult to determine daily requirements.[19] The estimated average requirements (EAR) and recommended daily allowances (RDA) for Mg intake are based on age and gender (Table 1.1). Current reference values stems from the fact that they were determined by measuring SMC in healthy normal individuals during data collection for National Health

and Nutrition Examination Survey I (NHANES I) in 1974.[20] Between 1971 and 1974, the average serum Mg level in U.S. adults was 0.85 mm/L.[20] In this same population a serum Mg deficiency of 21% in women and 1.5% in men was reported.[7,20] Since then there have been changes in the food supply and prevalence of diseases such as diabetes that affect Mg status, which may indicate a need to reevaluate daily requirements.[7] Reviews of the adequacy of the EAR question its validity.[4,7,15,21] Population studies over the past few decades assessing both food and supplement sources of Mg indicate a majority of U.S. adults consume amounts below the EAR (Table 1.2).[22-25] In fact, Mg was listed as a shortfall nutrient in the 2015 Dietary Guidelines, which indicates Mg status in the U.S. is a public health concern.[26] Women consume less Mg than men and black males and females consume less than their white counterparts, a trend that is well documented going back to the 1970s.[20]

Clinical Significance of Deficiency

The clinical consequences of inadequate Mg status have been reviewed extensively.[1-4] Hypomagnesaemia is associated with electrolyte, neuromuscular, neurologic, and cardiovascular abnormalities.[27] Mg plays a role in myocardial energy production, prevention of dysrhythmias, and promoting vasodilation.[5] Increased consumption of Mg can aid in treatment of CVD and prevention of sudden cardiac death.[2,4] Correcting Mg status can help control blood pressure and reduce risk factors for CVD, especially in those with hypertension and those that are depleted in Mg due to diuretic use or poor dietary intake.[2] Mg intake and serum Mg concentration are inversely proportional with c-reactive protein (CRP) levels.[4] CRP, a measure of inflammation, is

associated with risk of cardiovascular disease (CVD), metabolic syndrome, and diabetes.[4] This relationship with inflammation may help explain why inadequate intake and hypomagnesaemia are associated with CVD, arrhythmias, heart failure, diabetes, and metabolic syndrome.[2,28-31] Elevated risk of diseases even with SMC at higher levels than the present clinical cut off for deficiency further raise the question of the adequacy of the reference intervals.[7] Latent, or subclinical, deficiency is likely associated with risk of chronic diseases such as hypertension, cardiovascular disease (CVD), diabetes, and osteoporosis.[32]

The varied roles of Mg in the body have led to research on its impact on other chronic health conditions as well. The association between magnesium intake and depression is well documented.[23,33,34] Magnesium plays a role in many of the pathways involved in the pathophysiology of depression and is found in several enzymes, hormones, and neurotransmitters and depression is also associated with inflammation.[35,36] Recent randomized clinical trials have found supplementation with magnesium improves symptoms of depression in patient with hypomagnesaemia[37] and regardless of baseline Mg status.[38] Mg is involved in bone cell growth and inadequate intakes can lead to decreased bone formation and loss of bone mass. Animal studies have shown that Mg levels at 10%, 25% and 50% of adequate intake lead to bone loss, decreased osteoblast and increased osteoclast activity.[4] Adults suffering from migraines tend to be deficient in Mg and Mg's role as a smooth muscle relaxant may also make ensuring adequate status a priority for alleviating symptoms of asthma.[5] Recommendations for Mg supplementation

to alleviate symptoms of these clinical consequences of deficiency are currently under investigation.

Hypermagnesaemia, on the other hand, is not a concern. Overconsumption of Mg from food intake alone has never been documented and rarely occurs from intakes from supplemental Mg in people with adequate kidney function.[6]

Consumption Patterns

The negative health effects of inadequate Mg intake are not controversial, but the extent of the problem of deficiency deserves further exploration. The clinical significance of Mg deficiency in a majority of the U.S. is not inconsequential. A reliable and convenient clinical test for Mg status is not available to document changes in Mg status over time. Researchers rely on results from population-based studies to study changes in daily consumption throughout the past century. Daily intake has decreased from 400-500 mg per day in the early 20th century to 200-300 mg per day in the 21st century.[8-10] Dietary Mg intake is directly related to calorie intake but is influenced by the amount of Mg absorbed by the plant from the soil. Low Mg status may be an indicator of other suboptimal dietary and lifestyle patterns, such as inadequate intake of whole grains, fruits, and vegetables.[7] Unhealthy dietary patterns are often influenced by socioeconomic status.[39] Figure 1.1 illustrates the factors influencing Mg homeostasis. The following sections focus on factors impacting Mg consumption over the past century (Table 1.3). If the majority of the U.S. adult population is Mg deficient, the reasons for decreased consumption of Mg may prove to be an area for public health interventions.

Magnesium in Soil and Crops

A decrease of Mg in the food supply is likely a major contributor to inadequate consumption of Mg and perhaps chronic latent deficiency.[7] The mineral content of food differs according to the mineral content of the soil they are grown in, how the plant is grown and harvested, and the amount of processing prior to consumption. Wild plant foods consumed by hunter gatherers generally maintained higher micronutrient concentrations than do their domesticated counterparts.[40] Historical data of soil fertility indicate changes in concentrations of minerals in products from the 1940s to the end of the 20th century. Some studies report median declines of 5-40% or more of minerals in fruits and vegetables over the past 50 to 70 years.[13,41] Magnesium concentrations in cheese have decreased by 20% and meat by 15% due to decreased Mg in the feed given to animals.[42] The exact change is difficult to quantify due to the methods of purchasing, pretreating, and analyzing the food items by different researchers.[43] None the less, changes in the amount of Mg in the soil are reflected in crops. To increase the amount of Mg in food, there needs to be more Mg available in the soil.

The reason for the change in the amount of Mg in crops is hypothesized to stem from changes in agricultural processes that result in soil induced dilution effect and genetic dilution effect.[41,42] Soil dilution occurs as the result of environmental changes such as fertilization and irrigation, which tend to decrease concentrations of minerals in plants.[41] Phosphorus from fertilizers can be beneficial to Mg concentrations in the plant at low doses, but detrimental at very high rates of application.[42] Genetic dilution occurs when plant yield increases as a result of selective breeding.[42] This process came about

during the "green revolution" in the 1960s and 1970s, which encouraged increased yield of grains and other crops by 2 to 3 fold in developing countries.[41,44] For example, in fruits, vegetables, and grains approximately 80% to 90% of the dry weight yield is carbohydrate. When breeders select for a high yield they are selecting for high carbohydrate yield, with no assurance that any other nutrients are increasing in the same proportion.[41] Mg content in the food supply is affected by these agricultural processes. Twentieth century wheat can contain almost 30% less Mg.[44] Increasing grain yields over the past 40 years have provided additional food for the human population, but with a corresponding decrease in the availability of essential nutrients.

In addition to the amount of Mg available to the plant from the soil, factors related to the presence of other nutrients and the growth of the plant affect the Mg content of crops. The amount of Mg is influenced by competition with other ions (such as calcium), elevated concentrations of aluminum (which decreases Mg uptake[45]), and other factors that restrict the size of the root system.[42] Mg is found in high concentrations in the chlorophyll of plants,[2] but the developing layer of the plant actually becomes a barrier to absorption and less Mg is absorbed as the plant grows.[42] The edible portion of a plant can also determine Mg intake. Root crops store 25-33% of their Mg content in the tap root, which is usually not consumed.[42] Up to 50% of Mg is stored in the reproductive organs of plants such as seed or grain and are removed during processing.[42]

Magnesium in Water

Hard water is frequently considered an important source of Mg[42] and can account for up to 10% of daily intake.[2] The amount of Mg consumed from water varies greatly

depending on the mineral content of the water supply.[1,5] Soft water has decreased concentrations of dissolved Mg due to the process of distillation.[7] To meet the growing need for potable water, desalination has increased and the Mg content of desalinated water is less (0.8mg/L) than hard water (20-30 mg/L).[46] Geography also plays a role in the amount of Mg in the water supply. North American bottled and tap water contains much lower levels of Mg than European counterparts.[47] Levels of Mg in water differ significantly between states and even within areas of the same city.[47] Tap water accounts for two thirds of water consumed at home, but only half of water consumed away from home.[48] Per capita consumption of bottled water in the U.S. has increased from just under 2 gallons in 1976 to over 36 gallons in 2015, an increase of about 6% per year.[49,50] Filtered and bottled water contain less Mg than tap water, although, again, amounts vary greatly by the source of the water since mineral water contains higher amounts than spring water.[47]

Changes in Food Patterns

There are no excellent sources (providing 40% or more of the RDA per serving) or good sources (providing 25% or more of the RDA per serving) of Mg.[51] The highest levels of Mg are found in green vegetables, beans, peas, legumes, nuts, and whole unrefined grains. Meat, fish, dairy, and fat contain little Mg.[52] The amount of Mg in the U.S. food supply changed from 408 mg in the early 1900s to 349 mg in 1980, a 14% decrease.[53] Increased intake of processed grains and potatoes paired with increases in dairy, meat, poultry, and fish is thought to be a major reason for the decrease. From 1909-

1913 to 1980 the supply of protein from vegetables decreased by 33% while protein from animals increased by 24%, leading to a net reduction in Mg supply.[53]

With 72% of total energy in the current Western style diet coming from dairy products, cereals, refined vegetable oils, and alcohol, it is a poor source of Mg and often contains only 30-50% of the RDA for Mg.[2,54] Mg intake is directly related to calorie intake except when energy comes from high amounts of alcohol or refined sugars and oils.[1] As a result, eating a typical American diet has to include higher amounts of calories or include supplements to meet Mg recommendations.[55] Diets containing at least 3000 calories per day may be needed, in such cases, to achieve adequate intake of Mg from diet alone, which exceeds the calorie needs of the average adult.[56]

Sugar plus refined oil makes up over 36% of the U.S. diet.[40] Adults in the U.S. consume a large proportion of total energy from energy-dense, refined sugars such as cakes, cookies, pies, sodas and soft drinks and consuming large amounts of these foods reduces the total vitamin and mineral density of the diet.[57] Between 1909-1913 and 1980 use of sugars and other sweeteners increased by 50%, [53] and continued to climb. Per capita consumption of refined sugars in the U.S. increased from 55.5kg in 1970 to 69.1kg in 2000.[40] More recently, mean daily intake has decreased slightly from 21 teaspoons per day in 2003-2004 to just over 18 teaspoons in 2011-2012.[58] From 1909-1999 per capita consumption of vegetable oil increased by 130%, shortening increased by 136%, and margarine increased by 410%.[40] Changes in animal husbandry practices and decreased consumption of wild animals over the past two centuries led to the large scale addition of refined oils to the food supply.[40] Fat storage depots of wild animals are mostly saturated

fatty acids, while muscle and organ tissues supply mostly poly and mono unsaturated fats. Year round dietary intakes of high amounts of saturated fat are not possible when relying on wild animals for meat, due to the seasonal cyclic depletion of saturated fat. Animal husbandry has made it feasible to prevent this seasonal decline in body fat and to also slaughter at peak body fat percentage. The discovery of processing procedures that allow for the storage of products with high concentrations of animal saturated fats (cheese, butter, tallow, salted fatty meats) allows for year round consumption of these high fat products.[40]

Vegetables contain a high amount of Mg, but are consistently under consumed in the American diet. Use of processed vegetables increased 4 fold during the 20th century, while consumption of fresh vegetables increased only during the first half of the century.[53] Processing and boiling of vegetables leads to the loss of 80-90% of Mg and when these foods are the base of a person's diet, deficiency can occur.[1,13] From 1976-1980 (NHANES II) to 1988-1994 (NHANES III) the percent of adults consuming three or more servings of vegetables per day increased from 27% to 35%.[59,60] NHANES data from 1999-2002 indicate a small, but significant (P=0.03) decrease in mean daily intake with only 33% of adults consuming at least 3 servings of vegetables per day.[60] Other population-based studies confirm that vegetable intake stalled and then decreased in the late 1990s. Behavioral Risk Factor Surveillance System (BRFSS) data from 1990 to 1994 is consistent with the NHANES data from the early 1990s and indicates the percentage of U.S. adults meeting the guidelines for 5 servings of fruits and vegetables per day increased from 19% in 1990 to 22% in 1994, but then only increased to 23% in 1996.[61]

BRFSS data from 1994 to 2005 show an overall significant decrease in frequency of daily consumption of vegetables by U.S. adults from 2.03 times per day to 1.91 times (95% confidence interval -1.12, -0.10; $P<0.001$).[62] More recent data from BRFSS indicate the intake of vegetables remains poor. From 2007 to 2010, 13% of the adult population met the recommendations for daily vegetable intake of at least 1.5 cups per day and in 2013 the percentage decreased to 9%.[63]

Adults following a vegetarian diet tend to have higher intake of Mg from food.[8] Varying degrees of vegetarianism (i.e. lacto-ovo, or pesco-vegetarian) result in higher Mg consumption compared to a typical Western diet. In comparison to a typical U.S. diet pattern, a strict vegetarian diet significantly increases the amount of Mg consumed (mean intake of 509 mg per day vs. 652 mg per day; $P<0.05$).[64] The reason for the higher Mg intake is most likely a result of higher intakes of vegetables and legumes.[65] The percent of U.S. adults following a vegetarian diet has decreased from 2.3% in 2006 to 1.8% in 2016.[66]

Breakfast consumption was associated with a predicted increase in daily fruit and vegetable servings in a rural U.S. population (coefficient 0.255; $P<0.001$).[67] Mg intake is lowest and prevalence of inadequacy is highest in people not consuming breakfast and adequate intake is highest in those consuming ready to eat cereals (RTEC).[68] The adequacy seen with consumption of breakfast is thought to be a result of the inclusion of whole grains and dairy products. Although dairy is not a rich source of Mg, it is consumed so frequently that is acts as a significant source of Mg in U.S. diets. Dairy and dairy products provided 18% of daily Mg in the National Food Consumption Survey

(NFCS) of 1977-1978 and over 10% of adults' daily Mg in the Continuing Survey of Food by Individuals (CSFI) (1989-1991).[69,70] While still a large part of the Western diet, dairy intake has decreased over time. Between 2001 and 2004, 15% of Americans consumed the recommended daily servings of dairy, but in 2007-2010 only 11% met the recommendation.[71] Changes in the diet to meet the recommended servings predict a decrease of inadequate Mg intake in U.S. adults from 56% to 33%. The benefits were especially seen in older adults.[71]

However, conflicting research has shown that if RTEC and milk products are consumed more than fruit, vegetables, lean meat, and seafood, the overall micronutrient density in the diet is lowered.[40] The introduction of dairy and cereal grains as staples may have caused the average micronutrient content of the human diet to decline. The decline was worsened by milling techniques. In the latter part of the 19th century, nutritional characteristics of milled grain changed due to the germ and bran being removed during the milling process.[40] Only 16-18% of original Mg in many RTEC remains in the refined product.[18] Diets high in processed carbohydrates result in a significantly lower intake of Mg.[72] For example, a potato without the skin contains a third less Mg than one with skin. [42] White bread and cooked white rice contain almost a third less Mg than their whole grain counterparts.[52] From 2003-2004 to 2011-2012, a small but significant increase in the consumption of whole grains was seen in the U.S. population (0.6 g to 0.9 g equivalent per day; $P<0.01$). Nevertheless, consumption is still far below the recommendation to consume 50% of grains as whole.[58] These counter points regarding

dairy and RTEC intake reinforce the need to promote a balanced diet of various whole foods to attain nutritional adequacy.

Intake of beans, legumes, nuts, and seeds has remained mostly constant throughout the 21st century.[53] Between 2009 and 2010 40% of U.S. adults consumed nuts on a given day, but only 6% of the U.S. population consumes tree nuts regularly.[73] Tree nuts, similarly to dairy, are a great source of shortfall nutrients. Ninety-two percent of people eating tree nuts consume the EAR for Mg, compared to 40% of non-consumers and tree nut consumers exhibit a diet pattern of higher quality and nutrient adequacy overall.[54] Between 2005 and 2012 daily consumption of nuts and seeds has increased slightly (0.60 ounce equivalents to 0.70 ounce equivalents) as has the intake of legumes (0.09 cups to 0.12 cups).[74] While changes in consumption of these food items are not a reason for an overall decline in adequate Mg intake, they offer the potential for improving nutrient adequacy in the U.S. diet.

Magnesium Supplements

Supplements can be a major contributor to overall vitamin and mineral intake. In 1986, 15% of the population was taking an over the counter Mg supplement. The most common amount was 100 mg, although daily intake and the form of Mg was not confirmed.[6] A review of Mg supplement intake in the following decades using NHANES data shows that as of 2011-2012 Mg supplement use has increased to 28% of the population, although this is down from a high of 37% in 2005-2006.[75] Use is consistently higher in females[6,75] and increases with age.[76] People using supplements tend to consume healthier diets and have higher intakes of Mg from food as well.[48,76] Older adults taking

supplements are three times as likely to have adequate intake and older adults consuming a supplement also consume twice as much Mg from food alone.[48]

Socioeconomic Status

Individuals with a higher socioeconomic status (SES) consume healthier diets.[77] Higher income and education are associated with higher consumption of reduced or nonfat milk, lean meats, whole grains, and with consuming at least five servings of fruits and vegetables per day, while low SES is associated with higher consumption of refined grains and added fats.[39,60,77] Low educational status is associated with low earning potential, low purchasing power, and food insecurity.[39] The prevalence of food insecurity has remained stable at just over 14% throughout the 21st century.[26] Food costs are a barrier to consumption of nutrient dense foods in low SES groups.[77] Food insecure adults consume vegetables fewer times per month than food secure adults (69 vs. 76; $P<0.05$).[78] The need to maximize calorie intake and minimize food waste leads to not only the consumption of highly processed, shelf stable foods but also minimal variety.[77] The price of fruits and vegetables has increased more than foods high in sugar and fat in the past 20 years.[77,78] The increase in price affects those living in poverty to a greater extent and decreases access to healthy food. The disparity between SES and fruit and vegetable intake has increased over time. Results from the 5 A Day for Better Health Program indicate that though awareness of the program encouraging consumption of fruits and vegetable in the 1990s increased, intake declined in non-white racial and ethnic groups.[79] This finding may help explain the change in vegetable intake at the end of the 20th century. Americans living in poverty are more likely to be food insecure.[78]

Higher SES groups tend to consume higher amounts of most vitamins, minerals, and fiber regardless of overall energy intake.[77,80] NFCS from the 1970s through the 1990s indicate individuals living in poverty consume less Mg.[69] Gender, race, age, income and education level are associated with Mg intake as well as poverty level.[24,25,80,81] NHANES III (1988-1994) data indicate older adults experiencing food insecurity consume only 58% of the RDA for Mg while their food secure counterparts consume 77% of the RDA ($P<0.05$).[78] Older adults in the U.S. with higher income meet the EAR for Mg to a significantly higher extent than those with low income (39% vs. 22%; $P<0.05$) due to a healthier overall diet pattern.[39] NHANES 2011-2012 data indicate that the prevalence of U.S. adults meeting the EAR is greater for those with the highest income (~72%) versus those living in poverty (~50%; $P<0.001$) and those living in poverty are also less likely to take any dietary supplement (63% of those with higher income vs. 52% in the lowest poverty group; $P<0.001$) .[82] Although it is important to note that over half of adults in the high-income group still consume less than the EAR, and many well-educated, healthy adults also consume inadequate amounts of Mg.[83]

Mean changes in Mg intake over time

The data to this point supports the idea of a population with less access to and less consumption of Mg compared to the previous century. However, when comparing the NFCS from 1977-1978 and the NHANES from 2013-2014, mean Mg intake in men 20 years and older increased from 283 mg per day to 345 mg per day and in women of the same age from 204 mg per day to 268 mg per day (Figure 1.2; Joseph Goldman, MA, Food Surveys Research Group Agricultural Research Service, United States Department

of Agriculture, email communication, April 18, 2017). The data is consistent with the research indicating mean consumption in U.S adults is 200-300 mg per day, a decrease from a mean of 400-500 mg per day a century ago.[8-10] Yet, despite evidence to the contrary, Figure 1.2 indicates overall Mg intake in U.S. adults is recovering. These surveys confirm women consume less Mg than men and indicate older adults and females aged 20-29 years still do not currently meet the EAR, but mean intake in these age groups continues to increase along with the rest of the population.

Evidence for Inadequate Mg Status

The contradictory information gathered here does not resolve the question as to whether U.S. adults consume adequate amounts of Mg. According to several population-based studies investigating Mg intake in U.S. adults since the start of the 21st century, a majority do not consume the EAR. There is population-based data reviewing changes in dietary patterns and other factors affecting Mg consumption to support this conclusion. U.S. adults are consuming more amounts of processed grains, oils, and sugar, animal sources of protein, relying on soft water and bottled water more often, and consuming fewer fruits and vegetables and Mg supplements. At the same time, according to agricultural research, the amount of Mg in food is decreasing as a result of changing crop management practices. Yet 24-hour recall data from population-based surveys indicate an overall increase in Mg intake in all adults with mean intake reaching the EAR as of 2014.

Due to the limitations of consumption data from population-based studies, results should be interpreted with caution. Over the years, the way in which intake data is analyzed changes or differs by investigator and comparing results is difficult. Some

studies group foods according to conceptually and nutritionally similar characteristics, but do not disaggregate food mixtures.[84] The result is potentially inflated values for some macro and micronutrients.[70] Other studies separate food mixtures into individual ingredients and are then able to assess the nutrient contribution of each food, which results in a more accurate portrayal of percent distribution.[70] Comparing studies using differing methods may result in flawed conclusions about changes in consumption over time. Methods of surveys themselves can make it difficult to compare data if they do not properly weigh the data to the national population and use methodology that considers the complex sample design.[85] The 24-hour recall is the most common dietary data collection instrument used in surveillance and is the tool used in What We Eat in America (WWEIA), the dietary component of the NHANES.[86] A limitation of the 24-hour recall is that intake varies greatly from day to day and is not indicative of long term intake, although at the population level, it is thought to provide valid estimates of nutrient intake.[87] Interviewer training and interviewer inter reliability is also a limitation of 24-hour recalls. Decisions about the degree of probing for additional details for foods or recipes, as well as the use of default ingredients in recipes, impact the results. Trained interviewers are utilized for WWEIA and methods are validated.[88]

The availability of reliable food composition databases to analyze 24-hour intake data, in addition to appropriate statistical modeling to calculate the distribution of usual intake in a population, is essential to producing accurate dietary recall data.[86] There is evidence that the Mg in food has decreased over time due to agricultural processes. The amount of Mg reported in food varies with the seasons and can change frequently due to

manufacturer reformulations. Food composition data used to analyze intake must be continuously updated to reflect these changes. The United States Department of Agriculture (USDA) provides the food and nutrient databases used for population-based analyses. The National Database for Standard Reference (SR) is the main source of food composition data in the U.S.[89] It is updated annually and data are derived from USDA contracted analyses, the food industry, and the scientific literature. The Food and Nutrient Database for Dietary Studies (FNDDS) provides nutrient values and weights for typical food portions and is the underlying database for analyzing 24 hour recalls from survey responders in WWEIA.[89] There are no missing values in FNDDS and it is updated biennially. The nutrient values for the FNDDS are derived from SR. Food composition data are integral to the success of all federal dietary surveys by the USDA and Department of Health and Human Services. The ability of the agencies to keep pace with changes in the U.S. food system is commendable, but the databases are limited by the high cost of food analysis coupled with funding constraints.[90]

The Nutrition Data Set for Research (NDSR) is a Windows-based program designed for the collection and analysis of 24-hour dietary recalls, food records, menus, and recipes. It combines data from the USDA, food manufacturers, and scientific literature and includes more individual products than the FNDDS.[90] The database, developed and supported by the Nutrition Coordinating Center at the University of Minnesota, is used frequently in nutrition research. Due to the importance of knowing the nutrient content of food items, a recent study compared phosphorous values reported in NDSR for 46 products with results from a food analysis laboratory.[91] The results

indicated 78% of the products had higher levels of phosphorous than the NDSR reference values. This small study investigated the potential effects of inaccuracies in the nutrient database on study results. While it involved only one nutrient, it points to the possible limitations of current nutrient databases used in research and the ability to use results to make decisions about the nutritional status of the population.

Future Directions

In early 2015, as a result of the Dietary Guidelines Advisory Committee listing Mg as a shortfall nutrient, a workshop convened in the U.S. to assess the evidence for the need to revise the serum magnesium reference level. The group concluded that adequate scientific data exists to warrant an increase in the reference level to improve clinical care and public health.[7] To determine the reference level, a validated biomarker that most reflects Mg status is needed; whether it is a dietary, urinary, serum, or a combination marker is unknown. Other recommendations from the group include addressing methods of improving intake of Mg in crops and packaged foods, increasing public emphasis and education on the importance of Mg in the diet, and the development of systems to monitor Mg insufficiency.[7] While the development of a validated biomarker is essential, it will not be achieved quickly. The other recommendations are either already being implemented as part of larger public health initiatives or could be relatively easily.

Increasing the nutrient content of crops, minimizing loss during processing, and preserving nutrients during transport is possible. The amount of Mg that plant foods provide can be greatly improved by increasing the availability of Mg during growth and production.[92] Mg applications to the soil take time to become incorporated into crops;

however, foliar sprays of Epsom salts can increase Mg content of plants within 6 weeks.[93] Agronomic practices that encourage supplying adequate nutrients to the plant during vegetation, increasing the percent of edible plant parts, and use of high efficiency fertilizer along with low leaching techniques are additional suggested techniques for increasing Mg in food.[42] The quality and nutrient content of fruits and vegetables is also determined by the characteristics of the supply chain (time since harvest and type of processing).[94] Preservation methods can reduce the nutritional losses and increase shelf life, minimizing the impact of "food miles".[94]

Consuming a variety of foods high in Mg should be encouraged in all adults, regardless of the presence of lifestyle factors or chronic diseases that increase the risk of deficiency. Eating more whole grains, vegetables, legumes, nuts, and seeds can lead to higher intakes of Mg and other short fall nutrients. Decreased reliance on refined sugar and oils also decreases the risk of Mg deficiency. Modeling of various dietary scenarios indicate increasing plant foods by 100% of current intake and eliminating animal products decreases the percentage of people with inadequate Mg intake by 5-8%.[95] Increasing dairy products by 100% without changing the amount of intake from plant foods decreases the rate of inadequate Mg by 12%, but this model also increases calorie intake by almost 200 calories per day in.[95] An increase in total calorie intake with increased dairy intake would need to be counterbalanced with other dietary or lifestyle changes. The total amount of calcium consumption should be taken into account when recommending dairy to increase Mg intake, since very high calcium intake competes with Mg for absorption.[55]

Increasing the Mg concentration in the plant, and thus how much is consumed, might be more feasible than changing eating patterns since evidence that simply increasing awareness and knowledge of good nutrition practices leads to long term behavior change is lacking.[96] Education level can affect not only purchasing power but also exposure and understanding of dietary information and healthy behavior messages.[80] Strategies to encourage healthy eating patterns must be continually evaluated and revised to stay current with changes in the market and consumer needs. Due to the lower intake of Mg in minority groups, future programs hoping to improve diet patterns, and thus increase Mg intake, should focus not only on awareness around the benefits of increasing consumption of vegetables, legumes, nuts, and seeds but also the cultural aspects of dietary preferences.[97,98]

Not addressed by the working group is the use of supplements to fill the gap between food intake and the RDA. There have been no reported cases of hypermagnesemia from food alone, even in people with inadequate kidney function, and toxicity from supplements is rare.[6] Supplements can play a large role in meeting Mg needs.[83] Adults whose diet or medical history put them at higher risk for deficiency may benefit from Mg supplements in a highly absorbable forms, such as Mg salts. Generally tolerated in doses below the upper tolerable limit of 350 mg per day in those with adequate kidney function, higher doses can cause GI upset.[6] GI upset acts as a limiting factor in the amount of Mg that is consumed and leads to decreased intake or termination of consumption prior to reaching toxicity levels. Changes in SMC occur within weeks of initiation of Mg supplementation.[16]

A diagnosis of hypomagnesaemia due to inadequate dietary intake alone is rare.[1] As discussed, this may partly be due to the body's ability to utilize stores and maintain adequate SMC in times of deficiency. Several factors increase the requirement for Mg due to decreased absorption or increased excretion. However, many of the causes are not well understood or are not easily modifiable. Compounds in food such as phytic acid, oxalic acid, and protein, chronic conditions such as diabetes and gastrointestinal disorders, and behaviors such as smoking and alcohol consumption, as well as aging and medications may impact Mg absorption and excretion.[6,43,99-102] More research to determine the overall effect of these factors on net Mg levels is needed. Increasing Mg consumption through changes in agricultural processes and consumption of whole foods is likely a more realistic approach to ensuring adequate Mg status in U.S. adults at this time.

Conclusion

Until a valid biomarker for Mg status is discovered, continued monitoring of Mg intake via future population-based studies is essential. Despite the potential for deceased Mg intake as a result of changes in agricultural practices and dietary patterns, mean Mg intake in U.S. adults has improved over the past 40 years. However, positive dietary trends can stall and then decline and continued monitoring is essential. In the meantime, since there are no reported cases of hypermagnesemia from food alone, the health consequences of inadequate Mg are well established, and Mg is found in healthy foods adults should consume more often, there are few reasons not to encourage increased Mg intake from food. A public health campaign directed solely at Mg consumption in

addition to those to increase fruit, vegetable, and whole grain consumption is most likely not needed at this time.

Table 1.1 United States published requirements for magnesium[6]

Age	Male	Female	Pregnancy	Lactation
Estimated Average Requirement				
19-30 years	330	255	290	255
31-50 years	350	265	300	265
51-70 years	350	265		
>70 years	350	265		
Recommended Dietary Allowance				
19-30 years	400	310	350	310
31-50 years	420	320	360	320
51+ years	420	320		

Table 1.2 Percentage of adult population with intake below the EAR for magnesium

Reference	NHANES Years Represented	Magnesium Source	Ages Included	% Below EAR
Moshfegh, et al. (2005)[81]	2001-2002	food	19+	
Male				64%
Female				67%
Moshfegh, et al. (2009)[25]	2005-2006	food	19+	
Male				53%
Female				56%
Tarleton & Littenberg (2015)[23]	2007-2010	food + supplements	20+	54%
Papanikoloau, et al. (2015)[24]	2007-2010	food + supplements	19+	
White				43%
Male				44%
Female				41%
Black				69%
Male				69%
Female				69%
Cifelli, et al. (2016)[94]	2007-2010	food	19+	56%

Abbreviations: NHANES, National Health and Nutrition Examination Survey; EAR, Estimated Average Requirement

Figure 1.1 Factors influencing magnesium homeostasis

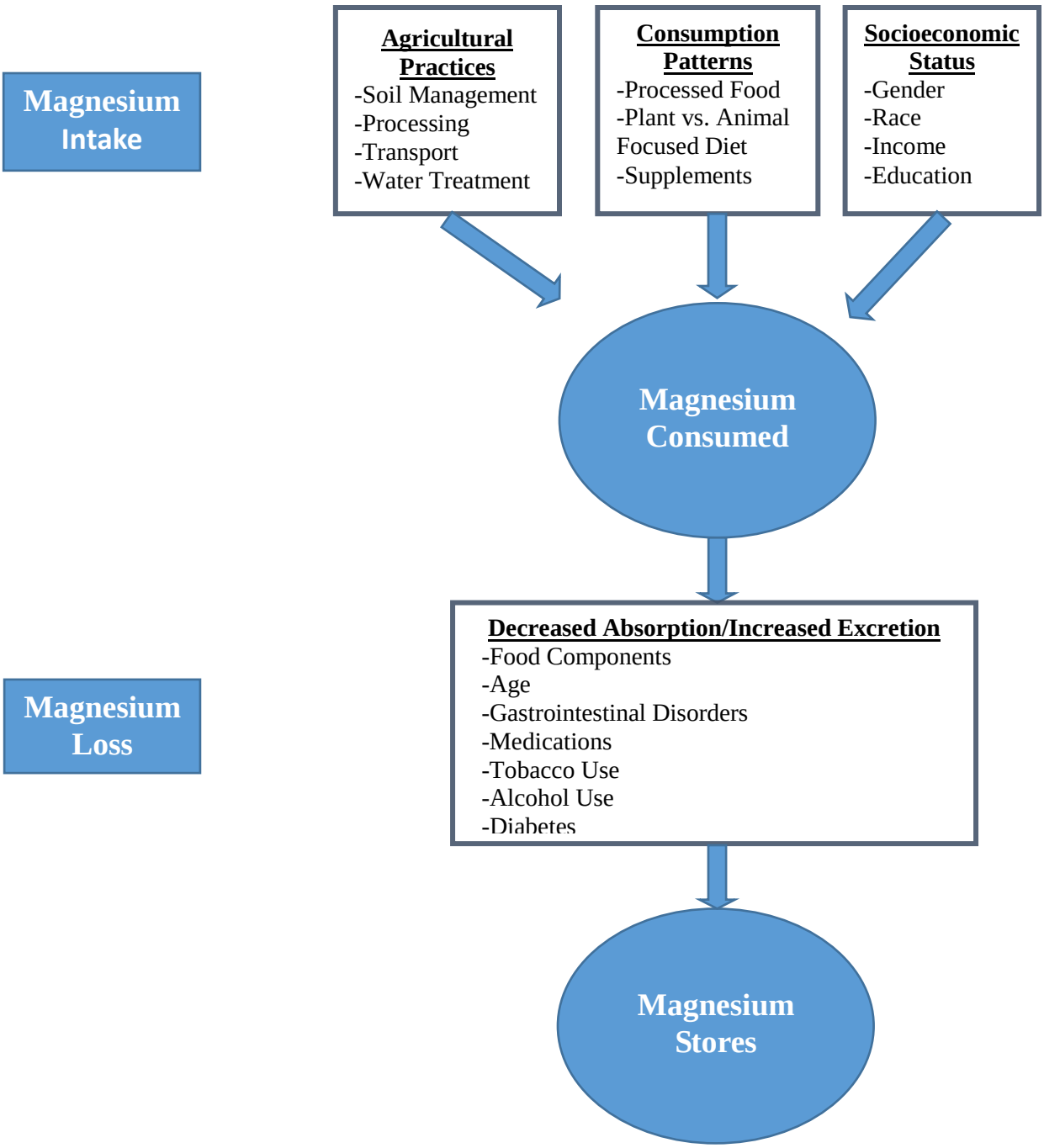


Table 1.3 Dietary factors negatively influencing consumption of magnesium: 20th to 21st century

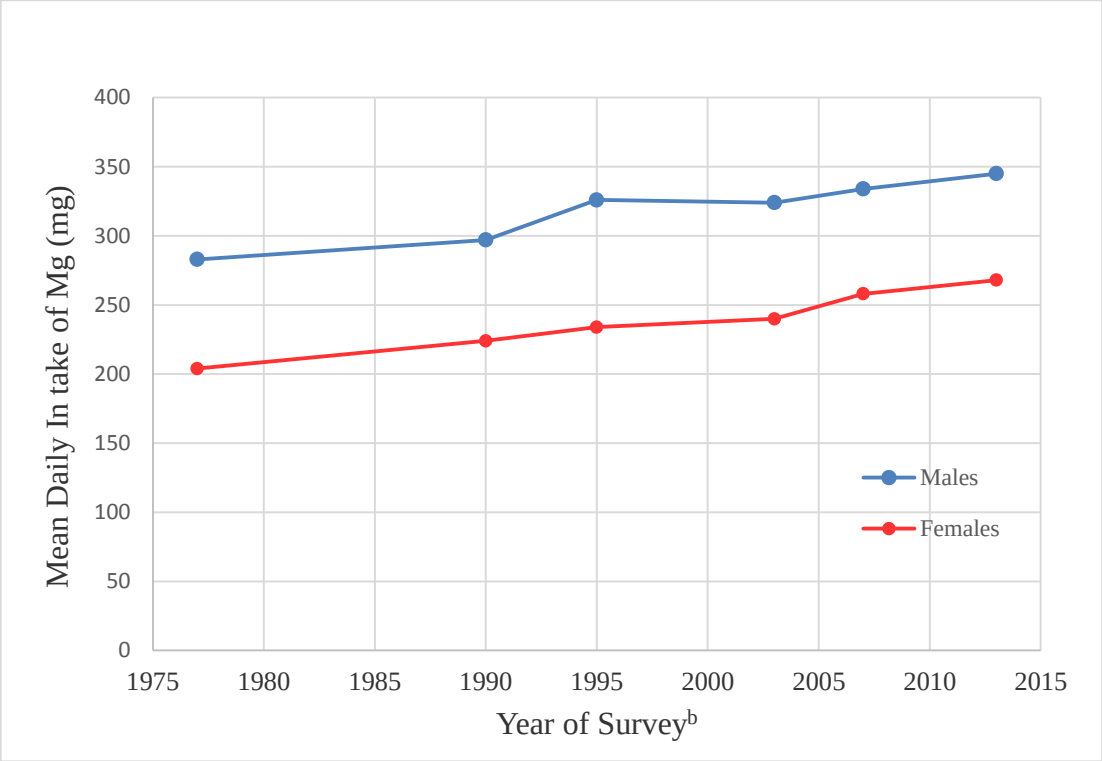
Decreased

- Magnesium in soil
- Magnesium in crops
- Consumption of plant based diets
- Consumption of dairy products

Increased

- Consumption of soft water and bottled water
- Reliance on animal protein
- Use of refined sugar and oils
- Consumption of processed grains and vegetables

Figure 1.2 Magnesium intake in U.S. adults over time[a]



[a] SOURCE: Joseph Goldman, MA, Food Surveys Research Group Agricultural Research Service, United States Department of Agriculture, email communication, April 18, 2017. All estimates from first day of intake collection which was collected in person. All statistics weighted to represent the national population using methodology that considered the complex sample design.
[b]National Food Consumption Survey 1977-1978; Continuing Survey of Food Intakes by Individuals 1989-1991, 1994-1996; What We Eat in America, National Health and Nutrition Examination Survey 2003-2004, 2007-2008, 2013-2014

References

1. Swaminathan R. Magnesium metabolism and its disorders. Clin Biochem Rev. 2003;24(2):47-66.
2. Grober U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients. 2015;7(9):8199-8226.
3. Long S, Romani AM. Role of cellular magnesium in human diseases. Austin J Nutr Food Sci. 2014;2(10):1-19.
4. Rosanoff A, Weaver CM, Rude RK. Suboptimal magnesium status in the United States: are the health consequences underestimated? Nutr Rev. 2012;70(3):153-164.
5. Beckstrand RL, Pickens JS. Beneficial effects of magnesium supplementation. J Evid Based Complement & Alt Med. 2011;16(3):181-189.
6. Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorous, Magnesium, Vitamin D, and Flouride*. Washington, DC: National Academy Press; 1997.
7. Costello RB, Elin RJ, Rosanoff A, Wallace TC. Perspective: the case for an evidence-based reference interval for serum magnesium: the time has come. Adv Nutr. 2016;7(6):977-993.
8. Altura BM, Altura BT. Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis. Cell Mol Biol Res. 1995;41(5):347-359.
9. Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended Dietary Allowances: Subcommittee on the Tenth Edition of the RDAs.* Washington DC: National Academy Press; 1989.
10. Marier J. Quantitative factors regarding magnesium status in the modern-day world. Magnesium. 1982;1(3-15):6.
11. Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kid J. 2012;5(Suppl 1):i3-i14.
12. Volpe SL. Magnesium in disease prevention and overall health. Adv Nutr. 2013;4(3):378s-383s.
13. de Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. Physiol Rev. 2015;95(1):1-46.
14. European Food Safety Authority Panel on Dietetic Products NaA. Scientific opinion on dietary reference values for magnesium. EFSA Journal. 2015;13(7):4186.
15. Nielsen FH, Johnson LA. Data from controlled metabolic ward studies provide guidance for the determination of status indicators and dietary requirements for magnesium. Biol Trace Elem Res. 2016;177(1):43-52.
16. Elin RJ. Assessment of magnesium status for diagnosis and therapy. Mag Res. 2010;23(4):S194-198.
17. Arnaud MJ. Update on the assessment of magnesium status. Br J Nutr. 2008;99(Suppl 3):S24-36.

18. Eby GA, Eby KL. Magnesium for treatment-resistant depression: a review and hypothesis. Med Hypotheses. 2010;74(4):649-660.
19. Felsby S, Nielsen J, Arendt-Nielsen L, Jensen TS. NMDA receptor blockade in chronic neuropathic pain: a comparison of ketamine and magnesium chloride. Pain. 1996;64(2):283-291.
20. Lowenstein FW, Stanton MF. Serum magnesium levels in the United States, 1971-1974. J Am Coll Nutr. 1986;5(4):399-414.
21. Hunt CD, Johnson LK. Magnesium requirements: new estimations for men and women by cross-sectional statistical analyses of metabolic magnesium balance data. Am J Clin Nutr. 2006;84(4):843-852.
22. Fulgoni VL, Keast DR, Bailey RL, Dwyer J. Foods, fortificants, and supplements: where do Americans get their nutrients? J Nutrition. 2011;141(10):1847-1854.
23. Tarleton EK, Littenberg B. Magnesium intake and depression in adults. J Am Board Fam Med. 2015;28(2):249-256.
24. Papanikolaou Y, Brooks J, Reider C, Fulgoni VL. Comparison of inadequate nutrient intakes in non-Hispanic blacks vs. non-Hispanic whites: an analysis of NHANES 2007-2010 in U.S. children and adults. J Health Care Poor Underserved. 2015;26(3):726-736.
25. Moshfegh A, Goldman J, Ahuja J, Rhodes D, LaComb R. What We Eat in America, NHANES 2005-2006: usual nutrient intakes from food and water compared to 1997 dietary reference intakes for vitamin D, calcium, phosphorous, and magnesium. 2009; https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/0506/usual_nutrient_intake_vitD_ca_phos_mg_2005-06.pdf. Accessed March 13, 2017.
26. United States Department of Health and Human Services, United States Department of Agriculture. *2015-2020 Dietary Guidelines for Americans.8th ed.* 2015; http://health.gov/dietaryguidelines/2015/guidelines/. Accessed March 7, 2017.
27. Martin KJ, González EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. J Am Soc Nephrol. 2009;20(11):2291-2295.
28. Geiger H, Wanner C. Magnesium in disease. Clin Kid J. 2012;5(Suppl 1):i25-i38.
29. Nielsen FH. Magnesium, inflammation, and obesity in chronic disease. Nutr Rev. 2010;68(6):333-340.
30. Moore-Schiltz L, Albert JM, Singer ME, Swain J, Nock NL. Dietary intake of calcium and magnesium and the metabolic syndrome in the National Health and Nutrition Examination (NHANES) 2001-2010 data. Br J Nutr. 2015;114(6):924-935.
31. Chacko SA, Sul J, Song Y, et al. Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. Am J Clin Nutr. 2011;93(2):463-473.
32. Elin RJ. Re-evaluation of the concept of chronic, latent, magnesium deficiency. Mag Res. 2011;24(4):225-227.

33. Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. Aust N Z J Psychiatry. 2009;43(1):45-52.
34. Yary T, Lehto SM, Tolmunen T, et al. Dietary magnesium intake and the incidence of depression: A 20-year follow-up study. J Affect Disord. 2016;193:94-98.
35. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(3):664-675.
36. Serefko A, Szopa A, Wlaz P, et al. Magnesium in depression. Pharmacol Rep. 2013;65(3):547-554.
37. Rajizadeh A, Mozaffari-Khosravi H, Yassini-Ardakani M, Dehghani A. Effect of magnesium supplementation on depression status in depressed patients with magnesium deficiency: a randomized, double-blind, placebo-controlled trial. Nutrition . 2017;35:56-60.
38. Tarleton EK, Littenberg B, MacLean CD, Kennedy AG, Daley C. Role of magnesium supplementation in the treatment of depression: a randomized clinical trial. PloS one. 2017;12(6):e0180067.
39. Bowman S. Low economic status is associated with suboptimal intakes of nutritious foods by adults in the National Health and Nutrition Examination Survey 1999-2002. Nutrition Res. 2007;27(9):515-523.
40. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81(2):341-354.
41. Davis DR. Declining fruit and vegetable nutrient composition: what is the evidence? Hort Science. 2009;44(1):15-19.
42. Grzebisz W. Magnesium–food and human health. J Elementol. 2011;16(2).
43. Topf JM, Murray PT. Hypomagnesemia and hypermagnesemia. Rev Endocr Metab Disord. 2003;4(2):195-206.
44. Rosanoff A. Changing crop magnesium concentrations: impact on human health. Plant Soil. 2013;368(1):139-153.
45. Mossor-Pietraszewska T. Effect of aluminium on plant growth and metabolism. Acta Biochim Pol. 2001;48(3):673-686.
46. Spungen JH, Goldsmith R, Stahl Z, Reifen R. Desalination of water: nutritional considerations. Isr Med Assoc J. 2013;15(4):164-168.
47. Azoulay A, Garzon P, Eisenberg MJ. Comparison of the mineral content of tap water and bottled waters. J Gen Intern Med. 2001;16(3):168-175.
48. Sebastian RS, Cleveland LE, Goldman JD, Moshfegh AJ. Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. J Am Diet Assoc. 2007;107(8):1322-1332.
49. Doria MF. Bottled water versus tap water: understanding consumers' preferences. J Water Health. 2006;4(2):271-276.

50. Gleick P. Bottled water sales: the shocking reality. 2013; http://scienceblogs.com/significantfigures/index.php/2013/04/25/bottled-water-sales-the-shocking-reality/. Accessed May 3, 2017.
51. Pennington JAT, Youngt B. Sodium, potassium, calcium, phosphorus, and magnesium in foods from the United States total diet study. J Food Comp Anal. 1990;3(2):145-165.
52. United States Department of Agriculture, Agricultural Research Service. USDA National FNutrient Database for Standard Reference, Release 28. 2015. https://ndb.nal.usda.gov/ndb/. Accessed March 20, 2017.
53. Welsh SO, Marston RM. Review of trends in food use in the United States, 1909 to 1980. J Am Diet Assoc. 1982;81(2):120-128.
54. O'Neil CE, Nicklas TA, Fulgoni VL, 3rd. Tree nut consumption is associated with better nutrient adequacy and diet quality in adults: National Health and Nutrition Examination Survey 2005-2010. Nutrients. 2015;7(1):595-607.
55. Flink EB. Nutritional aspects of magnesium metabolism. West J Med. 1980;133(4):304-312.
56. Lakshmanan FL, Rao RB, Kim WW, Kelsay JL. Magnesium intakes, balances, and blood levels of adults consuming self-selected diets. Am J Clin Nutr. 1984;40(6 Suppl):1380-1389.
57. O'Neil CE, Keast DR, Fulgoni VL, Nicklas TA. Food sources of energy and nutrients among adults in the US: NHANES 2003-2006. Nutrients. 2012;4(12):2097-2120.
58. Bowman S, Clemens J, Friday J, Thoerig R, Moshfegh A. Food Patterns Equivalents Intakes from Food: Mean Amounts Consumer per Individual, What We Eat in America, NHANES 2011-12; Tables 1-4. United States Department of Agriculture, Agricultural Research Service. https://www.ars.usda.gov/research/publications/publication/?seqNo115=312662. 2014. Accessed June 8, 2017.
59. Patterson BH, Block G, Rosenberger WF, Pee D, Kahle LL. Fruit and vegetables in the American diet: data from the NHANES II survey. Am J Public Health. 1990;80(12):1443-1449.
60. Casagrande SS, Wang Y, Anderson C, Gary TL. Have Americans increased their fruit and vegetable intake? The trends between 1988 and 2002. Am J Prev Med. 2007;32(4):257-263.
61. Li R, Serdula M, Bland S, Mokdad A, Bowman B, Nelson D. Trends in fruit and vegetable consumption among adults in 16 US states: Behavioral Risk Factor Surveillance System, 1990-1996. Am J Public Health. 2000;90(5):777.
62. Blanck HM, Gillespie C, Kimmons JE, Seymour JD, Serdula MK. Trends in fruit and vegetable consumption among U.S. men and women, 1994-2005. Prev Chronic Dis. 2008;5(2):A35.
63. Moore LV, Thompson FE. Adults meeting fruit and vegetable intake recommendations—United States, 2013. MMWR 2015;64(26):709-713.
64. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. J Acad Nutr Diet. 2013;113(12):1610-1619.

65. Haddad EH, Tanzman JS. What do vegetarians in the United States eat? Am J Clin Nutr. 2003;78(3 Suppl):626s-632s.
66. Stahler C. How many adults eat vegetarian? Vegetarian Journal. 2016;(4). http://www.vrg.org/journal/vj2006issue4/2006_issue4_poll.php. Accessed June 6, 2017.
67. Johnson CM, Sharkey JR, Dean WR. Eating behaviors and social capital are associated with fruit and vegetable intake among rural adults. J Hunger Environ Nutr. 2010;5(3):302-315.
68. Barr SI, DiFrancesco L, Fulgoni VL, 3rd. Consumption of breakfast and the type of breakfast consumed are positively associated with nutrient intakes and adequacy of Canadian adults. J Nutr. 2013;143(1):86-92.
69. United States Department of Agriculture, Agriculture Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group. USDA Nationwide Food Surveys, 1935-1998. https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/past-surveys/. Accessed April 10, 2017.
70. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. J Am Diet Assoc. 1998;98(5):537-547.
71. Quann EE, Fulgoni VL, 3rd, Auestad N. Consuming the daily recommended amounts of dairy products would reduce the prevalence of inadequate micronutrient intakes in the United States: diet modeling study based on NHANES 2007-2010. Nutr J. 2015;14:90.
72. Papanikolaou Y, Fulgoni VLF. Certain grain food patterns are associated with improved 2015 dietary guidelines shortfall nutrient intakes, diet quality, and lower body weight in US adults: results from the national health and nutrition examination survey, 2005–2010. Food Nutr Sci. 2016;7.
73. Nielsen SJ, Kit BK, Ogden CL. Nut consumption among US adults, 2009–2010. NCHS data brief. 2014;131:1-8.
74. United States Department of Agriculture, Agriculture Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group. Food Patterns Equivalents Database. https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-data-tables/. Accessed April 10, 2017.
75. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among us adults from 1999-2012. JAMA. 2016;316(14):1464-1474.
76. Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003–2006. J Nutr. 2011;141(2):261-266.
77. Darmon N, Drewnowski A. Does social class predict diet quality? Am J Clin Nutr. 2008;87(5):1107-1117.
78. Dixon LB, Winkleby MA, Radimer KL. Dietary intakes and serum nutrients differ between adults from food-insufficient and food-sufficient families: third National Health and Nutrition Examination Survey, 1988–1994. J Nutr. 2001;131(4):1232-1246.

79. Heimendinger J, Van Duyn MA, Chapelsky D, Foerster S, Stables G. The national 5 A Day for Better Health Program: a large-scale nutrition intervention. J Public Health Manag Pract. 1996;2(2):27-35.
80. Kant AK, Graubard BI. Secular trends in the association of socio-economic position with self-reported dietary attributes and biomarkers in the US population: National Health and Nutrition Examination Survey (NHANES) 1971-1975 to NHANES 1999-2002. Public Health Nutr. 2007;10(2):158-167.
81. Moshfegh A, Goldman J, Cleveland L. What We Eat in America, NHANES 2001-2002: Usual Nutrient Intakes from Food Compared to Dietary Reference Intakes. 2005; https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/0102/usualintaketables2001-02.pdf. Accessed March 28, 2017.
82. Bailey RL, Akabas SR, Paxson EE, Thuppal SV, Saklani S, Tucker KL. Total usual intake of shortfall nutrients varies with poverty among US adults. J Nutr Educ Behav. 2017;In Press.
83. Hallfrisch J, Muller DC. Does diet provide adequate amounts of calcium, iron, magnesium, and zinc in a well-educated adult population? Exp Gerentol. 1993;28(4–5):473-483.
84. Block G, Dresser CM, Hartman AM, Carroll MD. Nutrient sources in the American diet: quantitative data from the NHANES II survey. II. Macronutrients and fats. Am J Epidemiol. 1985;122(1):27-40.
85. Johnson CL, Paulose-Ram R, Ogden CL. National Health and Nutrition Examination Survey: Analytic Guidelines 1999-2010. Vital Health Stat. 2013;2(161).
86. Dodd KW, Guenther PM, Freedman LS, et al. Statistical methods for estimating usual intake of nutrients and foods: a review of the theory. J Am Diet Assoc. 2006;106(10):1640-1650.
87. Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of US adults. J Nutr. 2003;133(9):2879-2882.
88. Centers for Disease Control and Prevention. The National Health and Nutrition Examination Survey Documentation, Codebook, and Frequencies; Dietary Interview - Individual Foods, First Day. Atlanta, GA: CDC; 2008.
89. Ahuja JK, Moshfegh AJ, Holden JM, Harris E. USDA food and nutrient databases provide the infrastructure for food and nutrition research, policy, and practice. J Nutrition. 2013;143(2):241s-249s.
90. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. J Am Diet Assoc. 1988;88(10):1268-1271.
91. Moser M, White K, Henry B, et al. Phosphorus content of popular beverages. Am J Kid Dis. 2015;65(6):969-971.
92. Nielsen FH. Importance of plant sources of magnesium for human health. Crop Pasture Sci. 2016;66(12):1259-1264.
93. Boynton D. Nutrition by foliar application. Ann Rev Plant Phys. 1954;5(1):31-54.
94. Edwards-Jones G, i Canals LM, Hounsome N, et al. Testing the assertion that 'local food is best': the challenges of an evidence-based approach. Trends Food Sci Technol. 2008;19(5):265-274.

95. Cifelli CJ, Houchins JA, Demmer E, Fulgoni VL. Increasing Plant Based Foods or Dairy Foods Differentially Affects Nutrient Intakes: Dietary Scenarios Using NHANES 2007-2010. Nutrients. 2016;8(7):422.
96. Hackman RM, Aggarwal BB, Applebaum RS, et al. Forecasting nutrition research in 2020. J Am Coll Nutr. 2014;33(4):340-346.
97. Pawlak R, Colby S. Benefits, barriers, self-efficacy and knowledge regarding healthy foods; perception of African Americans living in eastern North Carolina. Nutr Res Pract. 2009;3(1):56-63.
98. Kant AK, Graubard BI. Ethnicity is an independent correlate of biomarkers of micronutrient intake and status in American adults. J Nutr. 2007;137(11):2456-2463.
99. Rude RK. Magnesium. In: Ross AC, Caballero B, Cousins RC, Tucker KL, Ziegler TR, eds. Modern *Nutrition in Health and Disease*. 11th ed. Baltimore, MA: Lippincott Williams & Wilkins; 2010:159-175.
100. Barbagallo M, Belvedere M, Dominguez LJ. Magnesium homeostasis and aging. Mag Res. 2009;22(4):235-246.
101. Kieboom BC, Kiefte-de Jong JC, Eijgelsheim M, et al. Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. Am J Kid Dis. 2015;66(5):775-782.
102. La Vecchia C, Negri E, Franceschi S, Parazzini F, Decarli A. Differences in dietary intake with smoking, alcohol, and education. Nutr Cancer. 1992;17(3):297-304.

CHAPTER 2: Magnesium Intake and Depression in U.S. Adults

Emily K. Tarleton, MS, RD and Benjamin Littenberg, MD

University of Vermont Center for Clinical and Translational Science

Abstract

Background: Depression is a common and often disabling disorder. Magnesium supplementation has been linked to improvement in depressive symptoms but consensus on the relationship between magnesium and depression has not been reached.

Methods: The purpose of this study was to test the existence of an association between dietary magnesium intake and depression in the adult U.S. population. A cross-sectional, population-based data set (National Health and Nutrition Examination Survey) was used to explore the relationship of magnesium intake and depression in 8,894 U.S. adults (mean age 46.1; 47.4% male) from 2007-2010. Using logistic regression to model the relationship between the presence of depression (Patient Health Questionnaire Score $\geq$5) and low magnesium intake (<184 mg/day), we examined the risk ratio (RR) of magnesium intake and its 95% confidence interval.

Results: After adjustment for all potential confounders, the strength of association of very low magnesium intake with depression was statistically significant (RR=1.16; 95%CI 1.06, 1.30; *P*=0.026). Adjusting for all other covariates, low magnesium intake was associated with depression in subjects under age 65 (RR 1.22; 95%CI 1.06, 1.40; *P*=0.007), but appeared protective in seniors (RR 0.75; 95%CI 0.56, 0.98; *P*=0.032).

Conclusions: We found a significant association between very low magnesium intake and depression, especially in younger adults. The finding of the potential protective effect of low magnesium intake in older adults is surprising and warrants further investigation.

Introduction

Depression is a common and disabling disorder. Almost 11% of adults older than 60 and 18.8% in those younger than 60 suffer from depression.[1] Although both pharmacologic and behavioral therapies are effective for many patients, they have important limitations. Medications can take weeks to have an effect, often have significant adverse effects, and fail to help many patients at all.[2] Non-pharmacologic approaches such as Cognitive Behavioral Therapy are also effective[3], but require highly trained therapists and weeks to achieve effectiveness.

As a result of the need for additional treatment options, interest in the role of nutrition in modulating depressive symptoms has grown. Magnesium plays a role in many of the pathways involved in the pathophysiology of depression and is found in several enzymes, hormones, and neurotransmitters.[4] Depression and magnesium are both associated with systemic inflammation.[5, 6] National data indicate a significant portion of the population has magnesium intake below the Estimated Average Requirement (EAR).[7]

Magnesium supplementation has been linked to improvement in symptoms of major depression[8], premenstrual symptoms[9], postpartum depression[8] and chronic fatigue syndrome.[10] Low magnesium status has been associated with increased depressive symptoms in several different age groups and ethnic populations.[11-14]

Issues in study design have led to inconclusive results and skepticism of magnesium's role in depression. Serum magnesium levels were used to indicate magnesium status in some studies,[11, 15] but its reliability is questionable.[16, 17] Clinical trials have suffered from limited sample sizes,[10, 11] the use of the supplement magnesium

oxide,[18] which is poorly absorbed,[17] and restrictive inclusion criteria.[11] With varying outcomes, different populations and age ranges, and limited sample sizes, consensus on the relationship between magnesium intake and depression has not been reached.

Some cross-sectional studies have reported an inverse relationship between magnesium intake and standardized depression scores in populations with low magnesium intake.[12-14, 19] Because these studies were conducted outside of the United States, their results should be validated in the U.S. population. One longitudinal study[20] did not find an inverse relationship, although it was underpowered to detect a significant reduction in depression.

If proven effective, increased magnesium consumption through diet or supplementation might address some of the limitations of currently available treatment. Magnesium is found in many common foods and emphasis on these foods can easily affect magnesium status. Although it can lead to hypermagnesemia and diarrhea, magnesium supplementation is, in general, a safe treatment with few unanticipated side effects. Magnesium supplementation provides very quick results. Case studies of magnesium supplementation reported improvements in depression, anxiety, and sleep within one week.[8, 11] Therefore, we sought to test the existence of a relationship between dietary magnesium intake and depression using a large, cross-sectional, population-based data set from the U.S.

Subjects and Methods

Data Source and Subjects

To investigate the question of whether there is an association between depression and magnesium intake, we conducted a cross-sectional study using the National Health and Nutritional Examination Survey (NHANES). NHANES participants undergo extensive interviews and laboratory assessments including measures of dietary intake, dietary supplements, socioeconomic factors, clinical characteristics, and personal habits.[21] By applying the weighting scheme supplied by the Centers for Disease Control and Prevention, NHANES can be used to represent the sex-, age-, race- and ethnicity-adjusted non-institutionalized population of the U.S. To increase the power of the analyses, we combined the data from two separate waves of the survey (2007-08, and 2009-10).[22] We included all subjects at least 20 years old with complete data for the outcome, predictor, and all the candidate confounders.

Variables

The main predictor variable was total magnesium intake in milligrams (mg)/day calculated from 24 hour dietary and supplement recall data. Intake was used because of the unreliability of serum magnesium levels[16] and because it is directly modifiable and could serve as an intervention. Low magnesium intake was defined as intake in the lowest quintile (<184 mg/day). Magnesium deficiency is defined with age- and sex-varying thresholds taken from the EAR as intake <350 mg/d for men over age 30, <330 mg/d for younger men, <265 for women over age 30, and <255 for younger women.[23]

The outcome variable was the Patient Health Questionnaire-9 (PHQ-9) score, a validated survey tool for measuring the presence and severity of depression in adults.[24] The PHQ-9 score is the sum of the responses to nine items representing symptoms of depression. Each is graded by the patient according to how often they have experienced the symptoms over the previous two weeks, from 0 (not at all) to 3 (nearly every day). PHQ-9 scores range from zero to 27 and were dichotomized into depressed (PHQ-9 score 5-27) or not (PHQ-9 score 0-4).

Based on review of the literature and our clinical experience, we considered age, sex, race, ethnicity, education, marital status, household income, food security, tobacco use, alcohol intake, diabetes, kidney disease, and folate intake as potential confounders of the relationship between depression and magnesium intake. Race and ethnicity were combined into a single dichotomous variable of non-Hispanic white *vs.* all others. Education was dichotomized as having a high school diploma (or equivalent) *vs.* not. Marital status was characterized as married or living as married *vs.* single, divorced, widowed or separated. Household income was dichotomized as low if it was reported to be $35,000 per year or less. Food insecurity was present if the subject endorsed any of the following three statements: "(I/we) worried whether (my/our) food would run out before (I/we) got money to buy more" or "The food that (I/we) bought just didn't last, and (I/we) didn't have money to get more" or "(I/we) couldn't afford to eat balanced meals." Tobacco use was considered present if the patient endorsed current smoking *vs.* absent for former smokers and those who never smoked. Alcohol use was coded as the average number of units consumed per day over the past year. A unit of alcohol is one can of

beer, one glass of wine, or one ounce of liquor. Non-drinkers were coded zero. Diabetes and kidney disease were considered present if the patient endorsed that a doctor or other health professional had told them they had the diagnosis. Folate intake in (micrograms per day) included dietary folate equivalents of food plus supplements and was dichotomized at <230 μg/d (the lowest quintile of daily folate intake).

Statistical Analysis

The primary hypothesis was that depression is associated with magnesium intake while adjusting for possible confounders. We used unadjusted nonparametric Wilcoxon-type tests of trend to assess the relationships between quintiles of magnesium intake and other subject characteristics.[25] We used logistic regression to model the relationship between the presence of depression (PHQ ≥5) and low magnesium intake (<184 mg/day, the lowest quintile) and tested the hypothesis by examining the odds ratio (OR) and relative risk (RR)[26] on magnesium intake and its 95% confidence interval (CI). Each potential confounder was tested in a separate univariate logistic regression for association with the outcome (depression) and the main predictor (low magnesium intake). If the variable was associated with both outcome and predictor with each $P<0.1$, it was considered a potential confounder and included in the multivariate model. We explored the use of the magnesium as a function of energy (milligrams of magnesium/1000 calories) as the predictor by following the same procedure. Because both magnesium intake[27] and depression[1] vary with age and gender, we constructed additional models including interaction terms to explore the possibility of interactions of magnesium with gender and magnesium with age. All analyses employed the

stratification and weighting scheme recommended for NHANES by the National Center for Health Statistics[22] using Stata13.1 (College Station, TX). *P* values $\leq$0.05 were considered to be statistically significant.

Results

Of the adult subjects in the NHANES data set, 73% met eligibility criteria, for a final sample size of 8,894 (see Figure 2.1). The characteristics of the sample are described in Table 2.1. All the selected covariates showed significant trends across the quintiles of magnesium intake. Depression was most prevalent in the lowest quintile of magnesium intake.

The univariate regression of low magnesium intake and depression demonstrated a strong statistically significant association with an OR of 1.73 (95%CI 1.48, 2.02; *P*<0.001) and an RR of 1.49 (95%CI 1.35, 1.66; *P*<0.001) (Table 2.2). All the potential confounders were associated with both low magnesium and depression (*P*<0.1) and were retained in the multivariate model (except household income because it was highly correlated with food insecurity). After adjustment for all potential confounders, the strength of association of low magnesium intake with depression was attenuated but remained statistically significant with an OR=1.21 (95%CI 1.02, 1.42; *P*=0.026). This is equivalent to a RR of 1.16 (95%CI 1.06, 1.30; *P*=0.026). The use of magnesium as a function of energy gave similar results.

Over half of the population (54%) reported deficient magnesium (intake less than the EAR). Deficiency was significantly associated with depression in the univariate model (OR 1.13; 95%CI 1.01, 1.27; RR 1.10; 95%CI 1.01, 1.20; *P*=0.04) but not in the

multivariate adjusted analyses (OR 0.97; 95%CI 0.85, 1.09; RR 0.98; 95%CI 0.88, 1.07; *P*=0.57).

Only one of the covariates had a significant interaction with depression. Older age interacted significantly with low magnesium intake (OR 0.51; 95%CI 0.37, 0.72; *P*<0.001). Adjusting for all other covariates, low magnesium intake was associated with depression in subjects under age 65 (OR 1.31; 95%CI 1.08, 1.58; RR=1.22; 95%CI 1.06, 1.40; *P*=0.007), but appeared protective in seniors (OR 0.69; 95%CI 0.49, 0.97; RR=0.75; 95%CI 0.56, 0.98; *P*=0.032) (Figure 2.2).

Discussion

Overall, we found a significant association between low magnesium intake and depression, especially in younger adults. The increased prevalence of depression was confined to the lowest levels of magnesium intake. Nonetheless, the effect is very strong, with a >50% higher rate of depression in the lowest quintile of intake compared to those consuming greater amounts. A very different pattern was observed in seniors (Figure 2.2 and Table 2.3). First, the overall rates of depression were lower. Second, the spread in rates across the levels of magnesium intake were much higher for younger adults (23% to 37%) than in seniors (15% to 21%). Third, the lowest quintile of intake among seniors did not have the highest prevalence of depression. Rather, the highest rates occurred in the group with the highest intake. Although the adjusted odds of depression were significantly greater in the highest intake group compared to the lowest quintile (Table 2.3), there was no clear dose-response relationship, and the clinical significance of this finding is uncertain. The large sample size available for analysis (372 to 435 seniors in

each quintile of magnesium intake) may be responsible for making a small or even negligible effect appear statistically significant. Even if we discount the apparent adverse effect of high magnesium intake in seniors, there is little doubt that the increased prevalence of depression with low intakes seen in younger subjects is absent after age 65.

By 2030, close to 20% of the population will be older than 65 (up from the current 12.9%).[28] Therefore, the number of people with late-life depression will also increase. Depression later in life increases risk for cardiovascular disease and mortality[29-31] and depressive symptoms lasting more than one year are associated with a significant increased risk of mortality.[29] Newly depressed older adults are at a higher risk for mortality and those with worsening depression have a 70% increase in mortality risk compared with patients with stable depression scores.[29] Therefore, understanding modifiable risk factors for depression in the older population is particularly useful.

Our data show over half of adults do not consume adequate amounts of magnesium. This finding is similar to other U.S. population studies.[7] Magnesium excretion increases while absorption decreases with age[32] because of various chronic diseases and decreased intake of foods high in magnesium. Compared with imipramine, magnesium supplementation was effective in treating depression in older adults with hypomagnesaemia and type 2 diabetes in a randomized control trial.[11] The current analysis differs by suggesting a detrimental effect of higher magnesium intake in older adults. The differences may be because this is a study of a general U.S. population with low intake rather than a group selected for low serum magnesium concentrations and diabetes.

Little is known about the mechanism of the possible effect of magnesium on depression. Even less is known about this mechanism in elderly and why the association might differ between age groups. The current findings might be due to unidentified confounders, reverse causality, or data error. The PHQ has been found to be comparable with the Geriatric Depression Screen in a convenience sample of elderly primary care patients.[33] However, the existence of an emotional paradox in elders,[34] in which older adults experience higher levels of well-being despite cognitive and physical decline, may influence how depression is identified and scaled in this group and make the PHQ less sensitive.

Several studies have looked at whether overall dietary pattern is more important than specific nutrients when looking at nutrition's influence on depression. Among adults with mood disorders, mineral intakes may be associated with psychiatric disorders more so than vitamin intakes.[35] We cannot rule out that a specific dietary pattern or combination of nutrients would show a synergistic effect and a stronger relationship with depression than magnesium alone. For instance, residents of Greece, where most people follow the Mediterranean Diet Pattern, have a lower rate of depression and mental disorders.[36, 37] Changing dietary patterns takes time, however, as well as commitment on the part of the patient. Emphasis on consumption of high magnesium foods such as green leafy vegetables, legumes, nuts, seeds and whole grains could offer a dietary approach to controlling symptoms of depression. Advocating for increased magnesium intake through food can lead to a healthier overall diet and might be attractive to patients that have previously experienced unwanted side effects from medications for depression.

Magnesium supplementation may be effective in as little as one week[8] but may lead to stomach upset such as nausea, vomiting, or diarrhea in some people. However, toxic levels are unlikely to occur when it is given in the recommended dose and kidney function is normal.[16] Whether increased dietary consumption of magnesium would lead to an improvement in symptoms just as quickly as supplements is unknown.

Strengths and Limitations

This study has several strengths. The sample size was large and representative of almost 180 million American adults. The analysis includes the most recent available data from 2007-2010 and captures both dietary and supplemental intake. Although the assessment of magnesium intake at only one time point may not reflect long term intake, trained interviewers were used to collect the data and the methods were validated and consistent over the four years of data collection.[38] In addition to social, demographic, behavioral and clinical covariates, this analysis also controlled for folate intake, which has not been included in many previous analyses.

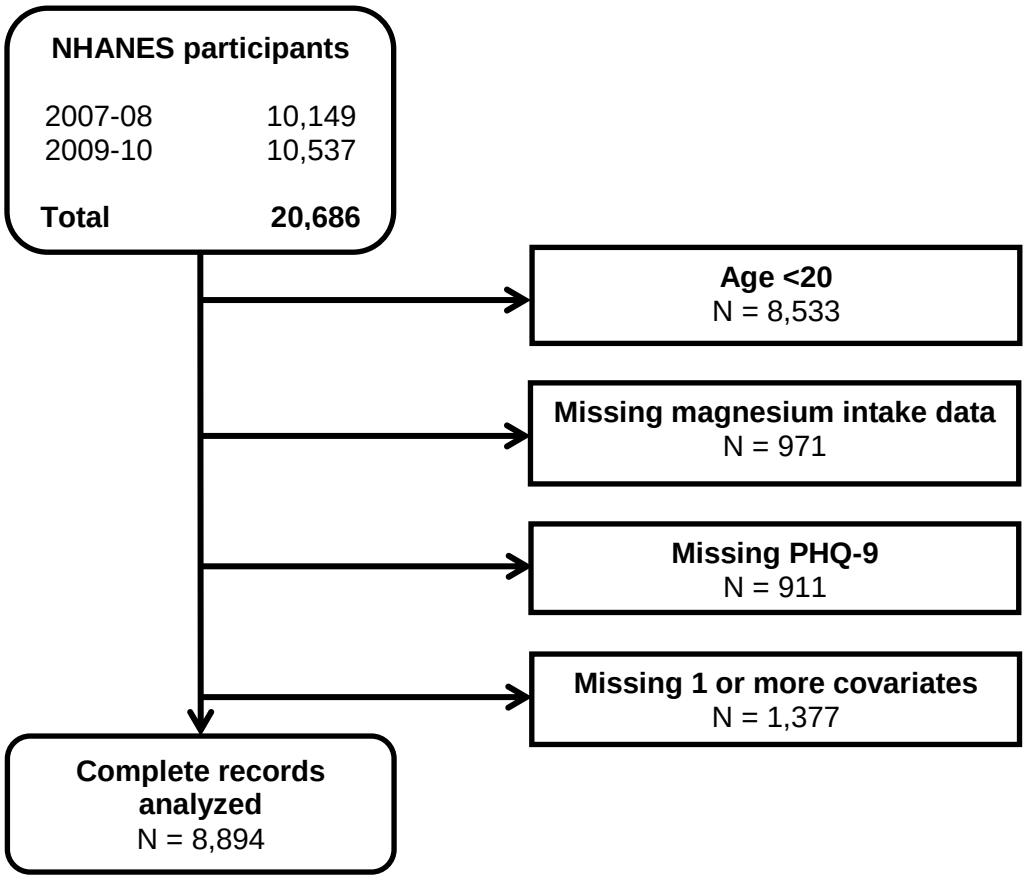
As with all observational studies, we cannot exclude the possibility of additional confounding not accounted for by the analysis. Likewise, we cannot rule out reverse causality to explain the association between magnesium intake and depression. In other words, poor dietary intake of magnesium could be a result of mental illness.

Conclusion

This study enlarges upon previous research finding a relationship between magnesium intake and depression. Although very low magnesium intake appeared protective for depression in seniors, it was associated with higher rates of depression in

younger adults. Rigorous, randomized clinical trials, with adequate power to analyze subgroups, are needed to confirm the effects of magnesium on depression.

Figure 2.1 Inclusion flow diagram



NHANES = National Health and Nutrition Examination Survey; PHQ-9 = Patient Health Questionnaire-9

Table 2.1 Subject characteristics by quintile of magnesium intake*

Characteristic	Quintile 1	2	3	4	5	Total
Sample size						
N	1,681	1,727	1,834	1,816	1,836	8,894
Magnesium intake						
Mean (mg/d)	138	216	281	361	581	334
Range (mg/d)	0-183	184-246	247-315	316-417	418-2,437	0-2,437
Deficient intake	100%	100%	58.5%	18.1%	0%	54%
Depression (PHQ-9 score)						
Mean	4.1	3.3	2.8	2.8	2.8	3.1
Range	0-27	0-27	0-24	0-25	0-27	0-27
Depressed (score $\geq$5)	32.2%	24.5%	20.5%	20.5%	21.1%	23.2%
Age						
Mean (y)	44.6	45.8	46.2	46.9	46.5	46.1
Senior (age 65+)	16.6%	16.5%	16.7%	14.7%	13.9%	15.5%
Race and ethnicity						
Mexican-American	15.9%	17.4%	18.5%	18.2%	17.7%	17.6%
Other Hispanic	12.6%	12.4%	11.1%	9.3%	8.7%	10.8%
Non-Hispanic White	39.2%	44.1%	46.6%	52.1%	57.3%	48.1%
Non-Hispanic Black	28.7%	21.8%	18.9%	15.9%	12.1%	19.3%
Other	3.6%	4.2%	4.9%	4.5%	4.3%	4.3%
Gender						
Male	26.9%	38.8%	46.2%	53.5%	63.2%	47.4%
Social						
High school graduate	73.6%	80.8%	82%	86.5%	86.7%	82.5%
Married (or living as married)	54.9%	58.2%	62.7%	66.1%	68.0%	62.6%
Food insecurity	23.4%	16.3%	13.5%	11.0%	10.8%	14.4%
Household income < $35,000/year	47.8%	33.2%	29.6%	23.2%	24.4%	30.5%
Habits						
Current smoker	31.2%	20.9%	20.5%	20%	17.7%	21.5%
Mean drinks per day	0.4	0.5	0.5	0.7	0.7	0.6
Chronic disease						
Diabetes	11%	9.6%	8.4%	8.4%	8.2%	9%
Kidney disease	3.7%	1.9%	1.2%	0.7%	1.1%	1.6%
Dietary Folate Equivalent intake						
Lowest quintile (< 230 µg/d)	58.6%	23.2%	9.1%	3.4%	1.5%	16.5%

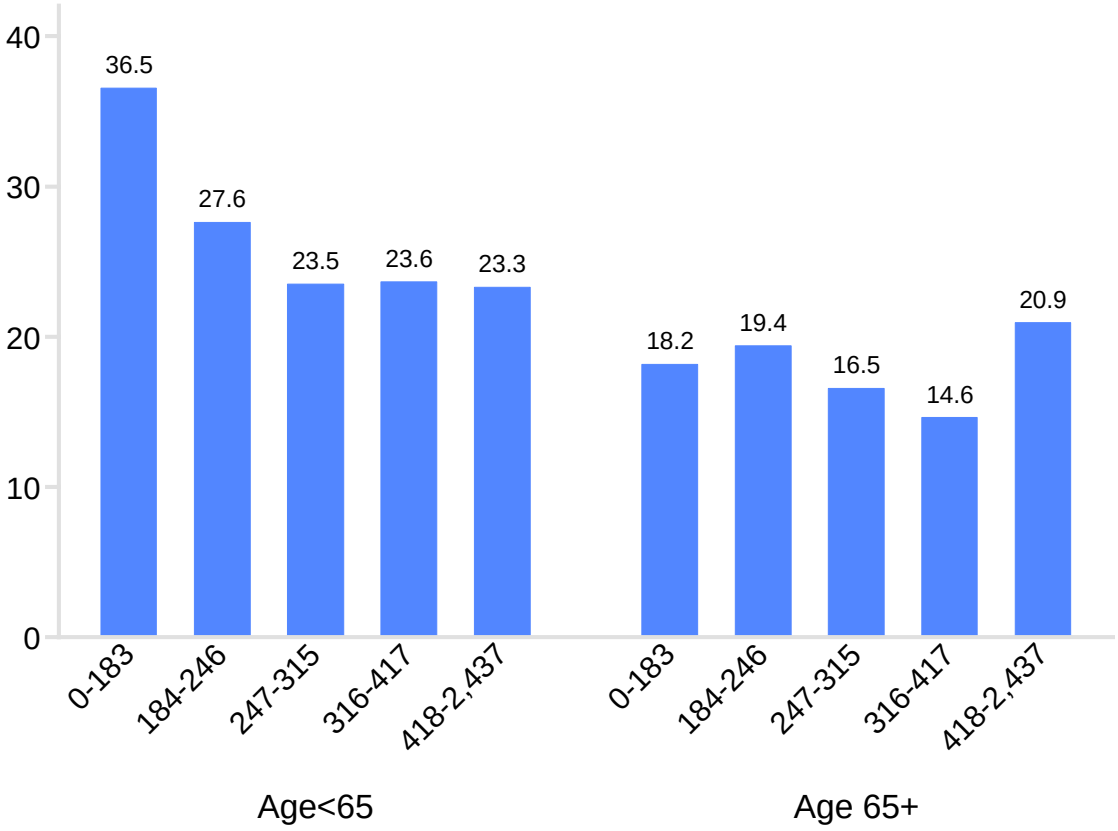
*The trend across quintiles of magnesium intake is significant with $P \leq 0.001$ for all characteristics using an unadjusted nonparametric test of trend.[25]
PHQ-9 = Patient Health Questionnaire-9

Table 2.2 Logistic regressions on depression

Independent Variable	**Odds Ratio**	**95% CI**	***P***
Univariate model			
Low magnesium	1.73	1.48, 2.02	<0.001
Multivariate model			
Low magnesium	1.21	1.02, 1.42	0.026
Male	0.61	0.53, 0.70	<0.001
Age 65+	0.65	0.54, 0.77	<0.001
Non-Hispanic white	0.95	0.68, 1.32	0.75
High school graduate	0.77	0.64, 0.93	0.007
Married	0.70	0.61, 0.80	<0.001
Drinker	1.06	0.99, 1.12	0.073
Chronic Kidney Disease	2.50	1.66, 3.79	<0.001
Smoker	1.78	1.52, 2.10	<0.001
Diabetes	1.63	1.29, 2.06	<0.001
Food insecurity	2.30	1.90, 2.78	<0.001
Low folate intake	1.11	0.92, 1.35	0.28

CI = Confidence Interval

Figure 2.2 Prevalence of depression adjusted by magnesium intake and age



The prevalence estimates for each quintile of magnesium intake for each age group were adjusted for gender, race, ethnicity, education, marital status, alcohol intake, smoking, kidney disease, diabetes, food insecurity and low dietary folate. Quintiles of magnesium intake are labeled as milligrams per day.

Table 2.3 Adjusted odds of depression by age and magnesium intake*

Magnesium Intake	**Odds Ratio**	**95% CI**	***P***
Age < 65			
0-183 mg/day	1		
184-246 mg/day	0.81	0.67, 0.98	0.032
247-315 mg/day	0.69	0.52, 0.92	0.012
316-417 mg/day	0.76	0.63, 0.91	0.005
418-2,437 mg/day	0.80	0.59, 1.09	0.15
Age 65+			
0-183 mg/day	1		
184-246 mg/day	1.38	0.87, 2.18	0.17
247-315 mg/day	1.29	0.79, 2.10	0.29
316-417 mg/day	1.30	0.83, 2.03	0.24
418-2,437 mg/day	2.15	1.34, 3.45	0.002

*Odds ratios and confidence intervals (CIs) were adjusted for sex, race, ethnicity, education, marital status, alcohol intake, smoking, kidney disease, diabetes, food insecurity and low dietary folate.

References

1. Centers for Disease Control and Prevention. Current Depression Among Adults---United States, 2006 and 2008. *MMWR.* 2010;59(38):1229-1235.
2. Zarate C, Duman RS, Liu G, Sartori S, Quiroz J, Murck H. New paradigms for treatment-resistant depression. *ANN NY Acad Scis.* 2013;1292(1):21-31.
3. Hoifodt RS, Strom C, Kolstrup N, Eisemann M, Waterloo K. Effectiveness of cognitive behavioural therapy in primary health care: a review. *Fam Pract.* 2011;28(5):489-504.
4. Serefko A, Szopa A, Wlaz P, Nowak G, Radziwon-Zaleska M, Skalski M, Poleszak E. Magnesium in depression. *Pharmacol Rep.* 2013;65(3):547-554.
5. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35(3):664-675.
6. Chacko SA, Sul J, Song Y, Li X, LeBlanc J, You Y, Butch A, Liu S. Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. *Am J Clin Nutr.* 2011;93(2):463-473.
7. Fulgoni VL, Keast DR, Bailey RL, Dwyer J. Foods, Fortificants, and Supplements: Where Do Americans Get Their Nutrients? *J Nutrition.* 2011;141(10):1847-1854.
8. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses.* 2006;67(2):362-370.
9. Walker AF, De Souza MC, Vickers MF, Abeyasekera S, Collins ML, Trinca LA. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *J Womens Health.* 1998;7(9):1157-1165.
10. Cox IM, Campbell MJ. Red blood cell magnesium and chronic fatigue syndrome. *Lancet.* 1991;337(8744):757.
11. Barragan-Rodriguez L, Rodriguez-Moran M, Guerrero-Romero F. Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. *Magnes Res.* 2008;21(4):218-223.
12. Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient intakes and the common mental disorders in women. *J Affect Disord.* 2012;141(1):79-85.
13. Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. *Aust N Z J Psychiatry.* 2009;43(1):45-52.
14. Yary T, Aazami S, Soleimannejad K. Dietary intake of magnesium may modulate depression. *Biol Trace Elem Res.* 2013;151(3):324-329.
15. Imada Y, Yoshioka S-I, Ueda T, Katayama S, Kuno Y, Kawahara R. Relationships between serum magnesium levels and clinical background factors in patients with mood disorders. *Psychiat Clin Neurosci.* 2002;56(5):509-514.

16. Ismail Y, Ismail AA. The underestimated problem of using serum magnesium measurements to exclude magnesium deficiency in adults; a health warning is needed for "normal" results. *Clin Chem Lab Med.* 2010;48(3):323-327.
17. Walker AF, Marakis G, Christie S, Byng M. Mg citrate found more bioavailable than other Mg preparations in a randomised, double-blind study. *Magnes Res.* 2003;16(3):183-191.
18. De Souza MC, Walker AF, Robinson PA, Bolland K. A Synergistic Effect of a Daily Supplement for 1 Month of 200 mg Magnesium plus 50 mg Vitamin B6 for the Relief of Anxiety-Related Premenstrual Symptoms: A Randomized, Double-Blind, Crossover Study. *J Women Health Gender-B.* 2000;9(2):131-139.
19. Huang JH, Lu YF, Cheng FC, Lee JN, Tsai LC. Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study. *Nutr J.* 2012;11:41.
20. Derom ML, Martinez-Gonzalez MA, Sayon-Orea Mdel C, Bes-Rastrollo M, Beunza JJ, Sanchez-Villegas A. Magnesium intake is not related to depression risk in Spanish university graduates. *J Nutr.* 2012;142(6):1053-1059.
21. Centers for Disease Control and Prevention. Questionnaires, Datasets, and Related Documentation. Vol 2013. http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm.
22. Johnson CL, Paulose-Ram R, Ogden CL. National Health and Nutrition Examination Survey: Analytic Guidelines 1999-2010. *Vital Health Stat.* 2013;2(161).
23. Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorous, Magnesium, Vitmain D, and Flouride*. Washington, DC: National Academy Press; 1997.
24. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Int Med.* 2001;16(9):606-613.
25. Cuzick J. A Wilcoxon-type test for trend. Stat Med. 1985;4:87-90.
26. Zhang J, Yu KF. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA.* 1998;280(19):1690-1691.
27. Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of US adults. *J Nutr.* 2003;133(9):2879-2882.
28. Administration on Aging. Profile of Older Americans. February 10, 2012; http://www.aoa.gov/AoARoot/Aging_Statistics/Profile/index.aspx. Accessed October 30, 2012.
29. Bogner HR, Morales KH, Reynolds CF, 3rd, Cary MS, Bruce ML. Course of depression and mortality among older primary care patients. *Am J Geriatr Psychiatry.* 2012;20(10):895-903.
30. St John PD, Montgomery PR. Do depressive symptoms predict mortality in older people? *Aging Ment Health.* 2009;13(5):674-681.
31. Hamer M, Bates CJ, Mishra GD. Depression, physical function, and risk of mortality: National Diet and Nutrition Survey in adults older than 65 years. *Am J Geriatr Psychiatry.* 2011;19(1):72-78.

32. Volpe SL. Magnesium. In: Erdman JW, Macdonald IA, eds. *Present Knowledge in Nutrition*. 10th ed. Ames, Iowa: Wiley & Sons; 2012:459-474.
33. Phelan E, Williams B, Meeker K, Bonn K, Frederick J, LoGerfo J, Snowden M. A study of the diagnostic accuracy of the PHQ-9 in primary care elderly. *BMC Fam Pract.* 2010;11(1):63.
34. Mather M. The emotion paradox in the aging brain. *Ann N Y Acad Sci.* 2012;1251:33-49.
35. Davison KM, Kaplan BJ. Nutrient intakes are correlated with overall psychiatric functioning in adults with mood disorders. *Can J Psychiatry.* 2012;57(2):85-92.
36. Panagiotakos DB, Chrysohoou C, Siasos G, Zisimos K, Skoumas J, Pitsavos C, Stefanadis C. Sociodemographic and lifestyle statistics of oldest old people (>80 years) living in ikaria island: the ikaria study. *Cardiol Res Pract.* 2011:679187.
37. Sanchez-Villegas A, Verberne L, De Irala J, Ruiz-Canela M, Toledo E, Serra-Majem L, Martinez-Gonzalez MA. Dietary fat intake and the risk of depression: the SUN Project. *PLoS ONE.* 2011;6(1):e16268.
38. Centers for Disease Control and Prevention. The National Health and Nutritiona Examination Survey Documentation, Codebook, and Frequencies; Dietary Interview - Individual Foods, First Day. Atlanta, GA: CDC; 2008.

CHAPTER 3: Role of magnesium supplementation in the treatment of depression:

A randomized clinical trial

Emily K. Tarleton[1], Benjamin Littenberg[1,2], Charles D. MacLean[1,2], Amanda G. Kennedy[1,2] Christopher Daley[3]

[1]Center for Clinical and Translational Science, University of Vermont, Burlington, Vermont, United States of America

[2] Department of Medicine, University of Vermont, Burlington, Vermont, United States of America

[3] Department of Psychiatry, University of Vermont, Burlington, Vermont, United States of America

Abstract

Current treatment options for depression are limited by efficacy, cost, availability, side effects, and acceptability to patients. Several studies have looked at the association between magnesium and depression, yet its role in symptom management is unclear. The objective of this trial was to test whether supplementation with over-the-counter magnesium chloride improves symptoms of depression. An open-label, blocked, randomized, cross-over trial was carried out in outpatient primary care clinics on 126 adults (mean age 52; 38% male) diagnosed with and currently experiencing mild-to-moderate symptoms with Patient Health Questionnaire-9 (PHQ-9) scores of 5-19. The intervention was 6 weeks of active treatment (248 mg of elemental magnesium per day) compared to 6 weeks of control (no treatment). Assessments of depression symptoms were completed at bi-weekly phone calls. The primary outcome was the net difference in the change in depression symptoms from baseline to the end of each treatment period. Secondary outcomes included changes in anxiety symptoms as well as adherence to the supplement regimen, appearance of adverse effects, and intention to use magnesium supplements in the future. Between June 2015 and May 2016, 112 participants provided analyzable data. Consumption of magnesium chloride for 6 weeks resulted in a clinically significant net improvement in PHQ-9 scores of -6.0 points (CI -7.9, -4.2; $P<0.001$) and net improvement in Generalized Anxiety Disorders-7 scores of -4.5 points (CI -6.6, -2.4; $P<0.001$). Average adherence was 83% by pill count. The supplements were well tolerated and 61% of participants reported they would use magnesium in the future. Similar effects were observed regardless of age, gender, baseline severity of depression,

baseline magnesium level, or use of antidepressant treatments. Effects were observed within two weeks. Magnesium is effective for mild-to-moderate depression in adults. It works quickly and is well tolerated without the need for close monitoring for toxicity.

Introduction

Depression affects 350 million people worldwide and is predicted to be the leading cause of disease burden by 2030, based on disability-adjusted-life-year [1]. Initial antidepressant trials of adequate dose and duration result in only about 50% of patients achieving remission [2]. Even after the addition of other treatments, 20% still suffer from symptoms after 2 years. Non-pharmacologic approaches such as Cognitive Behavioral Therapy and lifestyle interventions require highly trained therapists and several weeks to months to achieve effectiveness [3]. There is a great need for additional treatment options.

The association between magnesium intake and depression is well documented [4-7]. Improvement in depression with magnesium supplementation has been reported inconsistently [8, 9], although few clinical trials exist. One trial found magnesium chloride to be effective for depression in seniors with type 2 diabetes [10] while another trial found magnesium citrate decreased depression in patients with fibromyalgia [11]. One negative trial used magnesium oxide [12], known to be poorly absorbed.

The aim of this study was to test the hypothesis that 6 weeks of oral magnesium chloride ($MgCl_2$) supplementation will improve symptoms of mild-to-moderate depression in a primary care population.

Methods

Trial Design

This was a 12-week open label randomized cross-over control trial. Participants were recruited through primary care providers (PCPs) within a single academic medical center and randomized to begin $MgCl_2$ supplementation immediately or at week 7 (delayed). During the other 6-week period, they took no $MgCl_2$. Prior to the start of the study the Institutional Review Board of the University of Vermont approved the study. All subjects provided written informed consent. Trial registry can be found at clinicatrials.gov (Identifier: 02466087).

Participants

The target population was adults with mild-to-moderate depression. Inclusion criteria were: 1) 18 years of age or older; 2) no change in treatment plan for depression for the past 2 months and going forward (including no current treatment, stable use of antidepressant medication, or ongoing nonpharmacologic therapy); 3) Patient Health Questionnaire-9 (PHQ-9) score of 5-19 [13]. Exclusion criteria were: 1) Schizophrenia, bipolar disease, active delirium, dementia, kidney disease (due to the role of the kidneys in magnesium homeostasis), myasthenia gravis (magnesium may worsen symptoms of the disease), or gastrointestinal (GI) disease (diarrhea is a common side effect of magnesium); 2) pregnant or trying to get pregnant; 3) planned surgery in the next 3 months; 5) taking a medication known to interact with magnesium; 6) unwilling to stop taking non-study magnesium supplements for the duration of the study.

Magnesium supplements

Tablets of $MgCl_2$ (Alta Health Products, Idaho City, ID) were provided free of charge. Participants were instructed to take four 500 mg tablets of magnesium chloride daily for a total of 248 mg of elemental magnesium per day. $MgCl_2$ was used because of its high bioavailability and tolerability compared to other salts [14, 15].

Study procedures and randomization

PCPs reviewed lists of their patients with a diagnosis of depression in their medical record and indicated which ones may be sent a letter describing the study. PCPs were encouraged to remove patients from their list if they knew depression was no longer an active problem, the patient was also suffering from severe mental illness, or the patient was not able to start or stop taking magnesium. Those patients that did not opt out after receiving the letter were contacted by phone to determine interest and eligibility. Eligibility and diagnosis of depression was confirmed with an initial telephone PHQ-9 score between 5 and 19. Participants next met with study staff for a baseline visit during which they provided written informed consent and baseline data including demographics, medication use, the PHQ-9 [13], the Generalized Anxiety Disorders-7 (GAD-7) [16], the Modified Morisky Scale [17] to assess medication adherence behavior, the PhenX Tobacco Smoking Status Questionnaire for Adults, and the PhenX Alcohol 30 Day Quantity and Frequency Questionnaire [18]. Randomization to Immediate and Delayed treatment was stratified based on PHQ-9 score (5-9, 10-14, and 15-19) and blocked in groups of 10. Treatment assignments were sealed in an opaque envelope and shuffled and then numbered and opened in that order. The principal investigator (PI) assigned the

participants to their randomization order. The PI also gave the volunteers the supplements at either week 1 or week 7, based on randomization, and educated each participant on the dosage and possible side effects. Data were collected every 2 weeks via telephone and included the PHQ-9, GAD-7, questions about changes in medications, changes in treatment for depression, and side effects.

Outcome measures

The primary hypothesis was that magnesium supplementation decreases symptoms of depression and therefore the primary outcome was the difference in the change in PHQ-9 scores between baseline and the end of each six-week period (difference in differences). The PHQ-9 is a validated questionnaire with high sensitivity and specificity for the diagnosis of depression [13]. The PHQ-9 score can range from 0 to 27, with the following severity scores: 0-4 None; 5-9 Mild; 10-14 Moderate; 15-19 Moderate to Severe; 20-27 Severe. Telephone administration is comparable to in-person tracking [19].

Secondary outcomes were exploratory and included changes in the GAD-7 score as well as adherence to the supplement regimen and intention to use magnesium supplements in the future. GAD-7 score was recorded in the same fashion as the PHQ-9 and has been shown to be a valid indication of anxiety symptoms [16]. The GAD-7 score can range from 0 to 21, with the following severity scores: 0-4 None; 5-9 Mild; 10-14 Moderate; 15-21 Severe. To assess side effects, participants were asked to compare symptoms (headache, diarrhea, nausea, constipation, dizziness, oliguria, and polyuria) to baseline using a standardized 0-4 point scale (none, mild, moderate, or severe). At the

end of week 12, a pill count was used to calculate adherence to the supplement regimen and participants were asked whether they planned to continue using magnesium and why.

Data analysis

All data were analyzed based on the intention-to-treat principle. The age and gender of patients who were contacted but ineligible were compared to those who were randomized. Baseline characteristics of eligible participants were compared by randomization group. Student t-tests or Wilcoxon Rank Sum tests were used for continuous values and Chi-square tests for categorical values.

The change in outcome for each patient was calculated as the last value measured during that treatment arm minus the last value measured before that treatment arm. Before crossing over, this was the week 6 measure minus the baseline measure. After cross-over, this was the week 12 measure minus the week 6 measure. If a week 12 measure was not available, the week 10 or week 8 measure was used. Participants who did not provide at least one outcome measure in each treatment period were excluded. Treatment efficacy was assessed as the net improvement in outcome. The mean change in the outcomes during the 6 weeks of the control (no treatment) period was compared to the change in scores during the 6 weeks of treatment. Linear regression was used to test the significance in the net improvement in the outcome while controlling for potential confounders.

Each potential confounder was tested in a separate univariate linear regression for association ($P<0.05$) with the primary outcome and secondary outcome. Potential confounders were included in multivariate models. We explored the effectiveness of

treatment among various subgroups using multivariate models. Linear regression adjusting for randomization and clustering was used to identify adverse effects. Cuzick's test of trend [20] was used to explore the relationships between both the Modified Morisky score and treatment response with adherence. A two-sided $P<0.05$ was considered statistically significant. All analyses were completed using Stata14·1 (College Station, TX).

The targeted sample size was based on detection of a difference in difference in PHQ-9 scores of 1.5, which was felt to be clinically significant. The calculation, assuming a paired t-test, with 84% power, type I error rate of 5%, and a standard deviation of 5 [21], resulted in a sample size of 50 participants in each group.

Results

Recruitment occurred between June 2015 and May 2016. Of 1,930 patients identified from medical records, 1,340 (68%) were contacted and 126 (7%) were eligible and randomized (Figure 3.1). The mean age of the contacted patients was 50 years compared to a mean age of 52 years in the randomized group (P=0.06). The randomized group had fewer males than the other contacted patients (38% *vs.*47%; P=0.07).

Sixty-two participants (49%) were randomized to Immediate Treatment and 64 (51%) to Delayed Treatment (P=0.95). The two groups were similar in all baseline characteristics except age. The mean age in the Immediate group was 55.6 versus 49.1 in the Delayed group (P=0.006). All participants commenced treatment based on allocation. Seven participants withdrew from each group before crossing over (11%) (Figure 3.1). The most common reason was a change in other depression treatment (n=7) (Table 3.1).

No participants withdrew due to non-compliance. 108 participants completed all 12 weeks of the study. Four withdrew between week 8 and 12; their last results recorded before withdrawal were included in the final sample, resulting in 112 participants analyzed (Figure 3.1). The characteristics of the final analyzed sample appear in Table 3.2. The Immediate group was similar to the Delayed group except that they were 5.1 years older P=0.04).The characteristics of the 14 subjects who withdrew before crossing over were similar in all measured characteristics to the 112 in the final sample except that they were more anxious (GAD-7 12.5 *vs.* 8.6; P=0.01). There were no significant differences in age, gender, race, smoking, alcohol consumption, baseline PHQ-9 score, Modified Morisky score, or use of depression therapies at the time of randomization.

Outcomes

Unadjusted PHQ-9 depression scores improved during magnesium treatment (-4.3 points; 95% confidence interval (CI) -5.0, -3.6), but not during the control period (-0.1; CI -0.9, +0.7) for the final analyzable cohort of 112 adults. The net improvement was -4.2 points (CI -5.4, -2.9; P<0.001). Participants who were randomized to Immediate Treatment first experienced a decrease in PHQ-9 score within 2 weeks; their scores increased slightly towards baseline during the 6 weeks of control (Figure 3.2). Those in the Delayed Treatment group experienced a slight improvement in PHQ-9 score during the control weeks and a further improvement during the active treatment.

Age, gender, race, smoking status, drinks of alcohol per week, adherence to the supplement regimen, and other treatments for depression were not associated with response to treatment and were not included in the adjusted model. Mean PHQ-9 change

during the control weeks, randomization order, and use of selective serotonin reuptake inhibitors (SSRI) were retained in the multivariate analyses. When adjusted for these potential confounders, the net improvement with supplementation was -6.0 points (CI -7.9, -4.2; $P<0.001$). See Table 3.3. Data for all participants (N=126) follow a similar pattern (Table 3.4). Unadjusted GAD-7 anxiety scores improved during magnesium supplementation (-3.9 points; CI -4.7, -3.1), but worsened during the control period (+0.8; CI +0.02, +1.6) for a net benefit of -4.7 points (CI -6.0, -3.3; $P<0.001$) (Figure 3.3). After adjustment for potential confounders (Table 3.3), the net improvement in anxiety with magnesium supplementation was -4.5 points (CI -6.6, -2.4; $P<0.001$). Again, the data are similar for all participants as well (Table 3.4).

Subgroup analyses were performed using the adjusted models of the association of magnesium with PHQ-9 and GAD-7 scores. Subgroups were defined by gender, age above or below 55, PHQ above or below 9, GAD above or below 9, use of any antidepressant medications, use of specific medications (SSRIs, selective norepinephrine reuptake inhibitors, bupropion, monoamine oxidase inhibitors, antipsychotics), use of behavioral therapy or counseling, and adherence above or below 80% by pill count. The analyses indicated that magnesium was effective in all subgroups (Table 3.3).

Participants were less likely to report headaches while taking magnesium compared to the control period (unadjusted mean headache score 0.41 *vs.* 0.57 on the 0-3 scale). The adjusted difference was -0.16 (CI -0.25, -0.03; $P=0.013$). There was no difference in the reporting of diarrhea, constipation, nausea, dizziness or urinary symptoms (Table 3.5). Using the adjusted model, we explored the effect of magnesium

supplementation on the answers to individual PHQ-9 and GAD-7 items. All items in the PHQ-9 improved significantly during active treatment except question 8 (abnormal movement speed) and question 9 (thoughts of suicide). Of note, question 9 was positive on only 3 of 892 occasions. The only GAD-7 questions that did not improve significantly were questions 1 (feeling nervous, anxious, or on edge) and 5 (experiencing restlessness).

Percent adherence in the Immediate Treatment group (83%) and Delayed Treatment group (82%) were similar (P=0.85). Treatment response for both the PHQ-9 and GAD-7 tended to be greater with increased adherence; however, the trend was not significant for either at P=0.19 and P=0.64, respectively.

When asked whether they would take magnesium in the future, 68 (61%) answered yes, 22 (20%) answered maybe and 22 (20%) answered no. The most common reasons for a positive answer were “the magnesium helped my mood” (58%) and “it helped in other ways” (23%), such as by increasing energy, decreasing constipation, and decreasing muscle aches and cramps. The most common reason for a negative response was that “magnesium did not help mood” (46%), followed by side effects (20%). The most common side effect, diarrhea, was reported by 8 participants.

Discussion

This trial was conducted to test the efficacy and safety of over-the-counter magnesium and to determine its role in the treatment of depression. Consumption of 248 mg of elemental $MgCl_2$ daily for 6 weeks improved depression scores by a statistically and clinically significant mean of 6 points and anxiety symptoms by over 4 points. This effect was not due to natural history, regression to the mean, or confounding, and was

seen in a wide range of patients with varying ages, co-treatments, and severity of baseline symptoms. The similar effects seen in the univariate and multivariate models indicates that the potential confounders had little impact on the estimates of treatment effect.

As with other studies, [8, 11, 22] the improvement in symptoms was seen within weeks. The effect was somewhat diminished within 2 weeks of stopping supplementation, indicating relatively quick clearance as well. Although females are more likely to be diagnosed with depression [23], there was no difference in effect based on gender. The finding that high and low adherence subgroups had similar improvement suggests that a smaller dose may suffice with less risk for side effects and lower cost.

Adverse effects were not so severe as to lead to discontinuation except in one case in which nausea and lethargy led to withdrawal after two weeks. Participants did report experiencing other clinically significant, and well documented, positive effects of taking magnesium, such as decreases in headaches and muscle cramps [24]. The fact that nearly all specific PHQ-9 and GAD-7 items improved significantly while on treatment corresponds with the qualitative reports.

Although the association between magnesium and depression is well documented, the mechanism is unknown. However, magnesium plays a role in many of the pathways, enzymes, hormones, and neurotransmitters involved in mood regulation [25]. It is a calcium antagonist and voltage-dependent blocker of the *N*-methyl-D-aspartate channel which regulates the flow of calcium into the neuron [26]. In low magnesium states, high levels of calcium and glutamate may deregulate synaptic function, resulting in depression [9]. Depression and magnesium are also both associated

with systemic inflammation [27, 28]. The finding that those participants taking an SSRI experienced an even greater positive effect points toward magnesium's possible role in augmenting the effect of antidepressants. Since the mechanism of magnesium's role in depression is still not clear, it is difficult to say why this relationship with antidepressants may exist. In a sample of treatment resistant depressed patients with normal magnesium levels, those with high normal magnesium levels had a more robust response to antidepressants [29]. In another study, severity of depression correlated with reduced intracellular magnesium, and cellular levels normalized after successful treatment with antidepressants [30]. Patients may have normal plasma concentration of magnesium yet have depleted intracellular stores [31]. There may also be differential effects for SSRIs compared to other antidepressants. Some evidence to support adjunctive use of other nutraceuticals with antidepressants exists. The mechanism may be related to their anti-inflammatory properties or role in NMDA and glutamate activity [32]. Magnesium supplementation may allow for lower antidepressant dosage or avoid the need for use of a second medication, both of which could reduce overall side effect burden.

Implications for Practice

The net improvement in PHQ-9 score of 6 points is statistically and clinically significant. A change in score of 5 or greater reflects a clinically relevant change in individuals receiving depression treatment. After 6 weeks of psychological counseling, a drop in 5 points from baseline PHQ-9 indicates the treatment response is adequate and no treatment change is needed. The same guidelines can be applied to 4 weeks of an adequate dose of an antidepressant.[33] Magnesium supplementation provides a safe, fast

and inexpensive approach to controlling depressive symptoms. Most patients who experience improvement do so within two weeks of starting supplements. Oral magnesium supplementation is safe in adults with normal kidney function who are not taking medications that interact with the supplement and when used in dosages below the upper tolerable limit set by the Institute of Medicine (350 mg elemental magnesium per day) [34]. Hypermagnesemia is most commonly associated with the combination of impaired renal function and excessive intake of nonfood magnesium; few serious adverse effects are reported until very high doses are ingested [34].

Similar to national surveys [35], some participants with depression were not on any treatment. There are many barriers to treatment for depression including stigma associated with diagnosis, cost, side effects, non-adherence, and loss to follow-up [36]. Magnesium supplements do not come with the added stigma associated with other therapies and, while monitoring response is still important, the risk of side effects is not as great as from antidepressants. Over-the-counter magnesium can be offered as an alternative therapy to those patients hesitant to begin antidepressant treatment and is easily accessible without a prescription for around $14.00 per month.

Strengths

This is the first clinical trial done on magnesium for depression in the U.S. Exclusion criteria were minimal, increasing generalizability, and it used a well-absorbed form of magnesium. The paired analysis allowed each subject to serve as his or her own control, minimizing variance and improving statistical power. Random assignment of treatment order allowed for controlling for regression to the mean as an explanation for

the apparent treatment effects. Enrolling patients over a full year minimized the effects of seasonal changes in depression. The withdrawal rate was low and adherence was high, confirming patient reports of high acceptability.

Limitations

There was no placebo arm and randomization was not blinded for either the study team or the volunteer. The use of placebo and blinding are essential for a study that seeks to understand the mechanism of action of an intervention. However, they are not useful when the research seeks to assess the presence and magnitude of the effect of an intervention. Whether magnesium works because it induces a physiological change in the subject, or only because of the placebo effect (or a combination of the two), it remains that subjects do report better levels of depression and anxiety when taking magnesium than when not.

Enrolling patients with depression listed on their medical chart resulted in missing people with undiagnosed depression or who do not use Primary Care. PCPs may have introduced selection bias by differentially disapproving patients they thought were unlikely to be open to alternative treatments. This may not be an important limitation to generalizability since nutraceuticals would probably not be recommended for these patients anyway. The low response rate to our letter of invitation and follow up calls may have also introduced selection bias.

The study excluded subjects with malabsorption because the main known side effect of magnesium is diarrhea. However, because diarrhea was rare in the study, it would be worth determining the tolerance and effect in those with GI disease. Some of

the subgroups are small, limiting our ability to detect variation in efficacy, although none was seen. Due to the makeup of the local community, the study population lacked racial diversity.

Although improvement in symptoms occurred within two weeks and was maintained while on treatment, long-term effectiveness is unknown and longer trials are needed.

Measurement of serum magnesium was outside the scope of the study. A recent meta-analysis of observational studies found an overall 1.3-fold increased risk of depression in people with hypomagnesaemia [37] yet a previous meta-analysis was inconclusive [38]. It is not clear if hypomagnesaemia influences the efficacy of magnesium supplementation for depression.

Conclusions

Daily supplementation with 248 mg of elemental magnesium as four 500 mg tablets of magnesium chloride per day leads to a significant decrease in depression and anxiety symptoms regardless of age, gender, baseline severity of depression, or use of antidepressant medications. While the cross over design of this trial is robust in controlling for internal biases, it would be reassuring to see the results replicated in larger clinical trials that test long term efficacy and provide additional data on subgroups. However, this efficacy trial showed magnesium supplements may be a fast, safe, and easily accessible alternative, or adjunct, to starting or increasing the dose of antidepressant medications.

Figure 3.1 Consort diagram

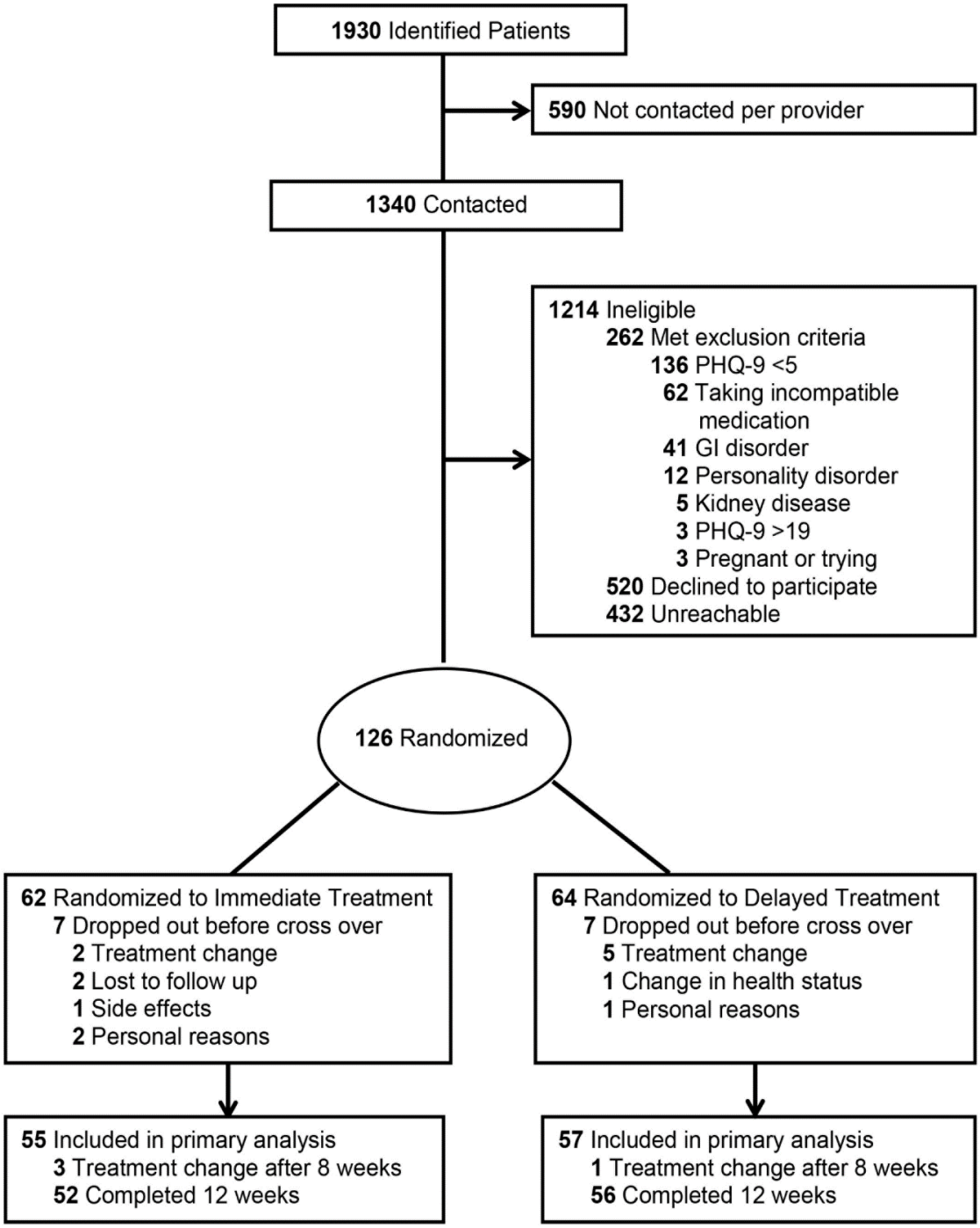


Table 3.1 Withdrawals by reason and time point

Reason for withdrawal	*Week 2*	*Week 4*	*Week 6*	×	*Week 8*	*Week 10*	*Week 12*	*Total*
Treatment Change for Depression	3	3	1	Cross-over		2[a]	2[a]	11
Side Effects	1							1
Change in Health Status		1						1
Personal Reasons			1					1
No Reason Given		1	1					2
Lost to Follow Up	1		1					2
Total number of withdrawals	5	5	4		0	2[a]	2[a]	18

[a]These participants were included in the final analysis using their last recorded values.

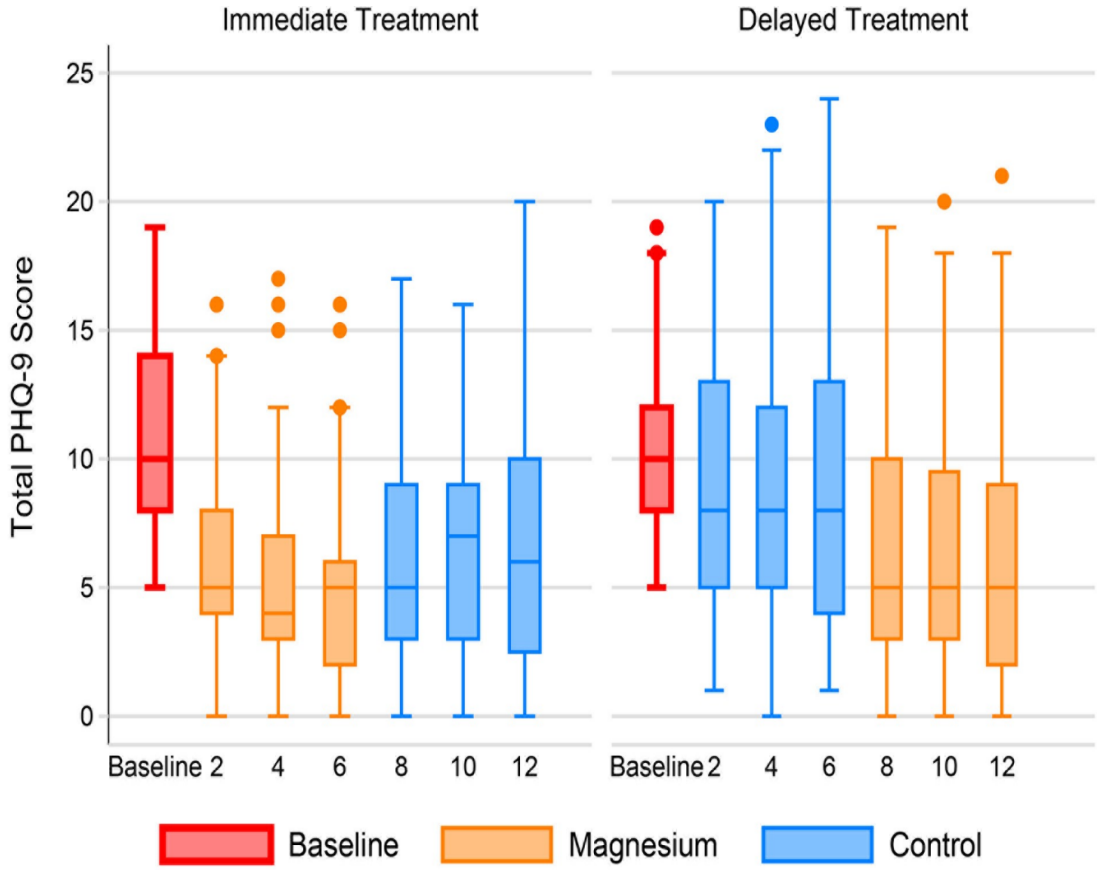
Table 3.2 Demographic characteristics of final sample (N=112)

Characteristic	*Randomization Group*		*P-Value*
	Immediate (N=55)	*Delayed (N=57)*	
Age, mean (SD)	55.2 (12.3)	50.1 (13.0)	0.038
Male Gender, N (%)	22 (40%)	22 (36%)	>0.99
Self-Report White Race, N (%)	53 (96%)	56 (98%)	0.62
Current Smoker, N (%)	7 (13%)	8 (12%)	>0.99
Servings of Alcohol Per Week, mean (SD)	3.3 (5.0)	4.9 (7.8)	0.19
Current Treatment for Depression, N (%)			
No Treatment	14 (25%)	17 (30%)	0.68
Self-management	1 (2%)	1 (2%)	>0.99
Non-pharmacologic Therapy	14 (26%)	11(19%)	0.50
One or more medications	35 (64%)	35 (61%)	0.85
Selective Serotonin Reuptake Inhibitors	19 (35%)	22 (39%)	0.70
Selective Norepinephrine Reuptake Inhibitors	8 (15%)	8 (14%)	>0.99
Tricyclic	2 (4%)	1 (2%)	0.61
Bupropion	7 (13%)	9 (16%)	0.80
Monoamine Oxidase Inhibitors	0	0	-
Antipsychotic	0	2 (4%)	0.50
Baseline Patient Health Questionnaire-9 Depression Score, mean (SD)	10.7 (3.7)	10.6 (3.8)	0.84
Baseline Generalized Anxiety Disorder-7 Anxiety Score, mean (SD)	8.6 (5.1)	8.7 (5.4)	0.92
Modified Morisky Score, mean (SD)	2.9 (0.9)	2.9 (1.0)	0.91

N=number; SD = standard deviation.

P-values calculated by Chi-square for categorical values and two-sample t-test or Wilcoxon Rank Sum for continuous values.

Figure 3.2 Patient Health Questionnaire-9 over time by group.



The individual box plots show the distribution of PHQ-9 scores by week in each randomization group. The middle line of each box represents the median score. The boxes range from the 25th to the 75th percentile. The whiskers demonstrate the range of scores with outliers shown by small circles.

Table 3.3 Adjusted net improvement with magnesium

			PHQ-9			*GAD-7*		
		N	*Change*	*95% CI*	*P*	*Change*	*95% CI*	*P*
All subjects	Magnesium	112	-4.9	-6.0, -3.9	<0.001	-3.6	-4.9, -2.3	<0.001
	Control	112	+1.1	-0.1, +2.3	0.08	+0.9	-0.4, +2.1	0.17
	Net Improvement		-6.0	-7.9, -4.2	<0.001	-4.5	-6.6, -2.4	<0.001
Subgroups			*Net Improvement*	*95% CI*	*P*	*Net Improvement*	*95% CI*	*P*
Gender	Female	68	-6.6	-9.1, -4.0	<0.001	-3.8	-6.4, -1.1	0.003
	Male	44	-5.3	-7.6, -3.1	<0.001	-5.5	-8.9, -2.1	0.001
Age	≤55 years	55	-5.3	-7.9, -2.8	<0.001	-5.1	-8.6, -1.5	0.002
	>55 years	57	-6.5	-9.0, -4.1	<0.001	-4.0	-6.6, -1.5	0.001
Baseline PHQ-9	≤9	49	-4.7	-6.3, -3.2	<0.001	-3.1	-4.8, -1.3	<0.001
	>9	63	-7.2	-10.1, -4.2	<0.001	-5.6	-9.2, -2.1	0.001
Baseline GAD-7	≤9	68	-4.7	-6.8, -2.6	<0.001	-2.2	-4.0, -0.5	0.005
	>9	44	-8.2	-11.0, -5.3	<0.001	-8.3	-12.6, -3.9	<0.001
Adherence	Low	56	-5.3	-8.2, -2.5	<0.001	-3.3	-5.9, -0.6	0.008
	High	56	-6.6	-8.7, -4.6	<0.001	-5.7	-8.7, -2.7	<0.001

PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; CI = confidence interval.

[a]Net Improvement = change in outcome during magnesium treatment – change in outcome during control.

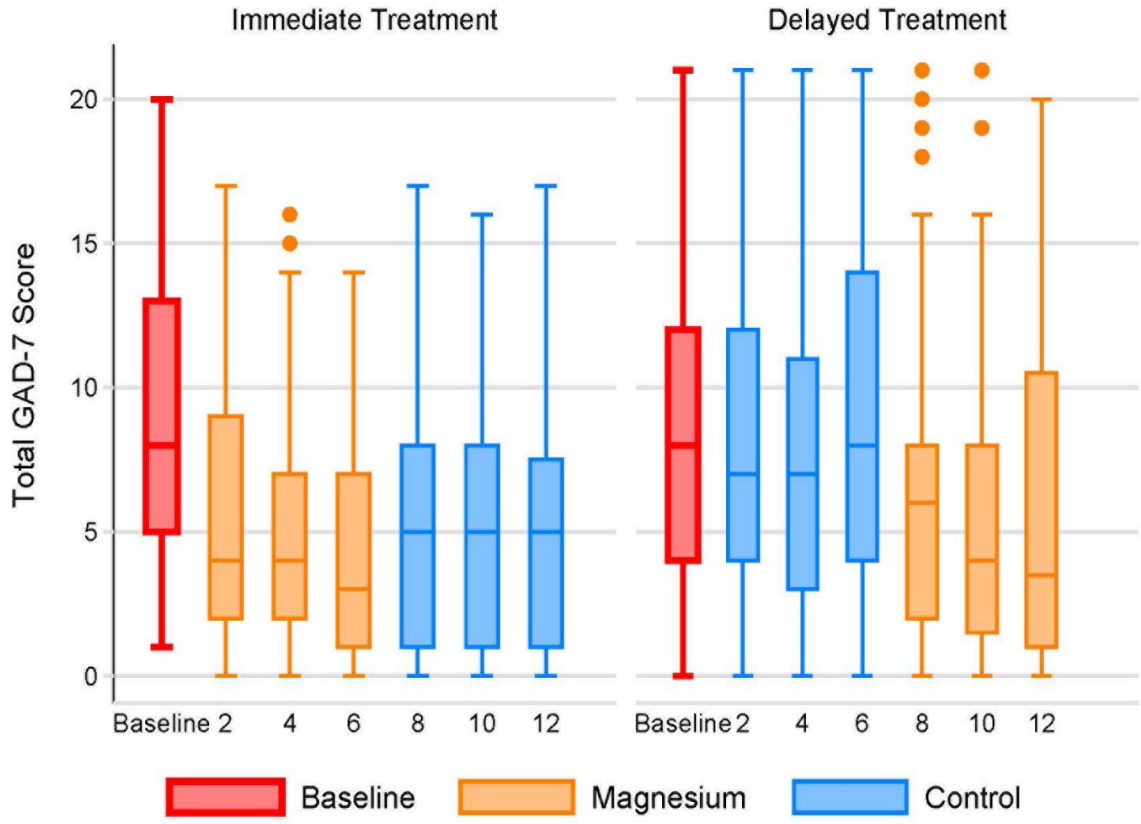
All results adjusted for mean PHQ-9 score during control weeks, treatment order (Immediate *vs.* Delayed), and selective serotonin reuptake inhibitor (SSRI) therapy.

Table 3.4 Unadjusted PHQ-9 and GAD-7 scores by event for all participants (N=126)

	Patient Health Questionnaire-9			*Generalized Anxiety Disorder-7*		
	Randomized Treatment Assignment			*Randomized Treatment Assignment*		
Event	*Immediate*	*Delayed*	*Total*	*Immediate*	*Delayed*	*Total*
Baseline, mean	10.9	10.8	10.8	8.9	9.2	9.0
SD	3.8	3.9	3.8	5.1	5.6	5.3
N	62	64	126	62	64	126
Week 2, mean	7.0	9.1	8.1	5.7	8.3	7.0
SD	4.7	4.9	4.9	4.7	5.4	5.2
N	60	63	123	60	63	123
Week 4, mean	5.8	8.9	7.4	4.9	7.8	6.4
SD	4.3	5.4	5.1	4.4	5.6	5.2
N	59	61	120	59	61	120
Week 6, mean	5.1	9.2	7.1	4.4	9.2	6.8
SD	3.9	5.6	5.2	4.0	5.9	5.6
N	57	57	114	57	57	114
Week 8, mean	6.1	6.8	6.5	5.5	6.2	5.9
SD	4.4	4.9	4.6	4.5	5.5	5.0
N	55	57	112	55	57	112
Week 10, mean	6.5	6.6	6.5	5.3	5.8	5.5
SD	3.9	4.5	4.2	4.3	5.4	4.9
N	52	56	108	52	56	108
Week 12, mean	6.3	6.3	6.3	5.2	5.8	5.5
SD	4.6	5.4	5.0	4.9	5.8	5.3
N	52	56	108	52	56	108

SD=standard deviation; N=number

Figure 3.3 Generalized Anxiety Disorders-7 over time by group.



The individual box plots show the distribution of PHQ-9 scores by week in each randomization group. The middle line of each box represents the median score. The boxes range from the 25th to the 75th percentile. The whiskers demonstrate the range of scores with outliers shown by small circles.

Table 3.5 Adverse effects during treatment.[a]

	Unadjusted			*Adjusted*[b]		
Adverse effect	*Control*	*Magnesium*	*Difference*	*Difference*	*95% CI*	*P*
Headache	0.57	0.41	-0.16	-0.14	-0.25, -0.03	0.01
Diarrhea	0.32	0.29	-0.02	-0.01	-0.11, +0.08	0.79
Nausea	0.22	0.24	+0.02	+0.02	-0.07, +0.11	0.64
Constipation	0.20	0.20	+0.00	-0.00	-0.08, +0.07	0.97
Dizziness	0.24	0.22	-0.02	-0.02	-0.09, +0.06	0.66
Oliguria	0.04	0.07	+0.03	+0.03	-0.02, +0.08	0.19
Polyuria	0.11	0.16	+0.05	+0.05	-0.01, +0.11	0.09

CI = confidence interval.

[a]Mean values of biweekly reports on a 0 to 4 scale.

[b]Adjusted for mean PHQ-9 score during control weeks, treatment order (Immediate *vs.* Delayed), use of SSRIs, and clustering within participant.

References

1. World Health Organization. Depression fact sheet no. 369 2012 [cited 2016 December 20]. Available from: http://www.who.int/mediacentre/factsheets/fs369/en/.
2. Trevino K, McClintock SM, McDonald Fischer N, Vora A, Husain MM. Defining treatment-resistant depression: a comprehensive review of the literature. Ann Clin Psych. 2014;26(3):222-32. PubMed PMID: 25166485.
3. Hoifodt RS, Strom C, Kolstrup N, Eisemann M, Waterloo K. Effectiveness of cognitive behavioural therapy in primary health care: a review. Fam Pract. 2011;28(5):489-504. doi: 10.1093/fampra/cmr017. PubMed PMID: 21555339.
4. Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. Aust N Z J Psychiatry. 2009;43(1):45-52. doi: 10.1080/00048670802534408. PubMed PMID: 19085527.
5. Huang JH, Lu YF, Cheng FC, Lee JN, Tsai LC. Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study. Nutrition J. 2012;11(1):41. doi: 10.1186/1475-2891-11-41. PubMed PMID: 22695027; PubMed Central PMCID: PMC3439347.
6. Tarleton EK, Littenberg B. Magnesium intake and depression in adults. J Am Board Fam Med. 2015;28(2):249-56. doi: 10.3122/jabfm.2015.02.140176.
7. Yary T, Lehto SM, Tolmunen T, Tuomainen T-P, Kauhanen J, Voutilainen S, et al. Dietary magnesium intake and the incidence of depression: a 20-year follow-up study. J Affect Disord. 2016;193:94-8. doi: http://dx.doi.org/10.1016/j.jad.2015.12.056.
8. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. Med Hypotheses. 2006;67(2):362-70. doi: http://dx.doi.org/10.1016/j.mehy.2006.01.047.
9. Derom ML, Martinez-Gonzalez MA, Sayon-Orea Mdel C, Bes-Rastrollo M, Beunza JJ, Sanchez-Villegas A. Magnesium intake is not related to depression risk in Spanish university graduates. J Nutrition. 2012;142(6):1053-9. doi: 10.3945/jn.111.155572. PubMed PMID: 22513990.
10. Barragan-Rodriguez L, Rodriguez-Moran M, Guerrero-Romero F. Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. Magnes Res. 2008;21(4):218-23. PubMed PMID: 19271419.
11. Bagis S, Karabiber M, As I, Tamer L, Erdogan C, Atalay A. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? Rheumatol Int. 2013;33(1):167-72. doi: 10.1007/s00296-011-2334-8. PubMed PMID: 22271372.
12. De Souza MC, Walker AF, Robinson PA, Bolland K. A synergistic effect of a daily supplement for 1 month of 200 mg magnesium plus 50 mg vitamin B6 for the relief of anxiety-related premenstrual symptoms: a randomized, double-blind, crossover study. J Womens Health Gend Based Med. 2000;9(2):131-9. doi: 10.1089/152460900318623. PubMed PMID: 5323857.

13. Kroenke K, Spitzer R, Williams J. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606 - 13. PubMed PMID: doi:10.1046/j.1525-1497.2001.016009606.x.
14. Durlach J, Guiet-Bara A, Pages N, Bac P, Bara M. Magnesium chloride or magnesium sulfate: a genuine question. Magnes Res. 2005;18(3):187-92. PubMed PMID: 16259379.
15. Martin RW, Perry KG, Jr., Martin JN, Jr., Seago DP, Roberts WE, Morrison JC. Oral magnesium for tocolysis: a comparison of magnesium gluconate and enteric-coated magnesium chloride. J Miss State Med Assoc. 1998;39(5):180-2. PubMed PMID: 9610075.
16. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Internal Med. 2006;166(10):1092-7.
17. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74. PubMed PMID: 3945130.
18. Hamilton CM, Strader LC, Pratt JG, Maiese D, Hendershot T, Kwok RK, et al. The PhenX Toolkit: get the most from your measures. Am J Epidemiol. 2011;174(3):253-60. doi: 10.1093/aje/kwr193. PubMed PMID: 21749974; PubMed Central PMCID: PMCPmc3141081.
19. Pinto-Meza A, Serrano-Blanco A, Peñarrubia MT, Blanco E, Haro JM. Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone? J Gen Intern Med. 2005;20(8):738-42. doi: 10.1111/j.1525-1497.2005.0144.x. PubMed PMID: PMC1490180.
20. Cuzick J. A Wilcoxon-type test for trend. Stat Med. 1985;4:87-90.
21. Littenberg B, MacLean C. Intra-cluster correlation coefficients in adults with diabetes in primary care practices: the Vermont Diabetes Information System field survey. BMC Med Res Methodol. 2006;6(1):20. PubMed PMID: doi:10.1186/1471-2288-6-20.
22. Rajizadeh A, Mozaffari-Khosravi H, Yassini-Ardakani M, Dehghani A. Effect of magnesium supplementation on depression status in depressed patients with magnesium deficiency: a randomized, double-blind, placebo-controlled trial. Nutrition. 2017;35:56-60. doi: 10.1016/j.nut.2016.10.014. PubMed PMID: 28241991.
23. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res. 2012;21(3):169-84. doi: 10.1002/mpr.1359. PubMed PMID: 22865617; PubMed Central PMCID: PMCPmc4005415.
24. Grober U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients. 2015;7(9):8199-226. doi: 10.3390/nu7095388. PubMed PMID: 26404370; PubMed Central PMCID: PMCPmc4586582.
25. Serefko A, Szopa A, Wlaz P, Nowak G, Radziwon-Zaleska M, Skalski M, et al. Magnesium in depression. Pharmacol Reports. 2013;65(3):547-54. PubMed PMID: 23950577.

26. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J. 1984;108(1):188-93. PubMed PMID: 6375330.
27. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(3):664-75. doi: 10.1016/j.pnpbp.2010.06.014. PubMed PMID: 20599581.
28. Chacko SA, Sul J, Song Y, Li X, LeBlanc J, You Y, et al. Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. Am J Clin Nutr. 2011;93(2):463-73. doi: 10.3945/ajcn.110.002949. PubMed PMID: 21159786; PubMed Central PMCID: PMCPMC3021435.
29. Camardese G, Risio LD, Pizi G, Mattioli B, Buccelletti F, Serrani R, et al. Plasma magnesium levels and treatment outcome in depressed patients. Nutr Neurosci. 2012;15(2):78-84. doi: doi:10.1179/1476830512Y.0000000002. PubMed PMID: 22564338.
30. Nechifor M. Magnesium in major depression. Magnes Res. 2009;22(3):163s-6s. PubMed PMID: 19780403.
31. Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kid J. 2012;5(Suppl 1):i3-i14. doi: 10.1093/ndtplus/sfr163.
32. Sarris J, Murphy J, Mischoulon D, Papakostas GI, Fava M, Berk M, et al. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. Am J Psychiatry. 2016;173(6):575-87. doi: 10.1176/appi.ajp.2016.15091228. PubMed PMID: 27113121.
33. Department of Veterans Affairs, Department of Defense. VA/DoD clinical practice guideline for management of major depressive disorder (MDD) Washington, D.C.2009 [cited 2017 May 17]. Available from: https://www.healthquality.va.gov/mdd/mdd_full09_c.pdf.
34. Institute of Medicine. *Dietary reference intakes: calcium, phosphorous, magnesium, vitmain D, and flouride.* Food and Nutrition Board, editor. Washington, DC: National Academy Press; 1997.
35. Wittayanukorn S, Qian J, Hansen RA. Prevalence of depressive symptoms and predictors of treatment among U.S. adults from 2005 to 2010. Gen Hosp Psychiatry. 2014;36(3):330-6. doi: http://dx.doi.org/10.1016/j.genhosppsych.2013.12.009.
36. Nutting PA, Rost K, Dickinson M, Werner JJ, Dickinson P, Smith JL, et al. Barriers to initiating depression treatment in primary care practice. J Gen Intern Med. 2002;17(2):103-11. PubMed PMID: 11841525; PubMed Central PMCID: PMCPmc1495010.
37. Cheungpasitporn W, Thongprayoon C, Mao MA, Srivali N, Ungprasert P, Varothai N, et al. Hypomagnesaemia linked to depression: a systematic review and meta-analysis. Intern Med J. 2015;45(4):436-40. doi: 10.1111/imj.12682. PubMed PMID: 25827510.
38. Derom ML, Sayon-Orea C, Martinez-Ortega JM, Martinez-Gonzalez MA. Magnesium and depression: a systematic review. Nutri Neurosci. 2013;16(5):191-206. doi: 10.1179/1476830512y.0000000044. PubMed PMID: 23321048

COMPREHENSIVE BIBLIOGRAPHY

Administration on Aging. Profile of Older Americans. February 10, 2012; http://www.aoa.gov/AoARoot/Aging_Statistics/Profile/index.aspx. Accessed October 30, 2012.

Ahuja JK, Moshfegh AJ, Holden JM, Harris E. USDA food and nutrient databases provide the infrastructure for food and nutrition research, policy, and practice. *J Nutrition*. 2013;143(2):241s-249s.

Altura BM, Altura BT. Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis. *Cell Mol Biol Res*. 1995;41(5):347-359.

Arnaud MJ. Update on the assessment of magnesium status. *Br J Nutr*. 2008;99(Suppl 3):S24-36.

Azoulay A, Garzon P, Eisenberg MJ. Comparison of the mineral content of tap water and bottled waters. *J Gen Intern Med. 2001*;16(3):168-175.

Bagis S, Karabiber M, As I, Tamer L, Erdogan C, Atalay A. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? *Rheumatol Int*. 2013;33(1):167-72.

Bailey RL, Akabas SR, Paxson EE, Thuppal SV, Saklani S, Tucker KL. Total usual intake of shortfall nutrients varies with poverty among US adults. *J Nutr Educ Behav*. 2017;In Press.

Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003–2006. *J Nutr.* 2011;141(2):261-266.

Barbagallo M, Belvedere M, Dominguez LJ. Magnesium homeostasis and aging. *Mag Res*. 2009;22(4):235-246.

Barr SI, DiFrancesco L, Fulgoni VL. Consumption of breakfast and the type of breakfast consumed are positively associated with nutrient intakes and adequacy of Canadian adults. *J Nutr*. 2013;143(1):86-92.

Barragan-Rodriguez L, Rodriguez-Moran M, Guerrero-Romero F. Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. *Magnes Res.* 2008;21(4):218-223.

Beckstrand RL, Pickens JS. Beneficial effects of magnesium supplementation. *J Evid Based Complement & Alt Med*. 2011;16(3):181-189.

Blanck HM, Gillespie C, Kimmons JE, Seymour JD, Serdula MK. Trends in fruit and vegetable consumption among U.S. men and women, 1994-2005. *Prev Chronic Dis*. 2008;5(2):A35.

Block G, Dresser CM, Hartman AM, Carroll MD. Nutrient sources in the American diet: quantitative data from the NHANES II survey. II. Macronutrients and fats. *Am J Epidemiol*. 1985;122(1):27-40.

Bogner HR, Morales KH, Reynolds CF, Cary MS, Bruce ML. Course of depression and mortality among older primary care patients. *Am J Geriatr Psychiatry.* 2012;20(10):895-903.

Bowman S. Low economic status is associated with suboptimal intakes of nutritious foods by adults in the National Health and Nutrition Examination Survey 1999-2002. *Nutrition Res.* 2007;27(9):515-523.

Bowman S, Clemens J, Friday J, Thoerig R, Moshfegh A. Food Patterns Equivalents Intakes from Food: Mean Amounts Consumer per Individual, What We Eat in America, NHANES 2011-12; Tables 1-4. United States Department of Agriculture, Agricultural Research Service. https://www.ars.usda.gov/research/publications/publication/?seqNo115=312662. 2014. Accessed June 8, 2017.

Boynton D. Nutrition by foliar application. *Ann Rev Plant Phys*. 1954;5(1):31-54.

Camardese G, Risio LD, Pizi G, Mattioli B, Buccelletti F, Serrani R, et al. Plasma magnesium levels and treatment outcome in depressed patients. *Nutr Neurosci*. 2012;15(2):78-84.

Casagrande SS, Wang Y, Anderson C, Gary TL. Have Americans increased their fruit and vegetable intake? The trends between 1988 and 2002. *Am J Prev Med*. 2007;32(4):257-263.

Centers for Disease Control and Prevention. The National Health and Nutrition Examination Survey Documentation, Codebook, and Frequencies; Dietary Interview - Individual Foods, First Day. Atlanta, GA: CDC; 2008.

Centers for Disease Control and Prevention. Current Depression Among Adults---United States, 2006 and 2008. *MMWR.* 2010;59(38):1229-1235.

Centers for Disease Control and Prevention. Questionnaires, Datasets, and Related Documentation. Vol 2013. http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm. Accessed May 30, 2017.

Chacko SA, Sul J, Song Y, et al. Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. *Am J Clin Nutr*. 2011;93(2):463-473.

Cheungpasitporn W, Thongprayoon C, Mao MA, et al. Hypomagnesaemia linked to depression: a systematic review and meta-analysis. *Intern Med J*. 2015;45(4):436-40.

Cifelli CJ, Houchins JA, Demmer E, Fulgoni VL. Increasing Plant Based Foods or Dairy Foods Differentially Affects Nutrient Intakes: Dietary Scenarios Using NHANES 2007-2010. *Nutrients*. 2016;8(7):422.

Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005;81(2):341-354.

Costello RB, Elin RJ, Rosanoff A, Wallace TC. Perspective: the case for an evidence-based reference interval for serum magnesium: the time has come. *Adv Nutr*. 2016;7(6):977-993.

Cox IM, Campbell MJ. Red blood cell magnesium and chronic fatigue syndrome. *Lancet.* 1991;337(8744):757.

Cuzick J. A Wilcoxon-type test for trend. *Stat Med.* 1985;4:87-90.

Darmon N, Drewnowski A. Does social class predict diet quality? *Am J Clin Nutr*. 2008;87(5):1107-1117.
Davis DR. Declining fruit and vegetable nutrient composition: what is the evidence? *Hort Science.* 2009;44(1):15-19.
Davison KM, Kaplan BJ. Nutrient intakes are correlated with overall psychiatric functioning in adults with mood disorders. *Can J Psychiatry.* 2012;57(2):85-92.
de Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. *Physiol Rev.* 2015;95(1):1-46.
Department of Veterans Affairs, Department of Defense. VA/DoD clinical practice guideline for management of major depressive disorder (MDD) Washington, D.C.2009 https://www.healthquality.va.gov/mdd/mdd_full09_c.pdf. Accesses May 17, 2017.
Derom ML, Martinez-Gonzalez MA, Sayon-Orea MC, et al. Magnesium intake is not related to depression risk in Spanish university graduates. *J Nutr.* 2012;142(6):1053-1059.
De Souza MC, Walker AF, Robinson PA, Bolland K. A Synergistic Effect of a Daily Supplement for 1 Month of 200 mg Magnesium plus 50 mg Vitamin B6 for the Relief of Anxiety-Related Premenstrual Symptoms: A Randomized, Double-Blind, Crossover Study. *J Women Health Gender-B.* 2000;9(2):131-139.
Dixon LB, Winkleby MA, Radimer KL. Dietary intakes and serum nutrients differ between adults from food-insufficient and food-sufficient families: third National Health and Nutrition Examination Survey, 1988–1994. *J Nutr*. 2001;131(4):1232-1246.
Dodd KW, Guenther PM, Freedman LS, et al. Statistical methods for estimating usual intake of nutrients and foods: a review of the theory. *J Am Diet Assoc*. 2006;106(10):1640-1650.
Doria MF. Bottled water versus tap water: understanding consumers' preferences. *J Water Health*. 2006;4(2):271-276.
Durlach J, Guiet-Bara A, Pages N, Bac P, Bara M. Magnesium chloride or magnesium sulfate: a genuine question. *Magnes Res*. 2005;18(3):187-92.
Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses.* 2006;67(2):362-370.
Eby GA, Eby KL. Magnesium for treatment-resistant depression: a review and hypothesis. *Med Hypotheses.* 2010;74(4):649-660.
Edwards-Jones G, Canals LM, Hounsome N, et al. Testing the assertion that 'local food is best': the challenges of an evidence-based approach. *Trends Food Sci Technol.* 2008;19(5):265-274.
Elin RJ. Assessment of magnesium status for diagnosis and therapy. *Mag Res*. 2010;23(4):S194-198.
Elin RJ. Re-evaluation of the concept of chronic, latent, magnesium deficiency. *Mag Res*. 2011;24(4):225-227.
European Food Safety Authority Panel on Dietetic Products NaA. Scientific opinion on dietary reference values for magnesium. *EFSA Journal*. 2015;13(7):4186.

Felsby S, Nielsen J, Arendt-Nielsen L, Jensen TS. NMDA receptor blockade in chronic neuropathic pain: a comparison of ketamine and magnesium chloride. *Pain*. 1996;64(2):283-291.
Flink EB. Nutritional aspects of magnesium metabolism. *West J Med*. 1980;133(4):304-312.
Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended Dietary Allowances: Subcommittee on the Tenth Edition of the RDAs.* Washington DC: National Academy Press; 1989.
Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of US adults. *J Nutr*. 2003;133(9):2879-2882.
Fulgoni VL, Keast DR, Bailey RL, Dwyer J. Foods, fortificants, and supplements: where do Americans get their nutrients? *J Nutrition*. 2011;141(10):1847-1854.
Geiger H, Wanner C. Magnesium in disease. *Clin Kid J*. 2012;5(Suppl 1):i25-i38.
Gleick P. Bottled water sales: the shocking reality. 2013; http://scienceblogs.com/significantfigures/index.php/2013/04/25/bottled-water-sales-the-shocking-reality/. Accessed May 3, 2017.
Grober U, Schmidt J, Kisters K. Magnesium in prevention and therapy. *Nutrients*. 2015;7(9):8199-8226.
Grzebisz W. Magnesium–food and human health. *J Elementol*. 2011;16(2).
Hackman RM, Aggarwal BB, Applebaum RS, et al. Forecasting nutrition research in 2020. *J Am Coll Nutr.* 2014;33(4):340-346.
Haddad EH, Tanzman JS. What do vegetarians in the United States eat? *Am J Clin Nutr*. 2003;78(3 Suppl):626s-632s.
Hallfrisch J, Muller DC. Does diet provide adequate amounts of calcium, iron, magnesium, and zinc in a well-educated adult population? *Exp Gerentol*. 1993;28(4–5):473-483.
Hamer M, Bates CJ, Mishra GD. Depression, physical function, and risk of mortality: National Diet and Nutrition Survey in adults older than 65 years. *Am J Geriatr Psychiatry.* 2011;19(1):72-78.
Hamilton CM, Strader LC, Pratt JG, Maiese D, Hendershot T, Kwok RK, et al. The PhenX Toolkit: get the most from your measures. *Am J Epidemiol*. 2011;174(3):253-60.
Heimendinger J, Van Duyn MA, Chapelsky D, Foerster S, Stables G. The national 5 A Day for Better Health Program: a large-scale nutrition intervention. *J Public Health Manag Pract*. 1996;2(2):27-35.
Hoifodt RS, Strom C, Kolstrup N, Eisemann M, Waterloo K. Effectiveness of cognitive behavioural therapy in primary health care: a review. *Fam Pract.* 2011;28(5):489-504.
Huang JH, Lu YF, Cheng FC, Lee JN, Tsai LC. Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study. *Nutr J.* 2012;11:41.
Hunt CD, Johnson LK. Magnesium requirements: new estimations for men and women by cross-sectional statistical analyses of metabolic magnesium balance data. *Am J Clin Nutr*. 2006;84(4):843-852.

Imada Y, Yoshioka S-I, Ueda T, Katayama S, Kuno Y, Kawahara R. Relationships between serum magnesium levels and clinical background factors in patients with mood disorders. *Psychiat Clin Neurosci.* 2002;56(5):509-514.
Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorous, Magnesium, Vitamin D, and Flouride*. Washington, DC: National Academy Press; 1997.
Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J*. 1984;108(1):188-93.
Ismail Y, Ismail AA. The underestimated problem of using serum magnesium measurements to exclude magnesium deficiency in adults; a health warning is needed for "normal" results. *Clin Chem Lab Med.* 2010;48(3):323-327.
Jacka FN, Maes M, Pasco JA, Williams LJ, Berk M. Nutrient intakes and the common mental disorders in women. *J Affect Disord.* 2012;141(1):79-85.
Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. *Aust N Z J Psychiatry*. 2009;43(1):45-52.
Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kid J*. 2012;5(Suppl 1):i3-i14.
Johnson CL, Paulose-Ram R, Ogden CL. National Health and Nutrition Examination Survey: Analytic Guidelines 1999-2010. *Vital Health Stat.* 2013;2(161).
Johnson CM, Sharkey JR, Dean WR. Eating behaviors and social capital are associated with fruit and vegetable intake among rural adults. *J Hunger Environ Nutr*. 2010;5(3):302-315.
Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J *Methods Psychiatr Res*. 2012;21(3):169-84.
Kant AK, Graubard BI. Ethnicity is an independent correlate of biomarkers of micronutrient intake and status in American adults. *J Nutr*. 2007;137(11):2456-2463.
Kant AK, Graubard BI. Secular trends in the association of socio-economic position with self-reported dietary attributes and biomarkers in the US population: National Health and Nutrition Examination Survey (NHANES) 1971-1975 to NHANES 1999-2002. *Public Health Nutr.* 2007;10(2):158-167.
Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among us adults from 1999-2012. *JAMA*. 2016;316(14):1464-1474.
Kieboom BC, Kiefte-de Jong JC, Eijgelsheim M, et al. Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. *Am J Kid Dis*. 2015;66(5):775-782.
Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Int Med.* 2001;16(9):606-613.
La Vecchia C, Negri E, Franceschi S, Parazzini F, Decarli A. Differences in dietary intake with smoking, alcohol, and education. *Nutr Cancer*. 1992;17(3):297-304.
Lakshmanan FL, Rao RB, Kim WW, Kelsay JL. Magnesium intakes, balances, and blood levels of adults consuming self-selected diets. *Am J Clin Nutr*. 1984;40(6 Suppl):1380-1389.

Li R, Serdula M, Bland S, Mokdad A, Bowman B, Nelson D. Trends in fruit and vegetable consumption among adults in 16 US states: Behavioral Risk Factor Surveillance System, 1990-1996. *Am J Public Health*. 2000;90(5):777.

Littenberg B, MacLean C. Intra-cluster correlation coefficients in adults with diabetes in primary care practices: the Vermont Diabetes Information System field survey. *BMC Med Res Methodol*. 2006;6(1):20.

Long S, Romani AM. Role of cellular magnesium in human diseases. *Austin J Nutr Food Sci*. 2014;2(10):1-19.

Lowenstein FW, Stanton MF. Serum magnesium levels in the United States, 1971-1974. *J Am Coll Nutr*. 1986;5(4):399-414.

Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(3):664-675.

Marier J. Quantitative factors regarding magnesium status in the modern-day world. *Magnesium*. 1982;1(3-15):6.

Martin KJ, González EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol*. 2009;20(11):2291-2295.

Martin RW, Perry KG, Jr., Martin JN, Jr., Seago DP, Roberts WE, Morrison JC. Oral magnesium for tocolysis: a comparison of magnesium gluconate and enteric-coated magnesium chloride. *J Miss State Med Assoc*. 1998;39(5):180-2.

Mather M. The emotion paradox in the aging brain. *Ann N Y Acad Sci*. 2012;1251:33-49.

Moore LV, Thompson FE. Adults meeting fruit and vegetable intake recommendations—United States, 2013. *MMWR*. 2015;64(26):709-713.

Moore-Schiltz L, Albert JM, Singer ME, Swain J, Nock NL. Dietary intake of calcium and magnesium and the metabolic syndrome in the National Health and Nutrition Examination (NHANES) 2001-2010 data. *Br J Nutr*. 2015;114(6):924-935.

Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24(1):67-74.

Moser M, White K, Henry B, et al. Phosphorus content of popular beverages. *Am J Kid Dis*. 2015;65(6):969-971.

Moshfegh A, Goldman J, Ahuja J, Rhodes D, LaComb R. What We Eat in America, NHANES 2005-2006: usual nutrient intakes from food and water compared to 1997 dietary reference intakes for vitamin D, calcium, phosphorous, and magnesium. 2009; https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/0506/usual_nutrient_intake_vitD_ca_phos_mg_2005-06.pdf. Accessed March 13, 2017.

Moshfegh A, Goldman J, Cleveland L. What We Eat in America, NHANES 2001-2002: Usual Nutrient Intakes from Food Compared to Dietary Reference Intakes. 2005; https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/0102/usualintaketables2001-02.pdf. Accessed March 28, 2017.

Mossor-Pietraszewska T. Effect of aluminium on plant growth and metabolism. *Acta Biochim Pol*. 2001;48(3):673-686.

Nechifor M. Magnesium in major depression. *Magnes Res*. 2009;22(3):163s-6s.

Nielsen FH. Magnesium, inflammation, and obesity in chronic disease. *Nutr Rev*. 2010;68(6):333-340.
Nielsen FH. Importance of plant sources of magnesium for human health. *Crop Pasture Sci*. 2016;66(12):1259-1264.
Nielsen FH, Johnson LA. Data from controlled metabolic ward studies provide guidance for the determination of status indicators and dietary requirements for magnesium. *Biol Trace Elem Res*. 2016;177(1):43-52.
Nielsen FH, Milne DB, Klevay LM, Gallagher S, Johnson L. Dietary Magnesium Deficiency Induces Heart Rhythm Changes, Impairs Glucose Tolerance, and Decreases Serum Cholesterol in Post Menopausal Women. *J Am Coll Nutr.* 2007;26(2):121-132.
Nielsen SJ, Kit BK, Ogden CL. Nut consumption among US adults, 2009–2010. *NCHS Data Brief*. 2014;131:1-8.
Nutting PA, Rost K, Dickinson M, Werner JJ, Dickinson P, Smith JL, et al. Barriers to initiating depression treatment in primary care practice. *J Gen Intern Med*. 2002;17(2):103-11.
O'Neil CE, Keast DR, Fulgoni VL, Nicklas TA. Food sources of energy and nutrients among adults in the US: NHANES 2003-2006. *Nutrients*. 2012;4(12):2097-2120.
O'Neil CE, Nicklas TA, Fulgoni VL, 3rd. Tree nut consumption is associated with better nutrient adequacy and diet quality in adults: National Health and Nutrition Examination Survey 2005-2010. *Nutrients*. 2015;7(1):595-607.
Panagiotakos DB, Chrysohoou C, Siasos G, Zisimos K, Skoumas J, Pitsavos C, Stefanadis C. Sociodemographic and lifestyle statistics of oldest old people (>80 years) living in ikaria island: the ikaria study. *Cardiol Res Pract.* 2011:679187.
Papanikolaou Y, Brooks J, Reider C, Fulgoni VL. Comparison of inadequate nutrient intakes in non-Hispanic blacks vs. non-Hispanic whites: an analysis of NHANES 2007-2010 in U.S. children and adults. *J Health Care Poor Underserved*. 2015;26(3):726-736.
Papanikolaou Y, Fulgoni VLF. Certain grain food patterns are associated with improved 2015 dietary guidelines shortfall nutrient intakes, diet quality, and lower body weight in US adults: results from the national health and nutrition examination survey, 2005–2010. *Food Nutr Sci*. 2016;7.
Patterson BH, Block G, Rosenberger WF, Pee D, Kahle LL. Fruit and vegetables in the American diet: data from the NHANES II survey. *Am J Public Health*. 1990;80(12):1443-1449.
Pawlak R, Colby S. Benefits, barriers, self-efficacy and knowledge regarding healthy foods; perception of African Americans living in eastern North Carolina. *Nutr Res Pract*. 2009;3(1):56-63.
Pennington JAT, Youngt B. Sodium, potassium, calcium, phosphorus, and magnesium in foods from the United States total diet study. *J Food Comp Anal*. 1990;3(2):145-165.
Phelan E, Williams B, Meeker K, et al. A study of the diagnostic accuracy of the PHQ-9 in primary care elderly. *BMC Fam Pract.* 2010;11(1):63.

Pinto-Meza A, Serrano-Blanco A, Peñarrubia MT, Blanco E, Haro JM. Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone? *J Gen Intern Med*. 2005;20(8):738-42.

Quann EE, Fulgoni VL, Auestad N. Consuming the daily recommended amounts of dairy products would reduce the prevalence of inadequate micronutrient intakes in the United States: diet modeling study based on NHANES 2007-2010. *Nutr J*. 2015;14:90.

Rajizadeh A, Mozaffari-Khosravi H, Yassini-Ardakani M, Dehghani A. Effect of magnesium supplementation on depression status in depressed patients with magnesium deficiency: a randomized, double-blind, placebo-controlled trial. *Nutrition*. 2017;35:56-60.

Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J Acad Nutr Diet*. 2013;113(12):1610-1619.

Rosanoff A. Changing crop magnesium concentrations: impact on human health. *Plant Soil*. 2013;368(1):139-153.

Rosanoff A, Weaver CM, Rude RK. Suboptimal magnesium status in the United States: are the health consequences underestimated? *Nutr Rev*. 2012;70(3):153-164.

Rude RK. Magnesium. In: Ross AC, Caballero B, Cousins RC, Tucker KL, Ziegler TR, eds. Modern *Nutrition in Health and Disease*. 11th ed. Baltimore, MA: Lippincott Williams & Wilkins; 2010:159-175.

Sanchez-Villegas A, Verberne L, De Irala J, et al. Dietary fat intake and the risk of depression: the SUN Project. *PLoS One.* 2011;6(1):e16268.

Sarris J, Murphy J, Mischoulon D, et al. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. *Am J Psychiatry*. 2016;173(6):575-87.

Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. *J Am Diet Assoc*. 1988;88(10):1268-1271.

Sebastian RS, Cleveland LE, Goldman JD, Moshfegh AJ. Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. *J Am Diet Assoc*. 2007;107(8):1322-1332.

Serefko A, Szopa A, Wlaz P, et al. Magnesium in depression. *Pharmacol Rep*. 2013;65(3):547-554.

Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Internal Med*. 2006;166(10):1092-7.

Spungen JH, Goldsmith R, Stahl Z, Reifen R. Desalination of water: nutritional considerations. *Isr Med Assoc J*. 2013;15(4):164-168.

St John PD, Montgomery PR. Do depressive symptoms predict mortality in older people? *Aging Ment Health.* 2009;13(5):674-681.

Stahler C. How many adults eat vegetarian? *Vegetarian Journal*. 2016;(4). http://www.vrg.org/journal/vj2006issue4/2006_issue4_poll.php. Accessed June 6, 2017.

Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. *J Am Diet Assoc*. 1998;98(5):537-547.

Swaminathan R. Magnesium metabolism and its disorders. *Clin Biochem Rev*. 2003;24(2):47-66.

Tarleton EK, Littenberg B. Magnesium intake and depression in adults. *J Am Board Fam Med*. 2015;28(2):249-256.
Tarleton EK, Littenberg B, MacLean CD, Kennedy AG, Daley C. Role of magnesium supplementation in the treatment of depression: a randomized clinical trial. *PloS One*. 2017;12(6):e0180067.
Topf JM, Murray PT. Hypomagnesemia and hypermagnesemia. *Rev Endocr Metab Disord*. 2003;4(2):195-206.
Trevino K, McClintock SM, McDonald Fischer N, Vora A, Husain MM. Defining treatment-resistant depression: a comprehensive review of the literature. *Ann Clin Psych*. 2014;26(3):222-32.
United States Department of Agriculture, Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 28. 2015. https://ndb.nal.usda.gov/ndb/. Accessed March 20, 2017.
United States Department of Agriculture, Agriculture Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group. Food Patterns Equivalents Database. https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-data-tables/. Accessed April 10, 2017.
United States Department of Agriculture, Agriculture Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group. USDA Nationwide Food Surveys, 1935-1998. https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/past-surveys/. Accessed April 10, 2017.
United States Department of Health and Human Services, United States Department of Agriculture. *2015-2020 Dietary Guidelines for Americans.* 8th ed. 2015; http://health.gov/dietaryguidelines/2015/guidelines/. Accessed March 7, 2017.
Walker AF, Marakis G, Christie S, Byng M. Mg citrate found more bioavailable than other Mg preparations in a randomised, double-blind study. *Magnes Res.* 2003;16(3):183-191.
Walker AF, De Souza MC, Vickers MF, Abeyasekera S, Collins ML, Trinca LA. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *J Womens Health.* 1998;7(9):1157-1165.
Welsh SO, Marston RM. Review of trends in food use in the United States, 1909 to 1980. *J Am Diet Assoc.* 1982;81(2):120-128.
Wittayanukorn S, Qian J, Hansen RA. Prevalence of depressive symptoms and predictors of treatment among U.S. adults from 2005 to 2010. *Gen Hosp Psychiatry*. 2014;36(3):330-6.
World Health Organization. Depression fact sheet no. 369. 2012; http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed December 20, 2016.
Volpe SL. Magnesium. In: Erdman JW, Macdonald IA, eds. *Present Knowledge in Nutrition*. 10th ed. Ames, Iowa: Wiley & Sons; 2012:459-474.
Volpe SL. Magnesium in disease prevention and overall health. *Adv Nutr*. 2013;4(3):378s-383s.

Yary T, Aazami S, Soleimannejad K. Dietary intake of magnesium may modulate depression. *Biol Trace Elem Res.* 2013;151(3):324-329.
Yary T, Lehto SM, Tolmunen T, et al. Dietary magnesium intake and the incidence of depression: A 20-year follow-up study. *J Affect Disord*. 2016;193:94-98.
Zarate C, Duman RS, Liu G, Sartori S, Quiroz J, Murck H. New paradigms for treatment-resistant depression. *Ann N Y Acad Sci.* 2013;1292(1):21-31.
Zhang J, Yu KF. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA.* 1998;280(19):1690-1691.