

Artículo Original / Original Article

Development of a food frequency questionnaire to determine vitamin K intake in anticoagulated patients: a pilot study

Desarrollo de un cuestionario de frecuencia de consumo para determinar la ingesta de vitamina K en pacientes con tratamiento anticoagulante: un estudio piloto

ABSTRACT

Our aim was to develop a food frequency questionnaire (FFQ) to estimate vitamin K intake in patients receiving warfarin. We conducted a cross-sectional study. The FFQ was designed based on a literature review, and included foods containing $\geq 5 \mu\text{g}/100 \text{ g}$ consumed by the study group. The correlation between the intake of vitamin K estimated by the questionnaire and habitual intake measured by two 24-hour dietary recalls was assessed, as well as correlations between FFQ, International Normalized Ratio (INR) and serum vitamin K levels. The mean intake of vitamin K, estimated by the FFQ, was $112.6 \pm 82.7 \mu\text{g}/\text{day}$, and the habitual dietary intake estimated by 24-hour dietary recalls was $85.1 \pm 75.5 \mu\text{g}/\text{day}$, with a significant correlation between both methods ($r = 0.756$; $p < 0.001$). There was no correlation between FFQ and INR ($r = 0.054$; $p = 0.716$), or between FFQ and serum vitamin K ($r = -0.005$; $p = 0.982$). The strong correlation between vitamin K intake measured by FFQ and habitual dietary intake measured by 24-hour dietary recalls suggests that the FFQ can be used to estimate vitamin K intake.

Keywords: Vitamin K; Surveys and Questionnaires; Eating; Warfarin.

RESUMEN

El objetivo de este trabajo fue desarrollar un cuestionario de frecuencia de consumo (CFC) para estimar la ingesta de vitamina K en pacientes que reciben warfarina. La investigación correspondió a un estudio transversal. El CFC se basó en una revisión de la literatura e incluyó alimentos que contenían $\geq 5 \mu\text{g}/100 \text{ g}$. Se evaluó la correlación entre la ingesta de vitamina K estimada por el CFC y la ingesta habitual medida por dos recordatorios del consumo de las últimas 24 horas (R24). También se evaluó las correlaciones entre CFC, relación normalizada internacional (RNI) y los niveles séricos de vitamina K. La ingesta media de vitamina K, estimada por el CFC, fue de $112.6 \pm 82.7 \mu\text{g}/\text{día}$, y la ingesta dietética habitual estimada por los R24 fue de $85.1 \pm 75.5 \mu\text{g}/\text{día}$, con una correlación significativa entre ambos métodos ($r = 0.756$;

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$p < 0.001$). No hubo correlación entre CFC e RNI ($r = 0.054$; $p = 0.716$), o entre CFC y vitamina K sérica ($r = -0.005$; $p = 0.982$). La fuerte correlación entre la ingesta de vitamina K medida por CFC y los dos R24 sugiere que el CFC puede usarse para estimar el consumo de vitamina K.

Palabras clave: Vitamina K; Encuestas y cuestionarios; Ingestión de alimentos; Warfarina.

INTRODUCTION

Vitamin K is a fat-soluble vitamin, found in green leafy vegetables, herbs, vegetable oils and its predominant

form is vitamin K1 or phylloquinone¹. The vitamin is historically known for its role in biological activation of proteins and factors involved in blood clotting. Oral anticoagulants, including warfarin, act as vitamin K antagonists (VKAs), inhibiting these coagulation factors².

The anticoagulation effect is monitored by the prothrombin time (PT), expressed as International Normalized Ratio (INR)³. Variations in vitamin K intake are an important and independent factor for changes in the INR in patients using oral anticoagulants⁴.

Adequate intake recommendation of vitamin K (Adequate Intake - AI) determined by the National Academy of Sciences is 120 µg/day for men and 90 µg/day for women⁵. Although there is no consensus, patients taking warfarin are encouraged to have a moderate consumption of vitamin K similar to that of adequate intake for adults, in order to prevent adverse events, such as bleeding and thromboembolic episodes⁶. Although the mechanisms of action of warfarin are well known, changes in the INR require dose adjustments of the drug, and hence continuous monitoring of vitamin K⁷.

Food frequency questionnaires (FFQ) are a cost-effective, practical method used to estimate habitual dietary intake, assess nutrients, foods and food group consumption, and classify individuals according to their eating patterns. Although questionnaires have been widely used in epidemiological studies, the FFQ needs to be adapted to and validated in different populations⁸.

Previous studies conducted in the United States of America (USA) have validated FFQs designed to measure dietary vitamin K intake^{9,10}. These tools, however, cannot be applied to the Brazilian population, since habitual intake is influenced by factors including food diversity and different content of vitamin K, which, per se, may vary with growth conditions, soil and climate. Observations such as these have made it necessary to develop a Brazilian dietary assessment tool to estimate vitamin K intake in anticoagulated patients using VKA. Therefore, the present study aimed to develop a FFQ to estimate vitamin K intake in patients receiving warfarin.

MATERIALS AND METHODS

Study population and study sample

Patients seen at the outpatient oral anticoagulation clinics of the Internal Medicine Service of Porto Alegre General Hospital were enrolled in the cross-sectional study. These clinics are administered by fully trained nurses and physicians.

Inclusion criteria were age ≥18 years, attendance at the outpatient anticoagulation clinics of this hospital, stable INR between 2.0 and 3.5 in the previous two visits, cognitive ability to answer the questionnaires, and warfarin therapy for at least 6 months before enrollment. Exclusion criteria included: metabolic

bone diseases, gastrointestinal malabsorption or other diseases that may affect biliary secretion, clinical evidence of bleeding or thrombosis, and use of mineral or vitamin supplements.

Sample size calculation, with 80% power and a level of significance of 5%, yielded a 33 individuals. This sample size would be needed to achieve a correlation coefficient of 0.7 with the minimal acceptable coefficient of 0.4 between the intake of vitamin K estimated by FFQ and that estimated by 24-hour dietary recall^{11,12}.

The sample was selected by convenience between July and September 2015. The study was approved by the Ethics Committee of the Research and Graduate Group of Porto Alegre General Hospital (protocol number 14-0705). The study was conducted according to the Declaration of Helsinki and all participants signed the informed consent form after receiving detailed explanation of the study procedures.

Development of the FFQ

First, a list of food items that could potentially be included in the FFQ was made, based on 24-hour dietary recalls available in previous studies conducted with a similar study population, and on a FFQ for vitamin K previously developed and validated in the USA^{10,13}. Second, a literature review of articles including food composition tables for vitamin K was conducted, to identify and select foods with ≥ 5µg of vitamin K/100g of food, to be included in the final version of the questionnaire^{1,14,15,16,17,18,19,20}. Of these, one study was carried out with food in Brazil¹⁹. The content of vitamin K in each portion of foods included in the questionnaire was calculated by the mean of the vitamin concentrations described in these tables.

Foods that were not commonly consumed by our study group were not included, unless the vitamin K content was higher than 100µg per 100g of food. Foods were categorized into food groups, and household measures were established according to 24 hour dietary recalls previously performed in a similar population¹³.

A pilot study was conducted with 14 subjects aiming to detect other sources of vitamin K or household measures used by the study group. A photo album was used as a visual aid to improve the quality of information provided by participants.

In total, the FFQ included 36 food items, and were categorized into six groups: "vegetables/seasoning", "grain/beans", "fruits", "meat", "oil/fats" and "different preparations". The FFQ is shown in Appendix 1, in which each item includes 0 to 10 grades of frequency of food intake per day, week or month. Subjects were asked to select a grade of frequency in the last 1 month.

Portion size were divided into small, medium and large for each food item. For each portion size the homemade measure was given with the amount in grams described.

Assessment of dietary intake using 24-hour dietary recall

Two 24-hour dietary recalls were administered to assess the intra-subject variability of vitamin K intake. The first was conducted along with the FFQ, and the second one 30 days later. The interviews were conducted by a dietitian qualified with respect to personal presentation and conduct toward the interviewee.

Participants were asked to recall the foods and beverages they consumed in the twenty-four hours prior to the interview, starting from the first meal of the day. The dietitian registered the amount consumed in household measures, the preparation of each item, the time they consumed the food, as well as the brand and characteristics of processed foods. The content of vitamin K per 100g of food was calculated based on the same food composition tables used in the development of the FFQ.

Study protocol

In the first meeting, participants answered the FFQ and the first 24-hour dietary recall. A data collection instrument for characterization of the study group, including body weight and height was also administered. Blood samples were collected for serum vitamin K and PT determination.

International normalized ratio (INR), prothrombin time and serum vitamin K

Monitoring of oral anticoagulation was performed by using the INR, calculated from the PT. Five mL of venous blood was collected into tubes prefilled with 3.2% sodium citrate. Total blood was centrifuged for 15 minutes, and the plasma was used for PT determination. The test was performed at the Laboratory of Hematology of Porto Alegre General Hospital, and results were obtained from patients' electronic medical records.

For determination of serum vitamin K, 5 mL of venous blood was collected for each test. Serum samples were collected following centrifugation, and stored in duplicate at -80°C at the Laboratory of Cardiovascular Research of the Experimental Research Center of Porto Alegre General Hospital. The vitamin concentrations were determined by high performance liquid chromatography (HPLC) with fluorescence detection. All measurements were performed at once, on the same day when the FFQ was administered.

Statistical analysis

Categorical variables were expressed as absolute frequency and percentage. The assumption of normality was examined for all evaluated variables by Shapiro-Wilk test. Continuous variables with symmetrical distribution were expressed as mean and standard deviation and continuous variables with asymmetric distribution are expressed as median and interquartile range. Nutrient intake was estimated from the ratio of the frequency to the

portion consumed. Correlations between FFQ, 24-hour dietary recall and blood measurements were assessed by Spearman rank correlation coefficients, and corrected by intra-subject variability. Habitual vitamin K intake was estimated by the Multiple Source Method, corrected by intra-subject variability. The other analyses were performed by the SPSS (Statistical Package for the Social Science) software, version 18.0. A p-value <0.05 was considered statistically significant.

RESULTS

From a total of 864 electronic medical records screened, 303 patients were considered eligible for the study. After considering the exclusion criteria and absence of consent to enter the study, 48 patients were included in the study. The sample was composed of 22 women and 26 men, aged 61.1 ± 13.8 years, with mean body mass index (BMI) of 29.2 ± 5.1 kg/m². The main cause of anticoagulation was atrial fibrillation (42%) (Table 1).

For the second 24-hour dietary recall, 5 patients could not be contacted using the telephone number provided in the first meeting. These patients were included in the analyses, but only the 24-hour dietary recall was used to estimate their habitual intake. The mean period between the first and the second interview was 51 days.

Thirty-six food items were included in the FFQ, and categorized into six groups: "vegetables/seasoning", "grains/beans", "fruits", "meat", "oils/fats" and "different preparations".

The mean vitamin K intake measured by FFQ and 24-hour dietary recall was 112.55 ± 82.66 µg/day and 85.13 ± 75.46 µg/day, respectively. The median intake of vitamin K measured by FFQ and 24-hour dietary recall was 89.13 ($53.39 - 168.81$) µg/day and 68.45 ($36.21 - 117.49$) µg/day, respectively. Both had an asymmetric distribution. Associations between FFQ, 24-hour dietary recall and blood measurements, assessed by Spearman rank correlation coefficients, are summarized in Table 2.

There was a strong correlation between FFQ and 24-hour dietary recall ($r = 0.756$, $p < 0.001$) (Figure 1). No correlation between the intake of vitamin K measured by FFQ and INR ($r = 0.054$, $p = 0.716$) was observed.

There was also no significant correlation between serum vitamin K levels and vitamin K intake measured either by FFQ ($r = -0.005$, $p = 0.982$) or the first 24-hour dietary recall ($r = 0.255$, $p = 0.278$). Serum vitamin K was measured in a consecutive sample of 20 patients (41.6%) of total sample, with mean values (0.67 ng/mL \pm 0.48 ng/mL) within the normal range (0.09 ng/mL - 2.22 ng/mL)²¹.

Food items that most contributed to vitamin K intake showed a moderate but significant correlation with the mean intake estimated by the FFQ. These foods were: watercress ($r = 0.45$), lettuce ($r = 0.53$), scallion ($r = 0.34$), sautéed cabbage ($r = 0.32$), arugula ($r = 0.52$), potato salad ($r = 0.44$), parsley ($r = 0.45$), green beans ($r = 0.37$), kale ($r = 0.34$), cauliflower ($r = 0.31$).

Table 1. Sociodemographic and clinical characteristics of the sample.

Variables	Total (n= 48)
Age (years)	61.1± 13.8 (25 – 93)
Sex (male)	26 (54%)
Ethnic group	
White	42 (88%)
Not-white	6 (12%)
Educational level	
Illiterate	2 (4%)
Primary education, incomplete	20 (42%)
Primary education, complete	14 (28%)
Secondary education, incomplete	6 (13%)
Secondary education, complete	6 (13%)
Body mass index (kg/m ²)	29. 2 ± 5.1 (19.39 – 42.84)
Smoking	6 (13%)
Alcohol consumption	1 (2%)
Duration of anticoagulant therapy (years)	3.65 (1.72 – 7.97)
Cause of anticoagulation	
Atrial fibrillation	20 (42%)
Cardiac prosthesis	16 (33%)
Others	12 (25%)

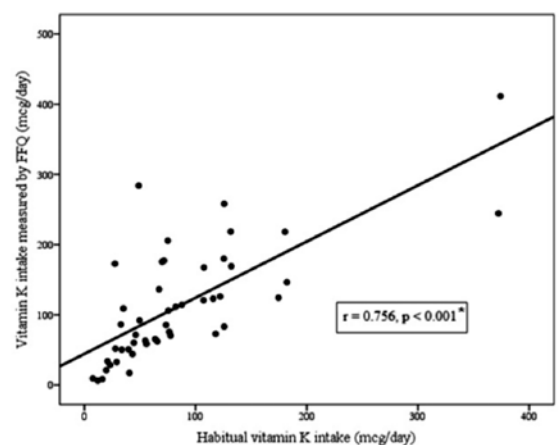
Data presented in number of patients with the analyzed characteristic (%), mean ± standard deviation (minimum - maximum) or median (interquartile range).

Table 2. Spearman correlation coefficients between vitamin K intake measured by food frequency questionnaire and other quantitative variables.

Variables	FFQ	p-value*
24-hour dietary recall (n=48)		
Correlation coefficient (r)	0.756	0,000
Serum vitamin K (n=20)		
Correlation coefficient (r)	- 0.005	0.982
INR (n=48)		
Correlation coefficient (r)	0.054	0.716

* p< 0.05 for all. Spearman correlation.

INR: International Normalized Ratio; FFQ: Food frequency questionnaire.

**Figure 1.** Spearman rank correlation between vitamin K intake measured by food frequency questionnaire (FFQ) and by 24-hour dietary recall.

* Spearman correlation.

DISCUSSION

This is the first Brazilian study to develop a FFQ to estimate the intake of vitamin K in anticoagulated patients. There was a strong, significant correlation ($r = 0.756$) between the FFQ and a 24-hour dietary recall, suggesting that the FFQ is a valid instrument to assess the intake of this vitamin in patients receiving warfarin.

The recommended adequate intake of vitamin K for adults is 120 $\mu\text{g}/\text{day}$ for men and 90 $\mu\text{g}/\text{day}$ for women⁵. In our study, habitual intake of vitamin K was slightly lower than these recommendations, whereas the intake estimated by the FFQ was closer to these values.

In Brazil, few studies have evaluated the usual intake of vitamin K. A study with healthy Brazilian adult subjects showed that regardless of gender or age, vitamin K intake was below the recommended adequate intake. The population had an average consumption of $110.7 \pm 55.8 \mu\text{g}/\text{day}$ ²².

Additionally, the current study FFQ estimates were lower than those reported in previous studies conducted in other countries^{9,10,23}. In a study by Couris et al (2000), subjects taking warfarin had a mean vitamin K intake of $138 \pm 15.7 \mu\text{g}/\text{day}$, which is higher than the recommended adequate intake¹⁰. This suggests that regardless of the use of warfarin, Brazilians tend to have insufficient vitamin K intake.

In general, a correlation coefficient of 0.4 - 0.7 is considered acceptable for a FFQ in relation to another dietary assessment method^{11,12}. In the present study, the correlation coefficient was 0.75, which was higher than the results of two previous studies on validations of FFQs ($r = 0.54$ and $r = 0.67$)^{22,24}. These studies evaluated not only vitamin K intake, but other nutrients involved in bone health.

Several studies have compared dietary data obtained from FFQs with those obtained from food records and 24-hour dietary recalls¹². Carrol et al (1997) demonstrated that two repeated measures were necessary to obtain appropriate coefficient correlations between dietary assessment methods²⁵.

Presse et al (2009) developed and validated a FFQ designed to measure vitamin K in 39 elderly subjects, and obtained a high correlation ($r = 0.83$) between this method and food records. Their results indicated that intake of vitamin K estimated by FFQ (222 $\mu\text{g}/\text{day}$) was higher than that obtained by the other method (135 $\mu\text{g}/\text{day}$)⁹, which is similar to what we observed in the present study, as we compared FFQ with 24-hour dietary recall. This would suggest a lack of accuracy of food records and 24-hour dietary recalls in assessing the intake of a specific nutrient, such as vitamin K, found in a limited number of foods commonly consumed by the general population⁹.

A self-assessment instrument, named K-Card, was developed and validated in a study conducted in the USA to determine daily intake of vitamin K and weekly variation in the intake for patients receiving anticoagulant therapy. The sample size was 36 subjects, and the correlation coefficients in the same subject at three different moments ($r = 0.995$, $r = 0.998$ and $r = 0.989$) showed a strong correlation with food records. The accuracy of K-Card results, in part, from the

inclusion of food items containing $\geq 5 \mu\text{g}$ of vitamin K per portion¹⁰. In our study, we used this same cut-off point to select the items to be included in the FFQ.

Although the INR is not a biomarker, it is the laboratory test of choice for monitoring the anticoagulation therapy of patients treated with oral anticoagulants, including warfarin³. Vitamin K intake is an independent factor that affects the stability of the anticoagulant effect⁴.

In the present study, we did not find a correlation between INR values and the vitamin intake estimated by the FFQ. It is worth mentioning that only patients with stable anticoagulation and receiving warfarin therapy for at least 6 months were enrolled in our study, which prevented a more accurate assessment of the effect of vitamin K intake on INR.

K-Card, which was previously mentioned, was used in a prospective study, and showed that a weekly change of 714 μg in vitamin K intake caused a significant increase by 1 unit in INR ($p < 0.01$)²⁶. The mean intake of the nutrient by our study group was much lower than this value, which may have contributed for the lack of correlation between INR and vitamin K intake.

It is well known that plasma phylloquinone levels depend on vitamin K intake in the last 24 hours and, for this reason, do not correlate well with nutritional status of vitamin K²⁷. This may partly explain the lack of correlation between the vitamin K intake estimated by the FFQ and serum vitamin K concentrations, since the questionnaire assessed dietary intake retrospectively over the last month, rather than the last 24 hours. Analysis of the first 24 dietary recall revealed that serum vitamin K levels tended to correlate with vitamin K intake ($r = 0.255$, $p = 0.278$). However, the literature recommends the assessment of dietary intake in the least four days. Booth et al (1995; 1997) demonstrated that a better correlation between these variables is achieved when multiple measurements of plasma phylloquinone and assessments of dietary intake are performed^{28,29}.

The study has some limitations that should be considered. First, serum vitamin K concentrations were measured in only 20 subjects (41.6% of the sample), which is different from previous studies in which larger samples of participants were included^{28,29}. Generally, the methods that evaluate dietary intake have some limitations, since the individual may have difficulty in estimating portions. Also, the consumption reporting can be altered because the participant knows that they are being evaluated, there was a variability of intake between subjects and the fact that reporting relies on the memory of the individual interviewed to recall past eating habits^{11,30}. However, QFA is a practical, cost-effective method that is used to estimate habitual dietary intake⁸. Another limitation is related to the scarcity of data on the content of vitamin K in foods produced in Brazil. Of the 36 items included in the FFQ, only 12 have been analyzed previously in a Brazilian study that determined the vitamin K content in foods consumed in the country¹⁹.

In conclusion, we found a strong correlation between vitamin K intake measured by FFQ and habitual dietary

intake measured by 24-hour dietary recalls. This finding suggests that the FFQ can be used to estimate vitamin K intake in anticoagulated patients receiving warfarin.

Variations in the intake of vitamin K may negatively affect the stability of anticoagulant therapy. In this context, the FFQ developed in this study can be useful in determining daily or weekly intake associated with anticoagulation stability. In addition to being easy-to-handle and quick to perform, this FFQ, specifically designed to measure the intake of vitamin K in anticoagulated patients, can be used in educational programs for this population.

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REFERENCES

- Bolton-Smith C, Price RJ, Fenton ST, Harrington DJ, Shearer MJ. Compilation of a provisional UK database for the phyloquinone (vitamin K1) content of foods. *Br J Nutr* 2000; 83: 389-399.
- Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K Antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 160S-198S.
- Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e152S-184S.
- Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *Am J Med* 2004; 116: 651-656.
- Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington (DC): National Academies Press (US). 2001. <http://www.nap.edu/openbook.php?isbn=0309072794>.
- Li RC, Finkelman BS, Chen J, Booth SL, Bershaw L, Brensinger C, et al. Dietary vitamin K intake and anticoagulation control during the initiation phase of warfarin therapy: a prospective cohort study. *Thromb Haemost*. 2013; 110: 195-196.
- Harshman SG, Saltzman E, Booth SL. Vitamin k: dietary intake and requirements in different clinical conditions. *Curr Opin Clin Nutr Metab Care* 2014; 17: 531-538.
- Willett WC. Future directions in the development of food-frequency questionnaires. *Am J Clin Nutr* 1994; 59: 171S-174S.
- Presse N, Shatenstein B, Kergoat MJ, Ferland G. Validation of semi-quantitative food frequency questionnaire measuring dietary vitamin k intake in elderly people. *J Am Diet Assoc* 2009; 109: 1251-1255.
- Couris RR, Tataronis GR, Booth SL, Dallal GE, Blumberg JB, Dwyer JT. Development of a self-assessment instrument to determine daily intake and variability of dietary vitamin k. *J Am Coll Nutr* 2000; 19: 801-807.
- Willett WC. *Nutritional Epidemiology*. Oxford University Press, New York, 1998.
- Cade J, Thompson R, Burley V, Warm D. Development validation and utilization of food frequency questionnaires—a review. *Public Health Nutr* 2002; 5: 567-587.
- Zuchinali P, Souza GC, Aliti G, Botton MR, Goldraich L, Santos KG, et al. Influence of VKORC1 gene polymorphisms on the effect of oral vitamin K supplementation in over-anticoagulated patients. *J Thromb Thrombolysis* 2014; 37: 338-344.
- Booth SL, Sadowski JA, Weihrauch JL, Ferland G. Vitamin K1 (Phylloquinone) Content of Foods: A Provisional Table. *J Food Compos Anal* 1993; 6: 109-120.
- Booth SL, Sadowski JA, Pennington JAT. Phylloquinone (Vitamin K1) Content of Foods in the U.S. Food and Drug Administration's Total Diet Study. *J Agric Food Chem* 1995; 43: 1574-1579.
- Damon M, Zhang NZ, Haytowitz DB, Booth SL. Phylloquinone (vitamin k1) content of vegetables. *J Food Compos Anal* 2005; 18: 751-758.
- Dismore ML, Haytowitz DB, Gebhardt SE, Peterson JW, Booth SL. Vitamin K content of nuts and fruits in the US diet. *J Am Diet Assoc* 2003; 103: 1650-1652.
- Elder SJ, Haytowitz DB, Howe J, Peterson JW, Booth SL. Vitamin k contents of meat, dairy, and fast food in the u.s. Diet. *J Agric Food Chem* 2006; 54: 463-467.
- Faria SASC, Arruda VAS de, Araújo ES, Penteado MVC. Vitamin K: content in food consumed in São Paulo, Brazil. *Braz J Pharm Sci* 2017; 53: 1-8.
- Shearer MJ, Bach A, Kohlmeier M. Chemistry, nutritional sources, tissue distribution and metabolism of vitamin K with special reference to bone health. *J Nutr* 1996; 126: 1181S-1186S.
- Olson RE. Vitamin K. In: *Modern nutrition in health and disease* (Shils ME, Olson JA, Shike M, Ross AC, eds) 9th. Baltimore: Williams & Wilkins, 1999.
- Souza WN, Rodrigues ML, Penteado MVC. Habitual adult and elderly intake of vitamin K. *Rev Nutr* 2012; 25: 507-515.
- Pritchard JM, Seechurn T, Atkinson SA. A food frequency questionnaire for the assessment of calcium, vitamin D and vitamin K: a pilot validation study. *Nutrients* 2010; 2: 805-819.
- Uenishi K, Ishida H, Nakamura K. Development of a simple food frequency questionnaire to estimate intakes of calcium and other nutrients for the prevention and management of osteoporosis. *J Nutr Sci Vitaminol* 2008; 54: 25-29.
- Carroll RJ, Pee D, Freedman LS, Brown CC. Statistical design of calibration studies. *Am J Clin Nutr* 1997; 65: 1187S-1189S.
- Couris R, Tataronis G, McCloskey W, Oertel L, Dallal G, Dwyer J, et al. Dietary vitamin K variability affects International Normalized Ratio (INR) coagulation indices. *Int J Vitam Nutr Res* 2006; 76: 65-74.
- Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. *J Nutr* 1998; 128: 785-788.
- Booth SL, Sokoll LJ, O'Brien ME, Tucker K, Dawson-Hughes B, Sadowski JA. Assessment of dietary phyloquinone intake and vitamin K status in postmenopausal women. *Eur J Clin Nutr* 1995; 49: 832-841.
- Booth SL, Tucker KL, McKeown NM, Davidson KW, Dallal GE, Sadowski JA. Relationships between dietary intakes and fasting plasma concentrations of fat-soluble vitamins in humans. *J Nutr* 1999; 127: 587-592.
- Kac G, Sichieri R, Gigante DP. *Epidemiologia Nutricional*. Fiocruz e Atheneu, Rio de Janeiro, 2007.

Appendix 1
Food frequency questionnaire for vitamin K

Food	Vitamin k (µg/100g)	How often do you eat?	Unit of time¹	Average portion size (g/ml)	Your portion²
VEGETABLES/SPICES					
Watercress		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 medium branch (5 g) 1 saucer (10 g) 1 dessert plate (25 g)	S M L ○ ○ ○
284.69 µg/100g					
Lettuce		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 medium leaf (10 g) 3 medium leaves (30 g) 5 medium leaves (50 g)	S M L ○ ○ ○
123.89 µg/100g					
Broccoli		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 small branch (30 g) 1 medium branch (60 g) 1 larger branch (90 g)	S M L ○ ○ ○
165.99 µg/100g					
Carrot (cooked)		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 dessert spoon (15 g) 1 tablespoon (30 g) 1 serving spoon (40 g)	S M L ○ ○ ○
15.56 µg/100g					
Carrot (raw)		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 tablespoon (15 g) 2 tablespoons (30 g) 1 serving spoon (35 g)	S M L ○ ○ ○
6.2 µg/100g					
Endive (raw)		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 medium leaf (12 g) 3 medium leaves (36 g) 5 medium leaves (60 g)	S M L ○ ○ ○
168.36 µg/100g					
Endive (cooked)		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 dessert spoon (20 g) 1 tablespoon (30 g) 1 serving spoon (50 g)	S M L ○ ○ ○
184.09 µg/100g					
Brussels sprouts		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 unit (16 g) 3 units (50 g) 5 units (80 g)	S M L ○ ○ ○
196 µg/100g					
Kale		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 dessert spoon (10 g) 1 tablespoon (20 g) 1 serving spoon (42 g)	S M L ○ ○ ○
341.35 µg/100g					
Cauliflower		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 small branch (30 g) 1 medium branch (60 g) 1 larger branch (85 g)	S M L ○ ○ ○
26.32 µg/100g					
Spinach		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 tablespoon (25 g) 2 tablespoons (50 g) 3 tablespoons (75 g)	S M L ○ ○ ○
434.53 µg/100g					
Mustard greens		0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 dessert spoon (20 g) 1 tablespoon (45 g) 1 serving spoon (75 g)	S M L ○ ○ ○
129 µg/100g					

Food	Vitamin k (µg/100g)	How often do you eat?	Unit of time¹	Average portion size (g/ml)	Your portion
Cabbage (raw)		0 1 2 3 4 5 6 7 8 9 10	D W M	1 tablespoon (10 g)	S M L
	256.87 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	2 tablespoons (20 g)	○ ○ ○
				1 serving spoon (25 g)	
Sautéed cabbage		0 1 2 3 4 5 6 7 8 9 10	D W M	1 tablespoon (20 g)	S M L
	162.36 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	2 tablespoons (40 g)	○ ○ ○
				1 serving spoon (45 g)	
Arugula		0 1 2 3 4 5 6 7 8 9 10	D W M	1 medium branch (5 g)	S M L
	259.11 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	1 saucer (10 g)	○ ○ ○
				1 dessert plate (25 g)	
Canned cabbage		0 1 2 3 4 5 6 7 8 9 10	D W M	1 dessert spoon (12 g)	S M L
Salad	19 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	1 tablespoon (20 g)	○ ○ ○
				1 serving spoon (45 g)	
Parsley		0 1 2 3 4 5 6 7 8 9 10	D W M	1table spoon (3 g)	S M L
	531.76 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	2 tablespoons (6 g)	○ ○ ○
Scallion		0 1 2 3 4 5 6 7 8 9 10	D W M	1 teaspoon (2 g)	S M L
	176.06 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	1 dessert spoon (3 g)	○ ○ ○
				1 tablespoon (5 g)	
Green beans		0 1 2 3 4 5 6 7 8 9 10	D W M	1 dessert spoon (15 g)	S M L
	16 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	1 tablespoon (22 g)	○ ○ ○
				1 serving spoon (50 g)	
GRAINS/BEANS					
Oats		0 1 2 3 4 5 6 7 8 9 10	D W M	1 tablespoon (12 g)	S M L
	10 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	2 tablespoons (24 g)	○ ○ ○
				3 tablespoons (36 g)	
Peas		0 1 2 3 4 5 6 7 8 9 10	D W M	1 dessert spoon (16 g)	S M L
	23.5 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	1 tablespoon (30 g)	○ ○ ○
				1 serving spoon (60 g)	
Beans		0 1 2 3 4 5 6 7 8 9 10	D W M	1 small ladle of bean (40 g)	S M L
	8.4 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	2 small ladles of bean (80 g)	○ ○ ○
				1 large ladle of bean (140 g)	
FRUITS					
Avocado		0 1 2 3 4 5 6 7 8 9 10	D W M	½ medium unit (200 g)	S M L
	25 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	1 medium unit (400 g)	○ ○ ○
				½ large unit (500 g)	
Red plum		0 1 2 3 4 5 6 7 8 9 10	D W M	1 small unit (108 g)	S M L
	8.4 µg/100g	○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	○ ○ ○	1 medium unit (147 g)	○ ○ ○
				1 large unit (201 g)	

Food Vitamin k ($\mu\text{g}/100\text{g}$)	How often do you eat?	Unit of time ¹	Average portion size (g/ml)	Your portion
Grape 10.25 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 small bunch (100 g) 1 medium bunch (170 g) 1 large bunch (270 g)	S M L ○ ○ ○
MEAT				
Hamburger (steak) 5.9 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	½ unit (28 g) 1 unit (56 g) 2 units (112 g)	S M L ○ ○ ○
OILS/FATS				
Butter with salt 7.1 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 teaspoon (8 g) 1 dessert spoon (23 g) 1 tablespoon (32 g)	S M L ○ ○ ○
Margarine with salt 42.33 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 teaspoon (8 g) 1 dessert spoon (23 g) 1 tablespoon (32 g)	S M L ○ ○ ○
Mayonnaise 55.1 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 teaspoon (6 g) 1 dessert spoon (17 g) 1 tablespoon (27 g)	S M L ○ ○ ○
MIXED PREPARATIONS				
Cake/Bread of corn 7.4 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 small slice (30 g) 1 medium slice (60 g) 1 large slice (100 g)	S M L ○ ○ ○
Meat lasagna 5.3 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 small piece (120 g) 1 medium piece (190 g) 1 large piece (250 g)	S M L ○ ○ ○
Pasta with Bolognese sauce 5.7 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 serving spoon (50 g) 2 serving spoons (110 g) 4 serving spoons (220 g)	S M L ○ ○ ○
Fried egg 6.9 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 unit (50 g) 2 units (100 g) 3 units (150 g)	S M L ○ ○ ○
Mashed potatoes 5.1 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 tablespoon (45 g) 1 serving spoon (80 g) 2 serving spoons (160 g)	S M L ○ ○ ○
Potato salad 11.02 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 tablespoon (50 g) 2 tablespoons (100 g) 2 serving spoons (200 g)	S M L ○ ○ ○
Salty snacks 12.5 $\mu\text{g}/100\text{g}$	0 1 2 3 4 5 6 7 8 9 10 ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○	D W M ○ ○ ○	1 unit (20 g) 5 units. (100 g) 10 units (200 g)	S M L ○ ○ ○
¹ D: daily, W: weekly, M: monthly. ² S: small, M: medium, L: large.				