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Vitamin K1 intake and incident diabetes in the Danish Diet Cancer and Health Study: Supplemental information

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Vitamin K_1 intake and incident diabetes in the Danish Diet Cancer and Health Study: Supplemental information

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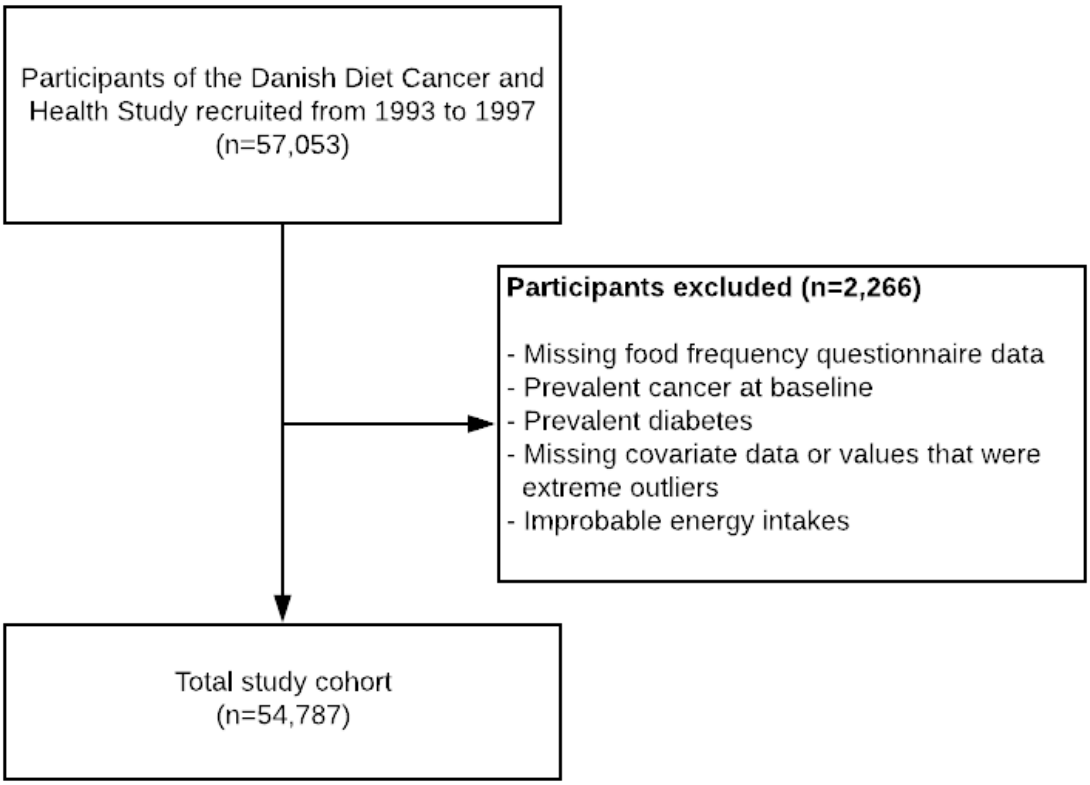
Table of contents

List of figures

List of tables



Supplemental Figure 1: Participant consort flow diagram.

Supplemental Table 1. Covariates included in models

Model 1a: Minimally-adjusted	Age and sex
Model 1b: Multivariable-adjusted	Age, sex, smoking status (current/former/never), physical activity (total daily metabolic equivalent categorised into quintiles), pure alcohol intake (0 grams per day/≤20 grams per day/20< and ≤40 grams per day/≥40 grams per day), social economic status (income categorised into quartiles), education, and hormone replacement therapy (females only; current/former/never)
Model 2: Multivariable-adjusted including covariates that are both potential confounders and potentially on the causal pathway	Age, sex, smoking status, physical activity, pure alcohol intake, social economic status, education, hormone replacement therapy, BMI (kg/m^2), hypertension (yes/no), hypercholesterolemia (yes/no), and prevalent disease (cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cancer; entered in the model separately)
Model 3: Multivariable-adjusted including energy intake and potential dietary confounders	Age, sex, smoking status, physical activity, pure alcohol intake, social economic status, education, hormone replacement therapy, energy intake (kJ/day), and intakes (g/d) of fish, red meat, processed meat, polyunsaturated fatty acids, monounsaturated fatty acids, saturated fatty acids, fibre, added sugar, wholegrains, refined grains, and fruit.

Supplemental Table 2. Association between vitamin K_1 intake and incident diabetes, stratified by diabetes risk factors

Stratification	Models	Vitamin K_1 intake quintiles				
		Q1	Q2	Q3	Q4	Q5
Sex						
Male	Model 1a	Ref.	0.87 (0.81, 0.92)	0.73 (0.68, 0.78)	0.60 (0.55, 0.65)	0.50 (0.45, 0.54)
	Model 1b	Ref.	0.95 (0.89, 1.01)	0.85 (0.79, 0.92)	0.74 (0.68, 0.81)	0.64 (0.59, 0.71)
	Model 2	Ref.	0.97 (0.91, 1.03)	0.91 (0.84, 0.97)	0.83 (0.76, 0.90)	0.76 (0.69, 0.84)
	Model 3	Ref.	0.97 (0.89, 1.05)	0.89 (0.80, 0.98)	0.8 (0.71, 0.89)	0.71 (0.62, 0.81)
Female	Model 1a	Ref.	0.83 (0.77, 0.88)	0.74 (0.68, 0.79)	0.67 (0.61, 0.74)	0.60 (0.54, 0.66)
	Model 1b	Ref.	0.91 (0.85, 0.98)	0.87 (0.80, 0.94)	0.83 (0.76, 0.92)	0.76 (0.69, 0.85)
	Model 2	Ref.	0.91 (0.85, 0.98)	0.89 (0.82, 0.96)	0.89 (0.81, 0.97)	0.84 (0.76, 0.94)
	Model 3	Ref.	0.87 (0.80, 0.96)	0.85 (0.76, 0.95)	0.85 (0.74, 0.98)	0.81 (0.69, 0.96)
Smoking status						
Never smoker	Model 1a	Ref.	0.84 (0.77, 0.92)	0.73 (0.65, 0.81)	0.63 (0.56, 0.71)	0.52 (0.46, 0.59)
	Model 1b	Ref.	0.91 (0.83, 1.00)	0.84 (0.75, 0.93)	0.75 (0.67, 0.85)	0.64 (0.57, 0.73)
	Model 2	Ref.	0.93 (0.85, 1.02)	0.89 (0.80, 1.00)	0.86 (0.76, 0.97)	0.78 (0.68, 0.89)
	Model 3	Ref.	0.90 (0.80, 1.01)	0.84 (0.72, 0.98)	0.79 (0.67, 0.93)	0.71 (0.58, 0.87)
Ever smoker	Model 1a	Ref.	0.86 (0.82, 0.91)	0.75 (0.70, 0.79)	0.65 (0.60, 0.69)	0.56 (0.52, 0.61)
	Model 1b	Ref.	0.95 (0.90, 1.00)	0.88 (0.83, 0.94)	0.81 (0.75, 0.87)	0.74 (0.68, 0.80)
	Model 2	Ref.	0.95 (0.90, 1.00)	0.89 (0.84, 0.95)	0.84 (0.78, 0.91)	0.79 (0.73, 0.86)
	Model 3	Ref.	0.94 (0.88, 1.01)	0.89 (0.82, 0.97)	0.85 (0.76, 0.94)	0.78 (0.69, 0.89)
BMI						
≤30 kg/m^2	Model 1a	Ref.	0.87 (0.82, 0.93)	0.75 (0.70, 0.80)	0.64 (0.59, 0.69)	0.54 (0.50, 0.59)
	Model 1b	Ref.	0.96 (0.90, 1.01)	0.88 (0.82, 0.94)	0.78 (0.72, 0.85)	0.69 (0.63, 0.75)
	Model 2	Ref.	0.96 (0.90, 1.02)	0.89 (0.83, 0.95)	0.81 (0.75, 0.88)	0.74 (0.68, 0.81)
	Model 3	Ref.	0.96 (0.89, 1.03)	0.90 (0.82, 0.99)	0.83 (0.74, 0.93)	0.75 (0.66, 0.86)
>30 kg/m^2	Model 1a	Ref.	0.86 (0.80, 0.93)	0.84 (0.78, 0.91)	0.83 (0.75, 0.92)	0.78 (0.70, 0.87)
	Model 1b	Ref.	0.91 (0.85, 0.98)	0.92 (0.85, 1.00)	0.93 (0.84, 1.03)	0.88 (0.79, 0.99)
	Model 2	Ref.	0.91 (0.84, 0.98)	0.92 (0.84, 1.00)	0.93 (0.84, 1.03)	0.89 (0.80, 1.00)
	Model 3	Ref.	0.90 (0.82, 0.99)	0.92 (0.82, 1.04)	0.95 (0.82, 1.10)	0.91 (0.76, 1.08)
MET score						
<56.5	Model 1a	Ref.	0.85 (0.80, 0.90)	0.74 (0.69, 0.79)	0.64 (0.59, 0.70)	0.54 (0.49, 0.59)
	Model 1b	Ref.	0.92 (0.87, 0.98)	0.86 (0.80, 0.92)	0.79 (0.73, 0.87)	0.69 (0.63, 0.76)
	Model 2	Ref.	0.92 (0.87, 0.98)	0.89 (0.83, 0.95)	0.85 (0.78, 0.93)	0.77 (0.70, 0.85)
	Model 3	Ref.	0.90 (0.84, 0.98)	0.85 (0.77, 0.94)	0.8 (0.71, 0.91)	0.70 (0.61, 0.81)
≥56.5	Model 1a	Ref.	0.86 (0.80, 0.92)	0.74 (0.68, 0.81)	0.63 (0.58, 0.69)	0.54 (0.49, 0.60)
	Model 1b	Ref.	0.94 (0.88, 1.01)	0.86 (0.79, 0.94)	0.77 (0.70, 0.84)	0.68 (0.62, 0.76)
	Model 2	Ref.	0.95 (0.89, 1.02)	0.90 (0.83, 0.98)	0.85 (0.77, 0.93)	0.80 (0.73, 0.89)
	Model 3	Ref.	0.93 (0.86, 1.02)	0.88 (0.78, 0.99)	0.83 (0.73, 0.94)	0.78 (0.67, 0.91)

Hazard ratios (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 – 5, to the median intake in quintile 1. Unless indicated by the stratification variable, model 1a adjusted for age and sex; Model 1b adjusted for age, sex, smoking status, physical activity, alcohol intake, social economic 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, wholegrains, refined grains, and fruit.

Supplemental Table 3. Association between vitamin K_1 intake and incident diabetes, stratified by tertiles of total vegetable intake

		Vitamin K_1 intake quintiles				
Baseline vegetable intake by tertile*		**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
1	No. events	1,530	807	306	84	11
84 [0 – 123] g/d	HR (95% CI)	Ref.	0.88 (0.80, 0.97)	0.80 (0.72, 0.89)	0.72 (0.61, 0.85)	0.61 (0.43, 0.86)
2	No. events	149	607	708	493	133
161 [123 – 203] g/d	HR (95% CI)	Ref.	0.91 (0.78, 1.06)	0.82 (0.68, 0.98)	0.72 (0.61, 0.85)	0.59 (0.46, 0.75)
3	No. events	17	114	292	614	835
266 [203 – 1529] g/d	HR (95% CI)	Ref.	0.85 (0.76, 0.95)	0.74 (0.60, 0.91)	0.64 (0.48, 0.85)	0.57 (0.44, 0.73)

Hazard ratios (95% CI) for incident diabetes during 23 years of follow-up, obtained from Cox proportional hazards models using Model 1b for adjustment: age, sex, smoking status, physical activity, alcohol intake, social economic status (income), education, and hormone replacement therapy.

*Median; range in parentheses (all such values)

Supplemental Table 4. Association between vitamin K_1 intake and incident diabetes, stratified by Nordic diet index

Nordic Diet Index (NDI)		Vitamin K_1 intake quintiles				
		Q1	**Q2**	**Q3**	**Q4**	**Q5**
Low NDI (0-2)	No. events	557	544	515	477	373
	HR (95% CI)	Ref.	0.91 (0.85, 0.98)	0.83 (0.75, 0.93)	0.78 (0.70, 0.88)	0.72 (0.59, 0.88)
Med NDI (3-4)	No. events	711	629	582	528	447
	HR (95% CI)	Ref.	0.90 (0.82, 0.99)	0.82 (0.74, 0.92)	0.76 (0.68, 0.85)	0.68 (0.61, 0.77)
High NDI (5-6)	No. events	315	303	267	239	213
	HR (95% CI)	Ref.	0.94 (0.82, 1.08)	0.89 (0.69, 1.16)	0.84 (0.60, 1.16)	0.74 (0.56, 0.98)

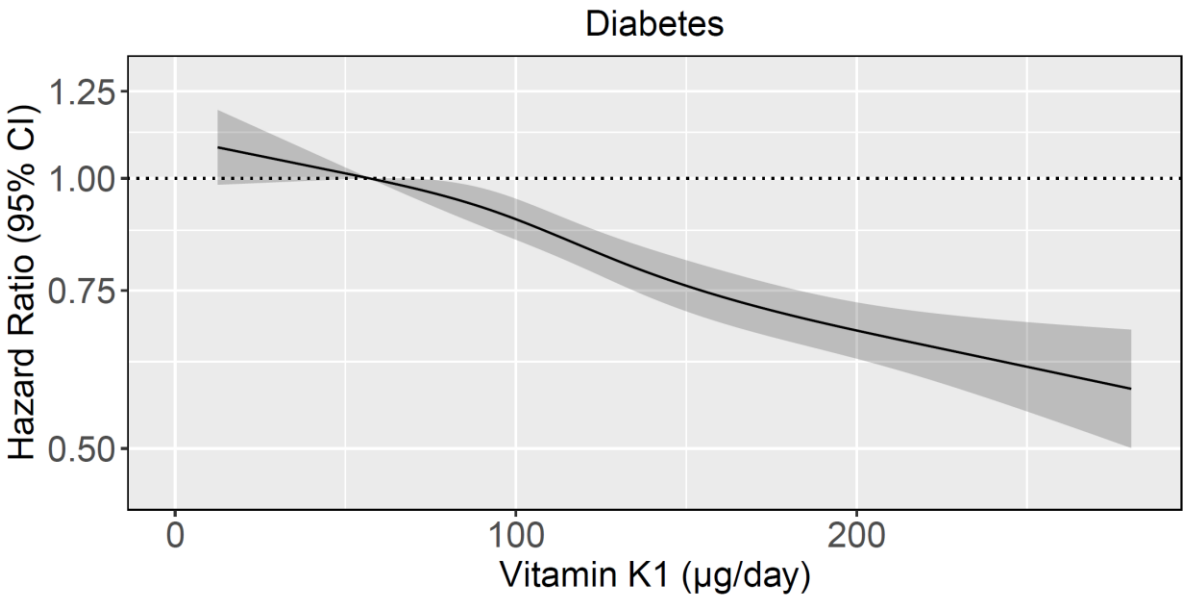
Hazard ratios (95% CI) for incident diabetes during 23 years of follow-up, obtained from Cox proportional hazards models using Model 1b for adjustment: age, sex, smoking status, physical activity, alcohol intake, social economic status (income), education, and hormone replacement therapy.

Supplemental Table 5. Hazard ratios of incident diabetes by statin therapy and quintiles of vitamin K_1 intake in a time-updated analysis

	Vitamin K_1 intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
P-value for interaction* = 0.002					
HR (95% CI)					
No statin therapy	ref.	0.88 (0.80, 0.97)	0.74 (0.67, 0.82)	0.71 (0.64, 0.78)	0.60 (0.54, 0.67)
Statin therapy	ref.	1.00 (0.90, 1.11)	0.93 (0.84, 1.04)	0.89 (0.79, 0.99)	0.78 (0.69, 0.88)

Hazard ratios (95% Confidence Intervals) for incident diabetes during 23 years of follow-up, obtained from time-updated Cox proportional hazards models. We used Model 1b adjustments: age, sex, smoking status, physical activity, alcohol intake, social economic status (income), education, hormone-replacement therapy.

*P value for the interaction term between vitamin K_1 intake and time-updated statin therapy.



Supplemental Figure 2: The association between vitamin K_1 intake (µg/day) and incident diabetes (n=6626), after censoring participants upon prescription of a vitamin K antagonist. Hazard ratios are derived from a Cox proportional hazards model with restricted cubic spline curves adjusting for age, sex, smoking status, physical activity, alcohol intake, social economic 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 (57 µg/d).