Review

Vitamin K intake and health, consideration from the epidemiological studies

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The most fundamental function of vitamin K is to activate the blood coagulation factors in the liver. Despite the recent recognition of its extra-hepatic actions, the current Dietary Reference Intakes for vitamin K is based on the amount necessary for maintaining the normal blood coagulation in many countries. To define the Dietary Reference Intake for vitamin K, appropriate biomarkers well-reflecting the vitamin K status are essential. Unfortunately, however, no markers are currently available with properties enabling us to properly define the vitamin K status; i.e., no interference by other factors and the presence of widely approved cut-off values. Thus, Adequate Intake is determined, which is an index based on the representative dietary intake data from healthy individuals. Recently, epidemiological studies have been reported regarding the relationship between vitamin K and noncommunicable diseases including osteoporotic fracture. Furthermore, studies focusing on the relationship between vitamin K intake and metabolic syndrome, physical function, depression, cognition, and all-cause mortality have become available, although limited in number. This review summarizes the recent findings in favor of the novel functions of vitamin K. More epidemiological studies are needed to define the appropriate vitamin K intake value based on the prevention of various disorders.

***Key Words*: vitamin K intake, Dietary Reference Intakes, noncommunicable diseases, all-cause mortality**

Vitamin K is a fat-soluble vitamin that occurs in two biologically active forms: phylloquinone (vitamin K_1) and menaquinone (vitamin K_2). Phylloquinone is predominantly found in leafy green vegetables such as spinach, broccoli, cabbage, whereas menaquinone is found mainly in meat, egg, and dairy products, with large variability of dietary intakes across different regions.[1] Natto, which is one of the Japanese traditional fermented foods, contains large amount of menaquinone-7. The most fundamental role of vitamin K is the one as a cofactor of gamma-glutamyl carboxylase (GGCX).[2] Although GGCX is present in various tissues, its role in the liver has received most attention until recently.[3,4] Historically, interest in vitamin K has been focused on its role in blood coagulation. Additionally, data have been reported regarding the relationship between phylloquinone or menaquinone intake and cardiovascular outcomes, bone health, diabetes mellitus, metabolic syndrome, cancer, and all-cause mortality.[5]

In this review, we will give an overview on some topics that are recently receiving concern; the Dietary Reference Intakes (DRIs) for vitamin K and the relationship between vitamin K intake and health consequence which have been newly obtained from clinical or epidemiological studies.

Methods

In this review article, data from observational studies were adopted. In substantial percentage of intervention studies with vitamin K, its large amount; i.e., pharmacological dose has been employed. Since our aim was to analyze the health consequence of vitamin K as a nutrient, we have considered it more appropriate to review the results from the epidemiological studies rather than the intervention studies. We assessed the overall quality of each epidemiological study by the Newcastle-Ottawa Scale (NOS).[6] NOS consists of 9 criteria (0–9 stars) including representativeness of the exposed cohort, the selection of the non-exposed cohort, ascertainment of exposure, and outcome of interest not present at the start of the study (maximum of 4 stars), comparability of the cohorts on the basis of study design and analysis (maximum of 2 stars), and finally, the assessment of the outcome (maximum of 3 stars). Two investigators (AK and KT) independently assessed the full text.

Dietary Reference Values for Vitamin K

What biomarkers are used for the assessment of vitamin K status? To determine the DRIs for vitamin K, the measurement of biomarkers well reflecting vitamin K status is required. Until recently, such biomarkers have been quite limited, and prothrombin time (PT) has been the only easy-to-use biomarker for vitamin K deficiency. PT, however, is not free from limitations. First, it is not so sensitive a marker reflecting vitamin K status.[7] Additionally, it is affected by factors other than vitamin K status such as hepatic dysfunctions, or hematological diseases.[8] Other possible biomarkers that have come to the clinical or research use include blood concentration of vitamin K, undercarboxylated forms of vitamin K dependent proteins [protein induced by vitamin K absence or antagonist-II (PIVKA-II), undercarboxylated osteocalcin (ucOC), dephosphorylated undercarboxylated form matrix gla protein (dp-ucMGP)], and urinary excretion of gamma carboxyglutamic acid (Gla).[5] These biomarkers show significant alteration according to phylloquinone intake, suggesting their usefulness. However, several problems still remain for the assessment of vitamin K status. First, since these markers are not solely affected by the phylloquinone intake, caution is required for using these markers for the assessment of vitamin K status. The second one is the unavailablity of widely approved cut-off values which enable us to properly assess the vitamin K status. Therefore, there is no decisive biomarkers at present for which a dose-

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response relationship with phylloquinone intake is established. Shea and Booth[9] also have described that there are no single biomarkers which can be considered a gold-standard for vitamin K status. Lack of appropriate biomarkers makes it practically impossible to define the DRIs for vitamin K based on the reliable experimental protocol such as the depletion-repletion study. Thus, DRIs for vitamin K in most countries are under the influence of the Adequate Intake (AI) from the Institute of Medicine (IOM). AI is an index basically based on the representative dietary intake data from healthy individuals.

The requirement of vitamin K intake in infants. Blood coagulation abnormality is the only overt clinical manifestation attributable to vitamin K deficiency, which, however, is rarely observed in healthy adults in developed countries. In contrast, newborn infants are quite vulnerable to vitamin K deficiency due to various reasons, such as poor transplacental vitamin K transport,[10] low vitamin K concentration in the breast milk,[11,12] and low production of vitamin K by the intestinal flora.[12] Some previous studies have also reported that the antenatal vitamin K supplementation is related to the vitamin K status of the newborn.[13,14] At present, however, the definite conclusion regarding the effect of maternal vitamin K supplementation has not been drawn.

As neonatal vitamin K deficiency is known to cause serious clinical consequences such as neonatal melena, a form of gastrointestinal bleeding, and intracranial bleeding, vitamin K is orally administered just after birth for their prevention.[15] Therefore, the reference intake of vitamin K in infants is determined based on the assumption that vitamin K is orally administered just after birth in clinical settings in many countries.

In the current review, we have summarized the DRIs for vitamin K from various sources (Table 1); DRIs for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc (IOM),[16] vitamin and mineral requirements in human nutrition [World Health Organization (WHO)],[17] Nutrient Reference Values for Australia and New Zealand [The Australian National Health and Medical Research Council (NHMRC) and the New Zealand Ministry of Health (MoH)],[18] Nordic Nutrition Recommendations 2012 (Nordic co-operation),[19] DRIs for Japanese (2020) (Ministry of Health, Labour and Welfare, Japan).[20] Most DRIs for vitamin K including the one in Japan are defined based on those of IOM. Vitamin K, however, is provided not only from food intake but also from the production by intestinal flora. Recently, it is reported that Japanese populations have different gut microbiome from that in other populations, which would be another basis for the different requirement of vitamin K intake in Japan from other countries.[21]

The Relationships between Vitamin K Intakes and Human Health in Epidemiological Studies

In the previous publications, the relationship between vitamin K intake and risks of low bone mineral density or fracture, cardiovascular diseases, cancer, diabetes has been published. Moreover, its association with physical function, depression, and mortality has been also reported. In this section, we have described the relationship between vitamin K intakes and the above-mentioned outcomes (Table 2). Each evidence level of the reviewed papers was assessed by the Newcastle-Ottawa Scale (NOS) (Supplemental Table 1*). Although the number of papers on mortality were limited, these papers showed a high level of evidence.

Fracture. One meta-analysis described the dose-response relationship between vitamin K intake and fracture risk.[22] Although the heterogeneity among studies was not observed, the authors have admitted that the epidemiologic studies focusing on the relationship between dietary vitamin K intake and the risk of fractures are quite few, and the results are inconsistent. To examine this relationship in detail, we have decided it necessary to evaluate the cited epidemiological studies individually in more detail. The results of our evaluation on the association between vitamin K intake and fractures from the epidemiological studies will be described below.

Results from five observational studies after adjustments for potential confounders, are shown in Table 2. In the largest observational study undertaken among women (nurses), subjects with baseline phylloquinone intake in quintile (Q) 3 (146–183 μg/day) had a significantly lower relative risk (RR) for hip fractures (RR: 0.70; 95% CI: 0.53, 0.93) compared with those in Q1 (<109 μg/day).[23] In addition, the RR of hip fracture was significantly lower (RR 0.70; 95% CI 0.53, 0.93) in combined Q2–Q5 with the baseline phylloquinone intake of 109 to >242 μg/day compared to Q1 (<109 μg/day), but this significant relation did not remain when updated dietary data during follow-up were taken into account.[23] Booth *et al.*[24] reported that subjects in the highest quartile (Q) of vitamin K intake (median: 254 μg/day) had a significantly lower fully adjusted RR (0.35; 95% CI: 0.13, 0.94) of hip fracture than those in the lowest Q of intake (median: 56 μg/day). In another study, the risk of hip fracture was significantly higher in the lowest Q of phylloquinone intake (Q1 <42.2 μg/day for women and 52.9 μg/day for men) when compared to the highest Q (Q4 >108.7 μg/day for women and 113.9 μg/day for men) with the hazard ratio (HR) of 1.63 (95% CI: 1.06, 2.49, p for trend: 0.015).[25] In this study, the HR of hip fractures was 0.98 (95% CI: 0.95, 1.00, $p = 0.030$) per 10 μg/day increment in phylloquinone intake. In the same study, however, the risk of hip fracture was not significantly associated with the intake of menaquinones expressed as the risk per 1 μg increment in intake, or even by the comparison of the lowest to the highest Qs of menaquinones intake [Q1; <7.2 μg/day (women) and 8.5 μg/day (men) vs Q4 >14.5 μg/day (women) and 16.2 μg/day (men)].[25] Some reports revealed the negative association between phylloquinone intake and fractures. In the nested case–control study in perimenopausal women, irrespective of the presence or absence of hormonal replacement therapy or the prevalent fracture at baseline, there was no significant association between the risk of vertebral fracture and phylloquinone intake, even by the comparison of the highest with the lowest Qs (>105 vs <25 μg/day).[22] In this study, the risk of fracture during the first 5 years of follow-up or 10 years were not significantly different between the phylloquinone intake categories.[26] In the interpretation of this data, however, caution is needed that vertebral bodies are mostly composed of trabecular bone, whereas proximal femur consists of both cortical and trabecular bone. In the observational study, there was no significant association between the risk of hip fracture and energy adjusted, log-transformed phylloquinone intake (per SD increment in intake) in either men or women aged 65 years and older.[27]

Although there have been some reports on the association of phylloquinone intake with fractures, those of menaquinone intake have not been reported, except for one study revealing that menaquinone intake had no significant association with fractures.[25] Considering the paucity of the previous reports, the relationship between the intake of phylloquinone or menaquinones and fractures is still to be established.

Metabolic syndrome (MetS). In a cross-sectional study, older women with higher body fat mass had lower vitamin K status, as assessed by lower plasma phylloquinone and higher PIVKA-II levels compared with women with lower body fat mass, after adjustment by the vitamin K intake. Men in the highest tertiles of percentage of body fat (%BF) had higher PIVKA-II, suggesting that increased adiposity is associated with lower vitamin K status.[28] Adipose tissue has been postulated to sequester fat-soluble nutrients, thereby

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Table 1. The summary of the dietary reference intake for vitamin K from various sources

The name of reference nutrients intake	Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc[16]	Vitamin and mineral requirements in human nutrition[17]	Nutrient Reference Values for Australia and New Zealand[18]	Nordic Nutrition Recommendations 2012[19]	Dietary Reference Intakes for Japanese (2020)[20]
Institution	Institute of Medicine (IOM)	World Health Organization (WHO)	The Australian National Health and Medical Research Council (NHMRC) and the New Zealand Ministry of Health (MoH)	Nordic co-operation (Denmark, Finland, Iceland, Norway, Sweden, and the Faroe Islands, Greenland, and Åland)	Ministry of Health, Labour and Welfare, Japan
Adults and elderly	Men	Males	Men	—	≥18 years 150 μg/day
	≥19 years 120 μg/day	19–65 years 65 μg/day	≥19 years 70 μg/day		
	Women	<65 years 65 μg/day	Women		
	≥19 years 90 μg/day	Females	≥19 years 60 μg/day		
		19–65 years 55 μg/day			
		<65 years 55 μg/day			
Method used to set the recommendation of vitamin K intake	The AI for adults is based on reported vitamin K dietary intakes in apparently healthy population groups (from NHANES III).	The recommended nutrient intake (RNI) of adult for maintaining classical function in coagulation have been set at a value of 1 μg/kg body weight/day	The AI for adults is based on median intake from a reanalysis of the National Nutrition Survey of Australia, 1995 and United States Department of Agriculture (USDA) data base.	No recommendation given due to lack of sufficient evidence	The AI for adults based on the average values of vitamin K intake from the 2016 NHNS data.
Infants	0–6 months 2.0 μg/day	0–6 months 5 μg/day	0–6 months 2.0 μg/day		0–5 months 4.0 μg/day
	7–12 months 2.5 μg/day	7–12 months 10 μg/day	7–12 months 2.5 μg/day		6–11 months 7.0 μg/day
Method used to set the recommendation of vitamin K intake	The AI for infants 0 through 6 months of age is based on a reported average intake of milk of 0.78 L/day and on an average phylloquinone concentration of 2.5 μg/L in human milk.	The RNI based on the adult RDA or adequate intake 1 μg/kg body weight/day	The AI for 0–6 months was calculated by multiplying the average intake of breast milk (0.78 L/day) by the average concentration of vitamin K in breast milk, and rounding.	No recommendation given due to lack of sufficient evidence	An AI of 4.0 mg/day for infants aged 0–5 months was determined by multiplying the average milk intake (0.78 L/day) and the average vitamin K content of milk (5.17 μg/L)
	*The AI assumes that infants also receive prophylactic vitamin K at birth in amounts suggested by the American and Canadian pediatric societies	*To prevent bleeding due to vitamin K deficiency, it is recommended that all breast-fed infants should receive vitamin K supplementation at birth according to nationally approved guidelines.			*Assuming the presence of the oral administration of vitamin K just after birth in clinical settings.
					For infants aged 6 to 11 months, the AI was determined to be 7 μg/day, *Considering the amount of vitamin K received from sources other than breast milk.
Children	1–3 years 30 μg/day	1–3 years 15 μg/day	1–3 years 25 μg/day		1–2 years 60 μg/day
	4–8 years 55 μg/day	4–6 years 20 μg/day	4–8 years 35 μg/day		3–5 years 70 μg/day
	Boys	7–9 years 25 μg/day	9–13 years 45 μg/day		6–7 years 85 μg/day
	9–13 years 60 μg/day	10–18 years 35–55 μg/day	14–18 years 55 μg/day		8–9 years 100 μg/day
	14–18 years 75 μg/day				10–11 years 120 μg/day
	Girls				12–14 years 150 μg/day
	9–13 years 60 μg/day				15–17 years 160 μg/day
	14–18 years 75 μg/day				
Method used to set the recommendation of vitamin K intake	The AIs are set on the basis of the highest median intake for each age group reported by the Third National Health and Nutrition Examination Survey (NHANES III)	The RNI of adult for maintaining classical function in coagulation have been set at a value of 1 μg/kg body weight/day	The AI for children is set based on median intakes from a re-analysis of the National Nutrition Survey of Australia, 1995	No recommendation given due to lack of sufficient evidence	The AI for children was determined by extrapolating the AI for adults by the 0.75th power of the BW ratio.
Pregnant or lactating women	Pregnancy	Pregnant women 55 μg/day	Pregnant and lactating women		Pregnant and lactating women
	14–18 years 75 μg/day	Lactating women 55 μg/day	14–18 years 60 μg/day		150 μg/day
	19–50 years 90 μg/day		19–30 years 60 μg/day		
	Lactation		31–50 years 60 μg/day		
	14–18 years 75 μg/day				
	19–50 years 90 μg/day				
Method used to set the recommendation of vitamin K intake	There is no basis as yet for making different recommendations for pregnant and lactating women. The AI are set at the level for non-pregnant and non-lactating women, respectively.	There is no basis as yet for making different recommendations for pregnant and lactating women. The RNI are set at the level for non-pregnant and non-lactating women, respectively.	There is no basis as yet for making different recommendations for pregnant and lactating women. The AI are set at the level for non-pregnant and non-lactating women, respectively.	No recommendation given due to lack of sufficient evidence	There is no basis as yet for making different recommendations for pregnant and lactating women. The AI are set at the level for non-pregnant and non-lactating women, respectively.

AI, adequate intake; RNI, recommended nutrient intake.

Table 2. The relationships between vitamin K intakes and health consequences in epidemiological studies

Outcome	Study design	County	population	Vitamin K intakes	Results	References
Hip fracture	Cohort study (10-years follow up)	United States	72,327 women (38–63 years)	median (1st–99th percentiles) PK: 169 (41–604) μg/day Adjustment for total energy 163 (45–563) μg/day	Compared with the lowest quintile (Q), 2–5 Qs of vitamin K intake had a significantly lower age-adjusted relative risk (RR: 0.70; 95% CI: 0.53, 0.93) Q1, <109 μg/day Q2, 109–145 μg/day Q3, 146–183 μg/day Q4, 184–242 μg/day Q5, >242 μg/day (Adjusted for age, follow-up period, BMI, menopausal status and use of estrogen replacement, medication, smoking, PA, and dietary intakes of calcium, vitamin D, protein, alcohol, and caffeine)	Am J Clin Nutr. 1999 Jan; 69(1): 74–9. [23]
Hip Fracture	Cohort study (7-years follow up)	United States	888 men and women (68–94 years)	PK: 210.3 ± 127.0 μg/day (men) 163 ± 115 μg/day (women)	Compared with the lowest Q, the highest Q of PK intake had a significantly lower fully adjusted relative risk (0.35; 95% CI: 0.13, 0.94) Q1, = 56 μg/day Q2, = 105 μg/day Q3, = 156 μg/day Q4, = 254 μg/day (Adjusted for femoral neck bone mineral density (BMD), sex, smoking status, calcium and vitamin D supplement use, alcohol consumption, BMI, age, energy intake, physical activity score, and vitamin D, calcium, and caffeine intakes)	Am J Clin Nutr. 2000 May; 71(5): 1201–8. [24]
Hip fracture	Cohort study (10-years follow up)	Norway	2,807 men and women (71–75 years)	PK [median (IQR)], 69 (67) μg/day (women); 75(62) μg/day (men) MK (median (IQR), 10 (7) μg/day (women); 12 (8) μg/day (men)	Compared with the highest Q, the lowest Q of PK intake had a significantly higher fully adjusted relative risk (1.63; 95% CI: 1.06, 2.49) MK intake was not associated with hip fracture PK intake Men Q1, <52.9 μg/day Q2, 52.9–77.4 μg/day Q3, 77.4–113.9 μg/day Q4, >113.9 μg/day Women Q1, <42.2 μg/day Q2,42.2–66.7 μg/day Q3, 66.8–108.6 μg/day Q4, >108.7 μg/day MK intake Men Q1, <8.5 μg/day Q2, 8.5–11.9 μg/day Q3, 11.9–16.2 μg/day Q4, >16.2 μg/day Women Q1, <7.2 μg/day Q2,7.2–10.7 μg/day Q3, 10.7–14.5 μg/day Q4, >14.5 μg/day (Adjusted for sex, total energy intake, smoking, body mass index (BMI), vitamin D- and calcium intake)	Bone. 2011 Nov; 49(5): 990–5. [25]
Fracture	Nested case-control study (subjects who sustained a fracture during the 10-year follow-up)	Denmark	1,800 women (43–58 years)	PK [median (25–75 percentiles)] Baseline: 67 (45–105) μg/day 5 years: 60 (37– 99) μg/day	PK intake was not associated with any fracture Q1, <25 μg/day Q2, 46–67 μg/day Q3, 68–105 μg/day Q4, >105 μg/day	Osteoporos Int. 2006; 17(8): 1122–32. [26]
Hip fracture and non-vertebral fracture	Cohort study (6.9-years follow up)	Hong Kong	2,944 men and women (>65 years)	PK [median (range)] 254 (157–362) μg/day (men) 239 (162–408) μg/day (women)	PK intake was not associated with fracture risks at all measured sites in men and women in either crude or adjusted models (Adjusted forage, baseline BMI, baseline hip BMD, PASE, education, current smoking status, current alcohol use, use of calcium supplement, and energy-adjusted intakes of protein, calcium and vitamin D)	Calcif Tissue Int. 2012 May; 90(5): 396–403. [27]
Obesity	Cross sectional study	United States	443 men and women (65–80 years)	No data of PK intake in all subjects. PK intake according to tertile of %body fat (%BF) Men T1: 157 ± 79 μg/day T2: 142 ± 75 μg/day T3: 148 ± 91 μg/day Women T1: 208 ± 129 μg/day T2: 196 ± 106 μg/day T3: 182 ± 133 μg/day	• PK intake was not associated with %BF • The inverse association was found between plasma PK level and %BF in women	J Nutr. 2010 May; 140(5): 1029–34. [28]

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Table 2. continued

Outcome	Study design	County	population	Vitamin K intakes	Results	References
Metabolic syndrome	Cohort study (10-years follow up)	Netherlands	625 men and women (40–80 years)	PK: 210.3 ± 127.0 μg/day MK: 31.1 ± 12.5 μg/day	• PK was not associated with both prevalence and incidence of MetS • High MK intakes were associated with a lower prevalence of MetS. (prevalence ratio: PR of 0.74 (95% CI: 0.54, 1.03) for the highest vs the lowest tertile. • The highest tertiles of MK intake (PR = 0.62; 95% CI: 0.40, 0.95) was associated with a lower occurrence of MetS. (Adjusted for age, sex, education, BMI, physical activity, smoking, alcohol, saturated fat, total protein, fiber)	J Clin Endocrinol Metab. 2015 Jun; 100(6): 2472–9. [32]
Physical function Usual 20-meter gait speed and chair stand completion time were used as Lower-extremity function markers)	Cohort study (6-years follow up)	United States	4,475 men and women (45–79 years)	No data of actual PK intake in all subjects. Subjects were divided into 4 groups. 1: Insufficient vitamin K and insufficient vitamin D 2: Insufficient vitamin K and sufficient vitamin D 3: Sufficient vitamin K and insufficient vitamin D 4: Sufficient vitamin K and sufficient vitamin D *Sufficient vitamin K intake was defined as ≥90 μg/day for women and ≥120 μg/day for men. Sufficient vitamin D intake was defined as ≥600 IU for men and women ages <70 years and ≥800 IU for men and women ages ≥71 years (included food and supplements)	Both sufficient intake of vitamin K and vitamin D at baseline was associated with overall faster 20-meter gait speed, chair stand completion time, and 400-meter walk time.	Arthritis Care Res (Hoboken). 2018 Aug; 70(8): 1150–1159. [35]
Depression (Center for Epidemiologic studies-depression: CES-D)	Cross sectional study	Japan	1,634 men and women (≥ 65 years)	No data of vitamin K intake in all subjects. VK intake Av ± SD (/1,000 kcal) Men 165.52 ± 89.82 μg/day (Non-Depressive Symptoms subjects) 148.69 ± 83.04 μg/day (Depressive Symptoms subjects) Women 194.94 ± 106.87 μg/day (Non-Depressive Symptoms subjects) 161.76 ± 94.01 μg/day (Depressive Symptoms subjects)	Higher dietary vitamin K intake was significantly associated with a lower presence of depressive symptoms in women (Adjusted for age, height, weight, BMI, living status, marital status, drinking alcohol, smoking status, energy, carbohydrates, hypertension, diabetes, and hyperlipidemia)	Nutrients 2017; 9: 1319. doi: 10.3390/nu9121319 [44]
Depression (Geriatric depression scale: GDS)	Cross sectional study	United Stetes	4,376 men and women (45–79 years)	PK [median (25–75 percentiles)] Baseline: 67 (45–105) μg/day 5 years: 60 (37–99) μg/day	Higher dietary PK intake was significantly associated with a lower presence of depressive symptoms in subjects not taking vitamin D supplementation. Energy-adjusted PK intake Q1, <83 μg/day Q2, 83–138 μg/day Q3, 139–232 μg/day Q4. >232 μg/day (Adjusted for age, sex, race (whites vs others), body mass index, education (degree vs others), smoking habits (current and previous vs others), yearly income (categorized as or <50,000$ and missing data). Physical Activity Scale for Elderly score, Charlson co-morbidity index, daily energy intake, adherence to Mediterranean diet)	Nutrients 2019; 11: 787. doi: 10.3390/nu11040788 [45]
Cognition	Case-control study	Canada	31 community-dwelling men and women with early-stage Alzheimer's disease (AD) and in 31 age- and sex-matched cognitively intact control subjects (≥65 years).	No data of PK intake in all subjects. PK intake mean ± SD, median (range) Control subjects (*n* = 31) 139 ± 233, 71 (2–1,797) μg/day patients with AD (*n* = 31) 63 ± 90, 38 (2–670) μg/day	PK intakes were significantly less in participants with AD even after adjusting for energy intakes.	J Am Diet Assoc. 2008 Dec; 108(12): 2095–9. [47]

Table 2. continued

Outcome	Study design	County	population	Vitamin K intakes	Results	References
Cognition [Mini-Mental State Examination (MMSE); behavior with Frontotemporal Behavioral Rating Scale (FBRS)]	Cross sectional study	France	192 men and women (≥65 years)	PK 319.9 ± 196.3 μg/day (*n* = 192)	PK intake was positively associated with MMSE score and inversely associated with FBRS. (Adjusted for age, gender, social problems, education level, body mass index, comorbidity burden, history of stroke, use of VKAs, regular fatty fish and eggs intakes, serum concentrations of thyroid-stimulating hormone (TSH), vitamin B12, albumin, and estimated glomerular filtration rate (eGFR))	Nutrients 2015; 7: 6739–6750; doi: 10.3390/nu7085306 [48]
Cognition Memory Complaint Questionnaire (MAC-Q; score 0–30, best)	Cross-sectional cohort study	France	160 men and women (≥65 years)	Vitamin K intake mean ± SD 328.0 ± 203.6 μg/day (*n* = 160)	• Subjects with serious subjective memory complaint had a lower vitamin K intake compared with those without serious subjective memory complaint, (298.0 ± 191.8 μg/day vs 393.8 ± 215.2 μg/day). • Increased vitamin K intake was positively associated with the MAC-Q score and inversely with serious subjective memory complaint. (Adjusted for age, sex, BMI, educational level, number of comorbidities, history of stroke, Mini-Mental State Examination (MMSE) score r<24, Instrumental Activities of Daily Living (IADL) score, geriatric depression scale (GDS) score, serum vitamin B12, serum thyroid-stimulating hormone (TSH), serum albumin, and estimated glomerular filtration rate (eGFR))	Maturitas. 2016 Nov; 93: 131–136. [49]
Mortality	Cohort study (7.2-years follow up)	Netherlands	4,807 men and women with no history of Myocardial infarction (≥55 years)	PK intake men 257.1 ± 116.1 μg/day Women 244.3 ± 131.9 μg/day MK intake Men 30.8 ± 18.0 μg/day (men) Women 27.0 ± 15.1 μg/day	• Energy-adjusted PK intake was not associated with coronary heart disease (CHD) mortality, and all-cause mortality • Energy-adjusted MK intake was an inverse relationship with CHD mortality and all-cause mortality. For CHD mortality RR in the mid and upper tertiles of energy-adjusted dietary menaquinone compared to the lower tertile were RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively. For all cause mortality RR in the mid and upper tertiles of energy-adjusted dietary menaquinone compared to the lower tertile were RR = 0.91 (95% CI: 0.75, 1.09) and 0.74 (95% CI: 0.59, 0.92), respectively. Energy-adjusted PK intake Q1, <200 μg/day Q2, 200–278 μg/day Q3, >278 μg/day Energy-adujusted MK intake Q1, <21.6 μg/day Q2, 21.6–32.7 μg/day Q3, >32.7 μg/day (Adjusted for age, gender, total energy intake, BMI, smoking status, pack-years of cigarette smoking, diabetes, education (3 categories), and intake of alcohol, SFA, PUFA, flavonoids (quercetin, myricetin, and kaempferol), and calcium.	J Nutr. 2004 Nov; 134(11): 3100–5. [55]

reduce their bioavailability,[29,30] and it is possible that the sequestration of phylloquinone in adipose tissue have contributed to the lower vitamin K status among those with higher %BF, although concentrations of phylloquinone, menaquinone-4, and dihydrophylloquinone did not differ between subcutaneous and visceral abdominal compartments in the study. An RCT with menaquinone-7 treatment for three years has reported that the fat mass ratio in the android and gynoid region increased by 1.4% (SE 0.6%) in the placebo group, whereas it did not change in the menaquinone-7 group [−0.5% (SE 0.6%), $p = 0.021$]. Although reports on this issue are limited, vitamin K may have a potential function of preventing the body fat increase.[31]

Only one observational study is available on the relationship between phylloquinone or menaquinone intake and MetS.[32] High menaquinones intakes were associated with the lower prevalence of MetS from the comparison of the highest vs the lowest tertiles (35–86 μg/day vs 6–25 μg/day). At follow up, to be in the highest tertiles of menaquinones intake and vitamin K status were associated with a lower occurrence of MetS [prevalence ratio (PR) of 0.62 (95% CI: 0.40, 0.95); p for trend = 0.01]. These associations were mainly driven by relations with lower triglyceride concentrations for menaquinones and lower waist circumference for vitamin K status. Phylloquinone intake was not associated with MetS prevalence in this study.

Physical function. Recently, the association of vitamin K status with physical function has been focused. Some papers have been published on the association of physical function with vitamin K status, as evaluated by circulating vitamin K level in two papers[33,34] and by vitamin K intake in one.[35] Some plausible vitamin K-dependent mechanisms for this relationship are shown below.[34] First, MGP is a negative regulator of vascular calcification, and high dp-ucMGP concentration, suggesting vitamin K deficiency in the vasculature, was reported to be associated with vascular calcium deposition.[36–39] Thus, vitamin K deficiency may impair neuromuscular as well as vascular function.

Alternatively, vitamin K promotes vascular smooth muscle differentiation, which may be associated with a better perfusion

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Table 2. continued

Outcome	Study design	County	population	Vitamin K intakes	Results	References
Mortality	Cohort study (4.8-years follow up)	Spain	7,216 men and women without CVD at enrollment, type 2 diabetes mellitus (T2DM) or ≥3 of the CVD risk factors (men: 55–80 years, women: 60–80 years)	No data of PK and MK intake in all subjects.	• Energy-adjusted PK intake was inversely associated with cancer mortality risk the highest and all-cause mortality compared with the lowest Q. HR for cancer mortality = 0.54 (95% CI: 0.30, 0.96) HR for all-cause mortality = 0.64 (95% CI: 0.45, 0.90) • Subjects who increased their intake of PK or MK during follow-up had a lower risk of cancer and all-cause mortality than subjects who decreased or did not change their intake. HR for cancer PK intake HR: 0.64 (95% CI: 0.43, 0.95) MK intake HR: 0.41 (95% CI: 0.26, 0.64) HR for all-cause mortality PK intake HR: 0.57 (95% CI: 0.44, 0.73) MK intake HR: 0.55 (95% CI: 0.42, 0.73) • Subjects who increased their intake of PK had a lower risk of cardiovascular mortality risk, while their intake of MK did not. HR for cardiovascular mortality risk PK intake HR: 0.52 (95% CI: 0.31, 0.86) MK intake HR: 0.76 (95% CI: 0.44, 1.29) Energy-adujusted PK intake Q1, 170.5 μg/day Q2, 276.1 μg/day Q3, 349.7 μg/day Q4. 626.4 μg/day Energy-adujusted MK intake Q1, 18.4 μg/day Q2, 29.9 μg/day Q3, 39.0 μg/day Q4, 57.5 μg/day (Adjusted for sex, age, changes in BMI, recruiting center, intervention group, smoking (never, current, past), changes in leisure time activity (metabolic equivalent of task/day), and education (primary education, secondary education, higher education), history of diabetes, hypertension, and hypercholesterolemia, use of oral antidiabetic medication, use of antihypertensive medication, and use of statins, dietary variables in energy-adjusted Qs (vegetables, fruits, legumes, cereals, dairy products, meat, fish, olive oil, nuts), alcohol and alcohol squared in grams per day, and changes in energy intake	J Nutr. 2014 May; 144(5): 743–50. [56]
Mortality	Cohort study (Av. 16.8 ± 2.9-years follow up)	Netherlands	33,289 men and women without history of MI (20–70 years)	No data of PK and MK intake in all subjects.	• PK intake was not associated with any of the outcomes. • A higher intake of menaquinones, especially long chain menaquinones associated with reduced CHD mortality with borderline significance ($HR_{10\mu g}$ 0.86 (95% CI: 0.74, 1.00) PK intake Q1, 87.7 μg/day Q2, 129.9 μg/day Q3, 169.9 μg/day Q4. 251.4 μg/day MK intake Q1, 26.2 μg/day Q2, 36.7 μg/day Q3, 45.8 μg/day Q4, 63.7 μg/day (Adjusted for age, gender, total energy intake, BMI, smoking status, pack-years of cigarette smoking, diabetes, education (3 categories), and intake of alcohol, SFA, PUFA, flavonoids (quercetin, myricetin, and kaempferol), and calcium)	Clin Nutr. 2017 Oct; 36(5): 1294–1300. [57]

PK, phylloquinone; MK, menaquinone; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid.

of muscle tissue.[40] In a cross-sectional study including 1,089 community-dwelling older adults,[33] higher plasma phylloquinone was significantly associated with better physical function, as indicated by short physical performance battery (SPPB) scores, which is an index used for the assessment of sarcopenia, and 20-m gait speed. Plasma phylloquinone

level of ≥1.0 nM is a concentration which is achieved when recommended intakes are met. Those with blood level higher than this cut-off value had better SPPB scores and 20-m gait speed after 4–5 years.

Lower plasma dp-ucMGP was associated with better SPPB scores and leg strength cross-sectionally, but not longitudinally. Another longitudinal cohort study including 633 community-dwelling adults described that those in the highest tertile of dp-ucMGP had significantly lower handgrip strength, smaller calf circumference, and poorer functional performance score compared with the lowest tertiles in women. A low vitamin K status, however, was not related to the 13-year decline in these measures.[34] There has been only one study on the association between vitamin K intake and physical function.[35] In the Osteoarthritis Initiative cohort (58% female, age 61 ± 9 years), those with sufficient intake of both vitamin D and vitamin K as defined according to the IOM recommendations; ≥90 μg/day for women and ≥120 μg/day for men for vitamin K, and ≥600 IU/day below <70 years and ≥800 IU/day over ≥70 years for vitamin D, had overall faster usual gait speed and chair stand completion time over 4–5 years follow up ($p = 0.029$). From these findings, vitamin K status is likely to have a positive association with physical function. Recently, intervention studies described that vitamin K supplementation had no effect on physical function.[41–43]

However, well-designed prospective cohort studies and clinical trials are required to confirm this relationship.

Depression. A few reports described the relationship between vitamin K intake and depression.[44,45] In a cross-sectional study with 1,634 elderly Japanese individuals (65 years and older), vitamin K intake was significantly lower in participants with depressive symptoms (148.69 ± 83.04 μg/1,000 kcal) than those without it (165.52 ± 89.82 μg/1,000 kcal), as assessed by the short version of the Geriatric Depression Scale (GDS). In the multiple regression analysis in the overweight participants, a significant correlation was observed between vitamin K intake and depressive symptoms.[44] Another study has reported the association of vitamin K status with depressive symptoms assessed by Center for Epidemiologic Studies-Depression (CES-D).[45] It was significantly lower in people with higher dietary vitamin K intake (>232 μg/day) than those with lower intake (<83 μg/day) (9.1% vs 11.9%, $p = 0.03$). Subjects with the highest dietary vitamin K intake had significant lower odds ratio (OR) of having depressive symptoms (OR = 0.58; 95% CI: 0.43, 0.80; $p = 0.001$) compared with those with the lowest dietary vitamin K intake in the logistic regression analysis after adjusted by potential confounders. Each increment of 100 μg vitamin K intake was associated with the significantly lower odds of 12% (OR = 0.88; 95% CI: 0.82, 0.95, $p = 0.001$) (p for trend = 0.003) only in subjects not taking vitamin D supplementation. Although the possible mechanism of vitamin K for depression has not been fully clarified, lifetime low-vitamin K diet was reported to be associated with higher levels of ceramides in the hippocampus *in vivo* study.[46] Since increased concentrations of ceramides have been related to pro-inflammatory processes, the production of reactive oxygen species, and the inhibition of neuronal survival,[46] the lack of neurogenesis in the hippocampus has been postulated as one of the possible pathogenetic causes of major depression.

Cognition. The relationship between vitamin K intake and cognition has been reported in some reports.[47–49] Mean vitamin K intake in patients with AD was significantly lower compared with those in control subjects (63 ± 90 μg/day vs 139 ± 233 μg/day), even after adjusting for energy intakes ($p = 0.0003$).[47] In a cross-sectional study in 192 consecutive participants aged 65 years and over, subjects with the second and highest tertiles of dietary phylloquinone intake (≥207 μg/day) had higher (i.e., better mean) Mini-Mental State Examination (MMSE) score (22.0 ± 5.7 vs 19.9 ± 6.2, $p = 0.024$) and lower (i.e., better) Frontotemporal Behavioral Rating Scale (FBRS) score (1.5 ± 1.2 vs 1.9 ± 1.3, $p = 0.042$) compared to those in the lowest tertiles of dietary phylloquinone intake (<207 μg/day). The multivariate linear regressions showed that log-transformed dietary phylloquinone intake was positively associated with MMSE score (adjusted $\beta = 1.66$, $p = 0.013$) and inversely associated with FBRS score (adjusted $\beta = -0.33$, $p = 0.037$).[48] In a cross-sectional study in 160 elderly subjects without taking vitamin K antagonists, subjects with serious subjective memory complaint had a significantly lower mean dietary vitamin K intake compared with those without serious subjective memory complaint (298.0 ± 191.8 μg/day vs 393.8 ± 215.2 μg/day, $p = 0.005$). Increased log-transformed dietary vitamin K intake was positively associated with the Memory Complaint Questionnaire (MAC-Q; score 0–30, best) (fully adjusted OR = 0.79, $p = 0.031$), and inversely with serious subjective memory complaint (fully adjusted OR = 0.34, $p = 0.017$).[49] Despite the apparent consistency of these findings, caution is needed for the interpretation. The second and third studies written above are from the same cohort [Cognition and LIPophilic vitamins (CLIP)].

Some previous reports from the basic research have been published describing the mechanisms of vitamin K (mostly menaquinone-4) action in the brain. Vitamin K modulates the synthesis and metabolism of sphingolipids, which are major constituents of the myelin sheath and neuronal cell membranes, and also key players in neuronal proliferation, differentiation, senescence, cell–cell interaction, and transformation.[50] Additionally, two vitamin K-dependent proteins (VKDPs), growth arrest-specific gene 6 (Gas6) and protein S, are also closely associated with the central nervous system (CNS) health and function.[46,50] Gas6 is involved in chemotaxis, mitogenesis, cell growth, and myelination, and has further been shown to rescue cortical neurons from amyloid β-induced apoptosis which is a specific marker of Alzheimer's disease (AD).[51] Since protein S offers neuronal protection during ischemic/hypoxic injury, both *in vivo* and *in vitro*,[52] it is plausible that protein S protects neurons from *N*-methyl-D-aspartate induced toxicity and apoptosis.[53]

Because of a limited number of subjects studied in these reports, it is premature to draw conclusion on the relationship between vitamin K intake and cognition.

Mortality. A recent meta-analysis described that, of the various outcomes analyzed, dietary phylloquinone was significantly associated only with the incidence of total coronary heart disease (CHD) (pooled HR comparing top with bottom tertiles 0.92; 95% CI: 0.84, 0.99; $p = 0.035$; $I^2 = 0\%$).[54] Regarding the dietary menaquinone, similar results were obtained for the incidence of total CHD (pooled HR comparing top with bottom tertiles 0.70; 95% CI: 0.53, 0.93; $p = 0.014$; $I^2 = 32.1\%$). However, some words of warning are given in this meta-analysis that causal relations cannot be established because of the limited number of available studies.

Three studies have been published on the relationship between vitamin K intake and mortality.[55–57] In a cohort study in 4,807 subjects aged 55 years and over with the available dietary data and no history of myocardial infarction at baseline, the RR of CHD mortality was reduced in the mid and upper tertiles of energy-adjusted dietary menaquinone (21.6–32.7 μg/day and >32.7 μg/day) compared to the lower tertile(<21.6 μg/day) [RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.91 (95% CI: 0.75, 1.09) and 0.74 (95% CI: 0.59, 0.92), respectively] after adjustment for covariates. In contrast, phylloquinone intake was not related to any of the outcomes.[55] A possibility has been suggested that inasmuch as menaquinone intake constitutes only 10% of the total vitamin

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K intake, its bioavailability is probably higher than that of phylloquinone that is strongly bound to vegetable fiber.[58] The authors ascribed the protective effect of menaquinone intake against CHD to the inhibition of arterial calcification. Another possibility is suggested that a sufficient intake of foods rich in menaquinones, such as curds and low-fat cheese, may contribute to CHD prevention.[55] Another prospective cohort analysis in 7,216 participants (men and women, aged 55–80 and 60–80 years respectively at baseline, median follow-up of 4.8 years) revealed that energy-adjusted baseline dietary phylloquinone intake was inversely associated with a significantly reduced risk of cancer and all-cause mortality after controlling for the potential confounders (HR: 0.54; 95% CI: 0.30, 0.96; and HR: 0.64; 95% CI: 0.45, 0.90, respectively).[56] In the longitudinal assessments, subjects who increased their intake of phylloquinone or menaquinone during the follow-up period had a lower risk of cancer (HR: 0.64; 95% CI: 0.43, 0.95; and HR: 0.41; 95% CI: 0.26, 0.64, respectively) and all-cause mortality (HR: 0.57; 95% CI: 0.44, 0.73; and HR: 0.55; 95% CI: 0.42, 0.73, respectively) than individuals who decreased or did not change their intake. Additionally, subjects who increased their intake of dietary phylloquinone had a lower risk of cardiovascular mortality risk (HR: 0.52; 95% CI: 0.31, 0.86). However, no association was observed between changes in menaquinone intake and cardiovascular mortality (HR: 0.76; 95% CI: 0.44, 1.29). Thus, higher phylloquinone dietary intake was associated with lower risk of developing age-related chronic diseases and mortality. The authors proposed that the basis for these findings would be the important involvement of vitamin K in such diverse areas as the pathophysiology of vascular calcification and atherosclerotic diseases, the modulation of bone metabolism and cancer initiation and progression.[25,59] The authors, however, have given some words of caution. Subjects in the highest Qs of dietary vitamin K intake generally had healthier diet, were more physically active and less likely to be smokers. Even by the Cox regression models adjusted by several dietary and lifestyle confounding variables, the possibility of residual or incompletely controlled confounding factors may have not been fully excluded.

In contrast, no significant associations were found between phylloquinone or menaquinones intake and all-cause mortality or cause-specific mortality such as the one due to cardiovascular disease (CVD), CHD, stroke, and cancer.[57] Higher intake of long chain menaquinones was associated with lower CHD mortality with borderline significance (p for trend = 0.06), HR 10 μg being 0.86 (95% CI: 0.74, 1.00) in the prospective cohort study including 33,289 participants aged 20–70 years 95% at baseline. These discrepancies from previous studies were explained by the difference in vitamin K intake level and study population.

Conclusion

Albeit the recent research progress, many issues remain to be further clarified. First, in the current DRIs in many countries, AI is defined for vitamin K, which is derived from the representative dietary intake data of the healthy individuals because of the insufficient data available for the determination of Estimated Average Requirement (EAR). Second, despite the previous reports suggesting the association of vitamin K intake with noncommunicable diseases (NCDs), such as osteoporosis, CVD, cancer, currently available data are not sufficient to determine the reference values for the circulating vitamin K level and vitamin K intake for their risk reduction. Third, notwithstanding the presence of some biomarkers for vitamin K status, they are subject to be affected by other variables, and not specific enough. Then, studies on the relationship between vitamin K intake and the risk of NCDs are necessary to determine the adequate value of vitamin K intake for preventing NCDs.

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Abbreviations

AD	Alzheimer's disease
AI	Adequate Intake
%BF	percentage of body fat
CES-D	Center for Epidemiologic Studies-Depression
CHD	coronary heart disease
CLIP	Cognition and LIPophilic vitamins
CVD	cardiovascular disease
dp-ucMGP	dephosphorylated undercarboxylated form matrix gla protein
DRIs	Dietary Reference Intakes
EAR	estimated average requirement
FBRS	Frontotemporal Behavioral Rating Scale
Gas6	growth arrest-specific gene 6
GDS	Geriatric Depression Scale
GGCX	gamma-glutamyl carboxylase
Gla	gamma carboxyglutamic acid
HR	hazard ratio
IOM	Institute of Medicine
MAC-Q	Memory Complaint Questionnaire
MetS	metabolic syndrome
MMSE	Mini-Mental State Examination
MoH	The New Zealand Ministry of Health
NCDs	noncommunicable disease
NHMRC	Nutrient Reference Values for Australia and New Zealand (The Australian National Health and Medical Research Council)
OR	odds ratio
PIVKA-II	protein induced by vitamin K absence or antagonist-II
PR	prevalence ratio
PT	prothrombin time
Q*	quintile or quartile
RR	relative risk
SPPB	short physical performance battery
ucOC	undercarboxylated osteocalcin
VKDPs	vitamin K-dependent proteins
WHO	World Health Organization

Conflict of Interest

No potential conflicts of interest were disclosed.

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