Phylloquinone intake, insulin sensitivity, and glycemic status in men and women

Makiko Yoshida, Sarah L Booth, James B Meigs, Edward Saltzman, and Paul F Jacques

ABSTRACT
Background: Limited evidence suggests that vitamin K may have a beneficial role in glucose homeostasis. No observational data exist on the associations between vitamin K intake and insulin sensitivity.

Objective: We aimed to examine associations between vitamin K intake and measures of insulin sensitivity and glycemic status in men and women aged 26–81 y.

Design: We assessed the cross-sectional associations of self-reported phylloquinone (vitamin K$_1$) intake with insulin sensitivity and glycemic status in the Framingham Offspring Cohort. Dietary and supplemental phylloquinone intakes were assessed by using a food-frequency questionnaire. Insulin sensitivity was measured by fasting and 2-h post-prandial glucose-tolerance test (OGTT) insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), and the insulin sensitivity index (ISI$_{0,120}$). Glycemic status was assessed by fasting and 2-h post-OGTT glucose and glycated hemoglobin (HbA$_{1c}$).

Results: Higher phylloquinone intake was associated with greater insulin sensitivity and glycemic status, as measured by 2-h post-OGTT insulin and glucose and ISI$_{0,120}$ after adjustment for age, sex, waist circumference, lifestyle characteristics, and diet quality [2-h post-OGTT insulin: lowest and highest quintile, 81.0 and 72.7 μU/mL, respectively (P for trend = 0.003); 2-h post-OGTT glucose: 106.3 and 101.9 mg/dL, respectively (P for trend = 0.009); ISI$_{0,120}$: 26.3 and 27.3 mg·L$^{-2}$·mmol·mU·min (P for trend = 0.009)]. Phylloquinone intake was not associated with fasting insulin and glucose concentrations, HOMA-IR, or HbA$_{1c}$.

Conclusion: Our findings support a potential beneficial role for phylloquinone in glucose homeostasis in men and women.

SUBJECTS AND METHODS

Subjects

The Framingham Offspring Study (FOS) is a longitudinal, community-based study of cardiovascular disease in the children of the participants in the original Framingham Heart Study cohort and their spouses (6). In 1971, 5135 participants were enrolled into the FOS (7). During examination cycle 5 (1991–1995), 3799 participants underwent an extensive examination, including

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comprehensive questionnaires, anthropometric measures, blood chemistries, and a physical examination by trained clinical personnel, with assessment of cardiovascular and other risk factors. Of the 3799 participants, 1080 were excluded from the current analyses for following reasons: invalid dietary information (n = 381), missing data on fasting insulin or glucose measures (n = 143), presence of diabetes (n = 324), use of anticoagulant including the vitamin K antagonist warfarin (n = 21), and missing information on major covariates (n = 211). The final sample size was 2719 (1247 men and 1472 women).

All of the participants in the FOS provided written informed consent. The institutional review boards for human research at Boston University and the Tufts Medical Center approved this study.

Phyloquinone intake assessment

Usual dietary intakes for previous 12 mo were assessed by using a semiquantitative food-frequency questionnaire (FFQ), as described elsewhere (8). This FFQ was validated for various nutrients and foods (8, 9), including phyloquinone (10, 11). A significant correlation was observed between the phyloquinone intake calculated from this FFQ and that from three 4-d diet records (r = 0.53) (10). A biomarker-based validation study has shown plasma that phyloquinone concentrations increased approximately twofold in a linear fashion across phyloquinone intakes between 50 and 250 μg/d, as assessed by the FFQ (11).

The questionnaire was mailed to participants before their study examination, and the participants were asked to bring the completed questionnaire with them to their appointment. The FFQ consisted of a list of foods with a standard serving size and a selection of 9 frequency categories ranging from never or <1 serving/mo to >6 servings/d. Phyloquinone intake was calculated by multiplying the frequency of consumption of each unit of food from the FFQ by the phyloquinone contents of the specific portion. Separate questions about the use of vitamin and mineral supplements were also included in the FFQ. Phyloquinone intakes reported here included intakes both from diets and supplements. Data from the FFQ were considered reliable if reported total energy intakes were ≥600 kcal/d (2.51 MJ/d) for men and women but <4200 kcal/d (17.54 MJ/d) for men or <4000 kcal/d (16.74 MJ/d) for women, and if fewer than 13 items were left blank.

Insulin sensitivity measures

Fasting blood samples (≥8 h) were collected at each examination cycle. Plasma and serum samples were stored at −70 °C. Plasma insulin concentrations were measured by using the Coat-A-Count 125I-radioimmunoassay (Diagnostic Products, Los Angeles, CA). This assay has cross-reactivity with proinsulin at the midcurve of 40%, intra-assay and interassay CVs of 5% to 10%, and a lower limit of sensitivity of 1.1 μU/mL (7.9 pmol/L). Plasma glucose concentrations were measured with a hexokinase regent kit (A-gent glucose test; Abbott Laboratories Inc, South Pasadena, CA). Glucose assays were performed in duplicate, and the CVs for this assay were <3%. The 75-g OGTT was administered, and the 2-h post-OGTT plasma insulin and glucose concentrations were measured. HbA1c was measured by using HPLC after an overnight dialysis against normal saline to remove the labile fraction. The interassay and intra-assay CVs were <2.5%. The assay was standardized against the HbA1c assay used in the Diabetes Control and Complication Trial (12).

We calculated 2 indexes of insulin sensitivity, HOMA-IR (13) and ISI0,120 (14). HOMA-IR is a surrogate measure of insulin sensitivity at basal state, and it tends to represent hepatic insulin sensitivity, whereas ISI0,120 reflects peripheral insulin resistance, glucose disposal, and β-cell response to an energy load (15). The HOMA-IR was calculated by using the following formula (13):

\[
\text{HOMA-IR} = \left( \frac{\text{fasting plasma insulin}}{\text{fasting plasma glucose}} \right) \times 22.5
\]

The ISI0,120 was calculated by using the following formula (14):

\[
\text{ISI0,120} = \frac{m}{\text{MPG}} / \log \text{MSI}
\]

where

\[
m = \left[ 75 000 \text{ mg} + (\text{fasting plasma glucose} - 2 - \text{h post-OGTT plasma glucose}) \times 0.19 \right] \times \text{body wt (kg)} / 120 \text{ min}
\]

\[
\text{MPG} = \frac{\text{fasting plasma glucose (mg/dL)}}{\text{2-h post-OGTT plasma glucose (mg/dL)}} / 2
\]

and

\[
\text{MSI} = \frac{\text{fasting serum insulin (μU/L)}}{\text{2-h post-OGTT serum insulin (μU/L)}} / 2
\]

where MPG = mean plasma glucose, and MSI = mean serum insulin.

Covariate information

Covariates used in these analyses were included because they were either determinants of insulin resistance and glycemic status, markers of a healthy (or unhealthy) lifestyle or diet quality, or other components of phyloquinone-containing foods. Covariates included age; sex; waist circumference; physical activity; cigarette smoking; alcohol consumption; estrogen use; multivitamin supplementation use; intakes of total energy, total fiber, potassium, saturated fatty acids, and n–3 fatty acids; and diet quality. Waist circumference was assessed at the level of the umbilicus while the participant was standing. Physical activity was determined as a metabolic equivalent–based score from a validated questionnaire of self-reported 24-h history of activity (16). We characterized cigarette smoking status as regularly smoking cigarettes in the past year (yes or no), and multivitamin supplementation use as current use at the time of the examination (yes or no), and estrogen use as reported current use of oral conjugated estrogen at the time of the examination (yes or no). Intakes of total energy (kcal/d), alcohol (g/d), total fiber (g/d), potassium (mg/d), saturated fatty acids (g/d), and n–3 fatty acids (g/d) were assessed by using the semiquantitative FFQ (8). Overall diet quality was measured by using the 2005 Dietary Guidelines for Americans Adherence Index (DGAI), as described elsewhere (17).

Statistical analysis

We used SAS statistical software (version 9; SAS institute, Cary, NC) for all statistical analyses. Statistical significance was
defined as \( P < 0.05 \). Normality of insulin sensitivity and glycemic status measures was tested. Because insulin concentrations and HOMA-IR were skewed to the right, we analyzed these variables with the natural logarithm transformation. Phylloquinone intake was categorized on the basis of quintiles of participants' intake levels. HbA1c was categorized into 2 groups (\(< 6.5%\) and \(\geq 6.5%\)) to capture participants with long-term hyperglycemia.

To describe subject characteristics across phylloquinone intake, analysis of covariance (ANCOVA) was performed. Age- and sex-adjusted means or percentages (95% CI) are presented.

To assess the association of phylloquinone intake with insulin sensitivity and glycemic status measures, we applied ANCOVA and logistic regression for continuous and dichotomous markers of insulin sensitivity and glycemic status, respectively. Phylloquinone intake is a potential surrogate marker for a healthy lifestyle and dietary pattern (18), which may relate to greater insulin sensitivity and improved glycemic status. As a result, lifestyle and diet quality potentially confound the association. Therefore, lifestyle characteristics were adjusted in model 1, and both lifestyle and dietary factors were controlled in model 2. Model 1 included age, sex, waist circumference, physical activity, cigarette smoking, alcohol consumption, estrogen use, and multivitamin supplementation use. Model 2 adjusted for total energy intake and diet quality measured by the DGAI in addition to covariates used in model 1. In addition, further adjustment for total fiber, saturated fatty acid, n-3 fatty acid, or potassium intake was performed. In all models, tests for trend by quintile category of phylloquinone intake were performed by assigning median values of phylloquinone intake for each quintile category and treating them as continuous variables. Because the Dietary Guideline Adherence Index score was calculated on the basis of age- and sex-specific criteria, \( P \) for trend was not adjusted for age and sex.

A higher phylloquinone intake was associated with indexes of insulin sensitivity after adjustment for age, sex, waist circumference, and lifestyle characteristics (Table 2). The associations of phylloquinone intake with fasting insulin concentrations and HOMA-IR became nonsignificant after adjustment for total energy and diet quality, as assessed by the DGAI. However, these associations remained significant when diet quality was adjusted by a healthy-choice subscore, a subcomponent of DGAI that does not include a dark green vegetable intake component (fasting insulin: \( P \) for trend = 0.01; HOMA-IR: \( P \) for trend = 0.01). In contrast, the associations of phylloquinone intake with 2-h postOGTT insulin and \( \text{ISI}_{0,120} \) remained significant with additional adjustment for total energy intake and DGAI. A higher phylloquinone intake was associated with lower 2-h post-OGTT glucose in the fully adjusted model. Further adjustment for other dietary factors, including total fiber, saturated fatty acid, n-3 fatty acids (EPA and DHA), and potassium, did not affect associations of phylloquinone with 2-h post-OGTT insulin and glucose or \( \text{ISI}_{0,120} \) (data not shown). There was no association between phylloquinone intake and fasting glucose concentrations or HbA1c.

Energy-adjusted phylloquinone intakes based on regression residuals provided the same results (data not shown).

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**TABLE 1**
Characteristics of men and women in the Framingham Offspring Cohort by quintile (Q) of phylloquinone intake

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Q1 (n = 543)</th>
<th>Q2 (n = 544)</th>
<th>Q3 (n = 544)</th>
<th>Q4 (n = 544)</th>
<th>Q5 (n = 544)</th>
<th>( P ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53.3 (52.5, 54.2)</td>
<td>54.2 (53.3, 55.0)</td>
<td>53.8 (53.0, 54.6)</td>
<td>54.6 (53.8, 55.4)</td>
<td>54.0 (53.2, 54.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Female (%)</td>
<td>42 (38, 47)</td>
<td>49 (45, 53)</td>
<td>52 (48, 56)</td>
<td>61 (57, 66)</td>
<td>66 (62, 70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.7 (91.6, 93.7)</td>
<td>92.4 (91.3, 93.4)</td>
<td>92.2 (91.2, 93.2)</td>
<td>92.4 (91.4, 93.5)</td>
<td>90.9 (89.8, 91.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (26.9, 27.6)</td>
<td>27.1 (26.8, 27.5)</td>
<td>27.1 (26.7, 27.5)</td>
<td>27.2 (26.8, 27.6)</td>
<td>26.9 (26.5, 27.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Physical activity score (MET-h/d)</td>
<td>34.6 (34.1, 35.1)</td>
<td>34.5 (34.0, 35.0)</td>
<td>35.0 (34.5, 35.5)</td>
<td>35.2 (34.7, 35.7)</td>
<td>35.2 (34.7, 35.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>27 (24, 31)</td>
<td>31 (28, 34)</td>
<td>35 (32, 38)</td>
<td>40 (37, 43)</td>
<td>45 (42, 49)</td>
<td>0.05</td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>10.5 (9.1, 11.8)</td>
<td>10.2 (8.8, 11.5)</td>
<td>11.1 (9.8, 12.4)</td>
<td>12.3 (10.9, 13.6)</td>
<td>12.1 (10.7, 13.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Estrogen use (% of women)</td>
<td>15 (10, 19)</td>
<td>16 (12, 20)</td>
<td>17 (13, 20)</td>
<td>18 (14, 22)</td>
<td>19 (15, 23)</td>
<td>0.01</td>
</tr>
<tr>
<td>Multivitamin use (%)</td>
<td>22 (18, 25)</td>
<td>22 (18, 26)</td>
<td>27 (23, 31)</td>
<td>32 (29, 36)</td>
<td>34 (30, 38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total energy (kcal/d)</td>
<td>1498 (1451, 1545)</td>
<td>1750 (1703, 1797)</td>
<td>1891 (1845, 1938)</td>
<td>2029 (1982, 2076)</td>
<td>2205 (2157, 2252)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dietary guideline adherence index score</td>
<td>7.2 (7.0, 7.4)</td>
<td>8.1 (7.9, 8.3)</td>
<td>9.2 (9.0, 9.3)</td>
<td>10.0 (9.8, 10.2)</td>
<td>11.2 (11.0, 11.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( ^{1} n = 2719 \). MET, metabolic equivalent. All values that are not percentages are least-squares means. Least-squares means and percentages were adjusted for sex and age; age was adjusted for sex only, and sex and estrogen use were adjusted for age only. ANCOVA was used to examine the participant characteristics by phylloquinone intake quintile categories.

\( ^{2} \) Phylloquinone intake medians (ranges) were 63 (10–83), 103 (84–120), 139 (120–160), 185 (160–218), and 282 (218–1975) \( \mu g/d \) for Q1, Q2, Q3, Q4, and Q5, respectively.

\( ^{3} P \) for trend by quintile category of phylloquinone intakes were performed by assigning median values of phylloquinone intake for each quintile category and treating them as continuous variables. Because the Dietary Guideline Adherence Index score was calculated on the basis of age- and sex-specific criteria, \( P \) for trend was not adjusted for age and sex.

\( ^{4} \) 95% CI in parentheses (all such values).
**DISCUSSION**

The major finding of the present study was that higher phylloquinone intake was associated with greater insulin sensitivity, as measured by 2-h post-OGTT insulin and ISI$_{0,120}$, and with better glycemic status, as measured by 2-h post-OGTT glucose concentrations, in a community-based sample of men and women. These observations are consistent with an earlier small metabolic study in which young men with lower vitamin K status, as assessed by biochemical markers, had higher 2-h post-OGTT insulin concentrations than did those with higher vitamin K status (3). Accordingly, it has been proposed that vitamin K may have a potential biological role in glucose homeostasis.

Although phylloquinone intake was significantly associated with insulin sensitivity and glycemic status, as assessed from 2-h post-OGTT measurements in the present study, we did not find significant associations of phylloquinone intake with insulin sensitivity and glycemic status measures assessed in the fasting state. We currently do not have an explanation for the observed state. We currently do not have an explanation for the observed

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**TABLE 2**

In insulin sensitivity and glycemic status measures by phylloquinone intake quintile (Q)$^d$

<table>
<thead>
<tr>
<th>Phylloquinone intake quintile category$^d$</th>
<th>Q1 (n = 543)</th>
<th>Q2 (n = 544)</th>
<th>Q3 (n = 544)</th>
<th>Q4 (n = 544)</th>
<th>Q5 (n = 544)</th>
<th>P for trend$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin sensitivity measures</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fasting insulin (µU/mL)$^d$</td>
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<td></td>
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</tr>
<tr>
<td>Model 1</td>
<td>29.2 (28.5, 29.8)</td>
<td>29.1 (28.4, 29.7)</td>
<td>28.3 (27.7, 28.9)</td>
<td>28.4 (27.8, 29.0)</td>
<td>27.9 (27.3, 28.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Model 2</td>
<td>29.0 (28.2, 29.7)</td>
<td>28.9 (28.3, 29.6)</td>
<td>28.3 (27.7, 28.9)</td>
<td>28.4 (27.8, 29.1)</td>
<td>28.1 (27.4, 28.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>2-h post-OGTT insulin (µU/mL)$^d$</td>
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<tr>
<td>Model 1</td>
<td>80.4 (76.8, 84.2)</td>
<td>81.1 (77.4, 84.8)</td>
<td>80.4 (76.8, 84.1)</td>
<td>78.6 (75.0, 82.3)</td>
<td>73.1 (69.8, 76.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>81.0 (76.8, 85.3)</td>
<td>81.0 (77.5, 84.9)</td>
<td>80.3 (76.7, 84.0)</td>
<td>78.4 (74.8, 82.2)</td>
<td>72.7 (68.9, 76.6)</td>
<td>0.003</td>
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<tr>
<td>HOMA-IR$^d$</td>
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<tr>
<td>Model 1</td>
<td>6.51 (6.35, 6.68)</td>
<td>6.53 (6.37, 6.70)</td>
<td>6.33 (6.17, 6.49)</td>
<td>6.37 (6.21, 6.53)</td>
<td>6.23 (6.07, 6.39)</td>
<td>0.007</td>
</tr>
<tr>
<td>Model 2</td>
<td>6.46 (6.27, 6.64)</td>
<td>6.48 (6.31, 6.65)</td>
<td>6.33 (6.17, 6.49)</td>
<td>6.38 (6.22, 6.55)</td>
<td>6.29 (6.11, 6.47)</td>
<td>0.22</td>
</tr>
<tr>
<td>ISI$_{0,120}$ (mg · L$^{-2}$·mmol · mU · min)$^d$</td>
<td></td>
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<td></td>
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<tr>
<td>Model 1</td>
<td>26.5 (26.0, 27.0)</td>
<td>26.1 (25.6, 26.6)</td>
<td>26.1 (25.6, 26.7)</td>
<td>26.5 (26.0, 27.1)</td>
<td>27.1 (26.6, 27.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 2</td>
<td>26.3 (25.7, 26.9)</td>
<td>26.1 (25.5, 26.6)</td>
<td>26.1 (25.6, 26.7)</td>
<td>26.6 (26.0, 27.2)</td>
<td>27.3 (26.7, 27.9)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Glycemic status measures</strong></td>
<td></td>
<td></td>
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<tr>
<td>Fasting glucose (mg/dL)$^d$</td>
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</tr>
<tr>
<td>Model 1</td>
<td>94.3 (93.6, 95.1)</td>
<td>95.0 (94.2, 95.7)</td>
<td>94.7 (94.0, 95.4)</td>
<td>94.8 (94.1, 95.6)</td>
<td>94.4 (93.6, 95.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>Model 2</td>
<td>94.2 (93.4, 95.0)</td>
<td>94.8 (94.0, 95.5)</td>
<td>94.7 (94.0, 95.4)</td>
<td>94.9 (94.2, 95.6)</td>
<td>94.6 (93.8, 95.4)</td>
<td>0.76</td>
</tr>
<tr>
<td>2-h post-OGTT glucose (mg/dL)$^d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>105.3 (103.0, 107.5)</td>
<td>106.5 (104.3, 108.7)</td>
<td>105.9 (103.7, 108.1)</td>
<td>105.0 (102.7, 107.3)</td>
<td>102.9 (100.6, 105.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Model 2</td>
<td>106.3 (103.8, 108.9)</td>
<td>106.9 (104.5, 109.2)</td>
<td>105.8 (103.6, 108.1)</td>
<td>104.6 (102.3, 106.9)</td>
<td>101.9 (99.9, 104.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>HbA$_{1c}$ (≥6.5% of total hemoglobin)$^d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>0.66 (0.30, 1.44)</td>
<td>0.81 (0.38, 1.75)</td>
<td>0.91 (0.43, 1.90)</td>
<td>0.39 (0.15, 1.00)</td>
<td>0.11</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>0.71 (0.32, 1.58)</td>
<td>0.91 (0.40, 2.09)</td>
<td>1.07 (0.45, 2.53)</td>
<td>0.50 (0.15, 1.55)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

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$^d$ Values for P for trend by quintile category of phylloquinone intakes were obtained by assigning median values of phylloquinone intake for each quintile trend state. We currently do not have an explanation for the observed state. We currently do not have an explanation for the observed

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1 $n = 2719$. Because of data availability, 2655 and 1992 subjects were included in the analyses for the association of phylloquinone intake with 2-h post-OGTT insulin and glucose with and HbA$_{1c}$, respectively. For 2-h post-OGTT insulin and glucose and ISI$_{0,120}$, the number of participants in each quintile was 534, 535, 532, 528, and 526 for Q1, Q2, Q3, Q4, and Q5, respectively. For HbA$_{1c}$ the sample size for each quintile was 391, 389, 403, 391, and 418, for Q1, Q2, Q3, Q4, and Q5, respectively. OGTT, oral-glucose-tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; HbA$_{1c}$, glycated hemoglobin. Model 1 was adjusted for age, sex, waist circumference, physical activity score, cigarette smoking, alcohol consumption, multivitamin use, and estrogen use. Model 2 was additionally adjusted for total energy intake and the Dietary Guidelines for Americans Adherence Index score. ANCOVA was performed to examine the association between phylloquinone intake quintile categories and measures of insulin sensitivity and glucose, and logistic regression was performed to examine the relationship between phylloquinone intake quintile categories and HbA$_{1c}$.

2 Phylloquinone intake medians (ranges) are 63 (10–83), 103 (84–120), 139 (120–160), 185 (160–218), and 282 (218–1975) µg/d for Q1, Q2, Q3, Q4, and Q5, respectively.

3 Values for P for trend by quintile category of phylloquinone intakes were obtained by assigning median values of phylloquinone intake for each quintile category and treating them as continuous variables. P values were based on the regression coefficients for median values of phylloquinone intake from linear regression for insulin sensitivity and glucose measures and logistic regression for HbA$_{1c}$ using median values of phylloquinone intake quintile as continuous variables.

4 Geometric least-squares $\bar{x}$; 95% CIs in parentheses (all such values).

5 Least-squares $\bar{x}$; 95% CIs in parentheses (all such values).

6 Odds ratios; 95% CIs in parentheses (all such values).
disparity in baseline and 2-h post-OGTT measures. However, our results are consistent with findings from a previous report from a small metabolic study of young men (2). Men with lower reported phylloquinone intake had lower insulin and higher glucose concentrations 30 min after oral glucose loading than did those with higher phylloquinone intake, but there was no association between phylloquinone intake and either fasting glucose or insulin concentrations (2). Potentially, delayed insulin release by the β-cells to oral glucose loading may explain observed elevation of 2-h post-OGTT insulin and glucose concentrations in persons with lower reported phylloquinone intake in the present study. However, our interpretation of data is limited because we did not assess the effect of phylloquinone intake on the acute insulin and glucose responses to oral glucose loading.

The nonsignificant association of phylloquinone intake with fasting insulin and HOMA-IR is potentially due to overadjustment in statistical models. Consumption of dark green vegetables, which are major sources of phylloquinone in this population, is part of the DGAI. When a subscore of the DGAI that did not include the dark green vegetable intake component was used instead of the overall DGAI in our statistical models, higher phylloquinone intake was associated with fasting insulin and HOMA-IR.

We also observed that higher phylloquinone intake was associated with higher ISI_{0,120}, which indicates greater insulin sensitivity. ISI_{0,120} may capture more of the complexity of the influence of insulin resistance and glucose homeostasis than may either HOMA-IR or the individual measures of insulin and glucose concentrations. The ISI_{0,120} incorporates body weight and both fasting and 2-h post-OGTT insulin and glucose concentrations. It is a complex assessment of insulin sensitivity that accounts for β-cell response to glucose loading, peripheral and hepatic insulin sensitivity, and glucose disposal (15). A previous study has shown a high correlation between ISI_{0,120} and insulin sensitivity, as measured by the hyperinsulinemic-euglycemic clamp technique (14). In the absence of appropriate measures, the current study cannot determine whether phylloquinone intake is associated with β-cell response, insulin sensitivity, or glucose disposal (or all). However, all of these components are involved in glucose homeostasis, and their dysfunction contributes to diabetes (19, 20).

The potential biological mechanisms relating phylloquinone to insulin resistance and glucose homeostasis are not understood. Two forms of vitamin K, phylloquinone and menaquinone-4, are found in the pancreas (21). However, vitamin K–dependent proteins specific to the pancreas have not been identified. A recent study proposed that osteocalcin, one of the vitamin K–dependent proteins in the bone, may improve insulin sensitivity and increase β-cell functions, partially through the enhancement of adiponectin expression (5). Alternatively, it has been suggested that vitamin K has potential physiologic functions in addition to its classical role as a cofactor for γ-carboxylation (22). In vivo, in vitro, and observational studies showed that vitamin K decreases inflammation–induced cytokines (23–25), so it is plausible that phylloquinone may improve insulin sensitivity and glycemic status by the suppression of inflammation.

The present study had several limitations. First, higher phylloquinone intake is a potential surrogate marker for a healthy dietary pattern, as characterized by higher intakes of fruit, vegetables, fish, and dietary fiber and lower intakes of saturated fat (18). Furthermore, because green leafy vegetables are also rich in other components (eg, dietary fiber and potassium) that have been reported to improve insulin sensitivity, phylloquinone intake may be only a marker for other components in green leafy vegetables that may be beneficial to insulin sensitivity and glycemic status. Although we cannot rule out the presence of residual confounding by overall lifestyle characteristics and diet quality (which may lead to the overestimation of the associations between phylloquinone intake and measures of insulin sensitivity and glycemic status), our finding does not support the hypothesis that these associations are due solely to diet quality. Additional adjustment for diet quality did not alter the significant associations between phylloquinone intake and measures of insulin sensitivity and glycemic status, as measured by ISI_{0,120} and by both 2-h post-OGTT insulin and glucose. Therefore, observed associations between phylloquinone intake and insulin sensitivity may indicate a biological role of phylloquinone in glucose homeostasis. A second limitation of the present study was its cross-sectional nature, which limited any causal inference from the observations. Finally, whereas most participants in the FOS have Northern European ancestry, the findings in the present study are consistent with those in Japanese young adults (2, 3). Thus, the similar findings in these 2 very distinct populations indicate that generalizability to other populations does not present a major limitation.

In summary, our findings suggest that phylloquinone intake may have a beneficial effect on glucose homeostasis, or it may serve as a surrogate marker of other dietary or lifestyle factors that were not controlled in the present analysis. These findings may lead to further areas of research that could help to elucidate potential novel functions of vitamin K. Future studies should focus on prospective relations between phylloquinone intakes and surrogate markers for insulin sensitivity, glycemic status, and type 2 diabetes, as well as on the putative biological mechanism explaining associations between phylloquinone and glucose homeostasis.

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