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Consumption of dairy products and cardiovascular disease 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 cardiovascular disease (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 24h-dietary records. Total dairy, milk, cheese, yogurts, fermented and reduced-fat dairy intakes were investigated. CVD cases (n=1,952) included cerebrovascular (n=878 cases) and coronary heart diseases (CHD, n=1,219 cases). Multivariable Cox models were performed to investigate associations. This analysis included n=104,805 French adults (mean age at baseline 42.8 years (SD 14.6), mean follow-up 5.5 years (SD 3.0, i.e. 579,155 persons 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 to intakes below 57 g/d (HR=0.81 [0.66-0.98], p-trend=0.01). 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 randomized controlled trials are needed to further assess the impact of consuming different dairy foods on CVD risk and potential underlying mechanisms.

1 Introduction

2 Cardiovascular diseases (CVD), including coronary heart diseases (CHD) and cerebrovascular diseases
3 such as strokes are still a leading cause of mortality worldwide, causing 17.9 million deaths every
4 year [1],[2]. In France, CVDs are the primary cause of death in women and the second most common
5 cause in men [3]. Beside smoking, lifestyle factors such as nutritional status and dietary habits, have
6 been identified as one of the main modifiable risk factors of CVD [4].Thus, public health guidelines
7 around the world target the consumption of specific nutrients and food groups as a strategy for
8 reducing CVD risk at a population level. In particular, reducing the dietary consumption of saturated
9 fat (SFA) is often recommended to help lower circulating levels of low-density lipoprotein
10 cholesterol, a well-established risk factor for CVD [5],[6]. In France, public health guidelines suggest a
11 consumption of SFA below 12% of dietary energy (without alcohol), with an emphasis on three fatty
12 acids that should remain below 8% of dietary energy (lauric C12:0, myristic C14:0 and palmitic C16:0
13 acids) [7]. In parallel, the French National Health and Nutrition Programme (PNNS) focuses on
14 recommendations related to food groups, and suggests a daily consumption of two servings of dairy
15 products per day for adults, to be chosen among milk, cheese and yogurts, but not including butter,
16 cream or dairy desserts (e.g. custard, ice cream and cheese cake) [8].

17

18 Dairy products are nutrient-rich foods containing various minerals and vitamins, such as calcium,
19 potassium, phosphorus, and vitamins B, K and D which are associated with health benefits. However,
20 full-fat dairy foods can also be energy-dense and may contain high levels of sodium and SFA. In
21 French adults, dairy contribute to 24% of total dietary SFA intake [9]. Despite this high contribution to
22 dietary SFA, epidemiological evidence on the association between dairy product consumption and
23 CVD risk remains unclear. Recent meta-analyses of prospective cohort studies suggest either null or
24 slightly inverse associations between total dairy foods and incident CVDs [10]–[13]. Similar trends were
25 also observed in more recent prospective cohort studies, such as the PURE study, which included
26 data from 21 countries across five continents and observed a reduced risk of CVD associated with
27 total dairy consumption [14]. In addition, epidemiological evidence on specific types of dairy remains
28 inconsistent, although a recent meta-analysis of nine prospective cohort studies suggested a
29 reduced CVD risk associated with the consumption of fermented dairy foods only, which included
30 cheese, yogurt and fermented milk, as opposed to intakes of total dairy or non-fermented milks [11].
31 These results raise the question of the importance of dairy food types and potential fermentation in
32 relation to cardiovascular health.

33

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

36 Material and Methods

37 The NutriNet-Santé cohort

38 The NutriNet-Santé study is an ongoing French web-based cohort, launched in 2009 with the aim of
39 investigating the associations between nutrition, dietary behaviours, determinants of nutrition
40 status, and health. Detail of this study has been published previously [15]. Briefly, since May 2009
41 participants aged 18 years and over with access to the Internet have been continuously recruited

42   among the French population using vast multimedia campaigns. All questionnaires are completed

43   online using a dedicated website (www.etude-nutrinet-sante.fr).

Ethical approval

45   The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines. It was

46   approved by the Institutional Review Board of the French Institute for Health and Medical Research

47   (IRB Inserm n°0000388FWA00005831) and the "Commission Nationale de l'Informatique et des

48   Libertés" (CNIL n°908450/n°909216). Each participant provides their informed consent

49   electronically. The study is registered at clinicaltrials.gov as NCT03335644.

Data collection

51   Upon inclusion, participants completed a set of five questionnaires related to socio-demographic

52   and lifestyle characteristics, such as sex, occupation, educational level (< high school degree, < 2

53   years after high school, ≥ 2 years after high school), smoking status (never smoked, former smoker,

54   current smoker), alcohol consumption (g/d), number of children [16], anthropometrics [17],[18] (e.g.

55   height and weight, which were validated against a random sample of participants), dietary intakes

56   [19], physical activity levels (as low, moderate of high, from validated seven day International Physical

57   Activity Questionnaire (IPAQ)) [20],[21], and health status (e.g. personal and family history of diseases,

58   prescribed medication).

Dietary data

60   Usual dietary intakes were assessed at inclusion and then every six months, using a series of three

61   non-consecutive web-based 24h-dietary records, randomly assigned over a 2-week period (2

62   weekdays and 1 weekend day). The web-based questionnaires used in the study have been tested

63   and validated against both in-person interviews by trained dietitians, and urinary and blood markers

64   [17],[22]. In this analysis, we calculated the usual baseline dietary intakes as the average of all 24h-

65   dietary records completed during the first two years of each participant's follow-up, with a

66   mandatory requirement of at least two 24h-dietary records during this period to be included in the

67   analysis.

68   At all times throughout their assigned dietary record period, participants had access to a dedicated

69   interface of the study website to declare all foods and beverages consumed during a 24h-period:

70   three main meals (breakfast, lunch, dinner) and any other eating occasion. When participants could

71   not provide weights for the food items consumed, they were invited to estimate portion sizes using

72   validated photographs or usual containers [23]. A French food composition database (>3,500 items)

73   [24] was used to estimate mean daily energy, alcohol, macro- and micro-nutrient intakes. These

74   estimates included contributions from composite dishes using French recipes validated by food and

75   nutrition professionals. Individual dietary data were not communicated to participants to avoid any

76   changes in dietary behaviours. Finally, those that under-reported total energy intake were identified

77   and excluded based on the method proposed by Black [25], using the basal metabolic rate, Goldberg

78   cut-off, and a physical activity level (PAL) cut-off of 1.55 which corresponds to the WHO value for

79   "light" activity. For this calculation, intra-individual coefficients of variations for BMR and PAL were

80   fixed using the values recommended by Black, i.e. 8.5 % and 15%, respectively. About 20.0% of

81 participants of the cohort were considered as under-reporters of energy intake and were excluded
82 from the analyses. There was no sign of over reporters as the highest energy intakes ranged within
83 plausible values (99th percentile = 3,289 kcal/d).

84 *Dairy products classification*

85 Trained dietitians categorised all dairy foods of the NutriNet-Santé composition table into one of the
86 five dairy groups defined in the PNNS: milk, cheese, yogurts, curd cheese and "petit-suisses". As per
87 the PNNS guidelines, milk-based products containing more than 12% of sugars were classified in a
88 separate "dairy desserts" category, while creams and butter which were considered as fat sources.
89 Thus, these three food groups were not included in this analysis. We calculated a larger "yogurt-like
90 dairy products" category which included the consumption of yogurt along with curd cheese and
91 petit-suisses, as those were not consumed frequently enough to be analysed separately. Total dairy
92 intakes were calculated by combining the consumption of each of the five dairy groups (milk,
93 cheese, yogurt, curd cheese and "petit-suisses"). In addition, we defined fermented dairy foods as
94 cheese, curd cheese, petit-suisses, yogurts and fermented milk, whereas non-fermented dairy
95 included all milks (UHT, pasteurised, concentrated and flavoured) except fermented ones. Finally,
96 reduced-fat dairy products included skimmed and semi-skimmed milk, low-fat yogurts, curd cheese,
97 petit-suisses and cheese containing less than 20g of fat per 100g final product.

98 **Case ascertainment**

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

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

118

119 **Statistical analyses**

120   As of the 1st January 2019, participants with no history of CVD who had completed at least two valid
121   24-h dietary records were included in the analyses. Mean daily dairy intakes (overall and by type of
122   dairy food) were coded as sex-specific quartiles, as potential distinctions in dietary patterns of
123   French adult men and women have been previously reported [26],[27]. Missing values represented less
124   than 5% for all covariates, except for physical activity, and were imputed with the modal or median
125   value for categorical and continuous variables, respectively. Physical activity scores were only
126   calculated when all the answers from the IPAQ were provided by the participants, which resulted in
127   a higher percentage of missing value for this variable (13.9%). Therefore, we introduced a missing
128   class for this variable in the main analysis. Nonetheless, we performed additional analyses including
129   complete cases and multiple imputation for missing values. We used the MICE method [28] to create
130   10 imputed datasets with fully conditional specification for the outcome [29] and the following
131   covariates: physical activity level, education level, smoking status and BMI. We used the SAS PROC
132   MIANALYZE procedure [30] to combine the results from the imputed datasets, based on the
133   combination rules proposed by Rubin [31],[32].

134   Two dietary patterns were identified using a principal component analysis based on 20 food
135   categories derived from the 58 food groups defined in the French PNNS (Appendix 1). The analysis
136   was conducted with the SAS PROC FACTOR procedure (SAS Institute Inc, Cary, NC). For easier
137   interpretation, we used the SAS "varimax" option to rotate the principal components orthogonally
138   and maximise the independence of the retained principal components. The first two principal
139   components explained 10.6% and 7.0% of the variance, respectively, which was consistent with
140   proportion of variance observed in other nutritional epidemiology studies [33]. The first principal
141   component was characterised by higher intakes of fruits, vegetables, soups and broths,
142   unsweetened soft drinks, and wholegrains, along with lower intakes of sweetened soft drinks, which
143   we defined as a "Healthy" dietary pattern. In contrast, the second principal component was
144   characterised by higher consumptions of fats and sauces (which included butter and dairy cream),
145   alcohol, meat, and starchy foods, which we defined as a "Western" dietary pattern. We calculated
146   an adherence score to each dietary pattern and for each participant, using the food categories factor
147   loadings to weigh the sum of all food categories observed consumption. Thus, the adherence score
148   measures a participant's diet conformity to the identified dietary pattern.

149   Multivariable Cox proportional hazard models with age as the primary time variable were used to
150   characterise the associations between each type of dairy consumption and incidence of CVD, CHD
151   and cerebrovascular diseases, and to calculate cause-specific hazard ratios and 95% confidence
152   intervals. In the CHD model, cerebrovascular disease cases were censored at the date of diagnosis
153   but were considered as non-cases for CHD, and reciprocally for the cerebrovascular disease model.
154   The Schoenfeld residuals were used to confirm risk proportionality assumptions [34]. P-values for
155   linear trends were obtained by coding quartiles of dairy consumption as an ordinal variable.
156   Participants contributed person-time to the Cox model until the date of CVD diagnosis, the date of
157   the last completed questionnaire, the date of death or 1st January 2019, whichever occurred first.
158   Models were adjusted for age (time-scale), sex, physical activity (low, moderate, high, missing,
159   computed following IPAQ recommendations), BMI (kg/m^2, continuous), education level (<high-
160   school degree, <2 years after high-school degree, ≥2 years after high-school degree), without alcohol
161   energy intake (kcal/d, continuous), alcohol intake (g/d, continuous), smoking status (never smoked,

162   former smoker, current smoker), number of dietary records (continuous), family history of CVD
163   (yes/no) (model 1).

164   In exploratory analyses, we performed two additional models to account for the potential influence
165   of the nutritional quality of the diet. This included adjusting model 1 for a healthy dietary pattern
166   derived from principal component analysis (Appendix 1) (model 2). Finally, further adjustments were
167   added to model 1 to include the influence of baseline prevalence and treatment of self-reported
168   type 2 diabetes, hypercholesterolemia, hypertension, and hypertriglyceridemia (model 3).

169   When Cox models revealed significant associations, sensitivity analyses were performed based on
170   model 1 by adding further adjustments for a Western dietary pattern derived from principal
171   component analysis (Appendix 1). Finally, CVD cases diagnosed in the first two years of each
172   participant's follow-up were excluded to account for reverse causation bias in statistically significant
173   associations. All tests were two-sided and p-values ≤ 0.05 were considered statistically significant. All
174   analyses were carried out with SAS software (version 9.4; SAS Institute Inc., Cary, NC).

Results
176   This analysis included 104,805 participants (see Figure 1. Flowchart) with a mean age of 42.8 years at
177   baseline (SD 14.6), among which 22,291 were men (21.3%) and 82,517 were women (78.7%).
178   Participants included in this analysis had completed on average 5.7 (SD 3.1) 24h-dietary records,
179   with 8.1% of the participants having only completed the minimum two dietary records for inclusion
180   in the analyses. The participants' baseline characteristics according to sex-specific quartiles of dairy
181   intake are shown in Table 1. Overall, there was no significant difference in baseline characteristics
182   between low consumers (1st quartile) and high consumers of dairy foods (4th quartile). In addition,
183   65% of our participants had moderate to high physical activity scores from the IPAQ, 65.4% had ≥ 2
184   years of education after high school and 82.8% did not smoke.

185   Participants consumed on average 222g/d of dairy foods (SD 151), including 110g/d of milk (SD 127),
186   37.7g/d of cheese (SD 28.3) and 79.1g/d of yogurt (SD 84.9), which was similar to the consumption
187   levels observed in the general French population [9]. In addition, dairy foods contributed to 18.3% of
188   total fat intakes (SD 13.7) and 28.9% of SFA intakes (SD 24.4) (Appendix 2).

Associations between dairy consumption and CVD risk

190   Between 2009 and 2019 and a mean follow-up of 5.5 years (SD 3.0, 579,155 person years), 2,098
191   cases of CVD were diagnosed, among which there were 1,220 cases of CHD (82 acute coronary
192   syndromes, 318 angina pectoris, 148 myocardial infarctions and 672 angioplasties) and 878 cases of
193   cerebrovascular diseases (118 strokes and 760 TIAs).

194   Schoenfeld residuals were not significantly associated with time, which supported the proportional
195   hazard assumption (Appendix 3). The associations between the consumption of dairy foods and the
196   risks of overall cardiovascular, coronary heart, and cerebrovascular diseases are presented in Table
197   2. The basic multivariable Cox proportional hazard (model 1) did not reveal any statistically
198   significant association between the consumption of any dairy type and overall or coronary heart
199   diseases. These associations remained statistically non-significant in models 2, 3 and 4 (data not

200 shown). However, high consumption (≥ 161.6g/d for males and , ≥ 160.9g/d for females) of
201 fermented dairy foods (yogurt, cheese and fermented milk) compared to low-consumption (< 57.3
202 g/d for males, < 54.3g/d for females) was associated with a 19% decreased risk of cerebrovascular
203 disease (HR = 0.81, 95%CI = 0.66-0.98, p-trend=0.01). This association was borderline significant
204 when considering the continuous intake of fermented dairy with an increment of 100g/d (HR = 0.98,
205 95%CI = 0.97-1.00, p-value=0.05). In addition, the restricted cubic spline presented in Figure 2
206 verified the linearity assumption between the consumption of fermented dairy foods and the risk of
207 cerebrovascular disease (p-value for non-linear association=0.23) [35].

208 **Exploratory and Sensitivity analyses**

209 The association between fermented dairy consumption and cerebrovascular risk remained
210 statistically significant when comparing the highest intake (4th quartile) to the lowest intake (1st
211 quartile), after further adjustments in models 2 and 3 (Table 3). Similarly, this association remained
212 stable in further exploratory analyses adjusting for a Western dietary pattern derived from principal
213 component analysis (HR = 0.81, 95%CI = 0.66-0.98, p-trend=0.01). Furthermore, the use of multiple
214 imputation with the MICE method to manage missing values strengthened the inverse association
215 between continuous consumption of fermented foods and cerebrovascular disease risk (HR = 0.91,
216 95%CI = 0.84-0.99, p-value=0.02), but did not significantly impact other associations between
217 continuous dairy consumption and overall, coronary heart or cerebrovascular disease risk. When
218 excluding CVD cases that required more extensive documentation to ascertain diagnosis (i.e. TIAs
219 and angina), all associations between dairy consumption and disease risk where non-significant,
220 likely due to a loss of statistical power.

221

222 Finally, the exclusion of cerebrovascular disease cases diagnosed during the first two years of follow-
223 up (n=144 cases excluded) suggested a 9% decreased risk of cerebrovascular disease associated with
224 each additional 100g of fermented dairy food consumed daily (n=734 cases / 103,927 non cases, HR
225 = 0.91, 95%CI = 0.83-0.99, p-trend=0.03), and a 21% decreased risk when comparing the highest (4th
226 quartile) to the lowest (1st quartile) consumption of fermented dairy (HR = 0.79, 95%CI = 0.64-0.98,
227 p-trend=0.001).

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

233 It is recommended to limit dietary SFA intakes for CVD prevention; however, this study did not
234 reveal any direct association between the consumption of dairy products and total CVD or CHD risk,
235 despite contributing to 28.9% of dietary SFA (Appendix 2b). This supports the existing
236 epidemiological evidence on the topic, especially from meta-analyses of prospective studies which
237 consistently reported null or weak inverse associations between the consumption of total dairy and

238 CVD risk [10]–[13],[36]. In a 2018 meta-analysis, Soedamah-Muthu and de Goede reported a non-
239 statistically significant association between total dairy and CHD risk when pooling the results from 15
240 prospective cohort studies, and reported an 8% reduced risk of stroke associated with an increment
241 of 200g of milk consumption per day (Risk Ratio (RR) = 0.92, 95% confidence interval (CI) = 0.88-0.97,
242 I^2 = 85%) [13]. Since then, the PURE prospective cohort study observed 5,855 CVD events over 9.1
243 years of follow-up from both urban and rural populations in 21 countries [14]. In this large prospective
244 study, authors reported that a total dairy consumption of >2 servings per day, compared to no dairy
245 consumption, was associated with a 22% risk reduction of major CVD (i.e. MI, stroke, or heart
246 failure) (Hazard Ratio (HR) =0.78, 95%CI = 0.67-0.90, p-trend=0.0001) and a 34% reduced risk of
247 incident stroke (HR = 0.66, 95%CI = 0.53-0.82, p-trend=0.0003). More recently, a small prospective
248 cohort study from Greece, which included 2,020 participants followed-up for 10 years, observed an
249 inverse association between total dairy intake and total CVD risk (HR = 0.48, 95%CI = 0.23-0.90) in
250 women only. This inverse association in women was stronger when the authors looked at yogurt
251 consumption, with a 14% CVD risk reduction associated with a 200g/d increment in yogurt intake
252 (HR = 0.86, 95%CI = 0.49-0.98) [37].

253 The inverse association between fermented dairy and cerebrovascular risk observed in this study
254 may suggest a differential effect of these types of dairy foods on cardiovascular health. In a 2019
255 meta-analysis of randomised controlled trials and prospective studies, Companys et al. observed
256 that the consumption of fermented milk was associated with a reduced risk of stroke and ischemic
257 heart disease (RR = 0.96, 95% CI 0.94 to 0.98, high heterogeneity I^2=95.9%) [38]. This finding was in
258 line with those reported in an extensive review of meta-analyses conducted by Fontecha et al. in
259 2019, which observed a reduced risk of stroke and stroke mortality associated with the consumption
260 of fermented dairy, including fermented milk [39] and cheese [12],[39]–[42], but not yogurt [10].

261 Another potential source of variation in the health effects of dairy consumption relates to the
262 nutrient content of specific types of dairy foods. In the large European EPIC-Netherlands study,
263 Laursen et al. observed 884 stroke cases over a 15.2-year follow-up. They reported that the
264 consumption of each additional daily serving of whole-fat yogurt as a substitution for any other dairy
265 group (low-fat yogurt, cheese, butter, buttermilk or milk) was associated with a lower risk of
266 ischemic stroke (HR between 0.33 and 0.36) [43]. These findings were in line with previous results
267 observed by the same authors in another European prospective study, the Danish Diet, Cancer and
268 Health cohort [44]. However, emerging evidence suggest that the nutrient content of dairy should be
269 considered in relation to the dairy food matrix, which refers to the physical structure of food and
270 may have an impact on nutrient absorption and biomarkers of CVD risk, such as blood pressure and
271 cholesterol metabolism. In particular, one hypothesis suggests that cheese, despite being high in fat,
272 possesses similar features to milk and yogurt, rather than to butter, due to its high calcium, protein
273 and milk fat globule membrane content [45]. In addition, the fermentation process involved in the
274 production of cheese and yogurt often results in the presence of bacteria within the food matrix,
275 which may produce short-chain fatty acids and bioactive peptides [45]. All these components of dairy,
276 particularly present in cheese and yogurt, may interfere with the intestinal absorption and
277 digestibility of fat (which is mostly SFA in dairy foods) and therefore attenuate the effect of SFA on
278 cholesterol metabolism and potentially provide a protective effect on cardiovascular health [46]–[49].
279 Although more well-controlled intervention studies in humans are necessary to further investigate

280 these potential mechanisms, this would be in line with observational evidence from meta-analyses
281 of prospective studies, which suggest that fermented dairy consumption may be associated with
282 lower total and low-density lipoprotein cholesterol levels [50]–[53]. Finally, a potential hypotensive
283 effect of bioactive peptides found in fermented dairy foods may reduce cerebrovascular diseases
284 risk, which would be in line with observational epidemiological studies, but still needs further
285 research to be fully elucidated [54].

286 The prospective design of this study contributed to its strengths, allowing the assessment of mid-
287 term associations of dairy consumption with CVD risks. In addition, this study used repeated 24h-
288 dietary records to provide detailed and up-to-date dietary intake assessment, as opposed to food
289 frequency questionnaires which are often used in nutritional epidemiology. In this study, we
290 identified two Healthy and Western dietary patterns using a principal component analysis (Appendix
291 1), and these patterns did not influence the associations observed between fermented dairy
292 consumption and cerebrovascular risk. Finally, the use of the SNIIRAM national register allowed the
293 maximisation of CVD case ascertainment, limiting the omission of cases when participants did not
294 report their disease to the study investigators. However, some limitations of this study also pertain
295 to its observational design. Indeed, residual confounding cannot be ruled out and a causal link
296 between the consumption of fermented dairy and a decreased risk of cerebrovascular disease
297 cannot be established from this prospective cohort study alone, although the inclusion of many
298 potential confounders in our main analyses suggest a robust inverse association. Furthermore, a
299 relatively limited statistical power precluded the investigation of specific types of CVDs. The
300 NutriNet-Santé cohort is volunteered-based, and as highlighted in Table 1, the participants included
301 in this study were generally more health-conscious, younger, more highly educated, more often
302 women, consumed more fruits and vegetables [9] and were less likely to smoke or be overweight [55],
303 compared to the general French population.

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

Conflicts of Interests/Competing Interests

Julie Lovegrove is Deputy Chair of the UK Scientific Advisory Committee for Nutrition (SACN) and was an expert on SACN's Saturated Fats working group. All others have no conflict of interest to declare.

Authors' contributions

LS, MT and JL designed the research. SH, PG, MT, CJ, LKF and EK-G conducted the research. LS performed the statistical analyses. BS supervised the statistical analyses. LS drafted the manuscript. MS, JL and KGJ supervised the writing. BS, KGJ, SH, PG, EK-G, CJ, LKF, MD, JL and MT contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. MT and JL had primary responsibility for the final content and are the guarantors. The corresponding author (BS) attests that all listed authors meet authorship criteria and that no other authors meeting criteria have been omitted.

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Table 1. Baseline characteristics of study population according to sex-specific quartiles of dairy consumption, NutriNet-Santé cohort, France, 2009-2019 (n=104,805).

Characteristics	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)		P-value [b]
						Quartiles of total dairy intake [a]					
Age, *years*	42.8	14.6	42.7	14.6	42.8	14.6	42.8	14.6	42.8	14.6	0.89
Sex											1.00
Female, *n*	82,517	78.7	20,629	78.7	20,629	78.7	20,630	78.7	20,629	78.7	
Male, *n*	22,291	21.3	5,572	21.3	5,573	21.3	5,573	21.3	5,573	21.3	
BMI, *kg/m²*	23.7	4.5	23.7	4.5	23.7	4.5	23.7	4.5	23.7	4.4	0.11
Physical Activity [c]											0.97
Low	2,2049	21.0	5,439	20.8	5,513	21.0	5,538	21.1	5,559	21.2	
Moderate	3,8712	36.9	9,710	37.1	9,676	36.9	9,633	36.8	9,693	37.0	
High	2,9447	28.1	7,366	28.1	7,376	28.2	7,370	28.1	7,335	28.0	
Education level											0.55
< High school degree	18,323	17.5	4,545	17.4	4,543	17.3	4,617	17.6	4,618	17.6	
< 2 years after high school	17,969	17.1	4,571	17.5	4,474	17.1	4,516	17.2	4,408	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	8,607	32.8	8,567	32.6	8,595	32.8	8,710	33.3	
Current	18,004	17.2	4,501	17.2	4,496	17.2	4,575	17.5	4,432	16.9	
Family history of CVD [d], *yes*	32,760	31.3	8,267	31.6	8,138	31.1	8,121	31.0	8,234	31.4	0.43
Prevalent morbidity, *yes*											
Type 2 diabetes	1,498	1.4	357	1.4	348	1.3	425	1.6	368	1.4	0.02
Hypertension	8,691	8.3	2,100	8.0	2,224	8.5	2,170	8.3	2,197	8.4	0.23
Hypercholesterolemia	8,396	8.0	2,073	8.0	2,135	8.0	2,097	8.0	2,091	8.0	0.79
Hypertriglyceridemia	1,536	1.5	383	1.5	378	1.4	390	1.5	385	1.5	0.98
Intakes of: [e]											
Energy, *kcal/d*	1,847	452	1,850	456	1,845	450	1,845	452	1,847	451	0.47
Alcohol, *g/d*	7.8	11.9	7.7	11.9	7.7	11.8	7.9	12.0	7.8	11.9	0.33
Total lipids, *g/d*	81.5	25.3	81.6	25.6	81.3	25.2	81.4	25.3	81.6	25.2	0.39
Carbohydrates, *g/d*	198.1	57.6	198.7	57.8	197.8	57.2	198.0	57.6	197.9	57.7	0.30
Proteins, *g/d*	78.8	21.5	78.9	21.6	79.0	21.5	78.7	21.4	78.8	21.5	0.58
Sodium, *g/d*	2.7	0.9	2.7	0.9	2.7	0.9	2.7	0.9	2.7	0.9	0.70
Total dietary fibre, *g/d*	19.5	7.2	19.5	7.2	19.5	7.1	19.5	7.3	19.4	7.2	0.54
Dietary Calcium, *mg/d*	921	299	922	299	922	299	919	299	921	299	0.61
Fruits and Vegetables, *g/d*	465	233	467	231	465	231	467	237	463	231	0.14
Total dairy, *g/d*	222	151	65	32	150	22	241	32	431	123	<0.001
Milk, *serving/d*	0.55	0.81	0.56	0.82	0.55	0.81	0.55	0.81	0.55	0.82	0.56
Cheese, *serving/d*	1.23	0.93	1.23	0.93	1.23	0.94	1.22	0.92	1.23	0.94	0.74
Yogurt, *serving/d*	0.47	0.55	0.09	0.16	0.38	0.33	0.64	0.51	0.77	0.77	<0.001

All values are presented as means ± SDs or *n* (%).
Abbreviations: **CVD**, cardiovascular disease. **d**, day.
[a] Sex-specific quartiles of total dairy consumption. Cut-offs were 112, 190 and 303g/d for males and 112, 191 and 301g/d for females.

Table 2. Associations between dairy consumption and cardiovascular disease risk from multivariable Cox proportional hazard models [a], NutriNet-Santé cohort, France, 2009-2019 (n=104,805).

		Continuous [c]	p-value	Quartiles of dairy food intakes [b]				p-trend
				First (low intake)	Second	Third	Fourth (high intake)	
Total CVD								
Milk	Cases/non-cases	1,952/102,856		484/25,717	514/25,688	468/25,735	486/25,716	
	HR (95% CI)	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	1,952/102,856		468/25,732	507/25,691	489/25,731	488/25,702	
	HR (95% CI)	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	1,952/102,856		530/30,180	405/21,173	544/26,781	473/24,722	
	HR (95% CI)	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	1,952/102,856		502/25,699	505/25,724	493/25,681	452/25,752	
	HR (95% CI)	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	1,952/102,856		461/25,740	502/25,700	513/25,690	476/25,726	
	HR (95% CI)	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	1,952/102,856		487/25,714	515/25,687	463/25,740	487/25,715	
	HR (95% CI)	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	1,952/102,856		686/35,249	401/22,536	435/22,543	430/22,528	
	HR (95% CI)	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	1,952/102,856		486/25,715	513/25,689	473/25,730	480/25,722	
	HR (95% CI)	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
Coronary Heart Disease [d]								
Milk	Cases/non-cases	1,219/103,586		296/25,905	347/25,853	301/25,902	275/25,926	
	HR (95% CI)	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	1,219/103,586		270/25,927	339/25,870	320/25,878	290/25,911	
	HR (95% CI)	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	1,219/103,586		297/30,135	280/21,690	321/26,162	321/25,599	
	HR (95% CI)	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	1,219/103,586		288/25,911	316/25,888	299/25,902	316/25,885	
	HR (95% CI)	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	1,219/103,586		287/25,915	339/25,861	305/25,897	288/25,913	
	HR (95% CI)	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	1,219/103,586		252/25,949	320/25,881	305/25,897	342/25,859	
	HR (95% CI)	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	1,219/103,586		298/25,903	349/25,852	293/25,909	279/25,922	
	HR (95% CI)	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	1,219/103,586		287/25,914	335/25,866	304/25,898	293/25,908	
	HR (95% CI)	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 [e]								
Milk	Cases/non-cases	878/103,927		207/25,994	248/25,952	227/25,976	196/26,005	
	HR (95% CI)	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	
	HR (95% CI)	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	
	HR (95% CI)	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	
	HR (95% CI)	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	
	HR (95% CI)	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	
	HR (95% CI)	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	
	HR (95% CI)	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	
	HR (95% CI)	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

Abbreviations: **CVD**, cardiovascular disease. **HR**, hazard ratio. **CI**, confidence interval.

[a] 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).

[b] 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, 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.

[c] Hazard Ratios 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.

[d] Includes myocardial infarction, angioplasty, acute coronary syndrome, and angina pectoris.

[e] Includes stroke and transient ischemic attack.

Table 3. Associations between fermented dairy foods and cerebrovascular disease risk from multivariable Cox proportional hazard models, NutriNet-Santé cohort, France, 2009-2019 (n=104,805). [a]

Proportional hazard Cox models [b,c]		Quartiles of fermented dairy food intakes [d]				p-trend
		First (low intake)	Second	Third	Fourth (high intake)	
	Cases/non-cases	180/26,021	229/25,972	232/25,970	237/25,964	
Model 1	HR (95% CI)	1	0.97 (0.79-1.18)	0.84 (0.69-1.02)	0.81 (0.66-0.98)	0.01
Model 2	HR (95% CI)	1	0.97 (0.79-1.18)	0.84 (0.69-1.02)	0.81 (0.66-0.98)	0.01
Model 2b	HR (95% CI)	1	0.97 (0.79-1.18)	0.84 (0.69-1.02)	0.81 (0.66-0.98)	0.01
Model 3	HR (95% CI)	1	0.96 (0.79-1.17)	0.83 (0.68-1.02)	0.80 (0.66-0.98)	0.01

Abbreviations: **HR**, hazard ratio. **CI**, confidence interval.

[a] Cerebrovascular disease included incident events of strokes and transient ischemic attacks.

[b] 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 hypertriglyceridemia.

[c] Hazard Ratios for an absolute increment of 100 g/d of fermented dairy foods

[d] 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.

Figures legends (Supplementary material)

Figure 1. Flowchart of participants included in the study, NutriNet-Santé cohort, France, 2009-2019

Figure 2. Spline plot for the linearity assumption of the association between the consumption of dairy foods and risk of cardiovascular diseases, NutriNet-Santé cohort, France, 2009-2019 (n=104,805). [a]
  a) Consumption of fermented dairy and risk of cerebrovascular diseases
  b) Consumption of total dairy and risk of total CVD
[a] Restricted cubic spline SAS macro developed by Desquilbet and Mariotti (35).