



*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

## Magnesium

### Evidence Summary

Evidence suggests that higher intake or circulating levels of magnesium (Mg) is associated with a reduced risk of dementia and a number of age-related diseases. Whether supplemental Mg above recommended levels is beneficial is unknown.

**Neuroprotective Benefit:** Observational data suggests that having sufficient levels of circulating Mg or higher-dietary intake of Mg may prevent dementia. Whether increasing Mg above recommended levels (with supplements) is beneficial is unknown.

**Aging and related health concerns:** Several meta-analyses suggest that increased consumption or circulating levels of Mg is associated with a decreased risk of several age-related diseases.

**Safety:** **Safe** when taken to correct or prevent Mg deficiency; however, there remains a risk of kidney damage with very high levels of Mg supplementation, particularly in older adults with pre-existing compromised kidney function. There is very little danger in obtaining too much Mg from the diet.



### **What is It?**

Mg is a divalent cation essential to many enzymatic biological processes. It is available in a variety of forms including magnesium sulfate, magnesium citrate, magnesium biglycinate and magnesium-L-threonate.

**Neuroprotective Benefit:** Observational data suggests that having sufficient levels of circulating Mg or higher-dietary intake of Mg may prevent dementia. Whether increasing Mg above recommended levels (with supplements) is beneficial is unknown.

#### Types of evidence:

- 1 pilot RCT
- 2 prospective observational studies
- 6 cross-sectional cohort studies of serum/CSF Mg levels
- Many preclinical *in vitro* and *in vivo* studies

#### Human research to suggest that magnesium may prevent dementia:

In one pilot RCT using magnesium L-threonate (MgT), 44 patients with subjective memory complaints and anxiety and sleep disorders were given 25 mg/kg/day of MgT for 12 weeks. The authors reported an improvement in overall cognitive ability in MgT patients vs controls ([Liu et al, 2015](#)). No other clinical trials in humans have tested if raising magnesium levels, either through diet or supplement use, can prevent dementia or cognitive impairment.

It has been speculated that some neurodegenerative diseases like Alzheimer's might arise from magnesium deficiency ([Durlach et al, 1990](#); [Ozturk et al, 2006](#)). A recent observational study that followed more than 1,400 cognitively healthy older adults for 8 years reported that dietary Mg intake greater than 400 mg/day was associated with an 84% reduced risk of developing MCI in men but not women ([Cherubin, 2014](#)). In a 2012 study that followed more than 1,000 cognitively healthy Japanese adults over 60 years old for 17 years, Mg intake over 196 mg/day was associated with a 37% reduced risk for all-cause dementia and a 74% reduced risk for vascular dementia ([Ozawa et al, 2012](#)). The association with lowered risk for vascular dementia is interesting in light of a recent report from the Framingham study that reported 58% lower risk of coronary artery calcification associated with dietary Mg intake greater than ~420 mg/day ([Hruby et al, 2014](#)). Coronary artery calcification may be indicative of calcification of brain microvasculature, a risk factor for developing vascular dementia. Magnesium



has also been shown to play a role in disaggregating fibrin-red blood cell clots, a common problem in atherosclerosis ([Lipinski et al, 2013](#)).

Many studies have reported associations between low plasma ([Cilliler et al, 2007](#); [Vural et al, 2010](#); [Barbagallo et al, 2011](#)) and brain levels ([Andrasi et al, 2005](#)) of Mg and incident dementia. Several of these studies also found direct correlations between cognitive function, disease severity and low serum Mg levels ([Cilliler et al, 2007](#); [Barbagallo et al, 2011](#)). Serum and CSF Mg levels in AD may be inversely related, as one study found elevated CSF levels of Mg in patients with AD compared to healthy age-matched controls ([Bostrom et al, 2009](#)).

*Human research to suggest that magnesium may benefit patients with dementia:*

No human research suggests that increasing magnesium can benefit patients with dementia. However, in a recent systematic review of 13 studies that compared Alzheimer's disease patients and healthy adults, no difference was observed in serum magnesium levels between the two groups. Yet, magnesium levels in the cerebrospinal fluid and hair were significantly lower for Alzheimer's disease patients than healthy adults ([Veronese et al, 2016](#)).

*Mechanisms from preclinical studies for how magnesium may benefit the brain:*

Magnesium is critical for the metabolism of many other trace metals in the human body and its absorption requires selenium and vitamins B<sub>6</sub> and D ([Johnson et al, 2001](#)). Magnesium deficiency is common in older adults and its study is complicated by the fact that Mg supplementation alone often does not suffice to increase serum Mg levels ([Johnson et al, 2001](#)). Magnesium supplementation is commonly prescribed to patients with AD who are taking the NMDA receptor antagonist memantine. Without adequate brain levels of Mg, memantine has unwanted activity against all NMDA receptor subtypes ([Kotermanski et al, 2009](#)).

Evidence from preclinical *in vitro* and *in vivo* experimentation suggests a rationale and mechanisms of action for Mg in many of the biological processes of AD and potential roles for Mg supplementation in the treatment of AD. Magnesium is a critical co-factor in the degradation of hyperphosphorylated (toxic) tau ([Zhang et al, 2005](#)) while it also may inhibit GSK-3 $\beta$  one of the kinases that pathogenically phosphorylates tau ([Gomez-Ramos et al, 2006](#); [Xu et al, 2014](#)). In cell culture, Mg also reduces APP processing into the pathogenic A $\beta$  form ([Yu et al, 2010](#)). Several recent studies in rodent models of AD suggest that elevating Mg levels, either by oral supplementation or direct brain injection, can prevent AD-related cognitive impairment and improve neuronal and synaptic health ([Li et al, 2013](#); [Xu et al, 2014](#)).



Oral magnesium threonate (MgT) has been the most extensively studied magnesium supplement and may also improve short- and long-term memory performance in healthy and aged rats ([Slutsky et al, 2010](#)). Additional preclinical studies suggest that MgT treatment may be able to suppress amyloid beta plaque formation, decrease levels of inflammation, and improve some measures of cognition in Alzheimer's disease mouse models ([Yu et al, 2015](#); [Wang et al, 2015](#)). In addition, preclinical evidence suggests that MgT may be able to increase the proliferation of new neurons in both young mice and after 12 months treatment in aged mice ([Jia et al, 2016](#)). An additional preclinical study suggests that threonate itself may increase intracellular Mg levels and increase synaptic density ([Sun et al, 2016](#)).

There is some preclinical evidence that Mg supplementation before traumatic brain injury in rats attenuates the cognitive effects of injury ([Enomoto et al, 2005](#); [Hoane et al, 2008](#); [Uysal et al, 2013](#)). Similarly, Mg treatment of rats after TBI may improve recovery and lessen post-TBI psychological dysfunction ([Fromm et al, 2004](#); [Turner et al, 2004](#)). However, a Cochrane meta-analysis of clinical trials with Mg supplementation with Mg suggested little or no benefit ([Arango et al, 2006](#)).

***APOE4 interactions:***

None reported

**Aging and health related concerns:** Several meta-analyses suggest that increased consumption or circulating levels of Mg is associated with a decreased risk of several age-related diseases.

***Types of evidence:***

- Several meta-analyses for dietary Mg and stroke, cardiovascular disease (CVD) and cancer risk
- 1 RCT for Mg supplementation and insomnia in elderly adults

There is little evidence to suggest that Mg supplementation can increase lifespan, per se. However, one study using rat cardiac tissue found that acute Mg deficiency can down-regulate telomerase activity, as well as increase oxidative damage to DNA and potentially contribute to the atherogenic disease process ([Shah et al, 2014](#)).

Meta-analyses suggest that circulating levels of Mg or dietary Mg intake may reduce risks for age-related diseases. Two meta-analyses of circulating Mg and magnesium intake reported a reduced risk of cardiovascular disease by 30% and 14%, respectively ([Del Gobbo et al, 2013](#); [Fang et al, 2016](#)). [Del](#)



[Gobbo et al \(2013\)](#) also reported that circulating Mg was associated with a trend toward a 27% reduced risk of ischemic heart disease and 39% reduced risk of fatal ischemic heart disease. A meta-analysis of 9 studies reported that higher consumption of dietary Mg was associated with a 27% reduced risk of metabolic syndrome ([Sarrafadegan et al, 2016](#)). A recent analysis of cancer risk found a significantly lower risk of colorectal cancer in women with dietary Mg intake in the highest quartile (RR: 0.77) ([Ko et al, 2014](#)). One 2012 double-blind RCT in 46 elderly adults with insomnia treated for 8 weeks with 500 mg magnesium sulfate daily reported improved sleep duration, lower cortisol levels and decreased early-morning waking ([Abbasi et al, 2012](#)).

**Safety:** Safe when taken to correct or prevent Mg deficiency; however, there remains a risk of kidney damage with very high levels of Mg supplementation, particularly in older adults with pre-existing compromised kidney function. There is very little danger in obtaining too much Mg from the diet.

Types of evidence:

- Observational studies for dietary Mg
- 1 RCT for supplemental Mg

Magnesium supplementation is relatively safe for most people. Common side effects include nausea, vomiting and diarrhea. Magnesium supplementation should also be avoided when using antibiotics of the aminoglycoside class, such as neomycin, gentamicin and streptomycin because of an increased risk of muscle paralysis ([Drugs.com](#)). It should be used with caution in older adults who may have compromised kidney function. Very high doses of Mg may result in nephrotoxicity. A pilot study of magnesium threonate reported no differences in adverse events between placebo and Mg groups.

**Dosing and Sources:**

The best studied supplement for brain health is magnesium threonate. Magnesium comes in a variety of forms that fall into three categories: magnesium salts, magnesium-acids and magnesium coupled to an amino acid. The human body uses elemental magnesium (i.e. magnesium that is not coupled to anything). The “carriers” attached to magnesium in supplements help deliver magnesium to the intestines, where it is broken apart and the elemental magnesium is absorbed. Different magnesium carriers break apart from magnesium at different rates, which can affect the “bioavailability” of elemental magnesium after ingestion and, thus, its absorption by our bodies. Although these different types of magnesium supplements offer differing degrees of bioavailable magnesium to our bodies, there is very little evidence that one type is superior to another at increasing brain magnesium levels.



- **Magnesium salts:** These include magnesium bicarbonate, magnesium carbonate, magnesium chloride, magnesium hydroxide, magnesium oxide, magnesium phosphate and magnesium sulfate. Of these, magnesium chloride offers the most free (“bioavailable”) magnesium after digestion in the gut. Magnesium sulfate offers somewhat less bioavailable magnesium, while magnesium carbonate, magnesium oxide and magnesium hydroxide (a laxative often called Milk of Magnesia™) offer very low bioavailable magnesium.
- **Magnesium acids:** Supplements containing magnesium acids include magnesium ascorbate, magnesium citrate, magnesium gluconate, magnesium lactate and magnesium fumarate. Of these, magnesium lactate and citrate offer the most bioavailable magnesium while magnesium fumarate and magnesium gluconate offer moderately bioavailable magnesium.
- **Magnesium amino acids:** Sometimes called “magnesium-amino acid chelates”, these forms of magnesium differ from the magnesium salts and magnesium acids in that they do not rely on absorption of elemental magnesium in the gut, but instead depend on biochemical pathways that break down proteins (since amino acids are the building blocks of proteins). These forms of magnesium include magnesium glycinate, magnesium lysinate, magnesium taurate, magnesium orotate and magnesium threonate. Most of these forms of magnesium offer similar high bioavailability as magnesium citrate and magnesium chloride, but because of the way they are manufactured, they also tend to be the most expensive magnesium supplements. Results from a small clinical trial of healthy human volunteers suggest magnesium citrate offers better bioavailability than most amino acid chelates.

Normal blood levels of magnesium for healthy adults range from 0.75 to 0.95 nmol/L. Magnesium deficiency is typically defined as serum levels lower than 0.75 nmol/L ([NIH](#)). The US RDA for magnesium is 310-320 mg/day for women and 400-420 mg/day for men ([NIH](#)), although it has been reported that actual daily intakes for U.S. adults are lower than that, typically 278–352 mg/day for men and 237–326 mg/day for women ([Ford et al, 2003](#)).

#### **Research underway:**

There is a 60-day RCT currently recruiting to test magnesium threonate supplementation as a treatment in patients with mild-to-moderate AD with Mg deficiency which should be reporting results in 2016 ([NCT02210286](#)).



**Search Terms:**

- Pubmed: “magnesium” + “Alzheimer’s”, “magnesium” + “cognitive”, “magnesium” + “dementia”, “magnesium” + “lifespan”, “magnesium” + “traumatic brain injury”, “magnesium” “longevity”, “magnesium” + “mortality”, “magnesium” with filters for “meta-analysis”, “systematic review”, “clinical trial”
- Clinicaltrials.gov: “magnesium” + “Alzheimer’s”, + “dementia”, + “cognitive”

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality's Rating page](#).