

Growing Evidence of a Proven Mechanism Shows Vitamin K2 Can Impact Health Conditions Beyond Bone and Cardiovascular

Katarzyna Maresz, PhD

Katarzyna Maresz, PhD, has published more than 30 scientific papers and is involved in Vitamin K2 clinical trials in Poland and Europe, cooperating with many research centers regarding the health effects and mechanism of action of Vitamin K2. She is the president of the International Science and Health Foundation and the scientific coordinator of the educational portal VitaminK2.org.

Vitamin K2 is a vital nutrient newly recognized for supporting bone and cardiovascular health, shown in observational and intervention trials, in healthy and patient populations, in adults and children. Even more recently, it has come to light that K2 status and the vitamin's mechanism of action impact other health areas, including but not limited to brain health, healthy joints, neuropathy, and vision health. This evidence lends itself to the argument that correcting a widespread vitamin K2 deficiency can significantly improve global health. The first step in remedying that deficiency is establishing a vitamin K2-specific recommended daily intake.

K2 For Cardio Health: A Foundation Of Evidence

The discovery of the role of vitamin K-dependent proteins in processes beyond coagulation and identification of various isoforms of vitamin K in the recent decades has

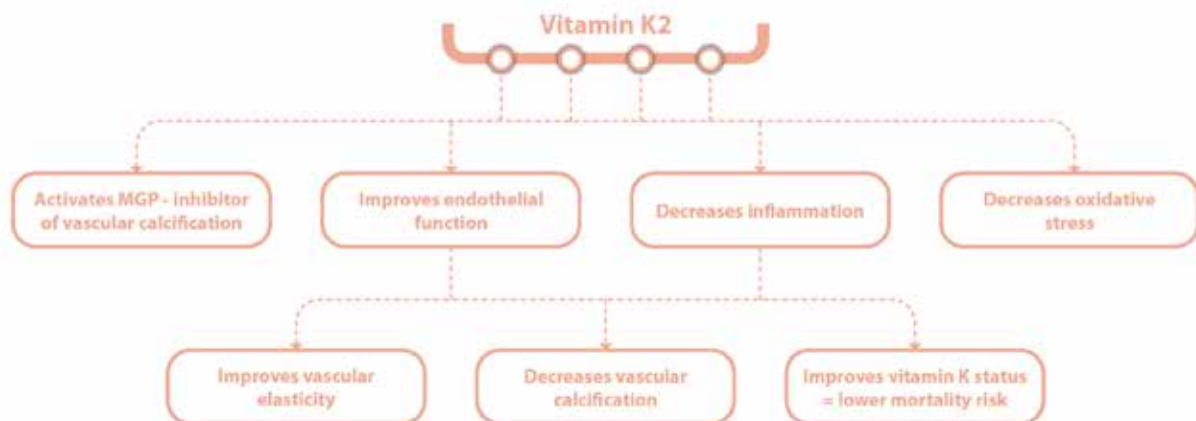
specifically highlighted vitamin K2 (menaquinone) as a crucial cardiovascular health nutrient. This is mainly due to K2's long half-life and extrahepatic activity, compared to a shorter half-life of the dietary form vitamin K1 (phylloquinone). Health-conscious consumers seek to meet the optimal intake of vitamin K2 to avoid calcium plaque buildup of atherosclerosis, thus keeping the risk and rate of calcification as low as possible.¹⁻³

Arterial calcification is considered an unfortunate result of aging, but fortunately, we can actively regulate this process by providing our body with adequate amounts of vitamin K2. This nutrient is essential to activate the most potent modulator of vascular calcification—Matrix Gla Protein (MGP)—and thus lower the risk of age-related cardiovascular decline.

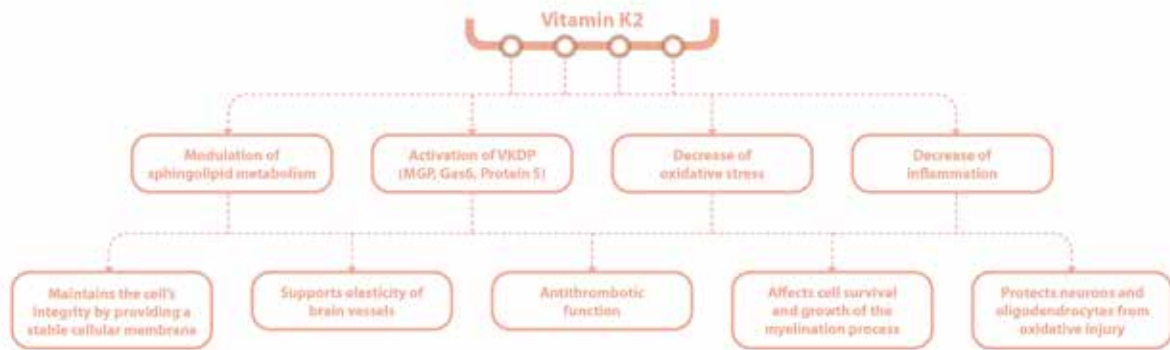
While observational data suggest a link between vitamin K2 intake and cardiovascular health, two groundbreaking intervention trials were published (a three-year and a one-year clinical study), which evaluated the effect of vitamin K2 vs. placebo on arterial stiffness in healthy people.

Results of a published, double-blind, randomized clinical trial, Knapen et al.⁴ show that when taken daily in nutritional doses (180 µg as MenaQ7®) for three years by a healthy population, vitamin K2 (MK-7) improves cardiovascular health. This study of 244 healthy

Vitamin K2 Cardiovascular Health Mechanism



Vitamin K2 Brain Health Mechanism



post-menopausal Dutch women, 55 to 65 years old, demonstrated substantial benefits in inhibiting age-related stiffening of arteries, resulting in increased pulse wave velocity (PWV) in the placebo group but not in the MK-7 group. Most remarkably, MK-7 not only suppressed arterial stiffening but also resulted in an unprecedented statistically significant improvement of vascular elasticity, both measured with ultrasound techniques and PWV in a healthy population.⁴

A 1-year follow-up placebo-controlled, randomized clinical trial study also showed cardiovascular benefit after K2 supplementation in both genders. In the total study group—243 subjects (40-70 years old) characterized by an elevated risk for cardiovascular disease due to vitamin K-insufficiency (i.e., dp-ucMGP > 400 pmol/L)—MK-7 (180 µg/day of K2 as MenaQ7®) induced a significant decrease of both dp-ucMGP and carotid-femoral pulse-wave velocity (cfPWV). The participants taking MenaQ7® maintained arterial flexibility, and the stiffness did not increase, whereas the placebo group became stiffer and less flexible.⁵

The significance of this clinical work has earned the medical community's attention, which is now in process with its trials that are using vitamin K2 as MK-7 (as MenaQ7®) as a possible therapy for patients whose conditions present symptoms of intense calcification.^{6,7}

The K2 Mechanism & Brain Health

Vitamin K2 as MK-7 is unique because it impacts arterial calcification, and no other compound (drug or vitamin) has been shown to do this. It turned out that this nutrient also lends a vital cardiovascular support to patients with chronic kidney disease who are on dialysis and renal transplant recipients.^{8,9}

Just as the K2 mechanism has lent itself to CKD patients, it is also being explored for its impact on other areas of brain health.

Vitamin K, a fat-soluble nutrient was historically discovered in 1935 for its role in blood coagulation, and as such has been thoroughly explored. In recent years, studies highlighted vitamin K2 involvement in brain cells

development and survival. In the brain vitamin K occurs predominantly as MK-4. Vitamin K2 has been involved in functions such as cell survival, chemotaxis, mitogenesis, cell growth, and myelination mediated by the activation of vitamin K-dependent proteins: Growth Arrest Specific Gene 6 (Gas6) and protein S.

Moreover, vitamin K2 is also involved in the synthesis of sphingolipids, an important class of lipids present in high concentrations in brain cell membranes. Initially appreciated for their role as essential structural components of cell membranes, sphingolipids are now known to participate in important cellular events such as signaling, proliferation, differentiation, senescence, transformation and survival of brain cells. In recent years, studies have linked alterations in sphingolipid metabolism to age-related cognitive decline and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.¹⁰⁻¹²

Alzheimer's Disease (AD) and Other Forms of Dementia

Human studies on the impact of vitamin K deficiency in brain function are limited, therefore it is still a matter of debate today whether vitamin K deficiency is associated to cognitive decline. Vitamin K antagonists (VKAs such as warfarin, acenocoumarol, and fluindion), used worldwide as oral anticoagulants, according to recent studies may have a negative influence on cognitive domains such as visual memory, verbal fluency and brain volume. The two most common types of dementia in Western countries are Alzheimer's disease (AD) and vascular dementia. The mechanism underlying AD is the deposition of β-amyloid peptide (Aβ) and the neurofibrillary tangles in the intracellular environment, neuronal death and the loss of synapses, all of which contribute to cognitive decline in a progressive manner.^{13,14}

Six studies demonstrated, in a population of 65 years and older, a direct correlation between low vitamin K dietary intake or serum concentration and deteriorated cognitive and behavioral performances.¹⁵⁻²⁰ Moreover, research findings show that vitamin K2 can protect neural cells against Aβ toxicity.²¹

Cui et al.²² connected aortic stiffness with an increased risk of dementia in older adults. More recently, *Nutrients* published a new review paper that examines the body of evidence connecting vitamin K2 to factors involved in AD pathogenesis, concluding that this demonstrates K2 as having the potential to slow the progression of AD and contribute to its prevention.²³ US researchers considered the antiapoptotic and antioxidant effects of vitamin K2 and its impact on neuroinflammation, mitochondrial dysfunction, cognition, cardiovascular health, and comorbidities in AD. They also examined the link between dysbiosis and vitamin K2 in the context of the microbiome's role in AD pathogenesis. According to the researchers, "Our review is the first to consider the physiological roles of vitamin K2 in the context of AD, and, given the recent shift in AD research toward nonpharmacological interventions, our findings emphasize the timeliness and need for clinical studies involving vitamin K2."

Considering the growing social and economic burden linked to the increasing number of patients suffering from cognitive impairment and dementia, further research on this topic can prove to be beneficial and applicable results can be expected.

Parkinson's Disease

Mitochondria are called the power plants of the cell, responsible for supplying the energy for its operation. Mitochondrial dysfunction was proposed to be an integral player in the development of Parkinson's disease (PD) nearly 40 years ago, and since those initial discoveries, evidence of the role it may play in this neurodegeneration continues to increase.²⁴

Parkinson's patients have several genetic defects, including PINK 1 and Parkin mutations, that lead to reduced mitochondrial activity. In one study, researchers found that fruit flies (*Drosophila*) with a PINK1 or Parkin mutation lost their ability to fly. They discovered that the mitochondria in these flies were defective, just as in Parkinson's patients. Because of this they generated less intracellular energy—energy the insects needed to fly. When the flies were given vitamin K2, the energy production in their mitochondria was restored and the insects' ability to fly improved. The researchers were also able to determine that the energy production was restored because the vitamin K2 had improved electron transport in the mitochondria. Vitamin K2 plays a role in the energy production of defective mitochondria. Because defective mitochondria are also found in Parkinson's patients with a PINK1 or Parkin mutation, vitamin K2 potentially offers hope for a new treatment for PD.²⁵

Recently, a case-control study was conducted that involved 93 PD patients and 95 healthy controls. The researchers found the serum vitamin K2 level in PD patients is lower than that in healthy controls. The decrease of vitamin K2 level may be related to the occurrence and progression of PD by loosening the regulation of inflammatory responses and coagulation cascades signal.²⁶

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a devastating neurological disease characterized by multifocal demyelinating lesions in the central nervous system. Although vitamin K participation in the brain pathology has not been fully explained, it is well known that oxidative stress has a critical role in neurodegenerative diseases. Further, vitamin K2 was found to have beneficial effects on the nervous system—it seems to protect neurons and oligodendrocytes from oxidative injury. Moreover, vitamin K2 can reduce inflammation and the consequences of autoimmune diseases, such as multiple sclerosis (MS). Because of the potential role of vitamin K2 in MS and the possibility that it may be associated with its clinical features, Austrian researchers decided to assess vitamin K2 serum levels in MS patients in comparison to healthy controls and correlate these levels with clinical appearance, medication, and disability status. Overall, 45 MS patients (31 females and 39 of the relapsing-remitting type) and 29 healthy controls (19 females) were included in the analysis. The vitamin K2 serum levels were more than three-fold higher in healthy controls as compared to MS patients healthy controls had a median level of 866ng/ml compared to a median level of 196ng/ml in MS cases. Vitamin K2 levels were lower with increasing numbers of attacks per year and were higher in patients with optic nerve lesions. This study showed that the substantially lower levels of vitamin K2 in MS patients could be due to depletion, lower production in the gut, diminished absorption or, less likely, reduced intake of precursor vitamin K1. The role of K2 in MS development and progress deserves further study.²⁷

Migraine

A better understanding of disease pathophysiology to help guide future research on migraine management is needed, since according to the WHO migraine is estimated as the fifth highest cause of years lost due to disability. In a case-control single-center observational study, Lebanese researchers compared arterial stiffness and markers of vitamin K2 status between a cohort of patients with untreated migraine vs. their age- and sex-matched non-migraine controls. The published outcome of their project constitutes an important message for migraineurs who are more prone to an increased risk of major cardiovascular events. Individuals with migraine have worse indices of arterial stiffness as compared with their age- and sex-matched control subjects. This increase in arterial stiffness is correlated with an increase in markers of vitamin K2 deficiency in the migraine with aura (MWA) group. It seems that people who suffer from migraine might benefit from MK-7 supplementation, however there is a need to direct the focus of research in this domain toward examining the effect of vitamin K2 supplementation on migraine frequency, arterial stiffness and cardiovascular outcome in patients with migraine.²⁸

Suboptimal K2 Status Linked to Cognitive Impairment



Peripheral neuropathy (PN)

Diabetic peripheral neuropathy is a frequent and severe complication of diabetes. A recent study aimed to evaluate factors associated with sensitive diabetic neuropathy in Type 2 Diabetes, and, in particular, dephospho-uncarboxylated Matrix-gla-protein (dp-ucMGP), the inactive form of MGP. Peripheral neuropathy was present in 15.7% of the patients and was significantly associated with dp-ucMGP levels. Since MGP is expressed in several components of the nervous system and is involved in some neurological disease, it is likely to play a role in peripheral nervous system homeostasis. Further studies are needed to determine if dp-ucMGP may be used as a biomarker of sensitive neuropathy.²⁹

Another study with the objective to assess the efficacy, tolerability and safety of vitamin K2 as MK7 in patients with peripheral neuropathy was conducted in 100 participants presenting with PN and suffering from either Vitamin B12 Deficiency (VBD, megaloblastic anaemia) or Type 2 Diabetes Mellitus (T2DM). For the first time, in larger sample size, it has been shown that K2 as MK7 at a dose of 100 mcg twice a day for 8 weeks has a therapeutic activity for the symptoms of PN in VBD and T2DM. It also helps in relieving the associated symptoms of PN such as cramps, burning pain, weakness, and fatigue. The reduction in symptoms was persistent even after the discontinuation of MK7. Vitamin K2 as MK7 was also well tolerated by all patients. Thus, it proves that vitamin K2 as

MK7 offers a confirming therapeutic effect in PN due to VBD or T2DM. Further, a multicentric placebo-controlled randomized double-blind trial can clearly establish the effect of vitamin K2 as MK7, also in case of residual neuropathy.³⁰

The Need For An RDI

Researchers formulated a nine-criteria standard in 2014 for the purpose of assessing whether sufficient grounds exist for a nutraceutical to be considered for Reference Daily Intake (RDI).³¹ The following factors need to be considered: (1) an accepted definition; (2) a reliable analysis method; (3) a food database with known amounts of the bioactive; (4) cohort studies; (5) clinical trials on metabolic processes; (6) clinical trials for dose-response and efficacy; (7) safety data; (8) systematic reviews and/or meta-analyses; and lastly, (9) a plausible biological rationale. By evaluating current knowledge and studies, either performed or still ongoing, a paper recently published in the journal *Nutrients* assessed whether vitamin K2 meets these nine criteria.³²

There is no doubt as to the differences between the pharmacokinetics of vitamin K1 and vitamin K2 in the human body. Vitamin K2 has been widely acknowledged for its extrahepatic activity; however, a detailed mechanistic description of K2 action has not been provided in the literature so far. The *Nutrients* paper showed that vitamin K2 clearly passes the nine criteria set out for establishing bioactive RDI recommendation. The concentration of

bioactive vitamin K2 in a range of fermented foods common to Western diets depends on factorial preparation methods, namely, the type of bacteria used in fermentation processes. Results of different clinical trials that tested the influence of vitamin K2 supplementation on human health status have shown that it either significantly improved it or strongly correlated. Researchers postulate that consistent consumption of vitamin K2 can reduce the risk of occurrence of cardiovascular diseases, bone loss, and, potentially, other age-related diseases. Bearing in mind this nature of vitamin K2 action on decreasing the development of diseases commonly linked to aging, steps should be taken by scientific and food policy makers to review the literature on the current state of vitamin K2 research and consider establishing an RDI for vitamin K2 to significantly improve global health and reduce the socioeconomic consequences of an aging population.

References

- Rheume-Bleue K. *Vitamin K2 and the Calcium Paradox: How a Little-Known Vitamin Could Save Your Life*. 2013. Harper; Reprint edition.
- Braam LA et al. *Thrombosis and Haemostasis*. 2004. 91(2): 373-80.
- Schurgers LJ et al. *Thrombosis and Haemostasis*. 2008. 100(4): 593-603.
- Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. A double-blind randomised clinical trial. *Thromb Haemost*. 2015;113(5):1135-1144. doi:10.1160/TH14-08-0675
- Vermeer C and Vik H. Effect of Menaquinone-7 (vitamin K2) on vascular elasticity in healthy subjects: results from a one-year study. *Vascul Dis Ther*, 2020;5. doi: 10.15761/VDT.1000179.
- Vossen LM et al. Menaquinone-7 supplementation to reduce vascular calcification in patients with coronary artery disease: rationale and study protocol (VitaK-CAC Trial). *Nutrients*. 2015; vol. 7, no. 11:8905-8915.
- Peeters FECM et al. Bicuspid aortic valve stenosis and the effect of K2 on calcification using sodium fluoride positron emission tomography/magnetic resonance: the BASIK2 trial design. *Nutrients*. 2018; vol.10, no. 4.
- Lee SM, An WS. Supplementary nutrients for prevention of vascular calcification in patients with chronic kidney disease, *Korean J Intern Med*. 2019;34(3):459-469. doi: 10.3904/kjim.2019.125
- Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, et al. Effect on vitamin K2 on progression of atherosclerosis and vascular calcification in nondialyzed patients with chronic kidney disease stages 3-5. *PolArchMedWewn*. 2015;125(9):631-40.
- Ferland G. 2012. Vitamin K, an emerging nutrient in brain function. *Biofactors* 38(2): 151-157. doi: 10.1002/biof.1004.
- Alisi L, Cao R, De Angelis C, et al. The Relationships Between Vitamin K and Cognition: A Review of Current Evidence. *Front Neurol*. 2019;10:239. Published 2019 Mar 19. doi:10.3389/fneur.2019.00239
- Carrié I, Portoukalian J, Vicaretti R, Rochford J, Potvin S, Ferland G. 2004. Menaquinone-4 Concentration Is Correlated with Sphingolipid Concentrations in Rat Brain, *The Journal of Nutrition* 134(1): 167-172. doi. org/10.1093/jn/134.1.167
- Kalaria RN, Maestre GE, Arizaga R, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors [published correction appears in *Lancet Neurol*. 2008 Oct;7(10):867]. *Lancet Neurol*. 2008;7(9):812-826. doi:10.1016/S1474-4422(08)70169-8
- Murphy MP, LeVine H 3rd. Alzheimer's disease and the amyloid-beta peptide. *J Alzheimers Dis*. 2010;19(1):311-323. doi:10.3233/JAD-2010-1221Poczatek formularzaDól formularza
- Sato Y, Honda Y, Hayashida N, Iwamoto J, Kanoko T, Satoh K. Vitamin K deficiency and osteopenia in elderly women with Alzheimer's disease. *Arch Phys Med Rehabil*. (2005) 86:576-81. 10.1016/j.apmr.2004.10.005
- Presse N, Shatenstein B, Kergoat MJ, Ferland G. Low vitamin K intakes in community-dwelling elders at an early stage of Alzheimer's disease. *J Am Diet Assoc*. (2008) 108:2095-9. 10.1016/j.jada.2008.09.013
- Presse N, Belleville S, Gaudreau P, Greenwood CE, Kergoat MJ, Morais JA, et al. Vitamin K status and cognitive function in healthy older adults. *Neurobiol Aging*. (2013) 34:2777-83. 10.1016/j.neurobiolaging.2013.05.031
- Chouet J, Ferland G, Féart C, Rolland Y, Presse N, Boucher K, et al. Dietary vitamin K intake is associated with cognition and behaviour among geriatric patients: the CLIP study. *Nutrients*. (2015) 7:6739-50. 10.3390/nu7085306
- Soutif-Veillon A, Ferland G, Rolland Y, Presse N, Boucher K, Féart C, et al. Increased dietary vitamin K intake is associated with less severe subjective memory complaint among older adults. *Maturitas*. (2016) 93:131-6. 10.1016/j.maturitas.2016.02.004
- Kiely A, Ferland G, Ouliass B, O'Toole PW, Purtil H, O'Connor EM. Vitamin K status and inflammation are associated with cognition in older Irish adults. *Nutr Neurosci*. (2018) 2018:1-9. 10.1080/1028415X.2018.1536411.
- Huang SH et al. Molecular Mechanism of Vitamin K2 Protection against Amyloid- β -Induced Cytotoxicity. *Biomolecules* 2021 Mar; 11(3):423.
- Cui C, et al. "Aortic stiffness is associated with increased risk of incident dementia in older adults." *J Alzheimer's Dis*. 2018;66(1):297-306.
- Popescu A and German M. "Vitamin K2 Holds Promise for Alzheimer's Prevention and Treatment." *Nutrients*. 2021,13,2206.
- Chen C, Turnbull DM, Reeve AK. Mitochondrial Dysfunction in Parkinson's Disease-Cause or Consequence?. *Biology (Basel)*. 2019;8(2):38. Published 2019 May 11. doi:10.3390/biology8020038
- Vos M, Esposito G, Edirisinghe JN, Vilain S, Haddad DM, Slabbaert JR, Van Meensel S, Schaap O, De Strooper B, Meganathan R, Morais VA, Verstreken P. Vitamin K2 Is a Mitochondrial Electron Carrier That Rescues Pink1 Deficiency. *Science*, 2012; DOI: 10.1126/science.1218632
- Yu YX, Yu XD, Cheng QZ, Tang L, Shen MQ. The association of serum vitamin K2 levels with Parkinson's disease: from basic case-control study to big data mining analysis. *Aging (Albany NY)*. 2020;12(16):16410-16419. doi:10.18632/aging.103691
- Lasemi R, Kundi M, Moghadam NB, et al. 2018. Vitamin K2 in multiple sclerosis patients. *Wiener klinische Wochenschrift* 130 (9-10): 307-313. doi: 10.1007/s00508-018-1328-x
- Mansour AG, Ahdab R, Daaboul Y, et al. Vitamin K2 Status and Arterial Stiffness Among Untreated Migraine Patients: A Case-Control Study. *Headache*. 2020;60(3):589-599. doi:10.1111/head.13715
- Jeannin AC, Salem JE, Massy Z, et al. Inactive matrix gla protein plasma levels are associated with peripheral neuropathy in Type 2 diabetes [published correction appears in *PLoS One*. 2020 May 5;15(5):e0232996]. *PLoS One*. 2020;15(2):e0229145. Published 2020 Feb 24. doi:10.1371/journal.pone.0229145
- Mehta DS, Dound YA, Jadhav SS, Bhawe AA, Devale M, Vaidya AD. A novel potential role of Vitamin K2-7 in relieving peripheral neuropathy. *J Pharmacol Pharmacother* 2018;9:180-5
- Lupton JR, Atkinson SA, Chang N, et al. Exploring the benefits and challenges of establishing a DRI-like process for bioactives. *Eur J Nutr* 53, 1-9 (2014), doi.org/10.1007/s00394-014-0666-3.
- Akbulut AC, Pavlic A, Petsophonsakul P, Halder M, Maresz K, Kramann R, Schurgers L. Vitamin K2 Needs an RDI Separate from Vitamin K1. *Nutrients* 2020, 12, 1852.