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Vitamin K_1 Intake and Incident Diabetes in the Danish Diet, Cancer, and Health Study

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Abstract

Context: Observational studies have reported lower risks of type 2 diabetes with higher vitamin K_1 intake, but these studies overlook effect modification due to known diabetes risk factors.

Objective: To identify subgroups that might benefit from vitamin K_1 intake, we examined associations between vitamin K_1 intake and incident diabetes overall and in subpopulations at risk of diabetes.

Methods: Participants from the prospective cohort, the Danish Diet, Cancer, and Health Study, with no history of diabetes were followed up for diabetes incidence. The association between intake of vitamin K_1, estimated from a food frequency questionnaire completed at baseline, and incident diabetes was determined using multivariable-adjusted Cox proportional-hazards models.

Results: In 54 787 Danish residents with a median (interquartile range) age of 56 (52-60) years at baseline, 6700 individuals were diagnosed with diabetes during 20.8 (17.3-21.6) years of follow-up. Vitamin K_1 intake was inversely and linearly associated with incident diabetes ($P < .0001$). Compared to participants with the lowest vitamin K_1 intake (median:57 µg/d), participants with the highest intakes (median:191 µg/d) had a 31% lower risk of diabetes (HR; 95% CI, 0.69; 0.64-0.74) after multivariable adjustments. The inverse association between vitamin K_1 intake and incident diabetes was present in all subgroups (namely, men and women, ever and never smokers, low and high physical activity groups, and in participants who were normal to overweight and obese), with differences in absolute risk between subgroups.

Conclusion: Higher intake of foods rich in vitamin K_1 was associated with a lower risk of diabetes. If the associations observed are causal, our results indicate that more cases of diabetes would be prevented in subgroups at higher risk (men, smokers, participants with obesity, and those with low physical activity).

Key Words: diet, non–insulin-dependent diabetes, nutrition epidemiology, obesity, phylloquinone, type 2 diabetes mellitus

Abbreviations: BMI, body mass index; EPIC-NL, European Prospective Investigation into Cancer and Nutrition–Netherlands study; FFQ, food-frequency questionnaire; ICD-10, International Classification of Diseases Tenth Revision; MET, metabolic equivalent; NDI, Nordic diet index; PREDIMED, Prevention with the Mediterranean Diet study; RCT, randomized controlled trial; T2D, type 2 diabetes; UBIAD1, UbiA prenyltransferase domain-containing protein 1; VKA, vitamin K antagonist; VKDP, vitamin K–dependent protein.

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Globally, it is estimated that 10.5% of the world's population has type 2 diabetes (T2D), with its prevalence expected to grow in the coming decades (1). T2D is a risk factor for chronic diseases such as cardiovascular disease, kidney disease, neuropathy, and retinopathy (1, 2), and was estimated to cause 6.7 million deaths alone in 2021 (1). Susceptibility to developing T2D is regulated by age, environment, and genetic factors but major contributors are dietary and lifestyle factors (3, 4). Therefore identifying modifiable risk factors that prevent or delay development of T2D (5) is a global challenge.

Evidence from observational studies suggest that dietary modifications, such as vegetarian and vegan diets; Mediterranean diet; and increased intake of whole grains, fruits, and vegetables, may lower the risk of T2D (6). Such diets are frequently used in interventions and are found to be effective in preventing T2D (7, 8). In fact, randomized controlled trials (RCTs) show that such interventions prove to be cost-effective and sustainable even after active intervention ends (8). However, poor adherence to altered diet and response bias are common issues in long-term interventions. We have recently demonstrated that vegetables—namely green leafy vegetables that are rich in dietary nitrate, lutein, folate, vitamin K_1, and β-carotene (9, 10)—may also play a protective role against T2D (11). Of these, there is mechanistic evidence for the association between vitamin K intake and T2D (12, 13).

Vitamin K_1, found abundantly in green leafy vegetables and some plant oils (14), may play a role in preventing T2D development (13). Though the exact mechanistic pathways are yet to be understood, vitamin K is hypothesized to play a role in insulin regulation via its carboxylation of vitamin K–dependent proteins (VKDPs), anti-inflammatory properties, lipid-lowering effects, and regulation of adipokine secretion (12, 15). There are 2 groups of dietary vitamin K: vitamin K_1 (phylloquinone), primarily found in green leafy vegetables and some plant oils, and vitamin K_2 (menaquinones—4 to 13 have been identified) limited to fermented foods and animal products (16). Differences lie in the absorption, metabolism, and bioactivity of different forms of vitamin K_2 (17, 18), and, unlike vitamin K_1, European food databases lack information on different forms of vitamin K_2, limiting the ability to examine associations between vitamin K_2 intake and health outcomes.

Observational studies reported a lower T2D incidence in participants with higher intake of dietary vitamin K_1 (19, 20) and total vitamin K ($K_1 + K_2$) (21, 22). However, these studies overlook effect modifications due to known risk factors of T2D. Additionally, studies suggest disruption in vitamin K metabolism (23) and increased risk of diabetes (24) with the use of statins. To our knowledge, no prior studies have explored whether the association between vitamin K_1 and incident diabetes differs with statin use. Therefore, we aimed to examine the prospective association between dietary vitamin K_1 intake and incident diabetes in a large Danish population. Secondary aims were to investigate whether associations were modified in the presence of known risk factors for diabetes and to identify subpopulations that may benefit the most from higher vitamin K_1 intake. In addition, we aimed to examine if the association between vitamin K_1 and incident diabetes varied by statin therapy (yes/no).

Materials and Methods

Study Population

Between 1993 and 1997, a total of 57 053 men and women between ages 50 and 64 years were recruited from the greater areas of Copenhagen and Aarhus, for participation in the Danish Diet, Cancer, and Health study (25). Using the Civil Personal Registration number, a personal identification number assigned to all Danish residents, data from participants were cross-linked to the following national registers: the Civil Registration System, the Integrated Database for Labor Market Research Database, the Danish Prescription Registry, and the Danish National Patient Register. Of the 57 053 individuals initially recruited into the study, 56 468 completed a food frequency questionnaire (FFQ) and had no diagnosis of cancer before study enrollment. Participants were excluded if they had improbable energy intake (<2092 kJ/day or >20 920 kJ/day; n = 198), missing data or extreme values for any covariates (n = 243), or if they had prevalent diabetes at baseline (n = 1240); prevalent diabetes was defined as self-reported diabetes, International Classification of Diseases, Tenth Revision (ICD-10) diagnosis of diabetes (E10, E11), or use of insulin and other glucose-lowering medications (ATC; A10A, A10B) at or before baseline. This left 54 787 participants remaining for analysis in the present study (Supplementary Fig. S1) (26).

This study was approved by the Danish Data Protection Agency (Ref No. 2012-58-0004 I-Suite No. 6357, VD-2018-117). Participants signed an informed consent for participation in the Diet, Cancer, and Health Study, and the investigations were carried in accordance with the principles of the Declaration of Helsinki.

Assessment of Exposure

The exposure of interest was intake of vitamin K_1, estimated from dietary data, collected using a validated 192-item, self-administered, semiquantitative FFQ (27, 28). The FFQ used in the Diet, Cancer, and Health study was validated for macronutrients and vitamins through comparison with 2 times 7 days' weighted diet record (28). While vitamin K was not included in this validation process, other vitamins such as A, C, and E were subject to validation. Results of the validation indicated that approximately 70% of participants were categorized in the same vitamin intake quintiles both for the FFQ and diet record methods. Details for the calculations used to determine intake of vitamin K_1 in this cohort have been provided previously (29, 30). Briefly, estimates of the vitamin K_1 content of most items in the FFQ were derived from the Frida Food Data database (31) and, where a vitamin K_1 value was not available, the US Department of Agriculture (32) nutrient database was used. Foods with no estimates available from either of the databases (vitamin $K_1 = 0$ µg/g, n = 44 foods) were assumed not to provide vitamin K_1. The amount of vitamin K_1 for each food item in microgram per day (µg/d) was quantified by the product of individual food item consumed (g/d) with the mean vitamin K_1 estimate from the respective food database in µg/g.

Assessment of Outcome

The outcome of interest was incident diabetes over a maximum of 23 years of follow-up. This was defined by either 1) a primary or secondary diagnosis of diabetes (ICD-10; E10, E11) for either inpatient and outpatient visits, or 2) a prescription for insulin or noninsulin medication for diabetes treatment (ATC; A10A, A10B). This definition for identifying patients with diabetes is based on an algorithm developed by the Danish Health Data Authority and has a positive

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predictive value of 96.9% (33). It is not possible to distinguish between patients with type 1 diabetes and T2D based on information from the Danish Health Registers (34).

Assessment of Covariates

Participants provided information on sex, date of birth, education, smoking habits, alcohol consumption, daily physical activity, use of hormone replacement therapy, and diet through questionnaires that they were asked to complete on enrollment. Anthropometric measures (height and weight) were taken at the study centers. Daily physical activity was based on metabolic equivalent (MET) score calculated by summing time spent per week on housework, do-it-yourself work, walking, cycling, sports, gardening, and leisure time activities. The details on calculation of MET score are described elsewhere (35). Socioeconomic status was represented by the average of each participant's household income over 5 years (defined as household income after taxation and interest, using the value of Danish currency in 2015). As an indicator of diet quality, we calculated the healthy Nordic diet index (NDI) of each participant as described previously (11, 36). Hypertension and hypercholesterolemia were self-reported. ICD-8 and ICD-10 codes combined with self-reported data were used to determine prevalent cardiovascular disease (ischemic heart disease, peripheral artery disease, stroke, atrial fibrillation, and heart failure), chronic kidney disease, and chronic obstructive pulmonary disease. Information on statin use was obtained from both the questionnaire and ATC codes in the Danish National Prescription Registry (ATC code: C10AA), while the use of vitamin K antagonists (VKAs) was determined through ATC codes (ATC code: B01AA).

Statistical Analyses

The statistical analysis plan was predetermined. Participants' time to event was based on a maximum of 23 years of follow-up from the date of enrollment until the date of death, emigration, diabetes diagnosis (as described earlier), or end of follow-up (August 2017), whichever came first. All deaths were censored and thus only each participant's respective time from study entry until death was used in the analysis to account for its competing risk (37). Cox proportional-hazards models were used to investigate the relationship between vitamin K_1 intake and incident diabetes; proportional-hazards assumptions were tested using log-log plots of the survival function vs time, which were assessed for parallel appearance, with no violation found. To allow associations to be nonlinear, all continuous covariates, including vitamin K_1, were modeled using restricted cubic splines. Hazard ratios (HRs) and 95% CI estimates are reported for the median intake in each quintile, with the first quintile median as the reference point, and were obtained from the model with the exposure fitted as a continuous variable through a restricted cubic spline. The graphs of HRs derived from the fitting of cubic splines had x-axis values restricted to intakes within 3 SDs of the mean. We tested for nonlinearity of the association using a chi-square test to compare nested models. Associations were investigated using 4 models of adjustment: 1a) minimally adjusted; 1b) multivariable-adjusted; 2) multivariable-adjusted including covariates that are both potential confounders and potential intermediates on the causal pathway; and 3) multivariable-adjusted including energy intake and potential dietary confounders (Supplementary Table S1) (26). Covariates were chosen a priori using knowledge of potential confounders of vitamin K intake and diabetes. To investigate whether associations were modified in the presence of established risk factors for diabetes, analyses were stratified by baseline smoking status (ever vs never smoker), body mass index BMI (≤30 vs >30), sex (male vs female), and median MET score (<56.5 vs ≥56.5) and *P* values for interaction terms were obtained from likelihood ratio tests of nested models. As there is potential for residual confounding, when stratifying by smoking status, and MET score, the corresponding continuous variables (smoking pack-years and, MET score, respectively) were included in the model where appropriate. To identify which subgroups may benefit the most from high intake of vitamin K_1, standard logistic regression models were used to obtain the 20-year absolute risk estimates of incident diabetes for the highest and lowest intake quintiles. For these analyses, a binary outcome indicating a diabetes diagnosis during 20 years of follow-up (the minimum follow-up time) was used. Unless indicated by the stratification variable, these estimates are for a nonsmoking participant, aged 56 years, with a BMI between 18.5 and 30, a total daily MET score between 33.3 and 48.5, with a mean household income of 394 701 and 570 930 Danish krone per year, 8 to 10 years of education, and an alcohol intake between 0 and 20 g/day. With the aim of understanding whether the association between vitamin K_1 and diabetes is explained by total vegetable intake, we stratified our analysis by tertiles of total vegetable intake. Further, stratification by NDI score was performed to understand if the association between vitamin K_1 and diabetes is influenced by diet quality. In a sensitivity analysis, participants were excluded if they were prescribed VKA at baseline (n = 301) and censored if they were prescribed a VKA during follow-up (n = 5933). In supplementary modeling, Cox proportional-hazards models were fitted with statin therapy as a time-updated covariate, with the same adjustments as model 1b. Participants were considered "on statin therapy" if the participants were on statin therapy at baseline or if the participants had claimed a statin prescription any time during follow-up. Vitamin K intake in quintiles was fitted in the model along with its interaction with the time-updated statin therapy, which was tested using a likelihood ratio test. All analyses were undertaken using STATA/IC 14.2 (StataCorp LLC) and R statistics (R Core Team, 2019).

Results

This cohort, composed of 54 787 Danish residents, had a median (interquartile range) age of 56 (52-60) years baseline. During the 20.8 (17.3-21.6) years of follow-up (1 010 191 person-years), 6700 participants were diagnosed with diabetes and 11 428 participants died during follow-up with no prior diabetes diagnosis.

Baseline Characteristics

The baseline characteristics of the study population, overall and stratified by vitamin K_1 intake quintiles, are shown in Table 1. The median intakes (interquartile range) of vitamin K_1 in this cohort was 113.0 µg/day (80.0-150.2 µg/d). Compared to participants with the lowest intake of vitamin K_1, those with the highest intake were more likely to be male, be more physically active, have a lower BMI, have a higher education degree, have a higher annual income, and were less likely to be current smokers or have a comorbidity. Furthermore, they tended to have a healthier underlying dietary pattern, eating more fish, fiber, fruits, and vegetables.

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Table 1. Baseline characteristics of study population

		Vitamin K_1 intake quintiles				
	Total population	Q1	Q2	Q3	Q4	Q5
	n = 54 787	n = 10 958	n = 10 957	n = 10 957	n = 10 957	n = 10 958
Total vitamin K_1 intake, µg/d	113 (80-150)	57 (47-65)	87 (80-94)	113 (107-120)	142 (134-150)	191 (173-219)
Sex (male)	25 903 (47.3)	5082 (46.4)	5303 (48.4)	5107 (46.6)	5199 (47.4)	5212 (47.6)
Age, y	56 (52-60)	56 (53-60)	56 (52-60)	55 (52-60)	55 (52-59)	56 (52-60)
BMI	25.5 (23.3-28.2)	26.0 (23.5-28.9)	25.9 (23.5-28.5)	25.6 (23.4-28.2)	25.3 (23.1-27.8)	24.9 (22.8-27.4)
MET score	56.5 (37.0-84.8)	49.5 (31.0-76.8)	54.0 (35.0-82.0)	57.0 (37.5-84.0)	59.5 (40.0-87.0)	63.5 (42.5-92.0)
Smoking status						
Never	19 281 (35.2)	2973 (27.1)	3684 (33.6)	4054 (37.0)	4273 (39.0)	4297 (39.2)
Former	15 746 (28.7)	2587 (23.6)	3013 (27.5)	3219 (29.4)	3324 (30.3)	3603 (32.9)
Current	19 760 (36.1)	5398 (49.3)	4260 (38.9)	3684 (33.6)	3360 (30.7)	3058 (27.9)
Education, y						
≤7	17 939 (32.7)	4916 (44.9)	4137 (37.8)	3598 (32.8)	2931 (26.8)	2357 (21.5)
8-10	25 286 (46.2)	4858 (44.3)	5150 (47.0)	5250 (47.9)	5168 (47.2)	4860 (44.4)
≥11	11 537 (21.1)	1178 (10.8)	1665 (15.2)	2103 (19.2)	2854 (26.0)	3737 (34.1)
Annual income, DKK/y						
≤394 700	13 473 (24.6)	3582 (32.7)	2772 (25.3)	2471 (22.6)	2304 (21.0)	2344 (21.4)
394 701-570 930	13 659 (24.9)	3125 (28.5)	2934 (26.8)	2761 (25.2)	2517 (23.0)	2322 (21.2)
570 931-758 297	13 794 (25.2)	2562 (23.4)	2902 (26.5)	2967 (27.1)	2850 (26.0)	2513 (22.9)
>758 297	13 861 (25.3)	1689 (15.4)	2349 (21.4)	2758 (25.2)	3286 (30.0)	3779 (34.5)
Hypertensive	8642 (15.8)	1829 (16.7)	1809 (16.5)	1760 (16.1)	1680 (15.3)	1564 (14.3)
Hypercholesterolemic	3964 (7.2)	839 (7.7)	789 (7.2)	841 (7.7)	799 (7.3)	696 (6.4)
Comorbidities						
Heart failure	194 (0.4)	60 (0.5)	35 (0.3)	34 (0.3)	36 (0.3)	29 (0.3)
Atrial fibrillation	263 (0.5)	57 (0.5)	49 (0.4)	53 (0.5)	51 (0.5)	53 (0.5)
COPD	820 (1.5)	233 (2.1)	163 (1.5)	155 (1.4)	131 (1.2)	138 (1.3)
CKD	136 (0.4)	24 (0.2)	41 (0.4)	32 (0.3)	24 (0.2)	15 (0.1)
IHD	2040 (3.7)	528 (5.0)	442 (4.2)	364 (3.4)	380 (3.6)	326 (3.1)
PAD	459 (0.8)	144 (1.4)	112 (1.1)	86 (0.8)	60 (0.6)	57 (0.5)
Stroke	715 (1.3)	187 (1.8)	172 (1.6)	137 (1.3)	108 (1.0)	111 (1.0)
Medication use						
Antihypertensive	6480 (11.8)	1379 (12.6)	1391 (12.7)	1302 (11.9)	1264 (11.5)	1144 (10.4)
Statin	1000 (1.8)	214 (2.0)	210 (1.9)	206 (1.9)	190 (1.7)	180 (1.6)
HRT (% female)						
Never	8707 (30.1)	3163 (53.8)	3002 (53.1)	3270 (55.9)	3178 (55.2)	3088 (53.7)
Current	4476 (15.5)	1721 (29.3)	1742 (30.8)	1750 (29.9)	1713 (29.7)	1781 (31.0)

(*continued*)

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Table 1. Continued

		Vitamin K_1 intake quintiles				
	Total population	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
	n = 54 787	**n = 10 958**	**n = 10 957**	**n = 10 957**	**n = 10 957**	**n = 10 958**
Former	17 760 (32.6)	992 (16.9)	910 (16.1)	830 (14.2)	867 (15.1)	877 (15.3)
NSAID	6908 (12.6)	3551 (32.7)	3546 (32.6)	3555 (32.6)	3575 (32.8)	3533 (32.4)
Aspirin	6480 (11.8)	1482 (13.5)	1415 (12.9)	1370 (12.5)	1325 (12.1)	1316 (12.0)
Dietary characteristics						
Energy, kJ	9498 (7855-11 363)	7887 (6553-9461)	8967 (7538-10 586)	9482 (8035-11 160)	10 125 (8637-11 846)	11 095 (9418-13 040)
Total fish intake, g/d	38 (25-55)	29 (18-42)	35 (24-50)	39 (27-54)	42 (29-59)	49 (33-68)
Red meat intake, g/d	78 (56-107)	69 (51-93)	78 (57-104)	80 (59-109)	82 (59-112)	83 (58-117)
Processed meat intake, g/d	24 (14-40)	24 (14-39)	26 (15-41)	25 (15-40)	24 (14-40)	23 (12-39)
Dietary fiber intake, g/d	20 (16-25)	14 (12-17)	18 (15-21)	20 (17-24)	23 (19-27)	27 (23-32)
Saturated FA, g/d	31 (24-39)	27 (21-35)	30 (23-38)	31 (24-39)	33 (25-41)	35 (27-44)
Polyunsaturated FA, g/d	13 (10-17)	10 (8-12)	12 (10-15)	13 (11-17)	15 (12-19]	17 (13-22)
Monounsaturated FA, g/d	27 (21-35)	23 (18-30)	26 (21-33)	27 (22-34)	29 (23-36]	31 (24-39)
Fruit intake, g/d	171 (94-281)	103 (46-181)	146 (82-237)	175 (104-272)	200 (125-311]	251 (156-387)
Vegetable intake, g/d	161 (104-230)	73 (51-98)	122 (95-153)	162 (131-198)	205 (168-248)	285 (230-351)
Alcohol intake, g/d	13 (6-31)	12 (4-33)	12 (6-31)	13 (6-30)	14 (7-31)	13 (7-30)

Data expressed as median (interquartile range) or n (%), unless otherwise stated.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DKK, Danish krone; FA, fatty acids; HRT, hormone replacement therapy, IHD, ischemic heart disease; MET, metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drug; PAD, peripheral artery disease; vitamin K_1, phylloquinone.

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Vitamin K_1 Intake and Incident Diabetes

Vitamin K_1 intake was linearly inversely associated with incident diabetes ($P < .0001$; $P_{nonlinearity} = .412$; Fig. 1). After multivariable adjustments for demographic and lifestyle confounders (model 1b), participants with the highest intake had a 31% lower risk of diabetes (HR_{Q5vsQ1}; 95% CI, 0.69 (0.64-0.74); Table 2). After adjustments were made for potential dietary confounders, the participants with the highest intake of vitamin K_1 had a 26% lower risk of diabetes (model 3: HR_{Q5vsQ1} 0.74; 95% CI, 0.67-0.83); see Table 2].

Stratified Analyses

Inverse associations between vitamin K_1 intake and incident diabetes were observed for all strata namely, male (HR_{Q5vsQ1}: 0.64; 0.59-0.71) and female (HR_{Q5vsQ1}: 0.76; 0.69-0.85), $P_{interaction} = .031$; ever (HR_{Q5vsQ1}: 0.74; 0.68-0.80) and never smokers (HR_{Q5vsQ1}: 0.64; 0.57-0.73), $P_{interaction} = .121$; normal to overweight (HR_{Q5vsQ1}: 0.69; 0.63-0.75) and obese participants (HR_{Q5vsQ1}: 0.88; 0.79-0.99), $P_{interaction} < .0001$; and those having lower (HR_{Q5vsQ1}: 0.69; 0.63-0.76) and higher physical activity level (HR_{Q5vsQ1}: 0.68; 0.62-0.76), $P_{interaction} = .694$ after multivariable adjustments (Supplementary Table S2) (26). The shape of the association was linear for all the subgroups except for obese participants, for whom the association was nonlinear (model 1b, Fig. 2). The absolute risk of diabetes was higher in men, smokers, those who were obese, and those with a lower level of physical activity; consequently, the absolute difference (vitamin K_1 intake quintile 5 – vitamin K_1 intake quintile 1) in the 20-year estimated risk of diabetes was greater for these subgroups than for their lower-risk counterparts (Table 3), even though the associations were similar on a relative scale.

There was a high correlation between vitamin K_1 intake and vegetable intake ($r = 0.79$; $P < .0001$). To explore if higher vitamin K_1 was just a marker of higher vegetable intake, we stratified our primary analysis by tertiles of total vegetable intake. The significant inverse association remained between vitamin K_1 intake and incident diabetes within each tertile, including among participants with the highest intakes of vegetables (Supplementary Table S3) (26). On stratification by categories of NDI, the associations between vitamin K_1 and incident diabetes were inverse for all categories of NDI (Supplementary Table S4) (26).

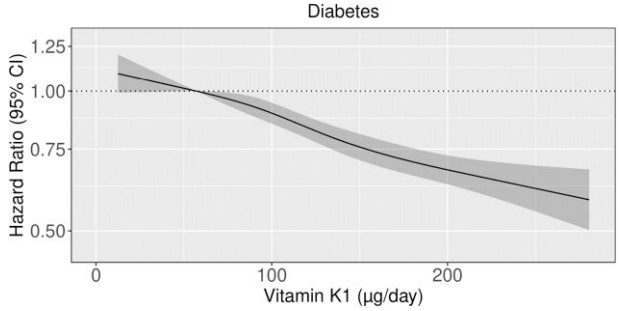

Figure 1. Hazard ratios from Cox proportional-hazards model with restricted cubic spline curves describing the association between vitamin K_1 intake (µg/day) and incident diabetes. Hazard ratios are based on models adjusted for age, sex, smoking status, physical activity, alcohol intake, socioeconomic status (income), education, hormone replacement therapy (model 1b), and are comparing the specific level of vitamin K_1 intake (horizontal axis) to the median intake for participants in the lowest intake quintile (K_1: 57 µg/day).

Sensitivity Analysis

The exclusion of participants prescribed a VKA did not change the relationship between vitamin K_1 intake and diabetes (HR_{Q5vsQ1}: 0.69; 0.64-0.74; model 1b) (Supplementary Fig. S2) (26).

Vitamin K_1 Intake and Time-updated Statin Analyses

By the end of follow-up, 23 507 participants had claimed a statin prescription. There was a statistically significant interaction between vitamin K_1 intake and statin therapy for incident diabetes ($P_{interaction} = .002$; Supplementary Table S5) (26). For the time during follow-up without statin therapy and compared to quintile 1, participants in the highest quintile had a 40% lower risk of diabetes (HR_{Q5vsQ1}: 0.60; 0.54-0.67). For the time during follow-up on statin therapy, participants in quintile 5 had a 22% lower risk of diabetes (HR_{Q5vsQ1}: 0.78; 0.69-0.88) after multivariable adjustments (model 1b; Supplementary Table S5) (26).

Discussion

In this large Danish prospective study, a higher dietary intake of vitamin K_1 was associated with a lower risk of diabetes among both men and women. We observed a linear inverse association with a 31% (CI, 26%-36%) lower risk of incident diabetes for the highest (median: 191 µg/d) vs lowest (median: 57 µg/d) quintile of vitamin K_1 intake. Differences in the absolute risk of diabetes, for high compared to low vitamin K_1 consumers, were greatest in men, current smokers, obese participants, and participants with lower physical activity. Statin use modified the association between vitamin K intake and incident diabetes.

To date, only 2 other observational studies have examined the association between dietary vitamin K_1 intake and incident diabetes (19, 20), both reporting a lower risk of T2D with higher dietary intake of vitamin K_1 intake. The Prevention with the Mediterranean Diet (PREDIMED) study observed a 17% (95% CI, 1%-29%) lower risk of T2D (131 incident cases among 1065 participants) for every 100 µg/d higher of vitamin K_1 over a median follow-up of 5.5 years (20), while the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) study observed a 19% (95% CI, 1%-34%) lower risk of T2D (918 incident cases among 38 094 participants) for the highest (mean: 333 µg/d) vs lowest (mean: 96 µg/d) quartile of vitamin K_1 over a median follow-up of 10 years (19). Our study was well powered with almost twice the follow-up duration and a greater number of incident cases (n = 6700); this may explain the clear inverse association observed compared to the previous 2 studies. Our findings add further support to the hypothesis that vitamin K_1 may play a role in preventing incident diabetes. The average intake of vitamin K_1 in the EPIC-NL study was 200 µg/d, while less than 10% of our study participants had an intake of 200 µg/d or more. This large difference in the intake of dietary vitamin K_1 may explain why a linear inverse association between vitamin K_1 intake and diabetes was observed in our study while the EPIC-NL study showed a nonlinear inverse association for incident T2D with a plateau at intakes higher than 200 µg/d. Likewise, in the Framingham Offspring Study, the associations between plasma phylloquinone and dietary phylloquinone

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Table 2. Hazard ratios of incident diabetes by quintiles of vitamin K_1 intake

	Vitamin K_1 intake quintiles				
	Q1	Q2	Q3	Q4	Q5
	n = 10 958	n = 10 957	n = 10 957	n = 10 957	n = 10 958
No. events	1696	1528	1306	1191	979
Intake, μg/d[a]	57 (4-73)	87 (73-100)	113 (100-127)	142 (127-161)	191 (161-800)
HR (95% CI)					
Model 1a	Reference	0.85 (0.81-0.89)	0.73 (0.69-0.77)	0.63 (0.59-0.67)	0.54 (0.50-0.57)
Model 1b	Reference	0.93 (0.89-0.98)	0.86 (0.81-0.90)	0.78 (0.73-0.83)	0.69 (0.64-0.74)
Model 2	Reference	0.94 (0.90-0.98)	0.89 (0.85-0.94)	0.85 (0.79-0.90)	0.79 (0.73-0.84)
Model 3	Reference	0.92 (0.87-0.98)	0.86 (0.80-0.93)	0.81 (0.74-0.89)	0.74 (0.67-0.83)

HRs (95% CI) for incident diabetes during 23 years of follow-up, obtained from restricted cubic splines in Cox proportional-hazards models, comparing the median intake in quintiles 2 to 5, to the median intake in quintile 1. Model 1a adjusted for age and sex; model 1b adjusted for age, sex, smoking status, physical activity, alcohol intake, socioeconomic status (income), education, hormone replacement therapy; model 2 adjusted for all covariates in model 1b plus BMI, hypertension, hypercholesterolemia, and prevalent disease (cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cancer, entered into the model separately); model 3 adjusted for all covariates in model 1b plus energy and intakes of fish, red meat, processed food, polyunsaturated fatty acids, monounsaturated fatty acids, saturated fatty acids, added sugar, whole grains, refined grains, and fruit.
Abbreviations: BMI, body mass index; HR, hazard ratio; vitamin K_1, phylloquinone.
[a]Median; range in parentheses (all such values).

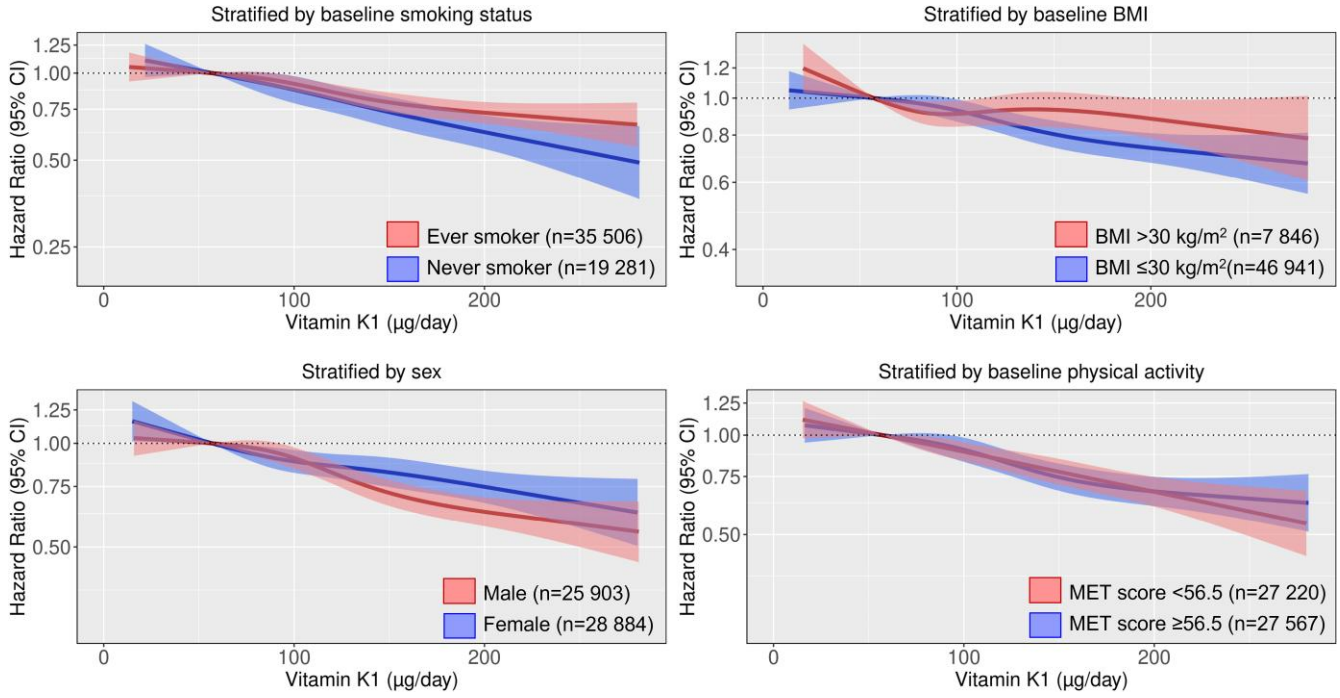

Figure 2. Multivariable-adjusted association between vitamin K_1 intake and incident diabetes stratified by baseline smoking status, BMI, sex, and physical activity. Hazard ratios are based on Cox proportional-hazards models and are comparing the specific level of vitamin K_1 intake (horizontal axis) to the median intake for participants in the lowest intake quintile (57 μg/day). All analyses were standardized for age, sex, smoking status, physical activity, alcohol intake, education, hormone replacement therapy, and socioeconomic status (income). BMI, body mass index; MET, metabolic equivalent.

intake plateaued beyond 200 μg/d (38). A review suggests that this could be due to overreporting of vegetable intake, and therefore caution is needed to interpret the finding above 200 μg/d of phylloquinone intake (16). Contrarily, the pharmaceutical supplementation of vitamin K1 greater than 500 μg/d has shown improvements in glycemic status and insulin sensitivity (39–41). Studies with a range of dietary intake along with diabetes-related biomarkers might help determine whether intake of vitamin K_1 beyond 200 μg/d is beneficial for reducing diabetes incidence.

A mendelian randomization study observed a causal association for a lower risk of T2D with each natural logarithm (nmol/L) higher circulating vitamin K_1 (RR: 0.93; 0.89-0.97) (42). It is important to consider that circulating vitamin K_1 levels denote a "snapshot" of recent consumption/vitamin K balance and are only modestly correlated with vitamin K_1 intake itself, and hence may not be representative of habitual vitamin K_1 consumption (16). Dietary intake of vitamin K_1, absorption and transportation of the vitamin, and other factors determine vitamin K status in the

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Table 3. Twenty-year predicted risk of diabetes

	Vitamin K_1 intake		
	Q1	Q5	Risk difference
	Risk (95% CI)	Risk (95% CI)	(%)
Male			
Nonsmoker	11.86 (10.75-13.08)	8.50 (7.63-9.46)	3.36
Former smoker	13.46 (12.25-14.78)	9.70 (8.73-10.75)	3.76
Current smoker	15.45 (14.16-16.84)	11.20 (10.11-12.39)	4.25
BMI ≤30	11.86 (10.75-13.08)	8.50 (7.63-9.46)	3.36
BMI >30	36.95 (34.34-39.64)	28.80 (26.35-31.37)	8.15
MET score <56.5	12.05 (10.96-13.23)	8.64 (7.76-9.60)	3.41
MET score ≥56.5	10.69 (9.65-11.83)	7.63 (6.86-8.48)	3.06
Female			
Nonsmoker	7.84 (7.11-8.63)	5.54 (4.98-6.16)	2.30
Former smoker	8.95 (8.10-9.88)	6.35 (5.70-7.08)	2.60
Current smoker	10.35 (9.44-11.33)	7.38 (6.63-8.20)	2.97
BMI ≤30	7.84 (7.11-8.63)	5.54 (4.98-6.16)	2.30
BMI >30	27.02 (24.94-29.20)	20.35 (18.51-22.33)	6.67
MET score <56.5	7.97 (7.24-8.75)	5.64 (5.06-6.27)	2.33
MET score ≥56.5	7.03 (6.36-7.77)	4.96 (4.46-5.51)	2.07

The 20-year predicted risks (%) of diabetes calculated from logistic regression models. Unless indicated by the stratification variable, these estimates are for a nonsmoking participant, aged 56 years, with a BMI between 18.5 and 30, a total daily MET score between 33.3 and 48.5, with a mean household income of 394 701 to 570 930 DKK/year, 8 to 10 years of education, and an alcohol intake between 0 and 20 g/day.
Abbreviations: BMI, body mass index; DKK, Danish krone; MET, metabolic equivalent; Q, quintile; vitamin K_1, phylloquinone.

human body so associations with vitamin K status/circulating vitamin K_1 have interpretations different from the association with dietary vitamin K intake itself (43).

In this study, the main dietary sources of vitamin K_1 were margarine, lettuce, broccoli, whole-meal bread, and spinach (30). Interestingly, we also observed a linear inverse trend for lower risk of diabetes across quintiles of vitamin K_1 for all vegetable tertiles as well as the categories of NDI when adjusted for several confounders. This suggests that phylloquinone, which is an important constituent of vegetables, might play a role in diabetes prevention irrespective of diet quality or vegetable consumption levels. However, we advocate a diverse intake of vegetables rich in phylloquinone as they offer additional health benefits (44, 45). Our findings of lower risk of diabetes for participants with higher vitamin K_1 intake, across the first, second, and third tertiles of total vegetable consumption, suggest that higher vitamin K_1 intake could help to alleviate diabetes burden and health care costs among populations with relatively low or higher levels of vegetable consumption.

Vitamin K acts as a cofactor in the carboxylation of glutamate residues in certain VKDP such as blood clotting proteins (16). Some VKDPs may be involved in glucose metabolism (eg, osteocalcin (46)) or processes that contribute to impaired glucose metabolism such as inflammation (eg, matrix Gla protein) (16, 47). However the mechanisms behind the role of vitamin K and VKDPs on glucose metabolism remain poorly understood and controversial (16, 46). Direct mechanisms, such as the role of vitamin K in altering the gut microbiome (48), preventing inflammation (12), and/or functioning as an incretin-like nutrient (49), may also be responsible for glucose metabolism. As such, further mechanistic work is needed to determine whether dietary vitamin K intake modifies glucose parameters and helps prevent T2D.

In this study, the absolute risk of incident diabetes was higher among men than women regardless of vitamin K_1 intake. In an RCT providing vitamin K_1 supplementation (500 µg/d), the beneficial effect on insulin resistance was limited to men after 36 months (40). There is no RCT on dietary vitamin K intake but only on vitamin K supplementation, which makes it difficult to understand if the effects of (non)dietary supplementation differ. In an observational study, a higher dietary vitamin K_1 intake was associated with greater insulin sensitivity among both men and women (50). It is speculated that the adipose tissue might sequester vitamin K, rendering it unavailable for use by other organs and tissues (51), which could be a potential explanation for the difference in association observed among men and women. Similarly, the clearer association for vitamin K_1 intake observed among normal to overweight participants compared to obese participants in the present study could be due to the higher proportion of adipose tissue among obese participants. In the present study, the 20-year estimated absolute risk difference of diabetes for high vs low vitamin K_1 intake was higher for all subgroups at high risk of T2D (men, smokers, obese participants, and those with low physical activity). Thus, promoting increased intake of vitamin K_1 among these subgroups may help to reduce T2D incidence in coming years at a population level. Given that FFQs are unreliable at estimating absolute intakes, participants in the lowest quintile of vitamin K_1 intake had only approximately 1 µg/kg body weight (median: 57 µg/d) of vitamin K_1 and it seemed insufficient to lower the risk of T2D in this study. In Europe, the current adequate intake for vitamin K is 1 µg/kg body weight per day for adults (52), so concern remains as to whether this is sufficient for other physiological needs of the body beyond blood clotting; also important to consider is whether this intake level is sufficient to prevent T2D.

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Mounting evidence suggests an increased risk of diabetes with the use of statins (24) but the mechanism for this relationship is unknown. Hypotheses include impaired insulin sensitivity from statin therapy, pancreatic β-cell deterioration, and changes in β-cell Ca^{2+} channel function (53). Statins inhibit UbiA prenyltransferase domain-containing protein 1 (UBIAD1) activity (23), an enzyme responsible for vitamin K degradation, and may inhibit synthesis of vitamin K_2 within the vasculature (54). Further, vitamin K_2 is also assumed to lower the risk of T2D (55). In addition, findings from a recent cross-sectional study suggest a functional deficiency of vitamin K among statin users compared to nonusers (56), though these observations are confounded by different patient characteristics and dietary vitamin K was not taken into consideration. Our study provides some evidence that statin therapy may modify the relationship between vitamin K_1 intake and diabetes; however, we need to be cautious while interpreting this finding as it could be due to confounding by indication for statin users compared to nonusers. While the benefit of statin therapy in cardiovascular disease prevention and treatment is unquestionable, further studies should clarify the mechanistic pathways between statin therapy and vitamin K metabolism, specific to insulin resistance, and the clinical effect of the potential interaction between vitamin K_1 and statin use.

The main strength of this study is the large sample size and use of population-based registries cross-linking socioeconomic and health-related data on an individual level. This enabled a long follow-up of 23 years with negligible loss to follow-up and, thus, the absolute risk prediction of incident diabetes. In addition, associations persisted after adjustment for key dietary confounders and among those with the highest vegetable intakes, indicating a role of vitamin K_1 in preventing diabetes. However, the strengths of the study must be balanced against its limitations. First, dietary intake was measured only at baseline and participants might have changed their diet during follow-up. This single measure might have introduced nondifferential misclassification in vitamin K_1 intake estimations and a bias in the association toward null. In addition, dietary vitamin K_1 estimates are derived from a combination of FFQ and food databases; we assumed that any misclassification of the exposure would be random, which would shift the association toward the null. Second, the incident diabetes outcome cannot distinguish between type 1 diabetes and T2D. However, given that type 1 diabetes usually accounts for only less than 10% of all diabetes, the early onset of most type 1 (aged <30 years) and the age range of the cohort (50-64 years) free of diabetes at baseline, the incident cases can be assumed to be predominantly T2D. We might have missed a few incident diabetes cases that are entirely on diet/lifestyle modifications and are missing from the Danish Prescription Register. In addition, some undiagnosed prevalent diabetes cases may have been included in this study, which likely biases our results toward null. Third, the associations observed could be attributed to other healthy behaviors apart from vitamin K_1 intake. To address this, we adjusted for several risk factors of T2D as well as other dietary behaviors and observed that the association remained inverse and statistically significant, but residual confounding cannot be ruled out. Further, there may have been unmeasured confounding such as gestational diabetes and pharmaceutical supplementation of vitamin K_1. Fourth, dietary vitamin K_1 intake may be a marker of other bioactives coexisting in vegetables (eg, β-carotene, ascorbic acid, nitrate, folate) (9) and plant oils (eg, monounsaturated and polyunsaturated fatty acids and vitamin E) (57) together with vitamin K_1. These components might act synergistically and maximize the effect observed, thereby preventing diabetes incidence so the study findings for vitamin K_1 alone could be an overestimate. Last, prevalent hypercholesterolemia was likely underreported as only 7.2% of participants reported hypercholesterolemia at baseline.

In summary, vitamin K_1 intake, from foods such as green leafy vegetables, cruciferous vegetables, and plant oils, were inversely associated with incident diabetes. Our findings emphasize the necessity of adequate intake of vitamin K_1, especially among high-risk subgroups (men, smokers, individuals with obesity, and those with low physical activity), as a potential means of reducing diabetes incidence at the population level.

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Author Contributions

L.C.B., C.P.B., J.M.H., and N.P.B. conceived the study design. P.P., K.M., and N.P.B. performed the analyses. P.P. and N.P.B. wrote the first draft of the paper. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript. N.P.B. is the guarantor of this work and as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Availability

Data described in the manuscript, code book, and analytic code will be made available on request pending application and approval by the Diet, Cancer, and Health Steering Committee at the Danish Cancer Society.

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