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 K1) and menaquinone (vitamin K2). 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. 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). Although GGCX is present in various tissues, its role in the liver has received most attention until recently. 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.

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). 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. Additionally, it is affected by factors other than vitamin K status such as hepatic dysfunctions, or hematological diseases. 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). 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 unavailability 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 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, the Dietary Reference Intakes (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, low vitamin K concentration in the breast milk, and low production of vitamin K by the intestinal flora. Some previous studies have also reported that the antenatal vitamin K supplementation is related to the vitamin K status of the newborn. 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. 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); Dietary Reference Intakes for Vitamin A, Vitamin K,Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (IOM), vitamin and mineral requirements in human nutrition (World Health Organization (WHO)), 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)), Nordic Nutrition Recommendations 2012 (Nordic co-operation), Dietary Reference Intakes for Japanese (2020) (Ministry of Health, Labour and Welfare, Japan).

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.

**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. 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). 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. Booth et al. 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).

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)]. 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). 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. 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.

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. 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

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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<sup>41</sup> | Vitamin and mineral requirements in human nutrition<sup>11</sup> | Nutrient Reference Values for Australia and New Zealand<sup>42</sup> | Nordic Nutrition Recommendations 2012<sup>43</sup> | Dietary Reference Intakes for Japanese (2020)<sup>44</sup> |
|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Institution                          | 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                                  |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| ≥19 years 120 μg/day                 |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Women                                |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| ≥19 years 90 μg/day                  |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Method used to set the recommendation of vitamin K intake |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Infants                              |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 0–6 months 2.0 μg/day                |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 7–12 months 2.5 μg/day               |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Method used to set the recommendation of vitamin K intake |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Children                             |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 1–3 years 30 μg/day                  |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 4–8 years 55 μg/day                  |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Boys                                 |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 9–13 years 60 μg/day                 |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 14–18 years 75 μg/day                |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Girls                                |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 9–13 years 60 μg/day                 |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 14–18 years 75 μg/day                |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Method used to set the recommendation of vitamin K intake |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Pregnant or lactating women          |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Pregnancy                            |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 14–18 years 75 μg/day                |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 19–50 years 80 μg/day                |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| Lactation                            |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |
| 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. |                                                                                                                                  |                                                                                                                 |                                                                                                                 |                                                                                                                 |                                                                                                                  |

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. 199 |
| 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 intake) | Am J Clin Nutr. 2000 May; 71(5): 1201–8. 196 |
| Hip fracture                 | Cohort study (10-years follow up) | Norway       | 2,807 men and women (71–75 years) | PK [median (IQR)], 69 (67) μg/day (men); 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. 197 |
| 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 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) | Osteoporos Int. 2006; 17(8): 1122–32. 198 |
| 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 %BF 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 | Calcif Tissue Int. 2012 May; 90(5): 396–403. 199 |
| 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. 200 |

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| Outcome                                                                 | Study design                  | Country                      | 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, 0.93) 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. (52) |
| 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. (60) |
| 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 (64) |
| Depression (Geriatric depression scale: GDS)                           | Cross sectional study         | United States                | 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 (65) |
| 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. (66) |
associated with lower vitamin K status. 

Adipose tissue has been postulated to sequester fat-soluble nutrients, thereby reduce their bioavailability, and it is possible that the sequestration of phyloquinone in adipose tissue have contributed to the lower vitamin K status among those with higher %BF, although concentrations of phyloquinone, menaquinone-4, and dihydropyloquinone 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.

Only one observational study is available on the relationship between phyloquinone or menaquinone intake and MetS. 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. Phyloquinone 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 and by vitamin K intake in one. Some plausible vitamin K-dependent mechanisms for this relationship are shown below. First, MGP is a negative regulator of vascular calcification, and high dp-uMGP concentration, suggesting vitamin K deficiency in the vasculature, was reported to be associated with vascular calcium deposition. 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 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.\(^\text{[34]}\) There has been only one study on the association between vitamin K intake and physical function.\(^\text{[35]}\) 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.\(^\text{[31,34]}\)

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.\(^\text{[4,44,45]}\) 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.\(^\text{[44]}\) Another study has reported the association of vitamin K status with depressive symptoms assessed by Center for Epidemiologic Studies-Depression (CES-D).\(^\text{[45]}\) 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.\(^\text{[46]}\) Since increased concentrations of ceramides have been related to pro-inflammatory processes, the production of reactive oxygen species, and the inhibition of neuronal survival, 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.\(^\text{[47,49]}\) 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).\(^\text{[47]}\) 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 (FRBS) 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 β = 1.66, p = 0.013) and inversely associated with FRBS score (adjusted β = −0.33, p = 0.037).\(^\text{[46]}\) 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 (298.8 ± 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).\(^\text{[46]}\) 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.\(^\text{[49]}\) 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.\(^\text{[46,50]}\) 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).\(^\text{[51]}\) Since protein S offers neuronal protection during ischemic/hypoxic injury, both in vivo and in vitro,\(^\text{[52]}\) it is plausible that protein S protects neurons from N-methyl-D-aspartate induced toxicity and apoptosis.\(^\text{[53]}\)

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; F = 9%).\(^\text{[45]}\) 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; F = 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.\(^\text{[55–57]}\) 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
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outcomes. The authors asserted 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. 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). 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. 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. 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 dietary reference intakes 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

| Abbreviation | Description |
|--------------|-------------|
| AD           | Alzheimer’s disease |
| AI           | Adequate Intake |
| BF           | percentage body fat |
| CES-D        | Center for Epidemiologic Studies-Depression |
| CHD          | coronary heart disease |
| CLIP         | Cognition and LI POPhilic 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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