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Substitutions between dairy products and risk of stroke: Results from the EPIC-NL cohort

Anne Sofie D. Laursen[1], Ivonne Sluijs[2], Jolanda M.A. Boer[3], W.M. Monique Verschuren[2,3], Yvonne T. van der Schouw[2], & Marianne U. Jakobsen[1,4]

[1]Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark

[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.

[3]Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

[4]National Food Institute, Division for Diet, Disease Prevention and Toxicology, Technical University of Denmark, Kongens Lyngby, Denmark

Corresponding author: Anne Sofie Dam Laursen
Bartholins Allé 2, DK-8000 Aarhus C, Denmark
E-mail: asdl@ph.au.dk
Phone: +45 21 84 42 84
Fax: +45 87 15 02 01

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Abstract

The association between intake of different dairy products and the risk of stroke remains unclear. We therefore investigated substitutions between dairy product subgroups and risk of stroke. We included 36,886 Dutch men and women. Information about dairy product intake was collected through a food frequency questionnaire. Dairy products were grouped as low-fat milk, whole-fat milk, buttermilk, low-fat yoghurt, whole-fat yoghurt, cheese and butter. Incident stroke cases were identified in national registers. We used Cox proportional hazards regression to calculate associations for substitutions between dairy products with the rate of stroke. During a median follow-up of 15.2 years we identified 884 stroke cases (503 ischemic and 244 hemorrhagic). Median intake of total dairy products was 4 servings/day. Low-fat yoghurt substituted for whole fat yoghurt was associated with a higher rate of ischemic stroke (HR=2.58, 95 % CI: 1.11, 5.97 per serving/day). Whole fat yoghurt as a substitution for any other subgroup was associated with a lower rate of ischemic stroke (HRs between 0.33 and 0.36 per serving/day). We did not observe any associations for hemorrhagic stroke. In conclusion, whole-fat yoghurt as a substitution for low-fat yoghurt, cheese, butter, buttermilk or milk regardless of fat content was associated with a lower rate of ischemic stroke.

Introduction

The Dietary Approaches to Stop Hypertension (DASH) diet [(1)] is recommended for stroke prevention [(2)]. The diet prescribes a high daily intake of low-fat dairy products, while restricting the intake of regular-fat or high-fat dairy. However, a study which compared a modified DASH diet including whole-fat dairy products and no low-fat dairy products with the original DASH diet, observed a similar beneficial effect on blood pressure as with the original DASH diet[(3)]. Also, the modified DASH diet was found to reduce plasma triglyceride and very-low density lipoprotein cholesterol concentrations without increasing low-density lipoprotein cholesterol[(3)], a potentially beneficial improvement in lipid profile. Most studies on dairy products and the risk of stroke have investigated intakes of total dairy products, total milk or dairy products categorized as either low-fat or whole-fat [(4; 5; 6; 7; 8)]. However, dairy products comprise a range of individual product types with individual nutritional properties [(9)] and therefore these categorizations may be too broad. For instance, in a recent meta-analysis of 18 follow-up studies investigating dairy product intake and the risk of stroke it was observed that intake of total whole-fat dairy products was associated with a lower risk of stroke while intake of whole-fat milk was associated with a higher risk of stroke [(10)]. Moreover, intake of total fermented dairy products including cheese was associated with a marginally statistically non-significant lower risk of stroke [(10)]. The authors thus call for future research with detailed information about product type and fat content. The studies included in this meta-analysis all investigated differences in intake of total dairy products or dairy product subgroups while adjusting for total energy intake, thus holding it constant. Once energy intake is held constant, the individuals with different intakes of dairy products will also differ in other non-specified energy-providing foods. Hence, these studies do not address whether one type of dairy product is to be preferred over another. Using specified food substitution analyses allows for direct comparison between different types of dairy products. Only one previous study has investigated substitutions between dairy products and risk of stroke, and observed that whole-fat yoghurt products as a substitution for low-fat yoghurt products, cheese or milk regardless of fat content was associated with a lower rate of stroke [(11)] but these results have yet to be confirmed by other studies.

Our aim was to investigate associations for substitutions between dairy product subgroups with incident stroke in a Dutch cohort with large quantities and varieties of dairy products habitually consumed.

Methods

Study population

We used data from the Dutch participants of the European Investigation into Cancer and Nutrition (EPIC-NL), which has previously been described [12]. The EPIC-NL cohort is comprised by two cohorts, Prospect and the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN). The Prospect study included 17,357 women aged 49-70 years and the MORGEN study included 22,654 men and women aged 21–64 years. All participants were recruited from 1993 through 1997 and the protocols for the cohorts were designed in collaboration, yielding compatible infrastructure. The studies complied with the Declaration of Helsinki and were approved by local medical ethical committees. All participants gave informed consent to participate in the study [12].

Of the 40,011 recruited participants we excluded 1,763 participants who did not give permission to register linkage for vital status or disease occurrence or for whom the cause of death was missing and 453 participants who reported having had a stroke prior to enrollment. Furthermore, we excluded participants in the top and bottom 0.5 % of the ratio of energy intake to estimated basal metabolic rate (n=352) and participants with missing exposure or covariate information (n=557), yielding a study sample of 36,886 men and women (Supplementary figure 1).

Dietary assessment

Information about food intake was obtained through a semi-quantitative food frequency questionnaire (FFQ) with 79 main items covering habitual consumption of 178 foods. Intake of dairy products was specifically addressed in items regarding breakfast cereals, butter and cheese eaten on bread, milk and yoghurt for drinking, dairy products used in coffee, butter used for cooking and dairy based desserts.

The reproducibility and validity of the questionnaire has been investigated [13]. The Spearman rank correlation coefficients for the validity assessed by comparison with 12 24-hr diet recalls were 0.64 and 0.38 for cheese among men and women, respectively and 0.71 and 0.79 for milk and milk products among men and women, respectively.

For the present study we divided dairy intake into the following groups: 1) low-fat milk (skimmed and semi-skimmed milk, <2 % fat), 2) whole-fat milk (whole-fat, raw and powdered milk, ≥3 % fat), 3) buttermilk, 4) low-fat yoghurt products (skimmed and semi-skimmed regular and drink yoghurt, <2 % fat, curd), 5) whole-fat yoghurt products (regular and drink yoghurt, ≥ 3 % fat), 6) cheese and 7) butter. The dairy product intake was expressed in servings/day and in kcal/day. For milk and yoghurt products the serving size was 200g and for cheese and butter it was 20g and 6g, respectively. We did not include intake of custard, whipped cream and chocolate milk in the analyses.

Stroke ascertainment

Stroke cases were defined according to the International Classification of Diseases 10th edition as codes I60-I66. Data on stroke occurrence were obtained through a standardized register for hospital discharge diagnoses administered by the Dutch Centre for Health Care Information since 1990. The register was linked to the cohort participants on the basis of birth date, sex, postal code and general practitioner by a validated probabilistic method as previously described [12; 14]. Information about vital status was collected via municipal registries. Subsequently, primary and secondary causes of death were obtained through linkage with data from Statistics Netherlands. The stroke cases were classified as ischemic or hemorrhagic. Participants were followed until the date of an incident stroke, death from another cause, loss to follow-up or were censored at 31st December 2010, whichever came first.

Covariate information

Baseline characteristics were collected using a self-administered questionnaire except for blood pressure and anthropometrical measurements which were collected at a physical examination.

Educational attainment was categorized as low (primary up to intermediate vocational education), intermediate (intermediate vocational education and higher secondary education) or high (higher vocational education and university). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Physical activity level was defined as inactive, moderately inactive, moderately active or active according to the Cambridge physical activity index [7; 12; 15]. Hypertension was defined on the basis of either self-reported physician-diagnosed hypertension, self-reported use of antihypertensive medication, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at the baseline examination. Hypercholesterolemia and previous myocardial infarction were self-reported. Prevalent diabetes mellitus was collected through self-report and linkage with hospital discharge diagnosis registers and was verified by the general practitioner [16]. Information about alcohol intake and intake of food groups other than dairy was collected with the FFQ. We also calculated a modified version of the Dutch Healthy Diet index 2015 (DHD2015) in order to adjust for overall diet quality [17]. The index measures adherence to the 2015 dietary guidelines from the Dutch Health Council [18]. With the data available, we were able to include 13 of the 15 original indicators: Fruit, vegetables, wholegrain products, legumes, nuts, dairy products, fish, tea, fat and oils, red meat, processed meat, sweetened beverages and fruit juices and alcohol. The dairy product component, however, was excluded because dairy products are our main exposure.

Statistical analyses

The associations for substitutions between subgroups of dairy products and the rate of total, ischemic and hemorrhagic stroke were investigated using Cox proportional hazard regression with age as the underlying time scale and adjusted for cohort (as stratum variable).

The substitution model (Model 1) included intake of all individual subgroups of dairy products (servings/day) except the dairy product subgroup to be substituted (i.e. 6 out of 7 subgroups were included in the model) and a variable representing the total number of servings of dairy products and total energy intake (kcal/day). It follows that the hazard ratio (HR) for each dairy product subgroup in the model can be interpreted as the difference in the rate of stroke for a one serving/day higher intake of the subgroups included in the model and a concomitant lower intake of the subgroup left out of the model. Using the same analytical approach, we also analyzed isocaloric substitutions of 100 kcal/d. The substitution analyses were adjusted as follows: education (categorical), BMI-adjusted waist circumference (residuals of waist circumference regressed on BMI) (continuous), smoking (categorical), physical activity (categorical), alcohol intake (5-knot spline) (Model 2) and DHD2015 (continuous) (Model 3). We further adjusted the analyses for the potential intermediate conditions hypertension, hypercholesterolemia, diabetes mellitus and myocardial infarction at baseline in a separate model (Model 4).

The assumption of independent delayed entry was investigated by including the date of enrollment in the models. As no association between the date of enrollment and stroke was found the assumption was deemed satisfied. The proportional hazards assumption tested with Schoenfeld residuals was satisfied. In order to determine departures from linearity in the substitution models, we plotted martingale residuals against the dairy product subgroup variables and included a lowess smooth and found no departure from linearity.

We further investigated potential effect modification between dairy product variables and the covariates sex age, BMI-adjusted waist circumference, smoking, alcohol, physical activity and DHD2015. We used likelihood ratio tests where we compared models (model 3) with and without interaction terms for the respective dairy product and covariate variables. We found no indication of effect modification (p-values between 0.07-0.99).

We performed sensitivity analyses where participants diagnosed with hypertension, hypercholesterolemia, diabetes mellitus or myocardial infarction at baseline were excluded, as the treatment for these conditions include dietary changes. These analyses were only performed for total and ischemic stroke due to too few cases of hemorrhagic stroke.

All analyses were performed using Stata 13.1 (College Station, Texas, USA).

Results

During a median follow-up of 15.2 years we identified 884 stroke cases including 503 ischemic, 244 hemorrhagic and 137 unclassified types of stroke. Participant characteristics across quintiles of dairy product subgroups are given in table 1 and supplementary tables 1-6. While there were no pronounced differences in characteristics between quintiles of low-fat milk intake (table 1), participants with a high intake of whole-fat milk or butter were more likely to be men, current smokers and have a higher alcohol intake (supplementary tables 1 and 6). For both low-fat and whole-fat yoghurt, those with high intakes compared to the lowest were more likely to be women and drink less alcohol and less likely to be current smokers or physically inactive. Moreover, participants with a high intake of yoghurt had higher intakes of fruit and vegetables and lower intakes of red and processed meat compared to participants with the lowest intake (supplementary tables 3 and 4).

For ischemic stroke, we did not observe an association for low-fat milk as a substitution for whole-fat milk (HR=0.97, 95% confidence interval (CI): 0.73, 1.30), whereas low-fat yoghurt products as a substitution for whole fat yoghurt products were associated with a higher rate (HR=2.58, 95 % CI: 1.11, 5.97). Also, whole-fat yoghurt products as a substitution for milk, buttermilk, cheese or butter were associated with a lower rate of ischemic stroke (low-fat milk: HR=0.34, 95 % CI: 0.15, 0.75, whole-fat milk: HR=0.33, 95 % CI: 0.14, 0.74, buttermilk: HR=0.35, 95 % CI: 0.16, 0.78, cheese: HR=0.35, 95 % CI: 0.16, 0.77, butter: HR= 0.36, 0.16, 0.79) (table 2). We did not observe any association for substitutions between dairy product subgroups with the rate of total or hemorrhagic stroke (supplementary table 7 and table 3).

When we repeated the analyses without the participants who reported a history of hypertension, hypercholesterolemia, diabetes mellitus or myocardial infarction at baseline, the patterns of associations remained the same, although the results did not reach statistical significance (supplementary tables 8 and 9).

When isocaloric substutions of 100 kcal/day were performed, we observed similar patterns of associations as for substitutions of servings (supplementary tables 10-12).

Discussion

In this prospective cohort study we observed that intake of whole-fat yoghurt products as a substitution for all other dairy product subgroups was associated with a lower rate of ischemic stroke. We did not observe any associations for substitutions between dairy products and the rate of total or hemorrhagic stroke.

Our study has important strengths but also limitations. We had detailed information about intake of several types of dairy products, which enabled us to directly compare individual diary product subgroups. We collected data on dairy product intake using a validated FFQ [(12)]. The correlation coefficients for the validity assessed by comparison with 12 24-hr diet recalls were 0.64 and 0.38 for men and women, respectively, for cheese and 0.71 and 0.79 for men and women, respectively, for milk and milk products, indicating that some non-differential misclassification of dairy product intake may be present. In the validation study, milk and yoghurt were grouped together and therefore we do not know the validity for individual types of milk and yoghurt. Although an FFQ is a suitable instrument to measure habitual diet in large-scale studies, the use of only one measurement may yield less precise risk estimates because the participants may have changed their diet during follow-up. The stroke diagnoses were identified by register linkage [(14)] but were not individually validated thus, non-differential misclassification of the outcome is possible [(19)].

Despite elaborate model adjustment, residual confounding from unknown or unmeasured stroke risk factors and misclassification of covariates may still be present. However, given the magnitude of the associations after adjustment for lifestyle and dietary risk factors, residual confounding is unlikely to fully explain the inverse association of whole-fat yoghurt as a substitution for other dairy products.

One other study has investigated substitutions between dairy product subgroups with the rate of stroke [(11)]. That study suggested that whole-fat yoghurt substituted for low-fat yoghurt, cheese, buttermilk or milk regardless of fat content was associated with a lower rate of ischemic stroke while no associations were observed for hemorrhagic stroke, which is in line with the results from the present study. The lack of association for substitutions between dairy product subgroups with hemorrhagic stroke could be due to a different etiology of hemorrhagic compared to ischemic stroke. However, both studies are likely underpowered to detect small associations, and therefore strong conclusions from those analyses cannot be drawn. Several prospective studies investigating dairy product intake and risk of stroke have been published [4; 5; 6; 7; 8; 20; 21]. These studies, however, did not specify a food substitution and therefore investigated the association of intake of dairy products in place of other non-specified energy-providing foods. Because what you choose to eat in place of a given dairy product may be population specific and may affect the association, the studies are not readily comparable and they do not directly address whether one type of dairy product is to be preferred over another.

Our results suggest that whole-fat yoghurt may be the better alternative to other dairy products for the prevention of ischemic stroke. In a randomized crossover study which compared the regular DASH diet with a modified high-fat DASH diet including whole-fat dairy products rather than low-fat dairy products, similar beneficial effects on blood pressure were observed for both diets as well as favorable effects on the lipid profile with the high-fat DASH diet [3]. The compared diets had similar total energy contents but differed in the energy content provided by dairy foods. Consequently the diets also differed in other energy-providing foods, in this case, particularly fruit juices and sugar from sweets. Therefore, the observed effects cannot solely be attributed to whole-fat dairy products because it is a joint effect of a higher intake of whole-fat dairy products and lower intake of fruit juices and sugars. In our study, the observed associations also represent a joint association, namely, the comparison of two specified dairy subgroups. However when we compare equal serving sizes of products differing in energy content or foods with different serving sizes, a difference in energy from other non-specified foods will remain unexplained by the model but this unexplained residual energy is much smaller than if we had not specified substitutions. In order to address the influence of unexplained residual energy intake in our analyses, we also performed isocaloric substitution analyses of 100 kcal/d, which roughly corresponds to the energy content of a glass of low-fat milk. The results from these analyses did not markedly differ from the results based on servings, which implies that unexplained energy intake may not be a major issue in the analyses of servings. This is perhaps because the difference in energy content of equal servings of milk and yoghurt is relatively small in the light of the total daily energy intake. Also, despite a large difference in energy density between milk products and cheese and butter, this difference is compensated for by the large difference in serving size. Consequently, in the case of substitution of dairy products, the two analytical approaches are comparable. This may however, not always be the case. For instance 100 kcal/d isocaloric substitutions between spinach and regular-fat cheese will approximately compare 400 grams of spinach with 30 grams of cheese. While such an analysis is not confounded by a difference in energy intake of other foods, it does not reflect choices of substitution made in the population. Thus, both analytical approaches hold important information but have limitations.

Multiple mechanisms might explain why whole-fat yoghurt products appear to be a better alternative than other dairy products. Dairy fat contains conjugated linoleic acid, which has been proposed to have beneficial health effects related to atherosclerosis, such as changes in body fat, lipid profile and blood pressure [22; 23]. Conjugated linoleic acid is formed in the rumen and mammary gland of the cow and to a lesser extent endogenously in humans by conversion of vaccenic acid in dairy fat [24; 25; 26]. Fermented milk products, such as yoghurt, contain probiotic cultures, such as lactobacilli and bifidobacteria, that may further increase the product content of conjugated linoleic acid through conversion of linoleic acid [27]. In addition, different probiotic cultures may also individually exert anti-atherosclerotic effects [23]. Therefore, our results may reflect a synergistic effect of high fat content and the presence of probiotic bacteria. The fat content alone does not appear to explain the found associations, as we did not find an association for the substitution between low-fat and whole-fat milk. Similarly, the presence of probiotic bacteria alone does not appear to explain the found associations, as we did not find an association for the substitution of low-fat yoghurt for low-fat milk. Furthermore, milk intake has been positively associated with urinary 8-iso-PGF2α, a biomarker of oxidative stress, whereas fermented milk intake has been negatively associated with 8-iso-PGF2α [28], offering an additional possible explanation for why whole-fat yoghurt products as a substitution for milk are associated with a lower rate of ischemic stroke in our study.

In conclusion, we observed that substitution of whole-fat yoghurt products for low-fat yoghurt products, cheese, butter, buttermilk or milk regardless of fat content was associated with a lower rate of ischemic but not hemorrhagic stroke.

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A.S.D.L. and M.U.J. designed the study; A.S.D.L. analyzed the data; A.S.D.L, M.U.J, I.S and Y.v.d.S. interpreted the data. A.S.D.L wrote the manuscript. J.M.A.B. and W.M.M.V. provided input to the manuscript. All authors read and approved the final version of the manuscript. The authors declare that there are no conflicts of interest.

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Table 1. Participant Characteristics in the EPIC-NL Cohort (N=36,886).

		Quintiles of low-fat milk				
	All participants	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
Total stroke (n)	884	181	171	161	201	170
Sex, men (%)	25.4	20.5	26.2	30.0	22.6	27.5
Age (years)	51.4	52.2	51.3	50.2	52.3	50.8
	(31.1 ; 63.4)	(35.2 ; 63.3)	(32.3 ; 63.2)	(28.7 ; 62.5)	(32.2 ; 64.8)	(27.8 ; 63.2)
Body mass index (kg/m^2)	25.1	25.1	25.1	24.9	25.3	25.2
	(22.9 ; 30.8)	(21.1 ; 31.3)	(21.1 ; 30.6)	(21.1 ; 30.3)	(21.4 ; 30.9)	(21.3 ; 30.9)
Waist circumference (cm)						
- Men	92.0	93.0	92.0	91.5	91.4	92.0
	(79.0 ; 106.3)	(80.0 ; 107.8)	(79.8 ; 106.5)	(78.5 ; 105.0)	(78.5 ; 106.0)	(79.0 ; 106.8)
- Women	81.5	81.3	81.0	80.5	82.0	82.0
	(70.2 ; 97.0)	(70.0 ; 97.6)	(70.0 ; 96.0)	(70.0 ; 95.7)	(71.0 ; 97.0)	(71.0 ; 97.5)
Low educational attainment (%)	57.9	58.3	58.0	57.6	60.0	55.4
Current smoker (%)	30.3	30.8	30.5	33.6	27.4	29.3
Physically inactive	7.4	9.0	7.9	7.3	6.6	6.2
Alcohol consumption (g/day)	5.0	6.8	4.8	5.0	4.4	4.4
	(0.0 ; 30.3)	(0.01 ; 34.6)	(0.02 ; 30.1)	(0.02 ; 29.7)	(0.02 ; 28.7)	(0.01 ; 28.1)
Hypertension (%)	37.2	40.6	36.5	33.7	39.0	36.3
Hypercholesterolemia (%)	8.5	9.4	8.4	7.4	8.3	8.8
Diabetes (%)	1.5	1.5	1.5	0.9	1.7	1.9
Prevalent myocardial infarction (%)	1.3	1.4	1.0	1.0	1.5	1.5
Habitual food consumption (servings/day)						

Total dairy	4.01	3.21	3.52	3.81	4.07	5.26
	(1.87 ; 7.19)	(1.12 ; 6.30)	(1.57 ; 6.58)	(1.94 ; 7.08)	(2.40 ; 6.81)	(3.39 ; 8.49)
Low-fat milk	0.46	0.05	0.19	0.46	0.88	1.71
	(0.05 ; 1.71)	(0.00 ; 0.10)	(0.13 ; 0.27)	(0.33 ; 0.66)	(0.77 ; 1.12)	(1.38 ; 3.02)
Whole-fat milk	0.15	0.01	0.06	0.13	0.19	0.37
	(0.01 ; 0.59)	(0.00 ; 0.10)	(0.02 ; 0.55)	(0.06 ; 1.10)	(0.15 ; 0.38)	(0.27 ; 0.72)
Buttermilk	0.00	0.00	0.00	0.00	0.00	0.00
	(0.00 ; 1.00)	(0.00 ; 2.00)	(0.00 ; 2.00)	(0.00 ; 1.00)	(0.00 ; 1.00)	(0.00 ; 1.00)
Low-fat yoghurt	0.15	0.09	0.15	0.14	0.17	0.17
	(0.01 ; 0.68)	(0.00 ; 0.63)	(0.01 ; 0.74)	(0.02 ; 0.65)	(0.02 ; 0.68)	(0.02 ; 0.65)
Whole-fat yoghurt	0.05	0.03	0.05	0.06	0.06	0.07
	(0.00 ; 0.28)	(0.00 ; 0.23)	(0.01 ; 0.29)	(0.01 ; 0.27)	(0.01 ; 0.29)	(0.01 ; 0.30)
Cheese	1.50	1.51	1.50	1.47	1.50	1.50
	(0.36 ; 3.38)	(0.30 ; 3.57)	(0.34 ; 3.39)	(0.36 ; 3.30)	(0.43 ; 3.25)	(0.41 ; 3.42)
Butter	0.46	0.40	0.48	0.53	0.44	0.44
	(0.12 ; 2.06)	(0.08 ; 2.08)	(0.13 ; 2.26)	(0.15 ; 2.34)	(0.12 ; 1.77)	(0.12 ; 1.74)
Fruit	2.41	2.39	2.36	2.20	2.48	2.53
	(0.77 ; 4.77)	(0.67 ; 4.92)	(0.69 ; 4.75)	(0.73 ; 4.53)	(0.92 ; 4.73)	(0.88 ; 4.87)
Vegetables	1.09	1.10	1.07	1.07	1.09	1.10
	(0.64 ; 1.74)	(0.61 ; 1.82)	(0.63 ; 1.72)	(0.63 ; 1.70)	(0.66 ; 1.72)	(0.63 ; 1.74)
Fresh red meat	0.41	0.39	0.41	0.43	0.40	0.40
	(0.11 ; 0.70)	(0.09 ; 0.70)	(0.11 ; 0.71)	(0.12 ; 0.72)	(0.12 ; 0.67)	(0.12 ; 0.69)
Processed red meat	1.37	1.24	1.36	1.50	1.34	1.43
	(0.20 ; 4.07)	(0.11 ; 4.05)	(0.18 ; 4.10)	(0.26 ; 4.25)	(0.23 ; 3.94)	(0.23 ; 4.07)

Fish	0.05 (0.00 ; 0.13)	0.06 (0.00 ; 0.13)	0.05 (0.00 ; 0.13)	0.05 (0.00 ; 0.13)	0.06 (0.01 ; 0.13)	0.06 (0.00 ; 0.13)

Q: quintile. Median (80 % central range) unless otherwise indicated.

Table 2. Associations for 1 Serving/Day Substitutions Between Dairy Products and Risk of Ischemic Stroke in the EPIC-NL Cohort.

Substitution	Model 1		Model 2		Model 3		Model 4	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Low-fat yoghurt for								
Whole-fat yoghurt	3.73	1.58,8.81	2.74	1.18,6.35	2.58	1.11,5.97	2.27	0.99,5.22
Low-fat milk	0.82	0.62,1.08	0.86	0.66,1.13	0.87	0.67,1.14	0.87	0.67,1.15
Whole-fat milk	0.72	0.52,1.00	0.83	0.60,1.15	0.85	0.61,1.17	0.80	0.58,1.11
Buttermilk	0.86	0.64,1.14	0.90	0.68,1.18	0.90	0.68,1.19	0.89	0.68,1.18
Cheese	0.85	0.65,1.10	0.89	0.70,1.15	0.91	0.71,1.17	0.88	0.69,1.14
Butter	0.84	0.65,1.08	0.91	0.71,1.17	0.93	0.72,1.19	0.88	0.69,1.13
Whole-fat yoghurt for								
Low-fat milk	0.22	0.10,0.49	0.32	0.14,0.70	0.34	0.15,0.75	0.38	0.18,0.85
Whole-fat milk	0.19	0.08,0.44	0.30	0.13,0.69	0.33	0.14,0.74	0.35	0.16,0.79
Buttermilk	0.23	0.10,0.52	0.33	0.15,0.73	0.35	0.16,0.78	0.39	0.18,0.87
Cheese	0.23	0.10,0.51	0.33	0.15,0.71	0.35	0.16,0.77	0.39	0.18,0.85
Butter	0.22	0.10,0.50	0.33	0.15,0.73	0.36	0.16,0.79	0.39	0.18,0.85
Low-fat milk for								
Whole-fat milk	0.88	0.66,1.17	0.96	0.72,1.29	0.97	0.73,1.30	0.92	0.68,1.23
Buttermilk	1.05	0.89,1.24	1.04	0.88,1.23	1.03	0.88,1.22	1.02	0.86,1.21
Cheese	1.04	0.90,1.20	1.04	0.90,1.19	1.04	0.90,1.20	1.01	0.88,1.17
Butter	1.02	0.89,1.17	1.05	0.92,1.21	1.06	0.92,1.22	1.01	0.88,1.16
Whole-fat milk for								
Buttermilk	1.19	0.92,1.54	1.08	0.83,1.39	1.06	0.82,1.38	1.12	0.86,1.44
Cheese	1.18	0.93,1.50	1.08	0.85,1.37	1.07	0.84,1.36	1.11	0.87,1.40
Butter	1.16	0.90,1.49	1.09	0.85,1.41	1.09	0.85,1.41	1.10	0.86,1.42
Buttermilk for								
Cheese	0.99	0.85,1.15	1.00	0.86,1.15	1.01	0.87,1.16	0.99	0.86,1.15
Butter	0.98	0.84,1.13	1.01	0.87,1.18	1.03	0.88,1.19	0.99	0.85,1.15
Cheese for								

Butter	0.98	0.88,1.10	1.02	0.91,1.13	1.02	0.91,1.14	1.00	0.89,1.11

CI: Confidence interval; HR: Hazard ratio. Model 1 was adjusted for energy intake and cohort (stratum variable). Model 2 was additionally adjusted for education, BMI-adjusted waist circumference, smoking, physical activity and alcohol. Model 3 was additionally adjusted for the Dutch Health Diet index 2015. Model 4 was additionally adjusted for baseline hypertension, hypercholesterolemia, diabetes mellitus and myocardial infarction.

Table 3. Associations for 1 Serving/Day Substitutions Between Dairy Products and Risk of Hemorrhagic Stroke in the EPIC-NL Cohort.

Substitution	Model 1		Model 2		Model 3		Model 4	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Low-fat yoghurt for								
Whole-fat yoghurt	1.06	0.37,3.02	0.82	0.29,2.28	0.75	0.27,2.09	0.70	0.25,1.93
Low-fat milk	0.88	0.60,1.28	0.90	0.62,1.30	0.91	0.63,1.31	0.90	0.63,1.30
Whole-fat milk	1.15	0.68,1.93	1.28	0.76,2.16	1.30	0.77,2.20	1.25	0.74,2.11
Buttermilk	1.01	0.69,1.49	1.02	0.70,1.49	1.02	0.71,1.49	1.02	0.70,1.47
Cheese	0.92	0.65,1.29	0.95	0.68,1.32	0.96	0.69,1.34	0.95	0.68,1.32
Butter	0.84	0.60,1.17	0.89	0.64,1.23	0.91	0.66,1.25	0.88	0.64,1.22
Whole-fat yoghurt for								
Low-fat milk	0.83	0.31,2.21	1.10	0.42,2.89	1.21	0.46,3.17	1.30	0.50,3.37
Whole-fat milk	1.08	0.37,3.12	1.57	0.55,4.48	1.74	0.61,4.96	1.79	0.63,5.08
Buttermilk	0.95	0.35,2.57	1.25	0.47,3.32	1.36	0.52,3.60	1.46	0.56,3.82
Cheese	0.87	0.33,2.27	1.16	0.45,2.99	1.28	0.50,3.30	1.36	0.53,3.47
Butter	0.79	0.30,2.07	1.09	0.42,2.81	1.21	0.47,3.12	1.27	0.50,3.24
Low-fat milk for								
Whole-fat milk	1.31	0.78,2.20	1.42	0.84,2.41	1.44	0.85,2.43	1.38	0.82,2.33
Buttermilk	1.15	0.90,1.48	1.14	0.89,1.46	1.13	0.88,1.44	1.12	0.88,1.44
Cheese	1.05	0.85,1.28	1.05	0.86,1.29	1.06	0.87,1.29	1.05	0.85,1.28
Butter	0.96	0.79,1.16	0.99	0.82,1.20	1.00	0.83,1.21	0.98	0.81,1.19
Whole-fat milk for								
Buttermilk	0.88	0.56,1.39	0.80	0.50,1.27	0.79	0.50,1.25	0.81	0.51,1.29
Cheese	0.80	0.52,1.23	0.74	0.48,1.15	0.74	0.48,1.14	0.76	0.49,1.17
Butter	0.73	0.47,1.14	0.70	0.44,1.10	0.70	0.44,1.10	0.71	0.45,1.11
Buttermilk for								
Cheese	0.91	0.73,1.13	0.93	0.75,1.14	0.94	0.76,1.16	0.93	0.76,1.15

Butter	0.83	0.67,1.02	0.87	0.71,1.07	0.89	0.72,1.09	0.87	0.71,1.07
Cheese for Butter	0.91	0.80,1.05	0.94	0.82,1.08	0.95	0.82,1.09	0.93	0.81,1.07

CI: Confidence interval; HR: Hazard ratio. Model 1 was adjusted for energy intake and cohort (stratum variable). Model 2 was additionally adjusted for education, BMI-adjusted waist circumference, smoking, physical activity and alcohol. Model 3 was additionally adjusted for the Dutch Health Diet index 2015. Model 4 was additionally adjusted for baseline hypertension, hypercholesterolemia, diabetes mellitus and myocardial infarction.