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SATURATED FAT FROM DAIRY SOURCES AND CARDIO-METABOLIC HEALTH: INSIGHTS FROM THE STANISLAS COHORT

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PURPOSE The health impact of dairy products is debated due to their high saturated fatty acid (SFA) content. Emerging evidence suggests that dairy products intake may reduce cardiovascular disease risk, despite their SFA-rich lipids, leading to the "dairy food matrix" concept. Nevertheless, the impact of lipid and SFA intake from whole dairy sources on cardio-metabolic health remains poorly understood. This study investigated the cross-sectional association of SFA intake from various types of dairy products and dairy fat sources with cardio-metabolic outcomes.

METHODS Data from 1619 participants of the STANISLAS cohort, who underwent extensive metabolic and cardiovascular phenotyping and completed a 133-item food frequency questionnaire covering dairy products and other dairy fat sources, were used. Associations of total dietary lipid, total dietary SFA, and SFA intakes from dairy products and dairy fat sources with metabolic outcomes (metabolic syndrome, hyperlipidemia, type 2 diabetes, prediabetes) and subclinical cardiovascular damages

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(i.e., arterial stiffness, atherosclerosis, left ventricular mass, diastolic dysfunction) were assessed using mixed models.

Results Median [interquartile range] lipid consumption via dairy products and dairy fat sources was 23 [15, 34] g/day. Higher total dietary lipid intake was associated with lower arterial stiffness (exp(β) [95%CI]: 0.96 [0.92–0.99]). Total dietary SFA and SFA from dairy products were both inversely associated with left ventricular mass (exp(β) [95%CI]: 0.85 [0.74– 0.98], and 0.99 [0.99–0.99], respectively). SFA from dairy fat sources, particularly from Butter, were inversely associated with hyperlipidemia (OR [95%CI]: 0.96 [0.93–0.99] for hypertriglyceridemia, 0.96 (0.93–0.99) for elevated LDLc, 0.95 (0.92–0.98) for elevated non-HDLc, 0.93 (0.89–0.96) for elevated Apolipoprotein B). SFA from Yogurt was inversely associated with Apolipoprotein B (OR [95%CI]: 0.92 [0.86–0.98]).

Conclusion Examining the specific diary matrix subtypes, our results suggest altogether neutral to beneficial associations of SFA from dairy products and dairy fat sources with cardio-metabolic health.

Keywords Dairy matrix · Saturated fatty acid · Cardiovascular damages · Metabolism · Food matrix · Epidemiology

Background

Milk and dairy products are a major nutritive food source worldwide, providing essential nutrients such as calcium, magnesium, selenium, riboflavin, vitamins B12 and B5. Milk lipids present a unique richness, including over 400 different fatty acids (including short-, medium-, natural trans-, branched-chain and conjugated species), polar lipids of the milk fat globule membrane, and fat-soluble vitamins [1]. Thus, milk and dairy products play a key role in healthy human nutrition and development throughout life. However, since the 1970s, the health effect of milk and dairy products has been questioned due to their high content in saturated fatty acids (SFA) [2, 3]. In the diet, SFA consist mainly of lauric, myristic and palmitic acids, which are atherogenic when consumed in excess (whereas stearic acid has a neutral effect) [4]. Excessive intake of SFA has been associated with poorer metabolic health and an increased risk of cardiovascular disease (CVD) [5]. Since 1980, recommendations have advised limiting SFA intake to less than 10% of total calories to reduce CVD risk [6, 7]. Nonetheless, more recent meta-analyses found no evidence that reducing SFA intake may reduce CVD incidence [8–10], whereas others report a mild beneficial effect [11]. These findings challenge the notion that further restricting dietary SFA will reduce clinical events [12]. Emerging evidence suggests that the effects of SFA intake vary according to food source [12–14], highlighting the so-called "food matrix effect". The term "food matrix" describes the overall structure of a food, the spatial organization of the nutrients and structures within it, and how these interact with each other; it can induce differential metabolic fate and impacts of nutrients ("food matrix effect") [15]. For instance, processed red meat contains SFA, but also high amounts of sodium and other preservatives that may have unfavorable effects on CVD risk factors. Conversely, dairy products (incl. milk, yogurt, cheese), an important source of SFA, also provide beneficial nutrients, including

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calcium, vitamin D, and proteins [1]. Some dairy products contain probiotics and bacterially-produced bioactive peptides that may also counterbalance the potentially unfavorable physiological effects of the atherogenic SFA [12, 16, 17]. In addition, blood lipid responses to milkderived SFA have been shown to differ based on food matrix structure. Meta-analyses of randomized controlled dietary intervention trials showed that cheese intake reduced LDLc and HDLc compared to butter [18, 19], whose matrix is a water-in-oil emulsion with a continuous fat phase and contains very few other nutrients, such as proteins and calcium. Recent clinical research has also highlighted the beneficial effects of polar lipids of the milk fat globule membrane on cholesterol metabolism [20, 21], and the mitigating impact of the viscous-to-rigid texture of certain dairy matrices in which the fat droplets/inclusions are embedded such as cheese, on digestion, intestinal absorption and satiety [22, 23]. Moreover, most national dietary guidelines emphasize the consumption of nutrient-dense dairy products such as milk, cheese, and yogurt [24]. However, other sources of dairy fat such as butter and cream are often excluded from this "dairy products" category [15, 24].

Notwithstanding, SFA are often studied as a whole, and despite these differences, few studies have explored the relationship between food sources of SFA and cardiometabolic health. In an epidemiological study from the Multi-Ethnic Study of Atherosclerosis, higher SFA intake from dairy products (excluding butter, considered as another SFA source) has been associated with lower CVD risk [13]. Of note, the association between butter SFA intake and CVD risk was neutral in this study: this non-deleterious association may be due to the presence of several favorable bioactive fatty acids in milk fat (e.g. short-chain species that are readily beta-oxidized, trans-vaccenic and trans-palmitoleic acids that have been associated with favorable metabolic effects [1]). However, no studies have thoroughly examined SFA intake stratified according to the various specific types of dairy products and dairy fat sources in this setting.

In light of the above, this study aimed to assess the cross-sectional associations of SFA from individual types of milk-related sources (dairy products per se vs. other dairy fat sources), as well as SFA from each type of milk-related products (i.e., dairy product categories: Milk, Yogurt, Unripened Cheese, Ripened Cheese; dairy fat source categories: Cream, Butter, Dairy desserts) with metabolic outcomes, i.e., pre-diabetes, metabolic syndrome and hyperlipidemia, as well as subclinical cardiovascular damages, i.e. carotidfemoral pulse wave velocity (cfPWV), a surrogate marker of arterial stiffness [25], carotid intima-media thickness (cIMT), a surrogate marker of atherosclerosis [26], left ventricular (LV) mass, and diastolic dysfunction (DD).

Methods

STUDY POPULATION

The STANISLAS cohort is a population-based study of 1,006 families (4,295 participants) from the Lorraine region in Eastern France recruited between 1993 and 1995 at the Center for Preventive

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Medicine. Participants were of French origin, living in the Lorraine region, and free of acute or chronic disease. Participants were followed every 5 to 10 years. From 2011 to 2016, 1,705 participants underwent their fourth examination. The STANISLAS study has been extensively described elsewhere [27].

The present study focused on the participants who underwent their fourth examination, where food data were collected, enabling us to acquire detailed information regarding milk-related lipids. Ten individuals with missing dietary data and 63 participants with daily energy intake either below 1,000 or above 5,000 kcal were excluded from the analysis. The exclusion of participants with daily energy intake below 1,000 kcal or above 5,000 kcal is a common approach in nutritional epidemiology to ensure data reliability and exclude implausible dietary reports. Thus, 1,632 participants were included in the initial descriptive analyses.

Thirteen participants were further excluded from the subsequent analyses due to missing values for at least one of the covariates. To maintain statistical power, the cross-sectional analyses for each outcome were conducted with the maximum number of individuals with available data (Fig. 1).

DATA COLLECTION

DIETARY ASSESSMENT

Dietary intake was assessed using a validated semi-quantitative food frequency questionnaire (FFQ) with 133 items [28]. The participants reported their consumption frequency and portion sizes of 133 food and beverage items over the previous 3 months. Consumption frequency was reported using 6 levels in the FFQ, ranging from "never or rarely" to "2 times or more a day." The portion size of each food or beverage item was estimated using standard serving sizes and food models. Daily nutrient intakes were calculated in grams per day by multiplying the consumption frequency of each item by the nutrient content of selected portions. Nutritional data were extracted from the French food composition database established by the French Data Center on Food Quality (Ciqual, last updated in 2013). The DASH score was calculated to evaluate global diet quality [29], and the number of servings of ultra-processed foods using the NOVA classification, which regroups the foods into 4 categories according to their level of processing, with ultraprocessed food (UPF) defined as the 4th category (NOVA4) [30]. A few dairy product items were classified under the UPF category such as flavored milk and flavored yogurt [31]. Low-fat butter and dairy dessert were also categorized under the UPF category [31].

TYPES OF DIETARY SOURCES OF MILK-RELATED LIPIDS/SFA

We first examined the 133-item FFQ to identify all individual milk-related products that are quantifiable sources of milk lipids (and SFA therein): this led to a list of 28 different milk-related products (Supplementary Table 1). Subsequent categories were then defined: (i) first globally, namely Dairy products vs. other Dairy fat sources, (ii) then more specifically, namely Milk, Yogurt, Cheese (among which Ripened vs. Unripened), Butter, Cream, and Dairy desserts (Supplementary Table 1). All types of milk and yogurt (skimmed, low-fat, and full-fat) were grouped together under

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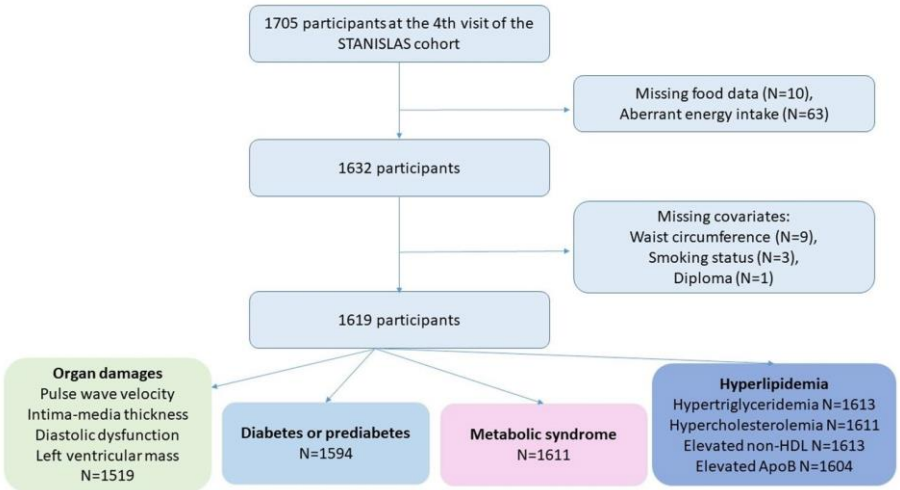
"Milk" and "Yogurt" categories, respectively, without distinction by fat content as SFA intake from the different products was the primary variable of interest (the differential fat/SFA content of skimmed, low-fat and full-fat products being *de facto* taken into account). Lipid and SFA intakes from these defined types of dairy products were calculated by adding the intakes from the corresponding individual products within. Total dietary lipids and SFA intakes were also calculated by adding the intakes from the whole foods from the FFQ.

METABOLIC OUTCOMES

Metabolic syndrome (MetS) was defined according to the National Cholesterol Education Program Adult Treatment Panel 3 (NCEP ATP 3) [32]. ATP 3 is one of the most widely used concepts for assessing MetS. It requires the presence of at least three of the following defined criteria: waist circumference > 102 cm in men and > 88 cm in women; office blood pressure ≥ 130/85 mmHg or treated by hypertensive drugs; elevated triglycerides ≥ 1.5 g/L or treated by lipidlowering drugs; fasting blood glucose ≥ 1.10 g/L or treated by antidiabetic drugs; reduced HDL cholesterol < 0.4 g/L in men and < 0.5 g/L in women.

Diabetes and prediabetes combined outcome was defined as fasting blood glucose ≥ 1.10 g/L or treated by antidiabetic drugs. To best account for the diversity of hyperlipidemia types and the emergence of new markers of cardiovascular risk such as non-HDL-cholesterol and Apolipoprotein B (ApoB), four different related outcomes were defined: (i) hypertriglyceridemia was defined as elevated triglycerides ≥ 1.5 g/L or treated by lipid-lowering drugs, (ii) hypercholesterolemia was defined as elevated LDLcholesterol ≥ 1.6 g/L or treated by lipid-lowering drugs, (iii) elevated non-HDL-cholesterol as non-HDL-cholesterol ≥ 1.9 g/L or treated by lipid-lowering drugs, and (iv) elevated ApoB as ApoB ≥ 1.3 g/L or treated by lipid-lowering drugs.

Fig. 1 Flowchart of the study



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CARDIOVASCULAR DAMAGE

CAROTID-FEMORAL PULSE WAVE VELOCITY (CFPWV)

cfPWV was assessed with the Complior® device (ALAM Medical, France), which simultaneously records arterial pulse waves at carotid and femoral sites, according to the recommendations of the European Network for Noninvasive Investigation of Large Arteries [33]. Two sensors were placed simultaneously on the carotid artery and femoral artery. Two measurements were made, with cfPWV calculated as their mean. If the 2 measurements differed by > 0.5 m/s, a third measurement was recorded, and the cfPWV was then calculated as the median of the 3 measurements. The onboard foot-to-foot algorithm based on the second-derivative waveforms was used to determine the transit time. The carotid-to-femoral, carotid-to-sternalnotch, and sternal-notch-to-carotid distances were measured with a measuring tape, and cfPWV (m/s) was obtained with the formula cfPWV = D × 0.8/(t).

CAROTID INTIMA-MEDIA THICKNESS (CIMT)

cIMT measurements were routinely performed by highresolution echo-tracking in a controlled environment at 22 ± 1 °C after 10 min of rest in the supine position as described elsewhere [34]. Carotid diameter, distension, and intima-media thickness were measured on the right common carotid artery. Four measurements were obtained per patient. Examinations were performed using the wall track system (WTS, ESOATE, Maastricht, The Netherlands) and the ART.LAB (ESAOTE, Maastricht, The Netherlands) in immediate succession.

DIASTOLIC DYSFUNCTION (DD)

Assessment of left ventricular DD was performed according to the recommendations of the American Society of Echocardiography and the Committee of the European Association of Echocardiography [35, 36], using the following grading scheme: mild or grade I (impaired relaxation pattern), moderate or grade II (pseudonormal filling) and, severe (restrictive filling) or grade III. Due to the relatively small number of subjects (n = 3) with grade III DD in our study population, it was decided to consider the variable as no DD, grade I and grade II/III.

LEFT VENTRICULAR MASS

Echocardiographic examinations of the subject in the left lateral decubitus position were performed by an experienced echocardiographer using a commercially available standard ultrasound scanner (Vivid E9, General Electric Medical Systems, Horten, Norway) with a 2.5-MHz phased-array transducer (M5S). The echo/Doppler examinations included exhaustive examinations in parasternal long- and short-axis views and in the standard apical views [35]. All acquired images and media were stored on a secured network server as digital videos with unique identification numbers and analyzed on a dedicated workstation (EchoPAC PC, version 110.1.0, GE Healthcare). Notably, the left ventricular internal diastolic diameter from the parasternal 2-dimensional long-axis view was measured. These measurements were subsequently used in the cube-function formula of the American Society of Echocardiography guidelines to calculate left ventricular mass (LVM) [37], which was then indexed for height to the 2.7 power [38].

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COVARIATES

During the fourth visit, all participants underwent a clinical examination measuring weight (kg), height (m), and waist circumference (cm). Body mass index was calculated as weight (kg) divided by the square of height (m). Blood samples were also collected, and serum concentrations of the following biomarkers were measured: fasting blood glucose, HDL cholesterol, and triglycerides. LDL cholesterol was calculated using the Friedewald formula: [LDL-cholesterol] = [total cholesterol] − [HDL-cholesterol] − ([triglycerides]/5) [39, 40]. Office blood pressure (BP) was also measured. After 10 min of rest in the supine position, systolic and diastolic blood pressures were measured with an automatic device (Dinamap Pro 400, CRITIKON). Office BP was measured 3 times at 1-minute intervals, and the mean of the 3 measurements was calculated. Blood samples were collected during the clinical examination.

Additionally, participants completed several questionnaires assessing their socio-demographic characteristics such as education level, medical history and treatment, as well as their level of physical activity using the International Physical Activity Questionnaire (IPAQ).

STATISTICAL ANALYSES

Participant characteristics were first assessed globally. The cohort was stratified into quartiles based on total lipid intake from milk-related sources (g/day), among which SFA represent 62.3%. Within each quartile, medians and interquartile ranges were calculated for each variable. Differences between quartiles were assessed using the Kruskal-Wallis test for quantitative variables and chi-square test or Fisher's exact test for qualitative variables, applying the BenjaminiHochberg correction for multiple testing.

Second, dairy lipid intakes were examined from six types of milk-related products: Milk, Yogurt, Ripened Cheese, Unripened Cheese, Cream, Butter (including dairy spreads), as well as Dairy desserts (Supplementary Table 1). The term 'dairy lipids' was used at this first stage since easier to visualize for a wide audience (62.3% of dairy lipids being composed of SFA). Dietary intakes and the distribution of milk-related lipid intake were calculated by quartile of dairy lipid consumption, with an additional stratification by generation: Generation 1 (parents - aged over 50) and Generation 2 (offspring aged over 18 and under 50).

Third, the relationships between dairy SFA intake and cardio-metabolic outcomes were assessed, analyzing the dietary intake and matrix effect at different levels: (1) total dietary lipids, (2) total dietary SFA, (3) SFA specifically from dairy products or from dairy fat sources, (4) SFA from six types of milk-related products (Milk, Yogurt, Ripened Cheese, Unripened Cheese, Butter (including dairy spreads), Cream and Dairy desserts). The latter were analyzed in association with seven different outcomes, divided into four categories: organ damages (i.e. cfPWV, cIMT, DD and LVM), combined pre-diabetes and diabetes, MetS and hyperlipidemia. Models were resolved using the lme4 package (v1.1.29) [41], with confidence intervals from broom mixed (v0.2.9.4) and p-values from lmerTest (v3.1.3) [41].

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Three levels of adjustment were applied for each model, progressively incorporating additional covariates: (1) adjusted for age and sex, (2) additionally adjusted for waist circumference, tobacco use, education level, DASH score, number of ultra-processed foods servings, total energy intake and alcohol intake, (3) additionally adjusted for the use of antihypertensive, antidiabetic, and lipid-lowering drugs, as well as adherence to a diet which allowed assessing changes in the usual diet, which is key information in a cross-sectional study.

For the diabetes/prediabetes outcome, the 'hypoglycemic treatment' variable was excluded from the predictors since individuals under treatment are systematically diabetic. Similarly, 'waist circumference' was omitted in models for MetS, as they are part of its criteria, as well as the variable "lipid-lowering drugs" for hyperlipidemia outcomes. In the context of a family cohort, mixed-effects models with a random family effect were used. Linear mixed-effects models (LMMs) were applied to quantitative outcomes, while generalized linear mixed-effects models (GLMMs) were used for qualitative outcomes. For LMMs, outcomes were log-transformed to address heteroskedasticity frequently observed in the data.

SENSITIVITY ANALYSES

Due to 291 missing values for physical activity, this variable was excluded from the main analyses to avoid loss of statistical power. Sensitivity analyses were conducted to assess its impact when included in the models. Two steps were followed: (1) *Dataset restriction*: Models were adjusted using data from individuals with physical activity information but without including this variable, assessing the loss of power due to the restricted sample size. (2) *Variable inclusion*: Physical activity was added to the models, using the same restricted dataset, to assess its influence on model coefficients.

Additionally, individuals were compared with and without missing physical activity data. Quantitative variables were analyzed using the Wilcoxon test, while qualitative variables were assessed using the chi-square test (for expected cell counts ≥ 5) or Fisher's exact test (for smaller counts).

All statistical analyses were performed using the R software (version 4.1.3).

Results

CHARACTERISTICS OF THE STUDY POPULATION

In the STANISLAS cohort, the median [Q1-Q3] consumption of lipids from all milk-related products (dairy products and dairy fat sources) was 23 [15, 34] g/day. The participants in the fourth quartile were more likely to be men, have a higher physical activity level, and less likely to be dieting or take lipid-lowering drugs (Table 1, and Supplementary Table 2). An increase in caloric and macronutrient intake from Q1 to Q4 was also observed (Table 2, Supplementary Table 2). Moreover, the

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contribution of dairy lipids to total lipid intake, assessed by the dairy lipids/total lipids ratio, also increased from 0.16 in Q1 to 0.36 in Q4. The participants in Q4 also had a higher intake of ultra-processed foods, and a lower DASH score, suggesting a lower overall nutritional quality (Supplementary Table 2). The prevalence of each binary outcome in the whole cohort was as follows: 40% (*N* = 637) diabetes/prediabetes, 25% (*N* = 402) MetS, and 18% (*N* = 273) diastolic dysfunction. Regarding hyperlipidemia, the prevalence was 27% (*N* = 440) for hypertriglyceridemia, 35% (*N* = 571) for elevated LDLc, 32% (*N* = 510) for elevated non-HDL-cholesterol, and 22% (*N* = 362) for elevated ApoB.

Table 1 *Participant characteristics according to quartiles of lipid intake from milk-related products*

		Quartile of lipid intake from milk-related products[2]				
Characteristics	Overall [0–120] (g/d)	Q1 [0–15] (g/d)	Q2 [15–23] (g/d)	Q3 [23–34] (g/d)	Q4 [34–120] (g/d)	*p*-value[1]
N	1632	408	408	408	408	
Age	56 (34, 60)	56 (35, 61)	56 (35, 60)	55 (35, 60)	55 (34, 60)	0.555
Male	794 (49%)	164 (40%)	200 (49%)	201 (49%)	229 (56%)	< 0.001
Blood glucose (g/L)	0.88 (0.82, 0.95)	0.88 (0.82, 0.94)	0.88 (0.83, 0.95)	0.88 (0.83, 0.95)	0.89 (0.82, 0.96)	0.861
Blood cholesterol (g/L)	2.10 (1.85, 2.41)	2.12 (1.83, 2.43)	2.10 (1.87, 2.41)	2.11 (1.86, 2.36)	2.08 (1.85, 2.39)	0.840
Triglycerides (g/L)	0.92 (0.67, 1.26)	0.96 (0.68, 1.26)	0.90 (0.67, 1.23)	0.93 (0.70, 1.31)	0.88 (0.65, 1.24)	0.448
HDL cholesterol (g/L)	0.57 (0.48, 0.66)	0.57 (0.48, 0.66)	0.56 (0.48, 0.66)	0.57 (0.48, 0.67)	0.55 (0.48, 0.66)	0.674
LDL cholesterol (g/L)	1.31 (1.11, 1.56)	1.32 (1.08, 1.58)	1.32 (1.13, 1.56)	1.30 (1.10, 1.53)	1.32 (1.10, 1.55)	0.724
Apolipoprotein A1 (g/L)	1.67 (1.49, 1.88)	1.69 (1.51, 1.90)	1.65 (1.49, 1.87)	1.67 (1.48, 1.88)	1.67 (1.50, 1.88)	0.674
Apolipoprotein B (g/L)	0.96 (0.81, 1.12)	0.97 (0.81, 1.15)	0.97 (0.84, 1.12)	0.96 (0.81, 1.10)	0.96 (0.80, 1.12)	0.747
Office SBP	123 (114, 135)	123 (113, 135)	123 (114, 135)	123 (115, 135)	124 (115, 135)	0.747
Antihypertensive treatment	333 (20%)	92 (23%)	79 (19%)	85 (21%)	77 (19%)	0.674
Lipid-lowering treatment	249 (15%)	79 (19%)	60 (15%)	62 (15%)	48 (12%)	0.040
Glucose-lowering treatment	60 (3.7%)	19 (4.7%)	16 (3.9%)	9 (2.2%)	16 (3.9%)	0.404
Metabolic syndrome	407 (25.1%)	116 (28.4%)	92 (22.8%)	93 (23.0%)	106 (26.0%)	0.191
Diabetes or prediabetes	640 (39.8%)	167 (41.4%)	156 (38.6%)	164 (40.6%)	153 (38.6%)	0.797
Hyperlipidemia						
Hypertriglyceridemia	442 (27.2%)	131 (32.3%)	104 (25.5%)	111 (27.2%)	96 (23.8%)	0.041
Elevated LDLc	576 (35.5%)	164 (40.5%)	144 (35.3%)	139 (34.2%)	129 (31.9%)	0.072
Elevated Non-HDLc	514 (31.6%)	149 (36.7%)	132 (32.4%)	117 (28.7%)	116 (28.7%)	0.043
Elevated ApoB	365 (22.6%)	116 (28.9%)	89 (22.0%)	83 (20.4%)	77 (19.1%)	0.004
Diastolic dysfunction	293 (18.4%)	79 (19.5%)	73 (18.3%)	71 (18.1%)	70 (17.6%)	0.910
Pulse wave velocity (m/s)	8.14 (7.28, 9.30)	8.22 (7.21, 9.48)	8.19 (7.37, 9.30)	8.16 (7.26, 9.33)	8.06 (7.28, 9.12)	0.898
Intima-media thickness (µm)	614.79 (522.00, 715.21)	612.17 (533.00, 706.00)	624.00 (515.96, 722.96)	613.92 (530.00, 715.00)	607.50 (510.75, 715.25)	0.594
Left ventricular mass (g/height$^{2.7}$)	32.68 (27.51, 39.59)	33.32 (27.73, 41.15)	32.67 (27.67, 39.73)	31.92 (26.82, 38.49)	33.12 (28.07, 39.33)	0.224

Continuous variables are expressed as mean ± SD or median (Q1, Q3) as appropriate. Categorical variables are presented as n(%). BMI, body mass index; SBP, systolic blood pressure; HDL, plasma high-density cholesterol; LDL, plasma low-density cholesterol; MET, metabolic equivalent task; SBP, systolic blood pressure. Generation 2 corresponds to the youngest individuals (aged over 18 years and under 50 years), related to Generation 1 (aged over 50 years)

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[1] Kruskal-Wallis rank sum test for continuous variables; Chi2 for categorical variables with all expected cell counts ≥ 5 and Fisher's exact test otherwise; BH correction
[2] Milk-related products include dairy products (Milk, Yogurt, Ripened Cheese, Unripened Cheese), but also Dairy fats and Dairy desserts (cf. Supplementary Table 1)

CONTRIBUTION OF THE VARIOUS DAIRY PRODUCT TYPES TO DAIRY LIPID INTAKE

Although 99.8% of participants consumed dairy products, the types of dairy products varied significantly. Cheese was the most consumed product (97.5% of consumers), while Milk was the least consumed (54.8% of consumers) (Supplementary Table 3). Most milk-related products contributed uniformly to increased milk-related lipid intake (Fig. 2), except Butter, which increased 4.5-fold from the first to the last quartile (3.8–17.2% of total milk-related lipids, respectively). Ripened cheese and Butter, the main sources of dairy lipids, showed generational differences—generation 1 consumed less Butter and more Ripened cheese, except among the highest dairy lipid consumers, where the generational difference in Butter intake disappeared (Fig. 3). Lipids from milk-related products represented 16 to 36% of total dietary lipid intake from the first to the last quartile (Supplementary Table 3). The contribution of milk-related SFA intake in the total dietary SFA intake ranged increasingly from 43 to 80% from Q1 to Q4, i.e. milk-related SFA represent the major SFA source for subjects in the second, third and fourth quartiles (Supplementary Table 3).

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Table 2 *Food intake characteristics according to quartiles of lipid intake from milk-related products*

Characteristics	Overall [0–120](g/d)	Quartile of lipid intake from milk-related products				
		Q1 [0–15](g/d)	Q2 [15–23](g/d)	Q3 [23–34](g/d)	Q4 [34–120](g/d)	*p*-value[1]
N	1632	408	408	408	408	
Dietary lipids (g/day)	89 (67, 120)	61 (50, 77)	82 (67, 100)	97 (78, 119)	131 (109, 161)	< 0.001
Lipids from milk-related products (g/day)[2,3]	23 (15, 34)	10 (7, 13)	19 (17, 21)	28 (25, 30)	45 (38, 55)	< 0.001
Lipids from dairy fat source (g/day)	7.11 (3.19, 13.50)	2.62 (1.46, 4.23)	6.26 (3.38, 9.75)	9.62 (4.69, 14.34)	17.17 (9.32, 24.34)	< 0.001
Lipids from dairy products (g/day)	14.00 (8.48, 22.02)	6.34 (3.86, 8.99)	12.53 (9.54, 15.58)	17.73 (13.47, 22.74)	28.69 (21.34, 37.01)	< 0.001
Dietary SFA (g/day)	34 (25, 46)	21 (17, 26)	30 (26, 36)	38 (32, 45)	54 (46, 64)	< 0.001
SFA from milk-related products (g/day)	14.47 (9.56, 21.07)	6.34 (4.39, 7.88)	12.05 (10.79, 13.28)	17.38 (15.82, 18.82)	27.91 (23.87, 34.28)	< 0.001
SFA from dairy fat source (g/day)	4.34 (1.94, 8.22)	1.61 (0.89, 2.61)	3.82 (2.04, 6.02)	6.03 (2.88, 8.99)	10.59 (5.64, 15.29)	< 0.001
SFA from dairy products (g/day)	8.75 (5.38, 13.86)	3.96 (2.41, 5.70)	7.91 (6.00, 9.82)	11.13 (8.44, 14.25)	17.98 (13.33, 23.13)	< 0.001
SFA from Milk (g/day)	0.08 (0.00, 1.19)	0.00 (0.00, 0.25)	0.07 (0.00, 1.19)	0.13 (0.00, 1.19)	0.25 (0.00, 1.36)	< 0.001
SFA from Yogurt (g/day)	1.15 (0.24, 2.94)	0.33 (0.05, 1.27)	1.15 (0.35, 2.41)	1.57 (0.36, 3.06)	2.41 (0.63, 4.83)	< 0.001
SFA from Cheese (g/day)	6.16 (3.25, 10.45)	2.58 (1.48, 3.99)	5.39 (3.26, 7.64)	7.84 (5.44, 10.98)	13.38 (8.73, 18.54)	< 0.001
SFA from Unripened cheese (g/day)	0.94 (0.37, 2.22)	0.58 (0.19, 1.12)	0.90 (0.39, 2.00)	1.17 (0.47, 2.50)	1.57 (0.54, 4.34)	< 0.001
SFA from Ripened cheese (g/day)	4.35 (1.82, 8.33)	1.67 (0.72, 2.82)	3.58 (1.93, 5.80)	5.90 (3.12, 8.92)	10.33 (5.39, 16.69)	< 0.001
SFA from Cream (g/day)	0.81 (0.32, 1.44)	0.41 (0.13, 0.81)	0.73 (0.32, 1.09)	1.00 (0.32, 1.90)	1.03 (0.41, 2.76)	< 0.001
SFA from Butter (g/day)	1.31 (0.00, 5.23)	0.18 (0.00, 1.12)	1.12 (0.17, 2.99)	2.62 (0.18, 5.23)	5.23 (1.68, 10.46)	< 0.001
SFA from Dairy dessert (g/day)	0.79 (0.12, 1.78)	0.36 (0.00, 0.92)	0.79 (0.12, 1.56)	0.96 (0.34, 2.01)	1.19 (0.45, 2.96)	< 0.001

Variables are expressed as median (Q1, Q3)

[1]Kruskal-Wallis rank sum test for continuous variables; Chi2 for categorical variables with all expected cell counts ≥ 5 and Fisher's exact test otherwise; BH correction

[2]Milk-related products include dairy products (Milk, Yogurt, Ripened Cheese, Unripened Cheese), but also Dairy fats, Dairy desserts (cf. Supplementary Table 1)

[3]Among these lipids, SFA represents 62.3%

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Fig. 2. *Contribution of lipids from each dairy item to total milk-related lipid intake across quartiles. (A) expressed in g/d for each item, (B) expressed as % of total milk-related lipid intake for each product type. Each milkrelated product types are defined in Supplementary Table 1.*

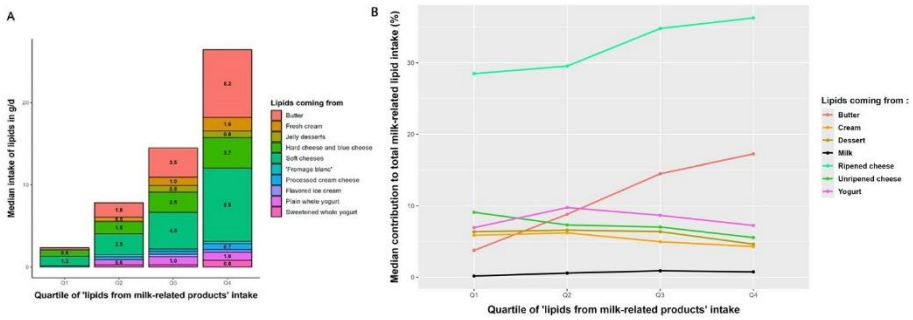
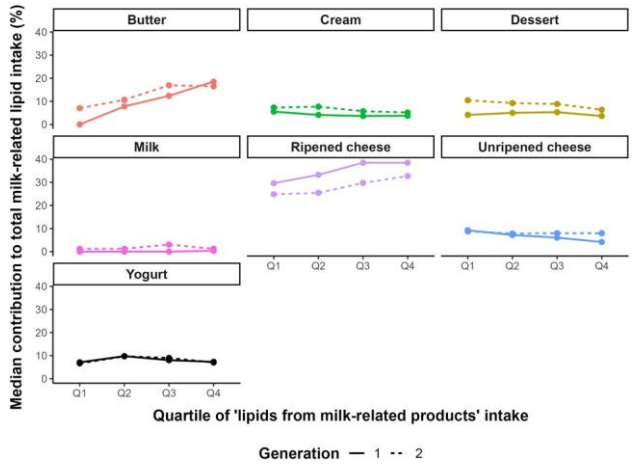


Fig. 3. *Contribution of each food group to lipid intake across quartiles of lipid intake according to generation. Generation 2 corresponds to the youngest individuals (aged under 50 years), and Generation 1 the oldest individuals (aged over 50 years). Each milk-related product types are defined in Supplementary Table 1.*



ASSOCIATION BETWEEN LIPIDS AND CARDIO-METABOLIC OUTCOMES

In these analyses, we investigated the association with cardio-metabolic outcomes in a step-by-step manner by refining the level of detail relative to the lipids. No significant associations were globally observed between total dietary lipids, total dietary SFA and SFA from dairy products and hyperlipidemia (Fig. 4), although in the fully adjusted models, total dietary SFA was significantly and negatively associated with elevated ApoB (Fig. 4D - OR [95% CI]: 0.970 [0.953–0.988]). SFA from dairy fat sources was significantly and negatively associated with the 4 hyperlipidemia variables (Figs. 4A, B, C, D): 0.962 [0.931–0.994] for hypertriglyceridemia, 0.962[0.933–0.991] for elevated LDLc, 0.950

[0.921–0.979] for elevated non-HDLc, 0.926 [0.892–0.961] for elevated ApoB. This association was driven by Butter, with SFA intake showing a similar inverse relationship with all hyperlipidemia variables: OR [95% CI]: 0.962 [0.931–0.994] for hypertriglyceridemia (Fig. 5, 0.962 [0.933– 0.991] for elevated LDLc (Fig. 6), 0.950 [0.921–0.979] for elevated non-HDLc (Fig. 7), 0.926 [0.892–0.961] for elevated ApoB (Fig. 8).

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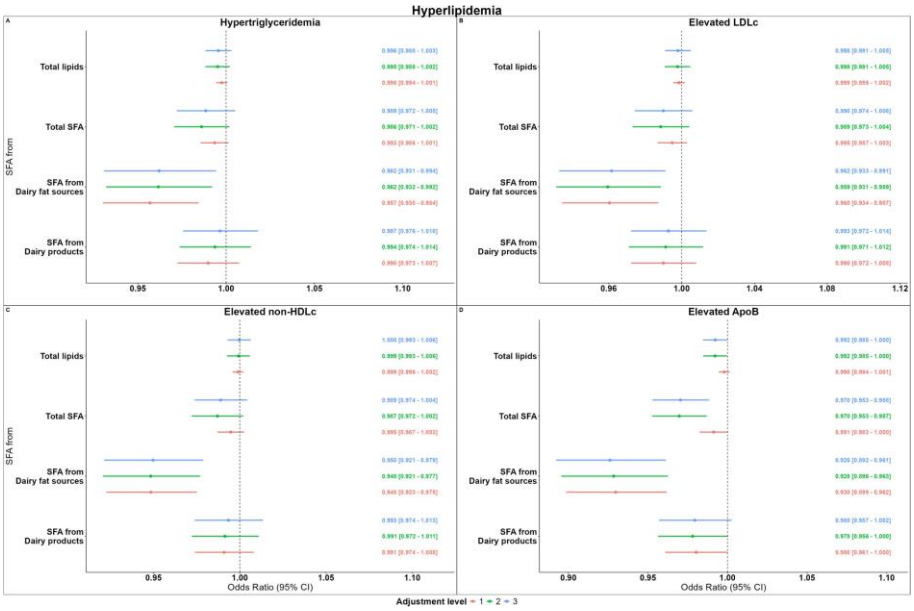
Fig. 4. *Associations between lipids as well as SFA and four different hyperlipidemia outcomes.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milk-related product types which are sources of SFA are defined in Supplementary Table 1. (A) Hypertriglyceridemia, defined as triglycerides ≥ 1.5 g/L or treated by lipid-lowering drugs, (B) Elevated LDLc, defined as LDLc ≥ 1.6 g/L or treated by lipid-lowering drugs, (C) elevated nonHDLc defined as non-HDLc ≥ 1.9 g/L or treated by lipid-lowering drugs, (D) elevated ApoB defined as ApoB ≥ 1.3 g/L or treated by lipid-lowering drugs. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, education level, DASH score, number of ultra-processed food servings), total energy intake and alcohol intake. For level 3, the models were additionally adjusted for the use of antihypertensive and antidiabetic drugs, as well as adherence to a diet.

In the sensitivity analyses, the association between SFA intake from Butter and non-HDLc and ApoB remained significant in the restricted cohort (by removing the participants with no data on physical activity without adjusting for the latter), and also by adjusting on physical activity in the restricted cohort (Figs. 7 and 8). However, although SFA from Butter were associated with hypertriglyceridemia in a model adjusted for age and sex (0.960 [0.931–0.991]), the significance was lost after further adjustment (0.972 [0.937– 1.008]) (Fig. 5B). Regardless of the adjustment or not for physical activity, the association with hypertriglyceridemia was no longer observed in the restricted cohort (Fig. 5C). Regarding elevated LDLc, the association with SFA from Butter became marginally significant in the restricted cohort in fully adjusted models (p = 0.051, Fig. 6). Of note, participants with available physical activity data and those without physical activity data, defining the differences between the whole and restricted cohorts, had altogether similar characteristics (Supplementary Table 4). Therefore, we cannot rule out that a lack of power may explain the loss of significant associations between Butter SFA intake and hypertriglyceridemia and elevated LDLc in the restricted cohort with the available physical activity data. Additionally, participants with hyperlipidemia had lower intake of Butter than participants without hyperlipidemia (Supplementary Table 5).

SFA from Yogurt showed no association with hypertriglyceridemia, elevated LDLc and elevated non-HDLc. However, SFA from Yogurt was significantly and negatively associated with elevated ApoB in

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the whole population (0.921 [0.864–0.981] - Fig. 8A), and in the restricted cohort, both with (0.913 [0.846–0.984] - Fig. 8C) or without adjustment on physical activity (0.912 [0.846–0.983] - Fig. 8B).

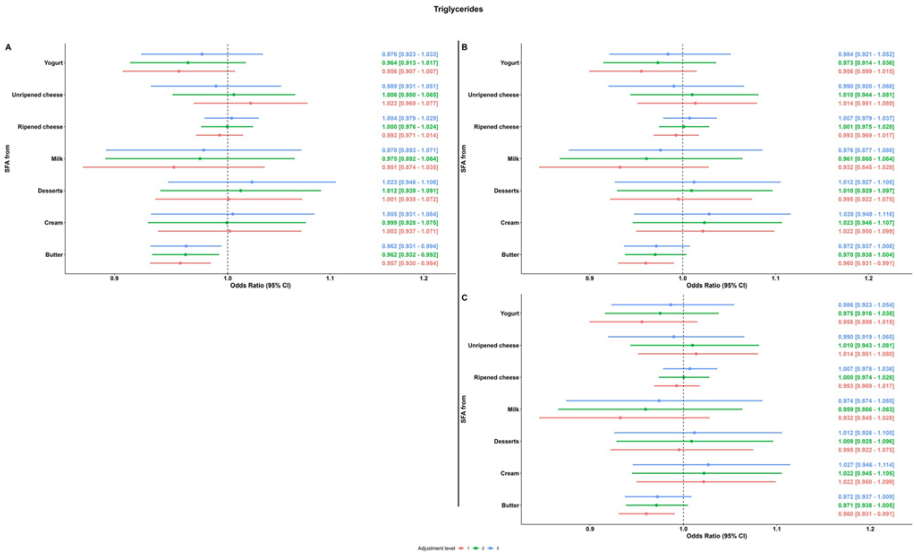
For left ventricular mass, the main analysis showed inverse associations with total dietary SFA (exp(β) [95% CI]: 0.849 [0.739–0.976]) and SFA from dairy products (0.997 [0.996–0.999]), although these associations disappeared in sensitivity analyses (Table 3). SFA from Yogurt were inversely associated with left ventricular mass, albeit marginally significant after adjusting for medications and dieting.

Pulse wave velocity was associated with total lipids in the fully adjusted models (0.961 [0.924–0.999]), with this association remaining in the sensitivity analysis (Supplementary Table 6). None of the SFA-related types of dairy products was associated with pulse wave velocity (Supplementary Table 6).

MetS was positively and significantly associated with SFA from Unripened cheese in the main analysis, although this association lost significance after adjustment for medications and dieting (Fig. 9). None of the other lipid sources was associated with MetS (Fig. 9).

Lastly, no association was observed between any of the milk-related lipids or SFA and any of the other outcomes, i.e. diabetes and prediabetes, DD and intima media-thickness, whether in the main (Figs. 10, and 11, Supplementary Table 7) or sensitivity analyses (data not shown).

Fig. 5. *Associations between SFA from seven types of milk-related products and hypertriglyceridemia.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milk-related product types which are sources of SFA are defined in Supplementary Table 1. Hypertriglyceridemia was defined as triglycerides ≥ 1.5 g/L or treated by lipid-lowering drugs (A) for the whole cohort, (B) for the restricted cohort, (C) for the restricted cohort with adjustment for physical activity. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, education level, DASH score, number of ultra-processed food servings, total energy intake and alcohol intake. For level 3, the models were additionally adjusted for the use of antihypertensive and antidiabetic as well as adherence to a diet (and physical activity in panel C only).

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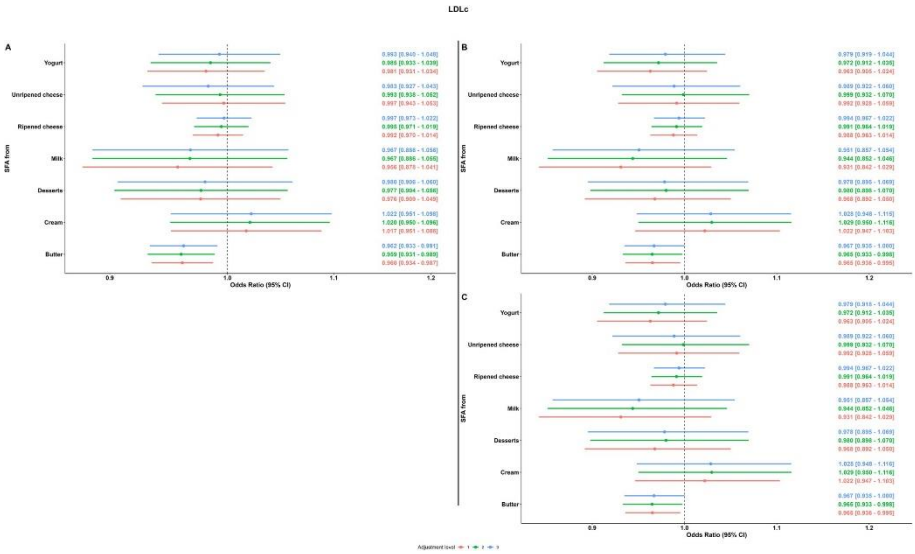
Fig. 6. *Associations between SFA from seven types of milk-related products and elevated LDLc.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milk-related products types which are source of SFA are defined in Supplementary Table 1. (A) for the full cohort, (B) for the restricted cohort, (C) for the restricted cohort with adjustment for physical activity. Elevated LDLc was defined as LDL-cholesterol ≥ 1.6 g/L or treated by lipid-lowering drugs. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, diploma, DASH score, number of ultra-processed foods servings, total energy intake and alcohol intake. For level 3, the models were adjusted taking also into account the use of antihypertensive and antidiabetic as well as adherence to a diet (and physical activity in panel C only).

Discussion

In the STANISLAS cohort, higher total dietary lipid intake was associated with lower arterial stiffness, while higher total dietary SFA and SFA from dairy products were favorably associated with lower left ventricular mass although all these latter associations were no longer significant in the sensitivity analysis. Higher SFA from dairy fat sources, particularly Butter, were associated with a lower occurrence of hyperlipidemia, namely hypertriglyceridemia, elevated LDLc, elevated non-HDLc, elevated ApoB. The associations of SFA from Butter with elevated non-HDLc and with elevated ApoB remained in the sensitivity analyses. However, this was not the case for hypertriglyceridemia and elevated LDLc where the associations were not significant anymore. SFA from Yogurt was associated with a lower occurrence of elevated ApoB in the main and sensitivity analyses. Total dietary SFA or from any of the milk-related products were not associated with any other cardio-metabolic outcomes.

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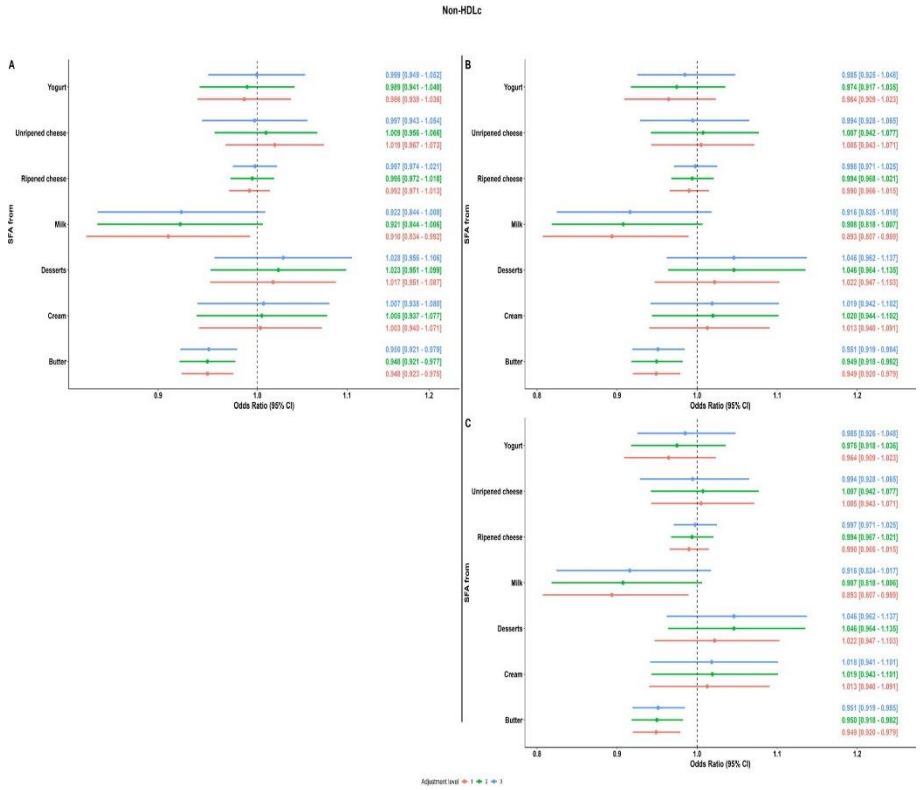
Fig. 7. *Associations between SFA from seven types of milk-related products and elevated non-HDLc.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milk-related products types which are source of SFA are defined in Supplementary Table 1. Elevated non-HDL-cholesterol as nonHDL-cholesterol ≥ 1.9 g/L or treated by lipid-lowering drugs. (**A**) for the full cohort, (**B**) for the restricted cohort, (**C**) for the restricted cohort with adjustment for physical activity. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, diploma, DASH score, number of ultra-processed foods servings, total energy intake and alcohol intake. For level 3, the models were adjusted taking also into account the use of antihypertensive and antidiabetic as well as adherence to a diet (and physical activity in panel C only).

Certain recent meta-analyses did not indicate any association between total dietary SFA intake and CVD [12], while others suggested different effects according to food matrix [13]. A food-based study approach in the Multi-Ethnic Study of Atherosclerosis cohort reported lower CVD risk with higher SFA intake from dairy products (incl. yogurts, ice creams, milks pure or in a beverage, cottage cheeses, socalled "regular" cheeses– i.e. Cheddar, American, Swiss…, cream sauce/soup, pizza, enchiladas without meat; excl. butter) but higher risk with SFA intake from meat (unprocessed and processed meats, pure or in meat-containing foods as hamburgers, burritos etc.) [13]. Authors highlight the role of food-specific fatty acids and nutrients, in addition to SFA, as well as other structural characteristics of the food [13]. The Framingham offspring study reports that adult men with higher intakes of "dairy SFA" had a less atherogenic profile than males with lower intakes of these fats [42]: in this study, SFA derived from all types of dairy products and dairy fat sources were considered (milk, yogurt, cheese, butter, cream, either as individual foods or as ingredients in other food products).

In this setting, our current study focusing mainly on SFA from specific subtypes of milk-related products providing dairy fat showed an inverse association between SFA intake from Dairy products

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and left ventricular mass in the main analyses, although not significant in the sensitivity analyses likely due to reduced power. While left ventricular hypertrophy is understudied, our findings align with evidence that frequent dairy consumption in children reduces the risk of left ventricular hypertrophy [43].

When considering CVD more globally, recent meta-analyses of prospective studies report null or weak inverse associations between total dairy consumption and CVD risk and mortality [44–47]. A recent review of dose-response results of large prospective cohort studies and meta-analyses examining the association of dairy food consumption and risk of cardiovascular outcomes concludes notably that: (i) total dairy intake is either not or favorably associated with CVD risk; (ii) there is no conclusive evidence that regularfat and low-fat dairy foods is differentially associated with any CVD-related clinical outcomes; and (iii) consumption of fermented dairy, primarily yogurt and cheese, in general shows no association with CVD risk [24]. Focusing on subclinical CV damages, our study reveals that only left ventricular mass was inversely associated with SFA intake from Dairy products, and not atherosclerosis or arterial stiffness. As increased left ventricular mass is a known risk factor for CVD [48], this result suggests a potential mechanism linking SFA from dairy products to CVD via left ventricular mass modulation. When examining associations at the product level, our findings show that SFA from Yogurt were significantly inversely associated with left ventricular mass. Although this association was no longer significant in the fully adjusted model, including medication and dieting, it nonetheless appears consistent with reviews that have concluded to a neutral to beneficial effect of fermented dairy on CVD [24, 49], and also more recently with the French Nutrinet Santé cohort study (no significant associations between total dairy, milk, cheese, yogurts, fermented and reduced-fat dairy intakes and CVD risk; but an observed reduced risk of cerebrovascular diseases, including stroke, with the consumption of fermented dairy, including cheese and yogurts) [50]. Furthermore, SFA from Yogurt were also significantly and inversely associated with elevated ApoB (an increasingly used marker of CVD risk) in both the main and sensitivity analyses, albeit not associated with other markers of hyperlipidemia. This finding may be explained by the fact that ApoB is not necessarily correlated with LDLc and non-HDLc, as ApoB more accurately reflects the concentration of atherogenic lipoprotein particles (i.e. LDL, VLDL, chylomicrons and their remnants) rather than the cholesterol within [51–53]. This result raises the question of a potential causal effect of SFA within yogurts on the amount of such lipoproteins. Supporting our finding, a 4-week randomized crossover trial comparing the effects of 1.5-2 portions/day of full-fat yogurt (4% fat), versus low-fat yogurt and butter (providing an equivalent fat amount than the full-fat yogurt), on cardiometabolic risk factors found that ApoB levels were significantly decreased following the full-fat yogurt intervention compared with the low-fat yogurt plus butter combination [54], while no differential effect was observed for TG, LDLc and non-HDLc in this trial. Altogether, as fermentation is reported to impact food lipid composition [55], this raises the question as of whether adjusted for the use of antihypertensive, antidiabetic, and lipid-lowering drugs, as well as adherence to a diet milk lipid fermentation by yogurt bacteria may ultimately in milk proteins and released by the proteolytic activity of contribute to a specific beneficial impact on ApoB levels. lactic acid bacteria [56]. These peptides exhibit antihyperMore generally, the fermentation of dairy products is known tensive properties, likely due to their ability to inhibit the

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to produce bioactive peptides that are initially embedded angiotensin-converting enzyme [57]. Additionally, yogurt naturally contains lactic acid bacteria with probiotic properties, promoting favorable changes in gut microbiota such as increased beneficial *Lactobacillus* and *Bifidobacterium* genera, which may help to prevent CVD [58]. Whether such mechanisms could contribute to the observed favorable associations of SFA from Yogurt with left ventricular mass and ApoB will deserve further investigation.

No associations were found between SFA intake (total or from milk-related sources) and pre-diabetes and diabetes in the present study. Nonetheless, there is conflicting evidence in the literature with one meta-analysis having found significant inverse associations between intakes of dairy products, low-fat dairy products, and cheese, and the risk of type 2 diabetes [59], whereas when focusing on total dietary SFA, others did not find any significant association with the risk of type 2 diabetes [60]. According to Soedamah-Muthu et al. [17], the results from all studied meta-analyses consistently showed neutral or inverse associations for total and low-fat dairy products, with the most striking inverse association observed for yogurt and type 2 diabetes. A more recent narrative review confirmed that consumption of yogurt appears to be associated with a lower risk of developing type 2 diabetes [49]. This was supported by the FDA in March 2024, which concluded that there is some credible evidence supporting a relationship between yogurt intake and reduced risk of type 2 diabetes, irrespective of fat content [61]. In the present study, we did not find any association between SFA from Yogurt and type 2 diabetes including pre-diabetes, supporting the fact that emphasis should not be placed on the SFA content of the yogurt matrix. Regarding hyperlipidemia, saturated fats are generally reported to raise blood LDL cholesterol and ApoB levels, key etiological CVD risk factors [4]. The Reading, Imperial, Surrey, Saturated fat Cholesterol Intervention ("RISSCI"-1) study showed that transitioning from higher-SFA/lower-Unsaturated FA (UFA) to a lowerSFA/higher-UFA diet significantly reduced fasting blood lipids such as LDLc, ApoB and non-HDLc [62]. In a dietary intervention RCT in men and women aged 50–75 years, consuming 50 g of butter per day during 4 weeks increased LDLc compared to 50 g/day of olive oil [63]. Here in a study population aged between 18 and 88 years and consuming lower butter amounts (maximum 10 [4–20] g/day in the higher quartile of milk-related lipid intake), we found that SFA from Butter was negatively associated with hypertriglyceridemia, elevated LDLc but also high non-HDLc and high ApoB. Importantly, among LDL particles, small- and medium-density LDL are considered more atherogenic due to decreased hepatic clearance by the LDL receptor and enhanced anchoring to LDL receptor-independent binding sites in extrahepatic tissues, including the arterial wall [64]. In this respect, a cross-over RCT [65] demonstrated that the observed increase in serum cholesterol from high-saturated fat diets stems from an increase in the concentration of large LDL particles, whereas small- and medium-sized LDL particles remain unaffected. Regarding Butter specifically, a RCT in obese individuals comparing diets rich in SFA from cheese or butter, or rich in MUFA or PUFA, or a low-fat, high-carbohydrate diet, suggests that SFA from butter and cheese have similar effects on features of the LDL particle size phenotype, and that consumption of SFA from butter may be associated with larger LDL particles, i.e., less atherogenic [66]. With regard to CV events, an epidemiological study reported that a higher intake of butter (> 1 serving per day) *versus* zero intake was not associated with a higher risk of the composite of mortality or major cardiovascular events

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(defined as death from cardiovascular causes, nonfatal myocardial infarction, stroke, or heart failure) [67]. Furthermore, several meta-analyses showed that butter consumption was not significantly associated with CVD, coronary heart disease and stroke [45, 47]. Altogether, the observation herein that Butter SFA was negatively associated with hyperlipidemia is consistent with the above latter. These favorable associations with Butter may be partly explained by (i) the butter consumption amount in the present cohort, which is close to the French recommendations i.e. not in excess, and (ii) the composition of this important milk fat source, containing several bioactive fatty acids (e.g. short chain, natural trans, branched chain, conjugated fatty acids). However, as these FA are also naturally present in dairy products but no association is observed here between other dairy SFA sources and hyperlipidemia, we cannot exclude a reverse causation in the observed crosssectional inverse association between Butter SFA intake and hyperlipidemia. Participants with hyperlipidemia had lower intake of SFA from Butter, compared to participants without hyperlipidemia: this can be the reflect of different long-term dietary habits but we cannot rule out that this could be the result of recent or older medical or dietary advices, even if our analyses adjusted on current dieting information to limit such a potential confounding behavior.

Altogether, increasing evidence supports that other components of milk lipid sources and of dairy products are more relevant than SFA content alone on cardio-metabolic health. As mentioned above, dairy products and dairy fat sources contain numerous other types of fatty acids with reported favorable biological activities (e.g. trans-vaccenic acid, trans-palmitoleic acid, conjugated linoleic acid) [1, 24]. In dairy products, other components may interfere with the intestinal absorption and digestibility of fat (e.g., calcium, notably in hard cheese, can reduce SFA absorption) and, therefore, attenuate the effect of SFA on cholesterol metabolism and potentially provide a protective effect on cardiovascular health [68]. Among lipid molecules carrying SFA in dairy products, milk polar lipids have been shown to reduce LDLc, ApoB and triglyceride concentrations as well as reduce intestinal cholesterol absorption in at-risk individuals in randomized dietary intervention trials [20, 21]. Suggested mechanisms are related to the impact of milk sphingomyelin that can reduce cholesterol absorption and improve circulating sphingolipid profile [69]. In a Chinese cohort study of ~ 2000 participants (dairy consumption being assessed as intake frequency and amount of milk, milk formula, yogurt, ice cream, milk tablet, cream, evaporated milk; i.e. excluding butter) (replicated in an intervention trial) [70] and in the large Spanish PREDIMED cohort (validated in confirmatory US cohorts, namely NHS, NHSII and HPFS) ("total dairy" being considered here as milk, yogurt, cheese, cream, ice cream and butter) [71], the circulating concentration of milk-specific sphingomyelin species (C14-SM) (i) was positively associated with total dairy intake, (ii) showed favorable associations with changes or incidences of blood pressure and fasting glucose in the Chinese participants with habitually low dairy consumption [70], and (iii) contributed to a dairy-intake score, a higher score being associated with a lower T2D risk [71]. Altogether, this supports a potential causal biological pathway between dairy intake (either including or excluding butter according to the studies), the identified circulating lipidomic profile, and the prevention of cardio-metabolic diseases [70, 72]. Finally, postprandial lipemia is another important independent risk factor for CVD: recent research shows that the structure and texture of the different SFA-containing dairy matrices (e.g. emulsified vs. spread milkfat; hard cheese vs. cream cheese) can modulate lipid

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digestion and postprandial lipemia [23, 73]. Hence, the health effect of the food as a whole rather than the content of any single nutrient may therefore be more relevant to understanding the associations between dietary consumption and health outcomes. Although the present work does not show major differences in the associations of SFA with cardiometabolic outcomes between the different matrices studied (Milk vs. Yogurt vs. Cheese vs. Butter vs. Cream notably), they align with recent reports that there is no deleterious association between dairy intake and CVD risk despite their SFA content [24].

The present study features several strengths. The analyses were based on a population-based cohort with the availability of detailed information on diet, in particular detailed information on milk-related products, lifestyle and clinical factors and outcomes, as well as extensive cardiovascular phenotyping. The present is also one of the first studies to focus on detailed milk-related products in relation to cardio metabolic health. However, certain limitations of this study should be acknowledged. First, the results are based on cross-sectional data, and causality cannot be implied due to the observational nature of the study. Second, physical activity data were not available for all participants and could therefore only be partially taken into account, despite its known importance in lifestyle-related diseases. Nonetheless, in a sensitivity analysis limited to individuals with available physical activity data, adjusting for physical activity did not alter the major results. Third, food intake may have changed over the life course because of age or disease diagnosis. However, our cross-sectional study design precluded us from recording these changes, which may influence the observed association, although dieting was accounted for as a confounder to minimize this effect. Longitudinal studies are needed to better understand the association between SFA intake from different dairy/milk-related matrix sources and cardio-metabolic outcomes. Lastly, the generalizability of our results may be limited due to the inclusion of participants solely from the Lorraine region, albeit with a similar intake of total dairy to that of the rest of France, but with less milk intake and greater cheese intake compared to Nutrinet Santé [50] and INCA3 [74] reports. Noteworthy, as dairy fat sources and dairy products provided up to 80% of total dietary SFA in the present cohort, observed associations between total dietary SFA and cardiometabolic outcomes may have been driven by the SFA from milk-related sources.

In conclusion, the present results align with recent literature indicating that SFA from dairy products present neutral to beneficial associations with cardio-metabolic health. They contribute to the "dairy matrix" concept in which the specific compositions and structures of dairy products and dairy fat sources more likely explain their relationship with cardiovascular health or some blood lipid markers of CVD risk than the SFA within. Our study also delves deeper into the specific subtypes of milk-related products, adding new insight to current knowledge exploring the dairy matrix effect. Further studies are needed to better understand these relationships in larger longitudinal cohorts and *via* RCTs in different populations, as well as exploring the health impact of other nutrients and micronutrients of the different dairy matrices, such as calcium, along with fermentation.

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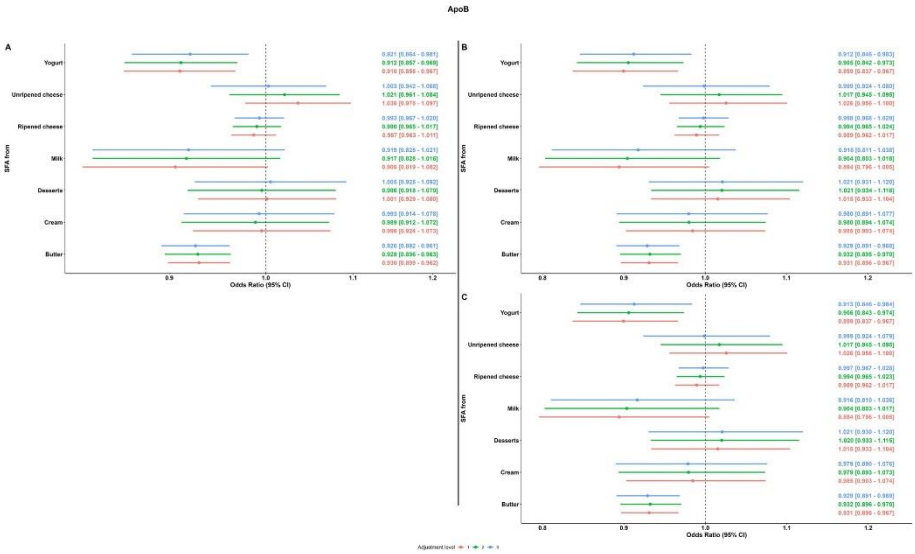
Fig. 8. *Associations between SFA from seven types of milk-related products and elevated ApoB.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milkrelated products types which are source of SFA are defined in Supplementary Table 1. Elevated ApoB as ApoB ≥ 1.3 g/L or treated by lipidlowering drugs. (A) for the full cohort, (B) for the restricted cohort, (C) for the restricted cohort with adjustment for physical activity. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, diploma, DASH score, number of ultra-processed foods servings, total energy intake and alcohol intake. For level 3, the models were adjusted taking also into account the use of antihypertensive and antidiabetic as well as adherence to a diet (and physical activity in panel C only).

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Table 3. *Association between milk-related lipids and SFA and left ventricular mass*

Left ventricular mass	Whole cohort Exp(β) [95% CI], *P*-value			Restricted cohort Exp(β) [95% CI], *P*-value			Restricted cohort with adjustment for physical activity Exp(β) [95% CI], P-value		
	Mod1	Mod2	Mod3	Mod1	Mod2	Mod3	Mod1	Mod2	Mod3
Total dietary lipids	1.014 [0.984–1.046], *p*= 0.4	0.967 [0.907–1.030], *p*= 0.3	0.979 [0.920–1.042], *p*= 0.5	1.019 [0.985–1.054], *p*= 0.3	0.979 [0.913–1.050], *p*= 0.6	0.991 [0.924–1.062], *p* = 0.8	1.019 [0.985–1.054], *p* = 0.3	0.976 [0.910–1.047], *p*= 0.5	0.987 [0.921–1.058], *p*= 0.7
Total dietary SFA	1.003 [0.930–1.083], *p* > 0.9	0.820 [0.712–0.945], *p* = **0.006**	0.849 [0.739–0.976], *p*= **0.022**	1.018 [0.935–1.108], *p*= 0.7	0.874 [0.747–1.023], *p*= 0.093	0.909 [0.778–1.062], *p*= 0.2	1.018 [0.935–1.108], *p*= 0.7	0.868 [0.742–1.016], *p*= 0.077	0.903 [0.773–1.054], *p*= 0.2
SFA from dairy fat sources	0.998 [0.995–1.000], *p* = 0.10	0.998 [0.995–1.000], *p*= 0.073	0.998 [0.996–1.001], *p*= 0.2	0.998 [0.995–1.001], *p*= 0.2	0.999 [0.996–1.001], *p*= 0.3	0.999 [0.996–1.002], *p*= 0.5	0.998 [0.995–1.001], *p* = 0.2	0.998 [0.996–1.001], *p*= 0.3	0.999 [0.996–1.002], *p*= 0.4
SFA from dairy products	0.999 [0.997–1.000], *p*= 0.14	0.997 [0.996–0.999], *p*= **0.006**	0.997 [0.996–0.999], *p*= **0.006**	0.999 [0.997–1.001], *p*= 0.4	0.998 [0.996–1.000], *p*= 0.10	0.998 [0.996, 1.000], *p*= 0.13	0.999 [0.997–1.001], *p*= 0.4	0.998 [0.996–1.000], *p*= 0.10	0.998 [0.996–1.000], *p*= 0.13
SFA from Butter	0.998 [0.995–1.000], *p*= 0.10	0.998 [0.995–1.000], *p*= 0.073	0.998 [0.996–1.001], *p* = 0.2	0.998 [0.995–1.001], *p*= 0.2	0.999 [0.996–1.001], *p*= 0.3	0.999 [0.996–1.002], *p*= 0.5	0.998 [0.995–1.001], *p*= 0.2	0.998 [0.996–1.001], *p*= 0.3	0.999 [0.996–1.002], *p*= 0.4
SFA from Cream	1.000 [0.994–1.007], *p*>0.9	0.998 [0.991–1.004], *p* = 0.5	0.998 [0.991–1.004], *p*= 0.5	1.000 [0.992–1.007], *p* > 0.9	0.997 [0.990–1.004], *p* = 0.4	0.997 [0.99–1.004], *p*= 0.4	1.000 [0.992–1.007], *p* > 0.9	0.997 [0.990–1.004], *p*= 0.4	0.997 [0.990, 1.004], *p* = 0.4
SFA from Dairy dessert	1.001 [0.994–1.008], *p*= 0.8	1.001 [0.994–1.008], *p*= 0.8	1.001 [0.995–1.008], *p*= 0.7	1.002 [0.994–1.009], *p*= 0.6	1.001 [0.994–1.009], *p*= 0.8	1.001 [0.994–1.009], *p*= 0.7	1.002 [0.994–1.009], *p*= 0.6	1.001 [0.994–1.008], *p*= 0.8	1.001 [0.994–1.009], *p*= 0.7
SFA from Milk	0.995 [0.987–1.003], *p*= 0.2	0.996 [0.988–1.003], *p*= 0.3	0.996 [0.989–1.003], *p* = 0.3	0.993 [0.984–1.002] *p*= 0.12	0.994 [0.986 – 1.003], *p*= 0.2	0.995 [0.987–1.004], *p*= 0.3	0.993 [0.984–1.002], *p*= 0.12	0.994 [0.986–1.002], *p*= 0.2	0.995 [0.987–1.003], *p*= 0.3
SFA from Ripened cheese	0.999 [0.997–1.001], *p*= 0.4	0.998 [0.996–1.000], *p*= 0.083	0.998 [0.996–1.000], *p*= 0.11	1.000 [0.997–1.002], *p*= 0.8	0.999 [0.996–1.001], *p*= 0.4	0.999 [0.997–1.002], *p*= 0.5	1.000 [0.997–1.002], *p*= 0.8	0.999 [0.997–1.001], *p*= 0.4	0.999 [0.997–1.002], *p*= 0.5
SFA from Unripened cheese	1.001 [0.996–1.006], *p*= 0.7	0.998 [0.993–1.003], *p*= 0.5	0.996 [0.991–1.001], *p*= 0.2	1.001 [0.995–1.007], *p* = 0.9	0.998 [0.992–1.004], *p*= 0.5	0.997 [0.991–1.003], *p*= 0.3	1.001 [0.995–1.007], *p*= 0.9	0.998 [0.993–1.004], *p*= 0.6	0.997 [0.991–1.003], *p*= 0.3
SFA from Yogurt	0.995 [0.990–0.999], *p*= **0.040**	0.995 [0.990–0.999], *p*= **0.045**	0.996 [0.991–0.999], *p*= 0.072	0.997 [0.991–1.002], *p*= 0.2	0.997 [0.992–1.003], *p*= 0.4	0.998 [0.993–1.003], *p*= 0.5	0.997 [0.991–1.002], *p*= 0.2	0.997 [0.992–1.003], *p* = 0.3	0.998 [0.993–1.003], *p*= 0.4

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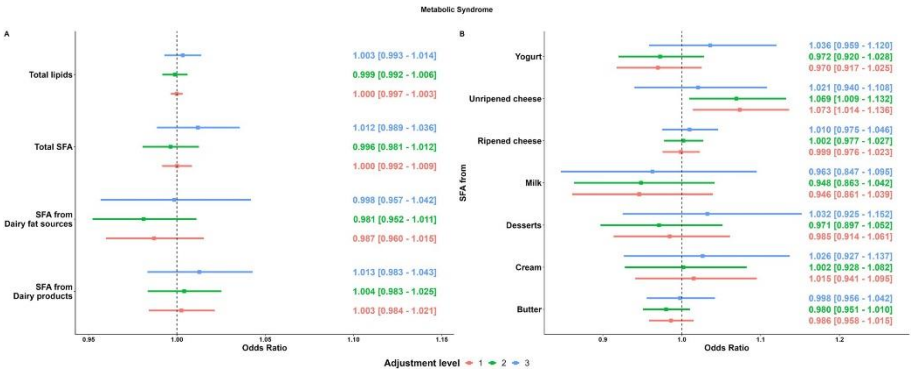
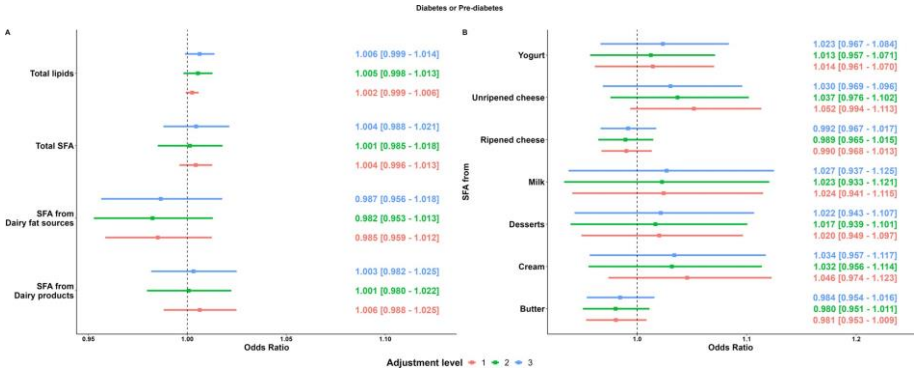
Exp(β) is the multiplicative factor for each 1 g/day increase in lipids or SFA. It is held that 100 x (exp(β) − 1) is the percent change in left ventricular mass associated with a 1 g/day increase of lipids or SFA
SFA, saturated fatty acids. Each milk-related product types which are sources of SFA are defined in Supplementary Table 1. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, education level, DASH score, number of ultra-processed food servings, total energy intake and alcohol intake. For level 3, the models were additionally adjusted for the use of antihypertensive, antidiabetic, and lipid-lowering drugs, as well as adherence to a diet.

Fig. 9. *Associations between milk-related lipids and SFA and metabolic syndrome.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milk-related product types which are sources of SFA are defined in Supplementary Table 1. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to tobacco use, education level, DASH score, number of ultra-processed food servings, total energy intake and alcohol intake. For level 3, the models were additionally adjusted for the use of antihypertensive, antidiabetic, and lipid-lowering drugs, as well as adherence to a diet.

Fig. 10. *Associations between milk-related lipids and SFA and diabetes/prediabetes.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milk-related product types which are sources of SFA are defined in Supplementary Table 1. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, education level, DASH score, number of ultra-processed food servings, total energy intake and alcohol intake. For level 3, the models were additionally adjusted for the use of antihypertensive, antidiabetic, and lipid-lowering drugs, as well as adherence to a diet.

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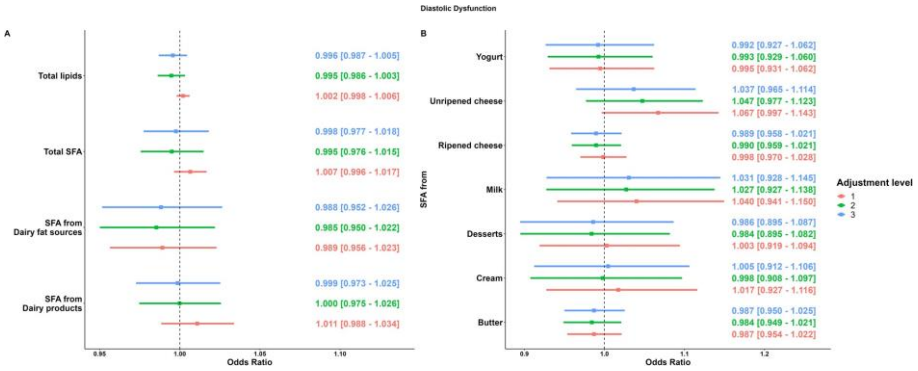
Fig. 11. *Association between milk-related lipids and SFA and diastolic dysfunction.*



Results are expressed for each increment of 1 g/day of lipids and SFA. SFA, saturated fatty acids. Each milk-related product types which are a source of SFA are defined in Supplementary Table 1. For adjustment level 1, the models were adjusted for age and sex. For level 2, the adjustment was extended to waist circumference, tobacco use, education level, DASH score, number of ultra-processed food servings, total energy intake and alcohol intake. For level 3, the models were additionally adjusted for the use of antihypertensive, antidiabetic, and lipid-lowering drugs, as well as adherence to a diet.

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AUTHOR CONTRIBUTIONS All authors have read and agreed to the published version of the manuscript. PR, NG, and JMB designed the fourth visit of the STANISLAS cohort. EB and NG supervised the cardiovascular (arterial stiffness and thickness, and echocardiography, respectively) assessments. LM performed the data management. SW, MCM, and NG designed the present research. TM, CL, KY performed the statistical analysis. SW and MCM drafted the first version of the manuscript. All authors were involved in the interpretation of the results and the critical review of the manuscript.

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DATA AVAILABILITY The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE The research protocols were all approved by the local Ethics Committee (Comité de Protection des Personnes Est III— Nancy— France), and all study participants gave informed written consent. The informed written consent was previously approved by the local Ethics Committee.

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