Consumption of dairy products and cardiovascular disease risk: results from the French prospective cohort NutriNet-Santé

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Consumption of dairy products and CVD risk: results from the French prospective cohort NutriNet-Santé

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Abstract

In France, dairy products contribute to dietary saturated fat intake, of which reduced consumption is often recommended for CVD prevention. Epidemiological evidence on the association between dairy consumption and CVD risk remains unclear, suggesting either null or inverse associations. This study aimed to investigate the associations between dairy consumption (overall and specific foods) and CVD risk in a large cohort of French adults. This prospective analysis included participants aged ≥18 years from the NutriNet-Santé cohort (2009–2019). Daily dietary intakes were collected using 24-h dietary records. Total dairy, milk, cheese, yogurts, fermented and reduced-fat dairy intakes were investigated. CVD cases (*n* 1952) included cerebrovascular disease (*n* 878 cases) and CHD (*n* 1219 cases). Multivariable Cox models were performed to investigate associations. This analysis included 104 805 French adults (mean age at baseline 42·8 (SD 14·6) years, mean follow-up 5·5 (SD 3·0) years, i.e. 579 155 person-years). There were no significant associations between dairy intakes and total CVD or CHD risks. However, the consumption of at least 160 g/d of fermented dairy (e.g. cheese and yogurts) was associated with a reduced risk of cerebrovascular diseases compared with intakes below 57 g/d (hazard ratio = 0·81 (95 % CI 0·66, 0·98), $P_{trend} = 0{\cdot}01$). Despite being a major dietary source of saturated fats, dairy consumption was not associated with CVD or CHD risks in this study. However, fermented dairy was associated with a lower cerebrovascular disease risk. Robust randomised controlled trials are needed to further assess the impact of consuming different dairy foods on CVD risk and potential underlying mechanisms.

Key words: **Dairy products: CVD: Fermented dairy: Cerebrovascular disease: Cheese: Yogurt**

CVD, including CHD and cerebrovascular diseases such as strokes, are still a leading cause of mortality worldwide, causing 17·9 million deaths every year[1,2]. In France, CVD are the primary cause of death in women and the second most common cause in men[3]. Beside smoking, lifestyle factors such as nutritional status and dietary habits have been identified as one of the main modifiable risk factors of CVD[4]. Thus, public health guidelines around the world target the consumption of specific nutrients and food groups as a strategy for reducing CVD risk at a population level. In particular, reducing the dietary consumption of SFA is often recommended to help lower circulating levels of LDL-cholesterol, a well-established risk factor for CVD[5–6]. In France, public health guidelines suggest a consumption of SFA below 12 % of dietary energy (without alcohol), with an emphasis on three fatty acids that should remain below 8 % of dietary energy (lauric C12 : 0, myristic C14 : 0 and palmitic C16 : 0 acids)[7]. In parallel, the French National Health and Nutrition Programme (PNNS) focuses on recommendations related to food groups and suggests a daily consumption of two servings of dairy products per d for adults, to be chosen among milk, cheese and yogurts, but not including butter, cream or dairy desserts (e.g. custard, ice cream and cheese cake)[8].

Dairy products are nutrient-rich foods containing various minerals and vitamins, such as Ca, K, P and vitamins B, K and

Abbreviations: HR, hazard ratio; TIA, transient ischaemic attack.

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D which are associated with health benefits. However, full-fat dairy foods can also be energy-dense and may contain high levels of Na and SFA. In French adults, dairy product contributes to 24 % of total dietary SFA intake[9]. Despite this high contribution to dietary SFA, epidemiological evidence on the association between dairy product consumption and CVD risk remains unclear. Recent meta-analyses of prospective cohort studies suggest either null or slightly inverse associations between total dairy foods and incident CVD[10,11]. Similar trends were also observed in more recent prospective cohort studies, such as the PURE study, which included data from twenty-one countries across five continents and observed a reduced risk of CVD associated with total dairy consumption[12]. In addition, epidemiological evidence on specific types of dairy products remains inconsistent, although a recent meta-analysis of nine prospective cohort studies suggested a reduced CVD risk associated with the consumption of fermented dairy foods only, which included cheese, yogurt and fermented milk, as opposed to intakes of total dairy or non-fermented milks[13]. These results raise the question of the importance of dairy food types and potential fermentation in relation to cardiovascular health.

This study aimed to investigate the associations between the consumption of dairy foods (overall and specific types) and CVD risk in a large cohort of French adults.

Materials and methods

The NutriNet-Santé cohort

The NutriNet-Santé study is an ongoing French web-based cohort, launched in 2009 with the aim of investigating the associations between nutrition, dietary behaviours, determinants of nutrition status and health. Detail of this study has been published previously[14]. Briefly, since May 2009, participants aged 18 years and over with access to the Internet have been continuously recruited among the French population using vast multimedia campaigns. All questionnaires are completed online using a dedicated website (www.etude-nutrinet-sante.fr).

Ethical approval

The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines. It was approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB Inserm n°0000388FWA00005831) and the 'Commission Nationale de l'Informatique et des Libertés' (CNIL n°908450/n°909216). Each participant provides their informed consent electronically. The study is registered at clinicaltrials.gov as NCT03335644.

Data collection

Upon inclusion, participants completed a set of five questionnaires related to sociodemographic and lifestyle characteristics, such as sex, occupation, educational level (<high-school degree, <2 years after high school, ≥2 years after high school), smoking status (never smoked, former smoker and current smoker), alcohol consumption (g/d), number of children[15], anthropometrics[16,17] (e.g. height and weight, which were validated against a random sample of participants), dietary intakes[18], physical activity levels (as low, moderate or high, from validated 7-d International Physical Activity Questionnaire)[19,20] and health status (e.g. personal and family history of diseases, prescribed medication).

Dietary data

Usual dietary intakes were assessed at inclusion and then every 6 months, using a series of three non-consecutive web-based 24-h dietary records, randomly assigned over a 2-week period (2 weekdays and 1 weekend day). The web-based questionnaires used in the study have been tested and validated against both in-person interviews by trained dietitians, and urinary and blood markers[16–21]. In this analysis, we calculated the usual baseline dietary intakes as the average of all 24-h dietary records completed during the first 2 years of each participant's follow-up, with a mandatory requirement of at least two 24-h dietary records during this period to be included in the analysis.

At all times throughout their assigned dietary record period, participants had access to a dedicated interface of the study website to declare all foods and beverages consumed during a 24-h period: three main meals (breakfast, lunch and dinner) and any other eating occasion. When participants could not provide weights for the food items consumed, they were invited to estimate portion sizes using validated photographs or usual containers[22]. A French food composition database (>3500 items)[23] was used to estimate mean daily energy, alcohol, macro- and micro-nutrient intakes. These estimates included contributions from composite dishes using French recipes validated by food and nutrition professionals. Individual dietary data were not communicated to participants to avoid any changes in dietary behaviours. Finally, those who under-reported total energy intake were identified and excluded based on the method proposed by Black[24], using the BMR, Goldberg cut-off and a physical activity level (PAL) cut-off of 1·55 which corresponds to the WHO value for 'light' activity. For this calculation, intra-individual CV for BMR and PAL were fixed using the values recommended by Black, i.e. 8·5 and 15%, respectively. About 20·0% of participants of the cohort were considered as under-reporters of energy intake and were excluded from the analyses. There was no sign of over-reporters as the highest energy intakes ranged within plausible values (99th percentile = 13,761 kJ/d).

Dairy products classification

Trained dietitians categorised all dairy foods of the NutriNet-Santé composition table into one of the five dairy groups defined in the PNNS: milk, cheese, yogurts, curd cheese and 'petit-suisses'. As per the PNNS guidelines, milk-based products containing more than 12 % of sugars were classified into a separate 'dairy desserts' category, while creams and butter were considered as fat sources. Thus, these three food groups were not included in this analysis. We calculated a larger 'yogurt-like dairy products' category which included the consumption of yogurt along with curd cheese and petit-suisses, as those were not consumed frequently enough to be analysed separately. Total dairy intakes were calculated by combining the

consumption of each of the five dairy groups (milk, cheese, yogurt, curd cheese and 'petit-suisses'). In addition, we defined fermented dairy foods as cheese, curd cheese, petit-suisses, yogurts and fermented milk, whereas non-fermented dairy included all milks (UHT, pasteurised, concentrated and flavoured) except fermented ones. Finally, reduced-fat dairy products included skimmed and semi-skimmed milk, low-fat yogurts, curd cheese, petit-suisses and cheese containing <20 g of fat per 100 g final product.

Case ascertainment

Participants were invited to declare any major health event on a dedicated interface on the study website, either through the yearly health status questionnaire, through a specific health check-up questionnaire sent out every 3 months, or spontaneously. We asked participants to send their medical records (e.g. complementary examinations for diagnosis, hospitalisations and electrocardiograms) to support any health event declaration. A physician expert committee validated every major health event after reviewing the participants' medical records and collecting additional information from the participants' treating physicians or medical practices. In the absence of any response to the study website for more than 1 year, the physician expert committee contacted the participants' family or physicians. In addition to this process, which constituted the main source of case ascertainment, cohort data from participants were linked to medico-administrative databases from the National Health Insurance (SNIIRAM, authorisation by the Council of State No 2013-175). Finally, deaths and potentially missed CVD events in deceased participants were identified using data from the French national cause-specific mortality registry (CépiDC).

The International Classification of Diseases-Clinical Modification codes (10th revision) were used to classify CVD cases. This study focused on first incident cases of myocardial infarction (I21), angioplasty (Z95.8), acute coronary syndrome (I20.0 and I21.4), angina pectoris (I20.1, I20.8 and I20.9), stroke (I64) and transient ischaemic attack (TIA, G45.8 and G45.9) occurring between inclusion and January 2019. CHD included all cases of myocardial infarction, angioplasty, acute coronary syndrome and angina pectoris, and cerebrovascular diseases included all cases of stroke and TIA.

Statistical analyses

As of 1 January 2019, participants with no history of CVD who had completed at least two valid 24-h dietary records were included in the analyses. Mean daily dairy intakes (overall and by type of dairy food) were coded as sex-specific quartiles, as potential distinctions in dietary patterns of French adult men and women have been previously reported[25,26]. Missing values represented <5 % for all covariates, except for physical activity and were imputed with the modal or median value for categorical and continuous variables, respectively. Physical activity scores were only calculated when all the answers from the International Physical Activity Questionnaire were provided by the participants, which resulted in a higher percentage of missing value for this variable (13·9 %). Therefore, we introduced a missing class for this variable in the main analysis. Nonetheless, we performed additional analyses including complete cases and multiple imputation for missing values. We used the MICE method[27] to create ten imputed data sets with fully conditional specification for the outcome[28] and the following covariates: physical activity level, education level, smoking status and BMI. We used the SAS PROC MIANALYZE procedure[29] to combine the results from the imputed data sets, based on the combination rules proposed by Rubin[30,31].

Two dietary patterns were identified using a principal component analysis based on twenty food categories derived from the fifty-eight food groups defined in the French PNNS (online Supplementary Table S1). The analysis was conducted with the SAS PROC FACTOR procedure (SAS Institute Inc.). For easier interpretation, we used the SAS 'varimax' option to rotate the principal components orthogonally and maximise the independence of the retained principal components. The first two principal components explained 10·6 % and 7·0 % of the variance, respectively, which was consistent with the proportion of variance observed in other nutritional epidemiology studies[32]. The first principal component was characterised by higher intakes of fruits, vegetables, soups and broths, unsweetened soft drinks and wholegrains, along with lower intakes of sweetened soft drinks, which we defined as a 'Healthy' dietary pattern. In contrast, the second principal component was characterised by higher consumptions of fats and sauces (which included butter and dairy cream), alcohol, meat and starchy foods, which we defined as a 'Western' dietary pattern. We calculated an adherence score to each dietary pattern and for each participant, using the food categories factor loadings to weigh the sum of all food categories observed consumption. Thus, the adherence score measures a participant's diet conformity to the identified dietary pattern.

Multivariable Cox proportional hazard models with age as the primary time variable were used to characterise the associations between each type of dairy consumption and incidence of CVD, CHD and cerebrovascular diseases, and to calculate cause-specific hazard ratios (HR) and 95 % CI. In the CHD model, cerebrovascular disease cases were censored at the date of diagnosis but were considered as non-cases for CHD, and reciprocally for the cerebrovascular disease model. The Schoenfeld residuals were used to confirm risk proportionality assumptions[33]. *P*-values for linear trends were obtained by coding quartiles of dairy consumption as an ordinal variable. Participants contributed person-time to the Cox model until the date of CVD diagnosis, the date of the last completed questionnaire and the date of death or 1 January 2019, whichever occurred first. Models were adjusted for age (time scale), sex, physical activity (low, moderate, high, missing, computed following International Physical Activity Questionnaire recommendations), BMI (kg/m^2, continuous), education level (<high-school degree, <2 years after high-school degree, ≥2 years after high-school degree), without alcohol energy intake (kcal/d, continuous), alcohol intake (g/d, continuous), smoking status (never smoked, former smoker and current smoker), number of dietary records (continuous) and family history of CVD (yes/no) (model 1).

In exploratory analyses, we performed an additional model to account for the potential influence of the nutritional quality

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of the diet. This included adjusting model 1 for a healthy dietary pattern derived by principal component analysis (model 2, online Supplementary Table S1). Finally, further adjustments were added to model 1 to include the influence of baseline prevalence and treatment of self-reported type 2 diabetes, hypercholesterolaemia, hypertension and hypertriglyceridaemia (model 3).

When Cox models revealed significant associations, sensitivity analyses were performed based on model 1 by adding further adjustments for a Western dietary pattern derived from principal component analysis (online Supplementary Table S1). Finally, CVD cases diagnosed in the first 2 years of each participant's follow-up were excluded to account for reverse causation bias in statistically significant associations. All tests were two-sided, and *P*-values $\leq 0{\cdot}05$ were considered statistically significant. All analyses were carried out with SAS software (version 9.4; SAS Institute Inc.).

Results

This analysis included 104 805 participants (see Fig. 1) with a mean age of 42·8 years at baseline (SD 14·6), among which 22 291 were men (21·3 %) and 82 517 were women (78·7 %). Participants included in this analysis had completed on average 5·7 (SD 3·1) 24-h dietary records, with 8·1 % of the participants having only completed the minimum two dietary records for inclusion in the analyses. The participants' baseline characteristics according to sex-specific quartiles of dairy intake are shown in Table 1. Overall, there was no significant difference in baseline characteristics between low consumers (1st quartile) and high consumers of dairy foods (4th quartile). In addition, 65 % of our participants had moderate to high physical activity scores from the International Physical Activity Questionnaire, 65·4 % had ≥2 years of education after high school and 82·8 % did not smoke.

Participants consumed on average 222 g/d of dairy foods (SD 151), including 110 g/d of milk (SD 127), 37·7 g/d of cheese (SD 28·3) and 79·1 g/d of yogurt (SD 84·9), which was similar to the consumption levels observed in the general French population[9]. In addition, dairy foods contributed to 18·3 % of total fat intakes (SD 13·7) and 28·9 % of SFA intakes (SD 24·4) (online Supplementary Table S2).

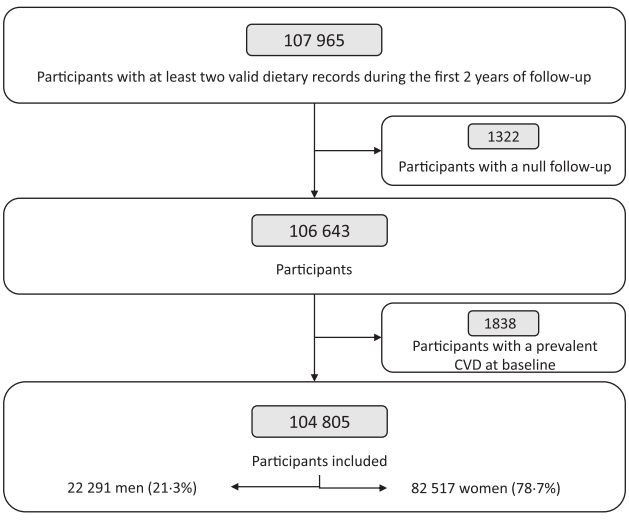

Fig. 1. Flow chart of participants included in the study, NutriNet-Santé cohort, France, 2009–2019.

Associations between dairy consumption and CVD risk

Between 2009 and 2019 and a mean follow-up of 5·5 years (SD 3·0, 579 155 person-years), 2098 cases of CVD were diagnosed, among which there were 1220 cases of CHD (eighty-two acute coronary syndromes, 318 angina pectoris, 148 myocardial infarctions and 672 angioplasties) and 878 cases of cerebrovascular diseases (118 strokes and 760 TIA).

Schoenfeld residuals were not significantly associated with time, which supported the proportional hazard assumption (online Supplementary Table S3). The associations between the consumption of dairy foods and the risks of overall CVD, CHD and cerebrovascular diseases are presented in Table 2. The basic multivariable Cox proportional hazard (model 1) did not reveal any statistically significant association between the consumption of any dairy type and overall or CHD. These associations remained statistically non-significant in models 2, 3 and 4 (data not shown). However, high consumption (≥161·6 g/d for males and ≥160·9 g/d for females) of fermented dairy foods (yogurt, cheese and fermented milk) compared with low consumption (<57·3 g/d for males, <54·3 g/d for females) was associated with a 19 % decreased risk of cerebrovascular disease (HR = 0·81, 95 % CI 0·66, 0·98, $P_{trend} = 0{\cdot}01$). This association was borderline significant when considering the continuous intake of fermented dairy with an increment of 100 g/d (HR = 0·98, 95 % CI 0·97, 1·00, *P*-value = 0·05). In addition, the restricted cubic spline presented in Fig. 2 verified the linearity assumption between the consumption of fermented dairy foods and the risk of cerebrovascular disease (*P*-value for non-linear association = 0·23)[34].

Exploratory and sensitivity analyses

The association between fermented dairy consumption and cerebrovascular risk remained statistically significant when comparing the highest intake (4th quartile) with the lowest intake (1st quartile), after further adjustments in models 2 and 3 (Table 3). Similarly, this association remained stable in further exploratory analyses adjusting for a Western dietary pattern derived from principal component analysis (HR = 0·81, 95 % CI 0·66, 0·98, $P_{trend} = 0{\cdot}01$). Furthermore, the use of multiple imputation with the MICE method to manage missing values strengthened the inverse association between continuous consumption of fermented foods and cerebrovascular disease risk (HR = 0·91, 95 % CI 0·84, 0·99, *P*-value = 0·02), but did not significantly impact other associations between continuous dairy consumption and overall, CHD or cerebrovascular disease risk. When excluding CVD cases that required more extensive documentation to ascertain diagnosis (i.e. TIA and angina), all associations between dairy consumption and disease risk were non-significant, likely due to a loss of statistical power.

Finally, the exclusion of cerebrovascular disease cases diagnosed during the first 2 years of follow-up (*n* 144 cases excluded) suggested a 9 % decreased risk of cerebrovascular disease

Table 1. Baseline characteristics of study population according to sex-specific quartiles of dairy consumption, NutriNet-Santé cohort, France, 2009–2019 (Mean values and standard deviations; numbers and percentages, *n* 104 805)

			Quartiles of total dairy intake*								
	All participants (*n* 104 805)		First (*n* 26 201) (lowest intake)		Second (*n* 26 202)		Third (*n* 26 203)		Fourth (*n* 26 202) (highest intake)		
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*P* †
Age (years)											0·89
Mean	42·8		42·7		42·8		42·8		42·8		
SD	14·6		14·6		14·6		14·6		14·6		
Sex											1·00
Female	82 517	78·7	20 629	78·7	20 629	78·7	20 630	78·7	20 629	78·7	
Male	22 291	21·3	5572	21·3	5573	21·3	5573	21·3	5573	21·3	
BMI (kg/m^2)											0·11
Mean	23·7		23·7		23·7		23·7		23·7		
SD	4·5		4·5		4·5		4·5		4·4		
Physical activity‡											0·97
Low	22 049	21·0	5439	20·8	5513	21·0	5538	21·1	5559	21·2	
Moderate	38 712	36·9	9710	37·1	9676	36·9	9633	36·8	9693	37·0	
High	29 447	28·1	7366	28·1	7376	28·2	7370	28·1	7335	28·0	
Education level											0·55
<High school degree	18 323	17·5	4545	17·4	4543	17·3	4617	17·6	4618	17·6	
<2 years after high school	17 969	17·1	4571	17·5	4474	17·1	4516	17·2	4408	16·8	
≥2 years after high school	68 516	65·4	17 085	65·2	17 185	65·6	17 070	65·2	17 176	65·6	
Smoking status											0·66
Never	52 325	49·9	13 093	50·0	13 139	50·2	13 033	49·7	13 060	49·8	
Former	34 479	32·9	8607	32·8	8567	32·6	8595	32·8	8710	33·3	
Current	18 004	17·2	4501	17·2	4496	17·2	4575	17·5	4432	16·9	
Family history of CVD§, yes	32 760	31·3	8267	31·6	8138	31·1	8121	31·0	8234	31·4	0·43
Prevalent morbidity, *yes*											
Type 2 diabetes	1498	1·4	357	1·4	348	1·3	425	1·6	368	1·4	0·02
Hypertension	8691	8·3	2100	8·0	2224	8·5	2170	8·3	2197	8·4	0·23
Hypercholesterolaemia	8396	8·0	2073	8·0	2135	8·0	2097	8·0	2091	8·0	0·79
Hypertriglyceridaemia	1536	1·5	383	1·5	378	1·4	390	1·5	385	1·5	0·98
Intakes of:‖											
Energy (kcal/d)											0·47
Mean	1847		1850		1845		1845		1847		
SD	452		456		450		452		451		
Alcohol (g/d)											0·33
Mean	7·8		7·7		7·7		7·9		7·8		
SD	11·9		11·9		11·8		12·0		11·9		
Total lipids (g/d)											0·39
Mean	81·5		81·6		81·3		81·4		81·6		
SD	25·3		25·6		25·2		25·3		25·2		
Carbohydrates (g/d)											0·30
Mean	198·1		198·7		197·8		198·0		197·9		
SD	57·6		57·8		57·2		57·6		57·7		
Proteins (g/d)											0·58
Mean	78·8		78·9		79·0		78·7		78·8		
SD	21·5		21·6		21·5		21·4		21·5		
Na (g/d)											0·70
Mean	2·7		2·7		2·7		2·7		2·7		
SD	0·9		0·9		0·9		0·9		0·9		
Total dietary fibre (g/d)											0·54
Mean	19·5		19·5		19·5		19·5		19·4		
SD	7·2		7·2		7·1		7·3		7·2		
Dietary Ca (mg/d)											0·61
Mean	921		922		922		919		921		
SD	299		299		299		299		299		
Fruits and vegetables (g/d)											0·14
Mean	465		467		465		467		463		
SD	233		231		231		237		231		
Total dairy (g/d)											<0·001
Mean	222		65		150		241		431		
SD	151		32		22		32		123		
Milk (serving/d)											0·56
Mean	0·55		0·56		0·55		0·55		0·55		
SD	0·81		0·82		0·81		0·81		0·82		
Cheese (serving/d)											0·74
Mean	1·23		1·23		1·23		1·22		1·23		
SD	0·93		0·93		0·94		0·92		0·94		

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Table 1. (*Continued*)

Characteristics	All participants (*n* 104 805)		Quartiles of total dairy intake*								
			First (*n* 26 201) (lowest intake)		Second (*n* 26 202)		Third (*n* 26 203)		Fourth (*n* 26 202) (highest intake)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*P* †
Yogurt (serving/d)											<0·001
Mean	0·47		0·09		0·38		0·64		0·77		
SD	0·55		0·16		0·33		0·51		0·77		

* Sex-specific quartiles of total dairy consumption. Cut-offs were 112, 190 and 303 g/d for males and 112, 191 and 301 g/d for females.
† *P*-value comparing quartiles of total dairy consumption, using two-sided χ^2 tests or Fisher tests as appropriate.
‡ Physical activity categories according to the International Physical Activity Questionnaire (IPAQ)[19] IPAQ data were missing for 14 600 participants (13·9 %).
§ Amongst first-degree relatives.
‖ Standard French serving sizes defined as 150 ml for milk, 30 g for cheese and 125 g for yogurts.

associated with each additional 100 g of fermented dairy food consumed daily (*n* 734 cases/103,927 non-cases, HR = 0·91, 95 % CI 0·83, 0·99, P_{trend} = 0·03), and a 21 % decreased risk when comparing the highest (4th quartile) with the lowest (1st quartile) consumption of fermented dairy (HR = 0·79, 95 % CI 0·64, 0·98, P_{trend} = 0·001).

Discussion

In this prospective cohort study of French adults, we did not observe a statistically significant association between the consumption of dairy food and the risk of CVD or CHD. However, our results suggest a possible lower risk of cerebrovascular disease (i.e. stroke and TIA) associated with a higher consumption of fermented dairy foods, such as cheese and yogurts.

It is recommended to limit dietary SFA intakes for CVD prevention; however, this study did not reveal any direct association between the consumption of dairy products and total CVD or CHD risk, despite contributing to 28·9 % of dietary SFA (online Supplementary Table S2b). This supports the existing epidemiological evidence on the topic, especially from meta-analyses of prospective studies which consistently reported null or weak inverse associations between the consumption of total dairy and CVD risk[10,11,35]. In a 2018 meta-analysis, Soedamah-Muthu & de Goede reported a non-statistically significant association between total dairy and CHD risk when pooling the results from fifteen prospective cohort studies and reported an 8 % reduced risk of stroke associated with an increment of 200 g of milk consumption per day (risk ratio = 0·92, 95 % CI 0·88, 0·97, I^2 = 85 %)[11]. Since then, the PURE prospective cohort study observed 5855 CVD events over 9·1 years of follow-up from both urban and rural populations in twenty-one countries[12]. In this large prospective study, authors reported that a total dairy consumption of > 2 servings per d, compared with no dairy consumption, was associated with a 22 % risk reduction of major CVD (i.e. MI, stroke or heart failure) (HR = 0·78, 95 % CI 0·67, 0·90, P_{trend} = 0·0001) and a 34 % reduced risk of incident stroke (HR = 0·66, 95 % CI 0·53, 0·82, P_{trend} = 0·0003). More recently, a small prospective cohort study from Greece, which included 2020 participants followed-up for 10 years, observed an inverse association between total dairy intake and total CVD risk (HR = 0·48, 95 % CI 0·23, 0·90) in women only. This inverse association in women was stronger when the authors looked at yogurt consumption, with a 14 % CVD risk reduction associated with a 200 g/d increment in yogurt intake (HR = 0·86, 95 % CI 0·49, 0·98)[36].

The inverse association between fermented dairy and cerebrovascular risk observed in this study may suggest a differential effect of these types of dairy foods on cardiovascular health. In a 2019 meta-analysis of randomised controlled trials and prospective studies, Companys *et al.* observed that the consumption of fermented milk was associated with a reduced risk of stroke and ischaemic heart disease (risk ratio = 0·96, 95 % CI 0·94, 0·98, high heterogeneity I^2 = 95·9 %)[37]. This finding was in line with those reported in an extensive review of meta-analyses conducted by Fontecha *et al.* in 2019, which observed a reduced risk of stroke and stroke mortality associated with the consumption of fermented dairy, including fermented milk[38] and cheese[38–42], but not yogurt[10].

Another potential source of variation in the health effects of dairy consumption relates to the nutrient content of specific types of dairy foods. In the large European EPIC-Netherlands study, Laursen *et al.* observed 884 stroke cases over a 15·2-year follow-up. They reported that the consumption of each additional daily serving of whole-fat yogurt as a substitution for any other dairy group (low-fat yogurt, cheese, butter, buttermilk or milk) was associated with a lower risk of ischaemic stroke (HR between 0·33 and 0·36)[43]. These findings were in line with previous results observed by the same authors in another European prospective study, the Danish Diet, Cancer and Health cohort[44]. However, emerging evidence suggests that the nutrient content of dairy should be considered in relation to the dairy food matrix, which refers to the physical structure of food and may have an impact on nutrient absorption and biomarkers of CVD risk, such as blood pressure and cholesterol metabolism. In particular, one hypothesis suggests that cheese, despite being high in fat, possesses similar features to milk and yogurt, rather than to butter, due to its high Ca, protein and milk fat globule membrane content[45]. In addition, the fermentation process involved in the production of cheese and yogurt often results in the presence of bacteria within the food matrix, which may produce SCFA and bioactive peptides[45]. All these components of dairy, particularly

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Table 2. Associations between dairy consumption and CVD risk from multivariable Cox proportional hazard models*, NutriNet-Santé cohort, France, 2009–2019
(Hazard ratios (HR) and 95 % confidence intervals, *n* 104 805)

					Quartiles of dairy food intakes†							
		Continuous‡				Second		Third		Fourth (high intake)		
Total CVD		HR	95 % CI	*P*	First (low intake)	HR	95 % CI	HR	95 % CI	HR	95 % CI	P_{trend}
Milk	Cases/non-cases	1952/102 856			484/25 717	514/25 688		468/25 735		486/25 716		
		0·99	0·93, 1·04	0·57	1	1·05	0·92, 1·19	0·96	0·84, 1·09	1·00	0·89, 1·14	0·70
Cheese	Cases/non-cases	1952/102 856			468/25 732	507/25 691		489/25 731		488/25 702		
		1·00	0·95, 1·04	0·86	1	1·09	0·96, 1·24	1·05	0·93, 1·20	1·06	0·93, 1·20	0·54
Yogurts	Cases/non-cases	1952/102 856			530/30 180	405/21 173		544/26 781		473/24 722		
		0·99	0·94, 1·04	0·72	1	1·09	0·96, 1·24	1·16	1·03, 1·30	1·09	0·96, 1·23	0·10
High-fat	Cases/non-cases	1952/102 856			502/25 699	505/25 724		493/25 681		452/25 752		
		0·92	0·85, 0·99	0·04	1	1·01	0·89, 1·14	0·99	0·87, 1·12	0·91	0·80, 1·03	0·12
Reduced fat	Cases/non-cases	1952/102 856			461/25 740	502/25 700		513/25 690		476/25 726		
		1·00	0·99, 1·01	0·93	1	1·09	0·96, 1·24	1·11	0·98, 1·26	1·04	0·91, 1·18	0·57
Fermented	Cases/non-cases	1952/102 856			487/25 714	515/25 687		463/25 740		487/25 715		
		1·00	0·99, 1·01	0·72	1	1·04	0·92, 1·18	0·94	0·83, 1·07	1·00	0·88, 1·13	0·60
Non-fermented	Cases/non-cases	1952/102 856			686/35 249	401/22 536		435/22 543		430/22 528		
		1·00	0·99, 1·01	0·55	1	0·91	0·81, 1·03	0·99	0·88, 1·12	0·99	0·87, 1·11	0·97
Total dairy	Cases/non-cases	1952/102 856			486/25 715	513/25 689		473/25 730		480/25 722		
		0·99	0·96, 1·02	0·48	1	1·06	0·94, 1·20	0·98	0·87, 1·12	0·99	0·88, 1·13	0·62
CHD§												
Milk	Cases/non-cases	1219/103 586			296/25 905	347/25 853		301/25 902		275/25 926		
		1·01	0·94, 1·08	0·83	1	1·12	0·96, 1·31	1·07	0·91, 1·26	1·10	0·93, 1·30	0·40
Cheese	Cases/non-cases	1219/103 586			270/25 927	339/25 870		320/25 878		290/25 911		
		0·99	0·93, 1·06	0·85	1	1·03	0·87, 1·21	0·93	0·79, 1·09	0·96	0·81, 1·15	0·42
Yogurts	Cases/non-cases	1219/103 586			297/30 135	280/21 690		321/26 162		321/25 599		
		0·96	0·89, 1·03	0·21	1	0·95	0·80, 1·13	0·97	0·83, 1·14	0·87	0·74, 1·02	0·12
High-fat	Cases/non-cases	1219/103 586			288/25 911	316/25 888		299/25 902		316/25 885		
		0·94	0·85, 1·04	0·23	1	0·89	0·76, 1·04	0·83	0·70, 0·98	0·86	0·73, 1·02	0·07
Reduced fat	Cases/non-cases	1219/103 586			287/25 915	339/25 861		305/25 897		288/25 913		
		1·00	0·96, 1·04	0·93	1	1·08	0·92, 1·27	0·95	0·81, 1·12	1·01	0·85, 1·19	0·63
Fermented	Cases/non-cases	1219/103 586			252/25 949	320/25 881		305/25 897		342/25 859		
		0·99	0·98, 1·01	0·21	1	1·00	0·84, 1·18	0·84	0·71, 0·99	0·89	0·75, 1·05	0·05
Non-fermented	Cases/non-cases	1219/103 586			298/25 903	349/25 852		293/25 909		279/25 922		
		1·00	0·99, 1·01	0·84	1	1·11	0·95, 1·30	1·05	0·89, 1·23	1·11	0·94, 1·31	0·39
Total dairy	Cases/non-cases	1219/103 586			287/25 914	335/25 866		304/25 898		293/25 908		
		0·99	0·95, 1·03	0·56	1	0·98	0·84, 1·15	0·88	0·75, 1·04	0·95	0·80, 1·12	0·30
Cerebrovascular disease‖												
Milk	Cases/non-cases	878/103 927			207/25 994	248/25 952		227/25 976		196/26 005		
		1·02	0·94, 1·11	0·65	1	1·11	0·92, 1·34	1·17	0·96, 1·41	1·13	0·92, 1·38	0·19
Cheese	Cases/non-cases	878/103 927			185/26 012	272/25 937		217/25 981		204/25 997		
		0·96	0·88, 1·04	0·33	1	1·19	0·99, 1·44	0·91	0·74, 1·11	0·99	0·80, 1·22	0·26
Yogurts	Cases/non-cases	878/103 927			187/30 245	221/21 749		235/26 248		235/25 685		
		0·93	0·85, 1·01	0·08	1	1·08	0·88, 1·32	1·04	0·86, 1·27	0·92	0·76, 1·12	0·30
High fat	Cases/non-cases	878/103 927			174/26 025	251/25 953		223/25 978		230/25 971		
		0·96	0·85, 1·08	0·45	1	1·16	0·96, 1·42	1·01	0·83, 1·42	1·00	0·81, 1·23	0·54
Reduced fat	Cases/non-cases	878/103 927			219/25 983	245/25 955		207/25 995		207/25 994		
		0·99	0·94, 1·04	0·62	1	1·02	0·85, 1·22	0·85	0·70, 1·03	0·94	0·78, 1·15	0·23
Fermented	Cases/non-cases	878/103 927			180/26 021	229/25 972		232/25 970		237/25 964		
		0·98	0·97, 1·00	0·05	1	0·97	0·79, 1·18	0·84	0·69, 1·02	0·81	0·66, 0·98	0·01
Non-fermented	Cases/non-cases	878/103 927			211/25 990	246/25 955		224/25 978		197/26 004		
		1·00	0·99, 1·01	0·67	1	1·08	0·90, 1·30	1·14	0·94, 1·38	1·12	0·91, 1·36	0·23
Total dairy	Cases/non-cases	878/103 927			212/25 989	244/25 957		205/25 997		217/25 984		
		0·98	0·94, 1·03	0·42	1	0·95	0·79, 1·14	0·79	0·65, 0·96	0·93	0·76, 1·13	0·19

* Cox models were adjusted for age (time scale), sex, physical activity (low, moderate, high, computed following IPAQ recommendations), BMI (kg/m^2, continuous), education level (<high-school degree, <2 years after high-school degree, ≥2 years after high-school degree), without alcohol energy intake (kcal/d, continuous), alcohol intake (g/d, continuous), smoking status (never smoked, former smoker, current smoker), number of dietary records (continuous), family history of CVD (yes/no) (model 1).
† Sex-specific cut-offs for milk were 16·1, 51·6 and 153·8 g/d in males and 16·3, 50·8 and 153·7 g/d in females. Cut-offs for cheese were 17·7, 32·9 and 51·4 g/d in males and 17·8, 33·0 and 51·6 g/d in females. Cut-offs for yogurt-like dairy were 0·04, 44·7 and 109·8 g/d in males and 11·9, 60·2 and 125·0 g/d in females. Cut-offs for high-fat dairy were 26·2, 50·5 and 84·6 g/d in males and 26·3, 50·0 and 83·9 g/d in females. Cut-offs for reduced-fat dairy were 46·7, 117·7 and 232·9 g/d for males and 47·1, 117·4 and 232·3 g/d in females. Cut-offs for fermented dairy were 57·3, 102·8 and 161·6 g/d for males and 54·3, 100·6 and 160·9 g/d in females. Cut-offs for non-fermented dairy were 16·8, 54·3 and 168·6 g/d in males and 15·9, 48·8 and 147·5 g/d in females. Cut-offs for total dairy were 112·0, 186·8 and 303·0 g/d in males and 111·7, 190·8 and 301·5 g/d in females.
‡ HR for an absolute increment of 150 g/d of milk, 30 g/d of cheese, and 100 g/d of yogurts, high-fat, reduced-fat, fermented, non-fermented and total dairy.
§ Includes myocardial infarction, angioplasty, acute coronary syndrome and angina pectoris.
‖ Includes stroke and transient ischaemic attack.

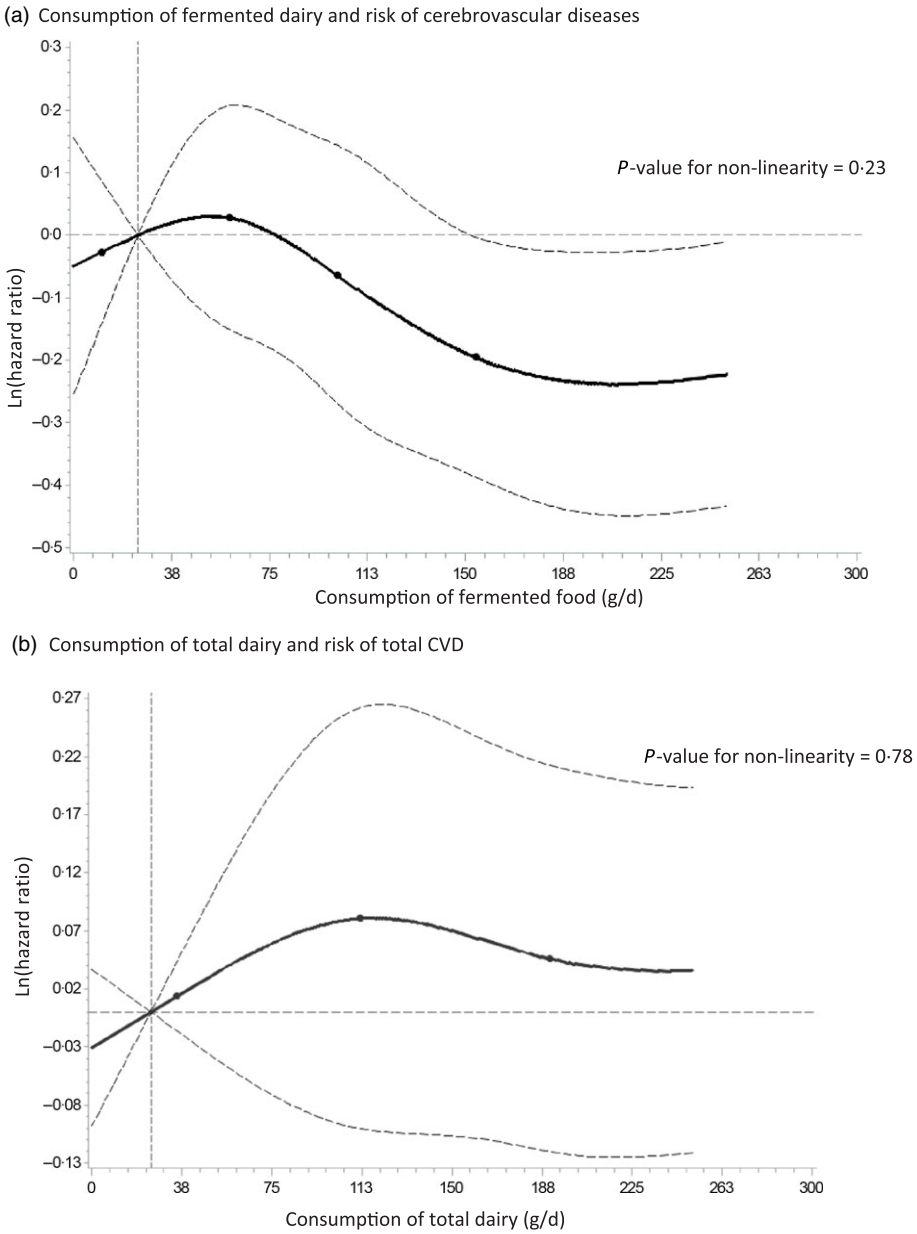

Fig. 2. Spline plot for the linearity assumption of the association between the consumption of dairy foods and risk of CVD, NutriNet-Santé cohort, France, 2009–2019 (*n* 104 805)[a]. Consumption of fermented dairy and risk of cerebrovascular diseases. Consumption of total dairy and risk of total CVD. [a]Restricted cubic spline SAS macro developed by Desquilbet & Mariotti[35]. —— Estimation; – – – Upper and lower confidence limit; • • • Knots.

present in cheese and yogurt, may interfere with the intestinal absorption and digestibility of fat (which is mostly SFA in dairy foods) and therefore attenuate the effect of SFA on cholesterol metabolism and potentially provide a protective effect on cardiovascular health[46–49]. Although more well-controlled intervention studies in humans are necessary to further investigate these potential mechanisms, this would be in line with observational evidence from meta-analyses of prospective studies, which suggest that fermented dairy consumption may be associated with lower total and LDL-cholesterol levels[50–53]. Finally, a potential hypotensive effect of bioactive peptides found in fermented dairy foods may reduce cerebrovascular diseases risk, which would be in line with observational epidemiological studies, but still needs further research to be fully elucidated[54].

The prospective design of this study contributed to its strengths, allowing the assessment of mid-term associations of dairy consumption with CVD risks. In addition, this study used repeated 24-h dietary records to provide detailed and up-to-date dietary intake assessment, as opposed to FFQ which are often used in nutritional epidemiology. In this study, we identified two Healthy and Western dietary patterns using a principal component analysis (online Supplementary Table S1) and these patterns did not influence the associations observed between fermented dairy consumption and cerebrovascular risk. Finally, the use of the SNIIRAM national register allowed

Table 3. Associations between fermented dairy foods and cerebrovascular disease risk from multivariable Cox proportional hazard models, NutriNet-Santé cohort, France, 2009–2019
(Hazard ratios (HR) and 95 % confidence intervals, *n* 104 805)*

	Quartiles of fermented dairy food intakes§							
		Second		Third		Fourth (high intake)		
Proportional hazard Cox models†,‡	First (low intake)	HR	95 % CI	HR	95 % CI	HR	95 % CI	P_{trend}
Cases/non-cases	180/26 021	229/25 972		232/25 970		237/25 964		
Model 1	1	0·97	0·79, 1·18	0·84	0·69, 1·02	0·81	0·66, 0·98	0·01
Model 2	1	0·97	0·79, 1·18	0·84	0·69, 1·02	0·81	0·66, 0·98	0·01
Model 2b	1	0·97	0·79, 1·18	0·84	0·69, 1·02	0·81	0·66, 0·98	0·01
Model 3	1	0·96	0·79, 1·17	0·83	0·68, 1·02	0·80	0·66, 0·98	0·01

* Cerebrovascular disease included incident events of strokes and transient ischaemic attacks.
† Cox models were adjusted for age (time scale), sex, physical activity (low, moderate, high, computed following IPAQ recommendations), BMI (kg/m^2, continuous), education level (<high-school degree, <2 years after high-school degree, ≥2 years after high-school degree), without alcohol energy intake (kcal/d, continuous), alcohol intake (g/d, continuous), smoking status (never smoked, former smoker, current smoker), number of dietary records (continuous), family history of CVD (yes/no) (model 1). Model 2 = Model 1 + healthy dietary pattern (derived by principal component analysis). Model 2b = Model 1 + Western dietary pattern derived by principal component analysis. Model 3 = Model 1 + prevalence and treatment of type 2 diabetes, dyslipidaemia, hypertension and hypertriglyceridaemia.
‡ HR for an absolute increment of 100 g/d of fermented dairy foods.
§ Sex-specific cut-offs for fermented dairy were 57·3, 102·8, 161·6 g/d for males and 54·3, 100·6 and 160·9 g/d in females. Fermented dairy foods included yogurt, cheese and fermented milk.

the maximisation of CVD case ascertainment, limiting the omission of cases when participants did not report their disease to the study investigators. However, some limitations of this study also pertain to its observational design. Indeed, residual confounding cannot be ruled out, and a causal link between the consumption of fermented dairy and a decreased risk of cerebrovascular disease cannot be established from this prospective cohort study alone, although the inclusion of many potential confounders in our main analyses suggests a robust inverse association. Furthermore, a relatively limited statistical power precluded the investigation of specific types of CVD. The NutriNet-Santé cohort is volunteered-based, and as highlighted in Table 1, the participants included in this study were generally more health-conscious, younger, more highly educated, more often women, consumed more fruits and vegetables[9] and were less likely to smoke or be overweight[55], compared with the general French population.

In conclusion, in this large prospective cohort study, we found that the consumption of dairy foods may not be associated with overall CVD or CHD risks in French adults. However, we observed a higher consumption of fermented dairy products (e.g. cheese and yogurt) to be associated with a lower risk of stroke and TIA. Overall, these observational findings provide insight on the potential role of specific dairy foods in cardiometabolic health. However, future randomised controlled trials are warranted to confirm these associations.

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L. S., M. T. and J. L. designed the research. S. H., P. G., M. T., C. J., L. K. F. and E. K.-G. conducted the research. L. S. performed the statistical analyses. B. S. supervised the statistical analyses. L. S. drafted the manuscript. M. S., J. L. and K. G. J. supervised the writing. B. S., K. G. J., S. H., P. G., E. K.-G., C. J., L. K. F., M. D., J. L. and M. T. contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. M. T. and J. L. had primary responsibility for the final content and are the guarantors. The corresponding author (B. S.) attests that all listed authors meet authorship criteria and that no other authors meeting criteria have been omitted.

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Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521001422

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