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.

Vitamin K_2

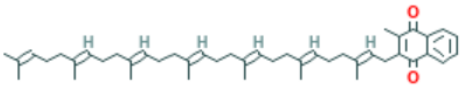
Evidence Summary

Some evidence suggests that vitamin K_2 may be beneficial for cardiovascular disease, cancer, and osteoporosis.

Neuroprotective Benefit: There is little evidence that supplementation with vitamin K_2 will benefit brain health, unless, perhaps, there is a vitamin K_2 deficiency.

Aging and related health concerns: Some epidemiological evidence suggests that high intake of vitamin K_2 may improve cardiovascular or metabolic outcomes, though the evidence for supplementation is mixed (except possibly for cancer or osteoporosis).

Safety: Vitamin K_2, in doses used in clinical trials, appears relatively safe for long-term use.

Availability: Available as a supplement (look for fermented forms of MK-7, preferably supplements that contain MenaQ7, e.g. link)	**Dose**: 100µg/day to 360µg/day	**Molecular Formula:** $C_{46}H_{64}O_2$ **Molecular weight:** 649g/mol  MK7 Source: Pubchem
Half-life: MK-7 ~ 70 hours	**BBB**: MK-4 Penetrant in animals	
Clinical trials: 28 completed, 16 ongoing (most studies <100 participants for MK-7; osteoporosis studies ~9,000 participants for vitamin K_2)	**Observational studies**: 11 completed (most dietary intake studies between 3,000-30,000 individuals).	

What is it?

Vitamin K represents several molecules including the phylloquinone (vitamin K_1) and the menaquinones (vitamin K_2). They play a role in coagulation (in fact, one class of anti-coagulants is vitamin K antagonists, such as warfarin). They are also thought to play a role in improving bone health, reducing vascular calcification, and reducing cardiovascular risk. Vitamin K_1 and K_2 act by interacting with vitamin K-dependent proteins (VKPDs) including those involved in the coagulation cascade (such as Factors II, VII, IX, X) and proteins involved in bone and soft-tissue mineralization (such as osteocalcin and Matrix Gla protein, respectively) (El Asmar et al, 2014).

Dietary vitamin K_1 is more common and comes primarily from green vegetables such as spinach, broccoli, kale, and Brussels sprouts. Dietary vitamin K_2 is of microbial origin and often comes from cheese, yogurt, and natto (fermented soybeans). Since dietary vitamin K_1 is more prevalent, the USDA recommendations for vitamin K intake refer to vitamin K_1. However, it is estimated that 10%-25% of vitamin K consumption is vitamin K_2. There is growing evidence that vitamin K_1 and K_2 play slightly different roles in the human body. There is currently no Recommended Dietary Intake (RDI) value for vitamin K_2, though calls have been made to make one (Akbulut et al, 2020).

There are several form of vitamin K_2, the most relevant to human health being menaquinone-4 (MK-4) and menaquinone-7 (MK-7). MK-4 is the most common dietary source of vitamin K_2 and is produced by the conversion in tissue and/or bacteria of vitamin K_1. It is water soluble and can be obtained from the consumption of animal products. Longer-chained menaquinones such as MK-7 (also MK-8 and MK-9) are primarily found in fermented foods, such as natto or hard cheese (Akbulut et al, 2020).

K vitamins are characterized by a quinone ring but have different chain lengths and degrees of saturation. The naming of the menaquinones is MK-n, where n is the number of isoprenoid side chain residues (e.g., MK-4 is a quinone ring with four isoprenoid side chains) (Beulens et al, 2013).

Trans MK-7

Long chain menaquinones, such as MK-7, can exist in several geometric isomers, *cis*, *trans*, and *cis/trans*. The *trans* isomer of MK-7 has the greatest biological activity (the *cis* form is estimated to have 1% of the biological activity of *trans*). *Trans* MK-7 exists in a linear formation while *cis* MK-7 is non-linear. The *cis* conformation impairs its ability to interact with subcellular proteins. Naturally occuring isomers of MK-7 are in the *trans* configuration. However, some commercial preparations may contain both *cis* and *trans* isomers. In addition, autoxidation by exposure to atmostpheric oxygen, light, and elevated temperature during storage may also convert *trans* MK-7 to *cis* MK-7 (Sitkowski et al, 2018).

Commercial supplements of MK-7 can be produced naturally, by fermentation, or through chemical synthesis. MK-7 is produced by fermentation using several bacterial strains, the preferred strain being *Bacillus subtilis natto.* It is assumed that natural synthesis of MK-7 using bacterial fermentation will produce all *trans* MK-7 (Lal and Berenjian, 2019). The amount of MK-7 in different supplements varies, with soft pills often having greater amounts of MK-7 than reported on the label and hard pills having less. Some commercial supplements claiming MK-7 was created using fermentation methods were reported to contain significant amounts of *cis* MK-7, suggesting that the provider is disingenous as to their production methods (see paragraph below on chemical synthesis (Szterk et al, 2018a, Szterk et al, 2018b).

MK-7 can also be produced through chemical synthesis. However, this method will often convert *trans* MK-7 to *cis/trans* MK-7 in ratios of 3:1 or 2:1. Therefore, the use of fermented forms of MK-7 is preferred. The largest supplier of fermented MK-7 is MenaQ7 from Nattopharma. It is not sold directly from Nattopharma to consumers. Rather they sell it to many supplement providers to use in their products (link).

This report is specific for vitamin K_2, so only studies that specify vitamin K_2 it will be included in the analysis. Of the individual menaquinones, MK-7 was primarily studied for age-related indications. MK-4 is the most prevalent form of vitamin K_2 in the brain (more than 98%) and was used in neuroprotection studies.

Neuroprotective benefit: There is little evidence that supplementation with vitamin K_2 will benefit brain health, unless, perhaps, there is a vitamin K_2 deficiency.

Types of evidence:

- One post-mortem study in humans
- Four preclinical studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Plasma and post-mortem tissue from 48 individuals (98-107 years of age, 25 demented, 23 nondemented) from the Georgia Centenarian study were collected and used to correlate MK-4 levels to cognition measured one year before death. MK-4 was the predominant type of vitamin K in brain tissue. Individuals taking anti-thrombotic drugs had up to 53.9% lower levels of MK-4 in the brain. Cognitive function was not associated with circulating MK-4 levels before or after excluding antithrombotic non-users. The authors suggested that once brain's MK-4 needs are met, higher levels are not necessarily better (Tanprasertsuk et al, 2019)

Human research to suggest benefits to patients with dementia:

None

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Alzheimer's – Preclinical Study

In a rat model of Alzheimer's disease (colchicine-induced memory impairment which decreases activity of acetylcholinesterase – AChE), treatment with a nutraceutical formulation from fermented soybeans (NN – contains nattokinase, daidzin, genistin, glycitin, and MK-7) over 28 days improved memory, reduced hippocampal protein carbonyl content, increased AChE activity, reduced lipid peroxidation levels, and increased antioxidant protein levels (glutathione, superoxide dismutase, and catalase) (Bhatt et al, 2017).

Cognition – Preclinical Studies

It was reported that MK-4 represents more than 98% of the total levels of vitamin K in the brain of young and old rats, and that MK-4 decreased as a function of age (note – some vitamin K_2-dependent proteins – anticoagulant proteins C and S, and Gas6 – also have functions in the brain). I*n vitro* studies suggest that MK-4 may have neuroprotective, antioxidant, and anti-inflammatory properties (Ferland, 2013). In a rat model of metabolic syndrome (high fat high fructose), 10-week treatment with vitamin K_2 improved anxiety and depression symptoms but had no effect on memory (Gancheva et al, 2016).

Stroke – Preclinical Studies

In a rat model of cerebral ischemia/reperfusion, treatment with a high dose of MK-4 (400mg/kg) reduced mortality after 24 hours. After seven days, MK-4 (400mg/kg) improved cognitive function, and reduced brain edema, cell death, neuronal death, gliosis, inflammatory markers (IL-6, IL-1β, TNFα), and nitrates (Moghadam and Fereidoni, 2020).

APOE4 Interactions:

Nothing reported for cognition. One study suggested that ApoE4 does not alter the risk of hip fracture due to low vitamin K_2 intake (Apalset et al, 2011).

Aging and related health concerns: Some epidemiological evidence suggests that high intake of vitamin K_2 may improve cardiovascular or metabolic outcomes, though the evidence for supplementation is mixed (except possibly for cancer or osteoporosis).

Types of evidence:

- One meta-analysis of vitamin K_2 supplementation for osteoporosis
- One meta-analysis of vitamin K_2 supplementation for hepatocellular cancer
- One systematic review of observational studies for coronary heart disease
- Five clinical trials of MK-7 for cardiovascular indications
- Three observational studies for mortality
- Three observational studies for cardiovascular indications
- One observational study for diabetes
- Two observational studies for cancer
- One case report for hypotension
- One preclinical study for diabetic neuropathy
- One review of preclinical studies in cancer

Mortality – Vitamin K_2 epidemiology studies: **Mixed evidence**
In an observational study of 33,289 participants (ages 20-70) from the EPIC-NL cohort followed over 16.8 years, dietary intake of vitamin K_2 (highest quartile versus lowest quartile – Q4 vs Q1) was not associated with all-cause, cardiovascular (CVD), coronary heart disease (CHD), stroke, or cancer-related mortality (Zwakenberg et al, 2016). Similar results were reported in another observational study of 7,216 participants with a high cardiovascular disease risk in the PREDIMED cohort followed over 4.8 years. Those in the highest quartile of vitamin K_2 intake had no change in risk for CVD, cancer, or all-cause mortality compared to those in the lowest quartile. However, individuals who increased their consumption of vitamin K_2 over the follow-up period had a reduced risk of cancer mortality (**HR = 0.41; 95%CI 0.26-0.64**) and all-cause mortality (**HR = 0.55; 95%CI 0.42-0.73**) (no effect on CVD mortality) (Juanola-Falgarona et al, 2014). In another observational study of 24,340 participants from the EPIC-Heidelberg cohort followed for more than 10 years (ages 35-64 years) greater consumption of vitamin K_2 (Q4 vs Q1) reduced cancer mortality risk (**HR = 0.72; 95%CI 0.53-0.98** – results were also significant for the other quartiles) (Nimptsch et al, 2010).

Coronary Heart Disease – Vitamin K_2 epidemiology studies: **Potential Benefit**
In a systematic review of two observational cohort studies, increased dietary intake of vitamin K_2 was associated with a reduced risk of CHD (**HR 0.59; 95%CI 0.40-0.86** for >32.7µg/day vs <21.6µg/day; and **HR = 0.91; 95%CI 0.85-1.00** per 10µg increase in consumption) (Rees et al, 2010). The authors suggest that the primary benefit comes from vitamin K_2 subtypes MK-7, MK-8, and MK-9 (Gast et al, 2009). In another cohort study of 2,987 Norwegian individuals followed over 11 years (ages 46-49), increased vitamin K_2 consumption (Q4 vs. Q1) was associated with a reduced risk of new-onset CHD (**HR = 0.52; 95%CI 0.29-0.94**). However, the results were no longer significant after controlling for calcium and saturated fatty acid intake (Haugsgjerd et al, 2020).

Coronary Calcification – Vitamin K_2 epidemiology studies: **Potential benefit**
In a cross-sectional study of 564 post-menopausal women, high consumption of vitamin K_2 (Q4 vs. Q1) was associated with a lower risk of coronary calcification (**prevalence rate = 0.80; 95%CI 0.65-0.98**) (Beulens et al, 2009). In a cross-sectional study of 103 patients (avg age 64), plasma levels of MK-4 and MK-7 were not associated with coronary artery calcification (CAC) score (Torii et al, 2016).

Cardiovascular disease – MK-7 Clinical Trials: **Mixed evidence**
80 community dwelling individuals under the age of 70 with a history of hypertension, diabetes, or previously diagnosed vascular disease were treated with 100µg/day of MK-7 (MenaQ7, Nattopharma) or placebo for six months. Levels of desphospho-uncarboxylated Matrix Gla Protein (dp-ucMGP – a protein

that plays a role in vascular calcification) decreased in the treated group. There were no significant differences in any cardiovascular outcome (endothelial function, carotid-radial pulse wave velocity, augmentation index, blood pressure, carotid intima-media thickness, cholesterol) (Fulton et al, 2015).

244 postmenopausal women (avg age 60) were treated with 180µg/day of MK-7 (MenaQ7, Nattopharma) for three years. MK-7 reduced local arterial stiffness in patients with high arterial stiffness at baseline (**p=0.018**). There were no changes in carotid intima-media thickness and a non-significant trend in a reduction in carotid-femoral pulse-wave velocity. Treatment reduced dp-ucMGP ~50% but had no effect on other circulating biomarkers (fasting glucose, hsCRP, IL-6, TNF-α, VCAM, E-selectin, advanced glycation end products) (Knapen et al, 2015).

In a study of 60 individuals (40-65 years of age) treated with 180 or 360µg/day of MK-7 (MenaQ7, Nattopharma) over 12 weeks, there was a reduction in dp-ucMGP in the treatment groups (31% and 46%, respectively), though there was no change in other plasma biomarkers (glucose, HOMA-IR, LDL-c, HDL-c, triglycerides, blood pressure) (Dalmeijer et al, 2012).

Vascular Calcification – MK-7 Clinical Trials: **No Benefit/Detrimental**
In a study of 68 participants with type 2 diabetes randomized to either 360µg/day of MK-7 (MenaQ7, Nattopharma) or placebo, treatment over six months had no effect on vascular calcification. However, there was an increase in a measure of active calcification (^{18}F-NaF PET target-to-background ration) (**p=0.03**) which was especially prominent in patients with no baseline vascular calcification. However, there was a high dropout rate in the placebo group, higher vascular calcification in the treatment group, and many of the patients took vitamin K_2 at baseline (Zwakenberg et al, 2019).

Hypotension – Case Report: **N/A**
There is one case report of a 62-year-old man who developed mild hypotension (100/50 mm Hg) after three days of taking 100µg/day of vitamin K_2 (Solgar). He developed hypotension again after rechallenged with vitamin K_2. The author speculates it could be due to a drug interaction with alfuzosin, an alpha blocker used to treat benign prostatic hyperplasia and hypertension (Eleftherios Teperikids, 2012).

Exercise – MK-7 Clinical Trials: **Potential Benefit**
26 aerobically trained athletes were treated with MK-7 (MyoMax, Nu Science Trading – 300µg/day for four weeks and 150µg/day for four weeks) or placebo over eight weeks. MK-7 increased cardiac output by 12% (**p=0.031**) (McFarlin et al, 2017).

Diabetes – Vitamin K_2 epidemiology studies: **Potential Benefit**
In a cross sectional and longitudinal study of 625 participants, high vitamin K_2 intake (highest tertile vs lowest tertile) was associated with a reduced prevalence of metabolic syndrome (**prevalence rate = 0.72, 95%CI 0.52-0.99**). In the longitudinal cohort, high intake of vitamin K_2 was also associated with a lower prevalence of metabolic syndrome (**prevalence rate = 0.62; 95%CI 0.40-0.95**) (Dam et al, 2015).

Diabetic Neuropathy – Vitamin K_2 preclinical study: **N/A**
One preclinical study suggested that vitamin K_2 improved the nociceptive threshold of both diabetic and non-diabetic mice, with no differences in improvements between the two (Onodera et al, 2001).

Cancer – Vitamin K_2 epidemiology studies: **No Benefit**
Preclinical studies suggest that vitamin K_2 has anti-cancer activity in several cell cancer lines (Hoyt et al, 2019). In an observational study from the EPIC-Heidelberg cohort with 24,340 participants followed for greater than 10 years (ages 35-64 years) cancer incidence was not different in participants who consumed greater vitamin K_2 (Q4 vs Q1) (Nimptsch et al, 2010). In an observational study with 28,356 patients followed over 11.8 years (avg age ~62), high intake of vitamin K_2 was not associated with a reduced prostate cancer risk (Hoyt et al, 2019).

Cancer – Vitamin K_2 Supplementation: **Potential Benefit**
In a meta-analysis of five randomized controlled trials, supplementation of vitamin K_2 for the recurrence of hepatocellular cancer after hepatic resection or local ablative therapy was not associated with a reduced risk of cancer recurrence after 1 year but was associated with a reduced risk of cancer recurrence at 2 years (**RR = 0.66; 95%CI 0.47-0.91**) and 3 years (**RR = 0.71; 95%CI 0.58-0.85**). However, the authors note there is insufficient data on the long-term survival of vitamin K_2 supplementation (Riaz et al, 2012).

Osteoporosis – Vitamin K_2 clinical trials: **Potential Benefit**
In a meta-analysis of 18 RCTs in patients with osteoporosis, vitamin K_2 was associated with increased lumbar bone mineral density (BMD) (five studies, **mean difference (MD) = 0.05g/cm^2; 95%CI 0.01-0.09g/cm^2**) with a non-significant effect on fractures (five studies) when compared with placebo. When compared with other anti-osteoporotic drugs, there were no significant differences with the use of vitamin K_2 (Su et al, 2019).

Safety: Vitamin K_2, in doses used in clinical trials, may be relatively safe for long-term use.

Types of evidence:

- One meta-analysis of clinical trials for osteoporosis
- A review from the European Food Safety Authority
- WebMD.com link

In a meta-analysis in patients with osteoporosis, vitamin K_2 was associated with an increased risk of adverse events (two studies, RR = 1.47; 95%CI 1.07-2.02) and adverse drug reactions (four studies, RR = 1.29; 95%CI 1.07-1.56) (note, many of the studies in these trials used vitamin K_2 in combination with another drug). There were no significant differences in the incidence of serious adverse events (Su et al, 2019).

The European Food Safety Authority conducted a review of clinical trials with MK-7 and concluded there were no adverse events on blood coagulation at doses up to 60µg/day for MK-7. In clinical trials of 180µg/day up to three years or 1080µg three times weekly for 8 weeks there were no significant adverse effects other than gastrointestinal issues due to the product's smell (Marles et al, 2017).

WebMD.com says that vitamin K_2 is likely safe for most people, with potential gastrointestinal side effects.

Drug interactions: Vitamin K_2 should not be used with vitamin K antagonists, such as warfarin, some anti-coagulants such as anisindione, dicumarol, and some cholesterol drugs, such as cholestyramine, colesevelam, and colestipol. Find a full list at drugs.com.

Sources and dosing: Check the label when buying vitamin K_2. Many supplements labeled vitamin K_2 actually contain MK-4 while MK-7 is thought to be the most important for age-related diseases (although MK-4 is most prevalent in the brain, there is little evidence that supplementation is beneficial for brain health). In addition, look for fermented forms of MK-7. The most commonly used form is MenaQ7. Doses have been used between 100µg/day to 360µg/day.

Research underway: Using search terms vitamin K_2 and menaquinone, 16 clinical trials were found on clinicaltrials.gov. Most of the trials were for vascular calcification, metabolic syndrom, or osteoporosis.

Search terms:

- menaquinone-4 + Alzheimer, cardiovascular, mortality, diabetes, cognition, neuropathy, hypotension, cancer, lifespan, apoe4, senomorphic
- vitamin K2 + alzheimer, cardiovascular, mortality, diabetes, cancer, cognition, neuopathy, hypotension, lifespan, apoe4, senomorphic
- menaquinone-7 + alzheimer, cardiovascular, diabetes, hypotension, neuropathy, cognition, lifespan, hypotension, cancer, apoe4, senomorphic

Websites visited:

- Clinicaltrials.gov
- Pubmed