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Dairy intake and coronary heart disease or stroke—A population-based cohort study ☆

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ABSTRACT

Aim: This study aimed to investigate the relationship between total dairy intake and dairy subtypes (high-fat dairy, low-fat dairy, milk and milk products, cheese and fermented dairy) with incident coronary heart disease (CHD) and stroke.
Methods: EPIC-NL is a prospective cohort study among 33,625 Dutch men and women. At baseline (1993–1997), dairy intake was measured with a validated food frequency questionnaire (FFQ). The incidence of both fatal and non-fatal CHD and stroke was obtained by linkage to the national registers.
Results: During 13 years follow-up, 1648 cases of CHD and 531 cases of stroke were documented. Total dairy intake was not significantly associated with risk of CHD (hazard ratio per standard deviation (SD) increase = 0.99; 95%-CI: 0.94–1.05) or stroke (0.95; 0.85–1.05) adjusted for lifestyle and dietary factors. None of the dairy subtypes was to CHD, while only fermented dairy tended to be associated (p = 0.07) with a lower risk of stroke (0.92; 0.83–1.01). Hypertension appeared to modify the association of total and low-fat dairy with CHD (p interaction < 0.02). Among participants without hypertension, but not among hypertensive participants, total (0.92; 0.85–1.02) and low-fat (0.94; 0.87–1.02) dairy tended to be associated with a lower risk of CHD.
Conclusion: Our results provide no evidence that dairy products are associated with risk of CHD or stroke. High intakes of total and low-fat dairy may be associated with a lower risk of CHD among participants without hypertension, while fermented dairy could be associated with a reduced risk of stroke.

1. Introduction

The intake of dairy products was thought to be associated with an increased risk of cardiovascular diseases (CVD) due to its relatively high content of saturated fat. Dietary recommendations target a diet limited in saturated fat, trans fat and cholesterol and therefore advise consuming fat-free or low-fat dairy products [1]. Such recommendations have been based on the positive linear relationship among dietary saturated fat, LDL cholesterol, and CVD risk [2].

However, a recent dose–response meta-analysis of 17 prospective studies investigated the relation of total dairy, milk, and low-fat and high-fat dairy with risk of CVD or all-cause mortality. The study indicated that milk intake was modestly inversely associated with CVD risk [3]. For coronary heart disease (CHD), stroke and all-cause mortality, no significant association with milk intake was observed. The authors also concluded that a limited number of studies are available to draw firm conclusions for specific subtypes of dairy like low- or high-fat dairy and cheese, in particular for stroke.

Meanwhile, different kinds of dairy products with varying nutrient compositions may have different effects on CHD or stroke risk. Minerals, protein and vitamins from dairy products can exert blood pressure- or cholesterol lowering effects, while saturated fat is associated with an increased risk of CHD [4]. Indeed, one study showed that in particular the ratio of high-fat dairy to low-fat dairy products is associated with an increased risk of CHD [5].

In The Netherlands, large quantities and varieties of dairy products are consumed, compared with other European countries [6]. Therefore the Dutch population provides an excellent opportunity to investigate the relation of dairy consumption and its subtypes in relation to CHD and stroke. The aim of this study is therefore to investigate the relationship of dairy intake, including the specific dairy subtypes high-fat dairy, low-fat dairy, milk and milk products, cheese and fermented dairy, with CHD and stroke in a large prospective cohort in the Netherlands.

2. Materials and methods

2.1. Study population and design

The EPIC-NL cohort is the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC) and consists of the Prospect-EPIC and MORGEN-EPIC cohorts [7]. The Prospect-EPIC study includes 17,357 women aged 49–70 years living in Utrecht and vicinity who participated in the nationwide Dutch breast cancer screening program between 1993 and 1997. The MORGEN-EPIC cohort consists of 22,654 men (n = 10,260) and women (n = 12,349) aged 21–64 years selected from random samples of the Dutch population in three different towns. Participants were recruited in both studies from 1993 to 1997. Right from the start, both Dutch cohorts collaborated closely to obtain maximal synergy on the design of the questionnaires and to follow identical protocols in the collection of biological samples. Therefore, both cohorts used standardized questionnaires and followed identical protocols in the collection of biological samples. Because of the efficiency gain in maintaining the cohort infrastructure and in conducting scientific analyses the two cohorts were merged into one EPIC-Netherlands cohort in 2006 [7]. At baseline, a general and a food-frequency questionnaire (FFQ) were administered, and a medical examination was performed for blood pressure measurements, anthropometry, and blood sampling. All participants provided informed consent before study inclusion. The study complies with the Declaration of Helsinki and was approved by the institutional board of the University Medical Center Utrecht (Prospect) and the Medical Ethical Committee of TNO Nutrition and Food Research (MORGEN).

From the total cohort (n = 40,011) subjects who did not give permission for linkage with vital status registries were excluded (n = 2717). Additionally, participants without information on dietary intake (n = 172) or with implausibly high or low scores for total food intake (outside the range of 800–4200 kcal/d for men and 500–3500 kcal/d for women) (n = 448) were excluded. Furthermore, subjects with known cardiovascular disease (n = 1099), cancer (n = 1485) or diabetes (n = 465) at baseline were excluded, leaving 33,625 participants for the present analysis.

2.2. Dietary assessment

Daily nutritional intakes were obtained from a self administered FFQ containing questions on the usual frequency of consumption of 79 main food items during the year preceding enrollment. This questionnaire allows estimation of the average daily consumption of 178 foods. A registered dietician checked the FFQ for inconsistencies, which were resolved by contacting the participant. The validity of the FFQ was assessed against 12 monthly 24-h recalls over a one-year period among 212 men and women. Spearman correlations were good for milk and milk products (r = 0.69 for men, r = 0.77 for women) and moderate for cheese (r = 0.56 and r = 0.32, respectively) [8,9].

Total dairy included all dairy food products except for butter and ice cream. Milk and milk products included all kinds of milk, yogurt, coffee creamers, curd, pudding, porridge, custard, and whipping cream. Cheese included all types of cheese except for curd. Low-fat dairy is defined as milk and milk products with a fat content <2 g/100 g (skimmed or semi-skimmed milk products) or cheese with a fat content, <20 g/100 g. High-fat dairy is defined as milk and milk products with a fat content ≥2 g/100 g (whole milk products) or cheese products with a fat content ≥20 g/100 g. Fermented dairy included buttermilk, yogurts, and cheese.

2.3. Outcome assessment

Morbidity follow-up data on coronary heart disease (CHD) events and stroke events were obtained from the Dutch Centre for Health Care Information which holds a standardized computerized register of hospital discharge diagnoses. All diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9). Follow-up was complete until the first of January 2008. The database was linked to the cohort on the basis of birth date, gender, postal code and general practitioner with a validated probabilistic method [10]. Information on vital status was obtained through linkage with the municipal registries. Causes of death were collected from Statistics Netherlands. Endpoints for the present analysis were CHD (ICD-9; 410–414, 427.5, 798.1, 798.2, 798.9) and stroke (ICD-9; 430-434, 436), whichever came first. These endpoints included both fatal and non-fatal cases of CHD and stroke. In a secondary analysis, we differentiated to non-fatal CHD obtained from hospital discharge diagnoses and CHD mortality based on causes of death. Finally, to compare our results with the meta-analysis [3], we used an endpoint of cardiovascular disease defined as a broad range of fatal and non-fatal vascular diseases including CHD, stroke, peripheral artery disease, congestive heart failure and pulmonary embolism (ICD-9: 410–414, 427.5, 428, 415.1, 443.9, 430–438, 440–442, 444, 798.1, 798.2, 798.9). In a subsample of our cohort, cases of CHD and acute myocardial infarction obtained from hospital discharge diagnoses were verified against hospital records. This showed that 91% of CHD events and 97% of acute myocardial infarction could be confirmed [11].

2.4. Other measurements

The general questionnaire contained questions on demographic characteristics, the presence of chronic diseases, and risk factors for chronic diseases. Smoking was categorized into current, past, and never smoker. Level of education was categorized as low (primary education up to those completing advanced elementary education),

average (intermediate vocational education and higher general secondary education) or high (higher vocational education and university). Physical activity was assessed using a questionnaire validated in an elderly population and categorized according to the Cambridge Physical Activity Index [12]. Because it was not possible to calculate a physical activity score for 14% of all participants missing scores were imputed using single linear regression modeling (SPSS MVA procedure). During the baseline physical examination screening, systolic and diastolic blood pressure measurements were performed twice in the supine position on the right arm using a Boso Oscillomat (Bosch & Son, Jungingen, Germany) (Prospect-EPIC) or on the left arm using a random zero sphygmomanometer (MORGEN-EPIC), from which the mean was taken. Hypertension was considered present when one or more of the following criteria were met: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported antihypertensive medication use, or self-report of physician-diagnosed hypertension. Height, and weight were measured, and BMI was calculated. All measurements were performed according to standard operating procedures. In a 6.5% random sample of the baseline cohort, total cholesterol was measured using enzymatic methods and HDL-cholesterol and LDL-cholesterol were measured using a homogeneous assay with enzymatic endpoint. These assays, including the haemolytic, icteric and lipemic indices (absorbance), were all performed on an autoanalyzer (LX20, Beckman Coulter, Mijndrecht, The Netherlands).

2.5. Data analysis

Participant characteristics are presented as medians, means with standard deviations or percentages. Intakes of total dairy and dairy subtypes were adjusted for total energy intake according to the residual method [13]. Total dairy and its subtypes were evaluated as continuous variables per standard deviation of the mean intake which is 265 g/d for total dairy, 34 g/d for high-fat dairy, 216 g/d for low-fat dairy, 265 g/d for milk and milk products, 13 g/d for cheese and 123 g/d for fermented dairy. Cox regression was used to estimate the hazard ratio and 95% confidence interval of the relation between total dairy intake and both fatal and non-fatal events of CHD or stroke. The analyses were repeated for different types of dairy, i.e. high-fat dairy, low-fat dairy, milk and milk products, cheese, fermented dairy and the ratio of high-fat to low-fat dairy. The presence of nonlinear associations of total dairy and its subtypes was explored by including the quadratic term of these intakes (per SD increase) in the model with the linear term. No evidence for nonlinear associations was found (with p values for quadratic terms ranging from 0.10 to 0.96).

All analyses were stratified for cohort. The duration of follow-up was calculated as the interval between date of study entry and the occurrence of a cardiovascular event, death, loss to follow-up, or January 1, 2008, whichever came first. The estimates were adjusted for age, sex and total energy intake (model 1). The second model additionally included smoking, BMI, education and physical activity. Further adjustment was made for the intake of coffee, ethanol, fruit, vegetables, fish, meat and bread (model 3).

The interaction between total dairy and possible effect modifiers, sex, age, BMI and hypertension was tested by including interaction terms into the model. In sensitivity analyses, we excluded cases occurring during the first 2 years and those participants censored in the first 2 years. To explore whether observed relations were explained by blood pressure, calcium or potassium, we adjusted for these variables in model 3. The proportionality assumption was checked visually by means of log minus log plots with no deviations detected. In the random sample (n = 2050), multivariable linear regression analysis was performed to assess the association between total dairy or its subtypes (independent variable) and total cholesterol, HDL- and LDL-cholesterol (dependent variable). Age, sex, total energy intake, smoking, BMI, education, physical activity, intake of coffee, ethanol, fruit, vegetables, fish, meat and bread were added as confounder.

Two-sided p-values below 0.05 were considered to be statistically significant. All statistical analyses were conducted SAS 9.2 (SAS Institute, Cary, US).

3. Results

During a mean follow-up of 13 years 1648 incident cases of CHD, including 211 CHD deaths, and 531 stroke cases, including 128 stroke deaths, were documented. Table 1 shows the baseline characteristics of the study population. The median energy-adjusted total dairy intake was 392 g/d (quartile 1 = 221 g/d; quartile 3 = 575 g/d). Low-fat dairy (median: 230 g/d) accounted for the largest part of dairy intake, compared with high-fat dairy (median: 46 g/d). The median daily intakes of milk and milk products, fermented dairy and cheese were 356 g/d, 85 g/d and 16 g/d, respectively. Participants with a high dairy intake were more active, smoked less often, drank less alcohol and consumed more fruit and vegetables (data not shown).

Adjusted for age, gender and energy intake, dairy intake was not associated with risk of CHD (HR per SD: 0.97; 95%-CI: 0.92–1.02). Adjustment for lifestyle and dietary factors further attenuated the association (HR: 0.99; 95%-CI: 0.94–1.05). None of the dairy subtypes was related to CHD risk, although for high-fat dairy we

Table 1
Mean ($\pm$ SD) baseline characteristics and dietary intakes of 33,625 men and women from the EPIC-NL cohort.

N	33,625
Follow up (years)	13.1
Gender (% male)	25.5
Age at recruitment (years)	49.0 ± 11.9
BMI (kg/m^2)	25.6 ± 4.0
Physically active CPAI (%)[a]	34.6
Systolic BP (mm Hg)	126.1 ± 18.7
Diastolic BP (mm Hg)	77.8 ± 10.6
Hypertension (%)	36.3
High education (%)	20.6
Current smoker (%)	30.1
Total energy (kcal/d)	2041.0 ± 583.6
Dietary intakes (g/d) [b,c]	
Total dairy	392 (234–574)
High-fat dairy	46 (30–67)
Low-fat dairy	230 (106–385)
Milk and milk products	356 (198–538)
Cheese	16.1 (9.7–25.8)
Fermented dairy	85 (45–176)
Fruit	240 (136–354)
Vegetables	130 (101–167)
Fish	7.6 (3.3–14.9)
Meat	105 (65–139)
Bread	134 (99–176)
Coffee	500 (375–750)
Tea	250 (54–500)
Alcohol	5.1 (0.7–15.8)

[a] CPAI = Cambridge Physical Activity Index.
[b] All dietary variables were adjusted for total energy.
[c] Intake of food groups and beverages is presented as median (interquartile range).

observed a slightly, but non-significantly decreased risk of CHD (HR: 0.97; 95%-CI: 0.92–1.02) (Table 2). Specifying these analyses to non-fatal CHD events and CHD mortality, we observed a borderline significant (p = 0.10) inverse relation with a HR of 0.96 (0.90–1.01) per SD increase for non-fatal events, while a non-significant increased risk was observed for CHD mortality (HR$_{SD}$ = 1.05; 0.92–1.20).

In additional analyses total dairy intake was categorized in quartiles. The association remains similar. After full-adjustment there was no association with CHD risk (HR 0.91; 0.91–1.06 for the highest versus lowest quartile).

Associations of dairy intake and risk of stroke were generally stronger than for CHD (Table 3). Total dairy consumption was associated with a lower risk of stroke adjusted for age, gender and total energy with a HR of 0.90 (0.82–0.99) per SD increase. Fermented dairy (0.86; 0.78–0.95) and low-fat dairy (0.89; 0.81–0.98) were also associated with a lower risk of stroke in model 1. However, after full adjustment,

Table 2
Univariable and adjusted hazard ratios (95%-CI) for the association of total dairy intake and dairy subtypes[a] with incident of (fatal or nonfatal) coronary heart disease among 33,625 subjects of the EPIC-NL study.

CHD (n = 1648)			
	Model 1[b]	Model 2[c]	Model 3[d]
Total dairy intake	0.97 (0.92–1.02)	1.00 (0.95–1.05)	0.99 (0.94–1.05)
Milk and milk products	0.97 (0.92–1.02)	1.00 (0.95–1.05)	0.99 (0.94–1.05)
Fermented dairy	0.95 (0.91–1.00)	0.99 (0.95–1.05)	1.00 (0.95–1.05)
Cheese	0.96 (0.91–1.01)	0.98 (0.93–1.03)	0.99 (0.94–1.04)
High-fat dairy	0.96 (0.92–1.01)	0.98 (0.93–1.03)	0.97 (0.92–1.02)
Low-fat dairy	0.98 (0.93–1.03)	1.01 (0.96–1.06)	1.01 (0.96–1.06)
Ratio high-fat to low-fat dairy	1.01 (0.97–1.05)	1.02 (0.98–1.06)	1.02 (0.98–1.06)

[a] All HRs are expressed per SD of the mean in g/d.
[b] Adjusted for gender, age and total energy intake.
[c] Adjusted for model 1 and physical activity, smoking, education and BMI.
[d] Adjusted for model 2 and intake of ethanol, coffee, fruit, vegetables, fish, meat and bread.

Table 3
Univariable and adjusted hazard ratios (95%-CI) for the association of total dairy intake and dairy subtypes[a] with incident (fatal or nonfatal) stroke among 33,625 subjects of the EPIC-NL study.

Stroke (n = 531)			
	Model 1[b]	Model 2[c]	Model 3[d]
Total dairy intake	0.90 (0.82–0.99)	0.93 (0.84–1.02)	0.95 (0.85–1.05)
Milk and milk products	0.91 (0.83–0.99)	0.93 (0.85–1.02)	0.95 (0.86–1.05)
Fermented dairy	0.86 (0.78–0.95)	0.90 (0.81–0.98)	0.92 (0.83–1.01)
Cheese	0.94 (0.86–1.02)	0.96 (0.88–1.05)	0.96 (0.88–1.06)
High-fat dairy	0.98 (0.90–1.07)	0.99 (0.91–1.07)	0.99 (0.91–1.09)
Low-fat dairy	0.89 (0.81–0.98)	0.92 (0.83–1.01)	0.94 (0.85–1.03)
Ratio high-fat to low-fat	0.98 (0.93–1.03)	0.98 (0.93–1.04)	0.98 (0.93–1.04)

[a] All HRs are expressed per SD of the mean in g/d.
[b] Adjusted for gender, age and total energy intake.
[c] Adjusted for model 1 and physical activity, smoking, education and BMI.
[d] Adjusted for model 2 and intake of ethanol, coffee, fruit, vegetables, fish, meat and bread.

these associations attenuated to non-significant with a HR of 0.95 (0.85–1.05) for total dairy. Only fermented dairy tended to be associated (p = 0.07) with a lower risk of stroke with a HR of 0.92 (0.83–1.01) per SD increase. Finally, when investigating the relation of milk and milk products with CVD, we observed a similar non-significant association as for CHD and stroke separately (HR = 1.01; 95%-CI: 0.96–1.05).

We did not observe interactions between total dairy intake and sex, age and BMI. Only for presence of hypertension, we observed an interaction (p<0.02) with total dairy. Among participants without hypertension, total dairy (0.92; 0.85–1.02) tended to be associated (p = 0.07) with a lower risk of CHD, while this was not apparent for those with hypertension. Similar results were observed for milk and milk products (0.92; 0.85–1.02) and low-fat dairy (0.94; 0.87–1.02) among normotensive participants.

Adjusting all associations for blood pressure or excluding cases occurring in the first 2 years did not change our results (data not shown). The associations of total dairy (HR: 0.94; 0.78–1.13) and milk and milk products (HR: 0.95; 0.81–1.11) with CHD among normotensive participants attenuated to non-significant when we adjusted for calcium and potassium. Including calcium and potassium almost completely explained the association of low-fat dairy (1.00; 0.87–1.15) with CHD among normotensive participants. In the random sample dairy intake or its subtypes were not associated with total cholesterol, HDL- or LDL-cholesterol levels (data not shown).

4. Discussion

In this large cohort of 33,625 Dutch men and women, total dairy consumption was not associated with risk of CHD or stroke. However, among participants without hypertension, total dairy, milk and milk products and low-fat dairy consumption tended to be associated with a reduced risk of CHD. Fermented dairy tended to be associated with a reduced risk of stroke.

Strengths of this study include its prospective design with over 10 years of follow-up and its large sample size. However, certain limitations need to be addressed. Firstly, we relied on self-reported intakes of dairy using an FFQ. This FFQ used was validated against 12 monthly 24-h recalls in a population of 121 subjects [9]. This study showed good reproducibility (r = 067–0.85) and good relative validity for milk and milk products (r = 0.69 for men, r = 0.77 for women), but lower relative validity for cheese intake (r = 0.56 and r = 0.32 respectively). This may have diluted the relation of cheese intake with CHD or stroke risk. Since dairy intake was assessed at baseline only, the effects of participants subsequently changing their pattern of dairy consumption are uncertain. However, we excluded participants with prevalent diseases and, in a sensitivity analysis, cases obtained in the first 2 years who are most likely to alter their dietary habits with similar results. Such reverse causation is therefore

unlikely to influence our results. Finally, as in any observational study, observed associations could be due to differences in other factors than dairy consumption. Despite adjustment for a large range of possible confounders, we cannot exclude unknown or unmeasured confounding.

The results from this study provided no evidence that total dairy or milk and milk products are associated with risk of either CHD or stroke. These findings are in line with a recent meta-analysis, that showed no significant association between total dairy or milk and milk products with risk of CHD (1.00; 0.96–1.04) or stroke (0.87; 0.72–1.07) [3]. Recently, the Netherlands Cohort Study could not detect an association between dairy products and all-cause or CVD mortality as well [14]. Only milk and milk products were inversely associated with risk of CVD in the meta-analysis with a HR of 0.94 (95%-CI: 0.89–0.99), an endpoint not primarily included in this study. However, when investigating the association of milk and milk products with a broad range of CVD in an additional analysis, we observed a similar non-significant association as we did for CHD and stroke. The previously reported reduced CVD risk for milk and milk products [3] seems to be mainly driven by effects of dairy consumption on stroke, since the association of milk intake with stroke was stronger than with CHD. Albeit not significant, the association of total dairy and milk and milk products with stroke in our study was also stronger than for CHD.

Distinguishing between high-fat and low-fat dairy, we could not detect significant associations with CHD or stroke as well, consistent with most previous studies [3]. Only the study by Hu et al. observed a lower risk of CHD with high intakes of low-fat dairy [5]. Surprisingly, in our study, only high-fat dairy tended to be associated with a lower risk of CHD events, while it was associated with a non-significantly higher risk of CHD mortality. This suggests a specific relation of high-fat dairy with fatal CHD that could perhaps be explained by the high saturated fat content of these dairy products. A recent meta-analysis indeed showed similar results for high saturated fat intakes with an increased risk of fatal CHD (RR = 1.32), while an RR of 0.99 was shown for total CHD [15,16].

Presence of hypertension appeared to modify the relation of total dairy, milk and milk products and low-fat dairy with risk of CHD. Only among participants without hypertension, total dairy, milk and milk products and low-fat dairy were associated with an approximately 8% reduced risk of CHD per 200–250 g/d, while no association was observed among participants with hypertension. These associations could be explained by effects of dairy consumption on blood pressure, since low-fat dairy intake is associated with reduced blood pressure (relative risk 0.87; 95%-CI 0.74–0.95) [17]. However, adjusting the associations between dairy and CHD for systolic and diastolic blood pressure did not alter our findings. Moreover, blood pressure is more strongly related to stroke than CHD [18]. Therefore, risk factors more strongly related to CHD like blood lipids could better explain our results. However, adjusting for baseline total and HDL cholesterol in part of cohort did not affect our results (data not shown). In addition, we could not detect any significant associations of total dairy intake and its subtypes with blood lipid concentrations. It is therefore more likely that other factors could be involved to explain these associations. Perhaps, minerals from dairy products could play a role, since adjusting for potassium and calcium explained part of the association between dairy and CHD. However, this would then have to be driven by effects on other risk factors than blood pressure or blood lipids like inflammatory factors [19]. Finally, residual confounding could be involved. The DASH-diet was reported to be more effective for participants with high sodium intakes [20]. Possibly, hypertensive participants in our cohort already slightly reduced their sodium intake, while normotensive participants did not. Unfortunately, a FFQ is not a valid tool to estimate sodium intake and we can therefore not address this effect.

We observed a borderline significant inverse association between intake of fermented dairy and risk of stroke. Larsson et al. investigated associations between fermented dairy products and risk of stroke and observed an inverse relation between cheese consumption and cerebral infarction, but not for other fermented dairy foods like yogurt or buttermilk [21]. Consistently, Goldbohm et al. observed an inverse relation of fermented full-fat milk with all-cause mortality and non-significantly with stroke mortality [14]. Altogether, these studies suggest an inverse relation between fermented dairy products and risk of stroke. Blood pressure- [22] and cholesterol- [23] lowering effects of fermented dairy could explain these relations. Specific tripeptides originating from milk fermentation, for example, have been suggested to reduce blood pressure [24], but a recent large randomized trial failed to confirm these results [25]. Another explanation could be the effect of vitamin K_2 that is mainly present in fermented dairy products. Vitamin K_2 has been previously shown to reduce vascular calcification and subsequent risk of CHD in two prospective cohorts [26,27], but the relation between vitamin K_2 and risk of stroke has not been investigated to date. Further research on the association between fermented dairy products and risk of stroke is therefore warranted.

In conclusion, our results provide no evidence that dairy products are associated with risk of CHD or stroke in a generally healthy Dutch population. Among participants without hypertension, high intakes of total and low-fat dairy could be associated with a lower risk of CHD, while fermented dairy may be associated with a reduced risk of stroke.

Acknowledgments

References

[1] Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114:82–96.

[2] Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002;288:2569–78.

[3] Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose–response meta-analysis of prospective cohort studies. Am J Clin Nutr 2011;93:158–71.

[4] Jakobsen MU, O'Reilly EJ, Heitmann BL, et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 2009;89:1425–32.

[5] Hu FB, Stampfer MJ, Manson JE, et al. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. Am J Clin Nutr 1999;70: 1001–8.

[6] Hjartaker A, Lagiou A, Slimani N, et al. Consumption of dairy products in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort: data from 35 955 24-hour dietary recalls in 10 European countries. Public Health Nutr 2002;5:1259–71.

[7] Beulens JW, Monninkhof EM, Verschuren WM, et al. Cohort profile: the EPIC-NL study. Int J Epidemiol 2010;39:1170–8.

[8] Ocke MC, Bueno-de-Mesquita HB, Pols MA, Smit HA, van Staveren WA, Kromhout D. The Dutch EPIC food frequency questionnaire. II. Relative validity and reproducibility for nutrients. Int J Epidemiol 1997;26:S49–58.

[9] Ocke MC, Bueno-de-Mesquita HB, Goddijn HE, et al. The Dutch EPIC food frequency questionnaire. I. Description of the questionnaire, and relative validity and reproducibility for food groups. Int J Epidemiol 1997;26:S37–48.

[10] Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. J Epidemiol Community Health 1992;46:136–40.

[11] Merry AH, Boer JM, Schouten LJ, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study. Eur J Epidemiol 2009;24: 237–47.

[12] Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6:407–13.

[13] Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65:1220S–8S.

[14] Goldbohm RA, Chorus AM, Galindo GF, Schouten LJ, van den Brandt PA. Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands. Am J Clin Nutr 2011;93:615–27.

[15] Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr 2010;91:535–46.

[16] Stamler J. Diet-heart: a problematic revisit. Am J Clin Nutr 2010;91:497–9.

[17] Ralston RA, Lee JH, Truby H, Palermo CE, Walker KZ. A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. J Hum Hypertens 2012;26:3–13.

[18] Chrysant SG, Chrysant GS. Effectiveness of lowering blood pressure to prevent stroke versus to prevent coronary events. Am J Cardiol 2010;106:825–9.

[19] German JB, Gibson RA, Krauss RM, et al. A reappraisal of the impact of dairy foods and milk fat on cardiovascular disease risk. Eur J Nutr 2009;48:191–203.

[20] Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336:1117–24 [17].

[21] Larsson SC, Mannisto S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Dairy foods and risk of stroke. Epidemiology 2009;20:355–60.

[22] Usinger L, Ibsen H, Jensen LT. Does fermented milk possess antihypertensive effect in humans? J Hypertens 2009;27:1115–20.

[23] St-Onge MP, Farnworth ER, Jones PJ. Consumption of fermented and nonfermented dairy products: effects on cholesterol concentrations and metabolism. Am J Clin Nutr 2000;71:674–81.

[24] Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. Nutrition 2008;24:933–40.

[25] Engberink MF, Schouten EG, Kok FJ, van Mierlo LA, Brouwer IA, Geleijnse JM. Lactotripeptides show no effect on human blood pressure: results from a double-blind randomized controlled trial. Hypertension 2008;51:399–405.

[26] Gast GC, de Roos NM, Sluijs I, et al. A high menaquinone intake reduces the incidence of coronary heart disease. Nutr Metab Cardiovasc Dis 2009;19:504–10 [28].

[27] Geleijnse JM, Vermeer C, Grobbee DE, et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr 2004;134:3100–5.