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## Randomized Control Trials

## The effect of dairy products on liver fat and metabolic risk markers in males with abdominal obesity – a four-arm randomized controlled trial



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## SUMMARY

**Background & aims:** In recent years, epidemiological studies have reported links between the consumption of fermented dairy products, such as yogurt, and health; however, evidence from human intervention trials is scarce and inconsistent. We aimed to investigate the effect of consumption of four different types of dairy products (two fermented and two non-fermented) on liver fat (primary outcome) and metabolic risk markers in males with abdominal obesity.

**Methods:** In this parallel randomized controlled trial with four arms, 100 males aged 30–70 years, with body mass index 28.0–45.0 kg/m<sup>2</sup>, and waist circumference ≥102 cm underwent a 16-weeks intervention where they were instructed to consume 400 g/day of either milk, yogurt, heat-treated yogurt, or acidified milk as part of their habitual diet. Liver fat was measured by magnetic resonance imaging.

**Results:** In the complete case analyses (n = 80), no effects of the intervention or differences between groups were detected in anthropometry or body composition including liver fat. Moreover, no effects were detected in inflammatory markers. Main effects of time were detected in blood pressure (decrease; P < 0.001), insulin (decrease; P < 0.001), C-peptide (decrease; P = 0.040), homeostatic model assessment for insulin resistance (decrease; P < 0.001), total cholesterol (decrease; P = 0.016), low-density lipoprotein (decrease; P = 0.033), high-density lipoprotein (decrease; P = 0.006), and alanine transaminase (decrease; P = 0.019). Interactions between group and time failed to reach significance.

**Conclusions:** In conclusion, findings from our study do not confirm that fermented yogurt products are superior in reducing liver fat or improving metabolic risk markers compared to non-fermented milk products. In fact, all intervention products (both fermented yogurt products and non-fermented milk products) did not affect liver fat and caused largely similar modest favorable changes in some metabolic risk markers. The study was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (# NCT04755530).

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**Abbreviations:** Metabolic syndrome, (MetS); Non-alcoholic fatty liver disease, (NAFLD).

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## 1. Introduction

The metabolic syndrome (MetS) reflects a cluster of metabolic abnormalities including abdominal obesity, elevated blood pressure, dyslipidemia, and impaired glucose tolerance, which incre

ases risk of CVD and type 2 diabetes [1–3]. Insulin resistance is central in the pathogenesis of impaired glucose tolerance and is also considered one of the leading etiologic factors in non-alcoholic fatty liver disease (NAFLD) [4,5]. NAFLD is defined by the presence of steatosis in  $\geq 5\%$  of the hepatocytes on histological analysis or  $\geq 5.6\%$  fat by volume on magnetic resonance spectroscopy and not due to secondary causes (e.g., drug-induced liver injury, viral hepatitis, or autoimmune liver disease) and excessive alcohol consumption [6]. NAFLD is frequently associated with the same metabolic abnormalities as MetS, which emphasizes NAFLD as the hepatic manifestation of MetS [4,5].

The current management options for MetS and NAFLD include lifestyle interventions implementing various dietary and physical activity regimens that generally focus on weight reduction, as well as pharmacotherapy for the individual components of MetS [1,6]. Little, however, is known about how qualitative changes in the diet can affect these conditions [7]. In recent years, focus on potential health effects of fermented dairy products, such as yogurt, has emerged [8–14]. Dairy products are nutrient-dense foods supplying high-quality protein and various micronutrients. Yogurt deviates from other dairy products with the fermentation process, which is induced by lactic acid bacteria, and alters the physical structure as well as the nutritive and bioactive properties of the yogurt products [11]. Many epidemiological studies have reported associations between consumption of fermented dairy products and lower risk of CVD, type 2 diabetes, and obesity [15–22]. However, because consumption of fermented dairy products, especially yogurt, is also linked to an overall healthy dietary and lifestyle pattern [23,24], it is difficult to dissect these confounding factors from the specific health benefits linked to yogurt in epidemiological studies. Only a small number of intervention trials have investigated the effect of consumption of fermented dairy products, including yogurt, on health outcomes such as glucose metabolism, lipid profile, and abdominal fat content [25–32]. However, these studies are small and inconsistent, and vary in the type of dairy product, nutrient content, bioactive components, physical structure, and processing methods – but also the control intervention – all of which seem to be important for the observed health effects [14].

Accordingly, we conducted a 16-week randomized controlled intervention with four arms. The aim was to investigate the effect two fermented dairy products (whole milk yogurt with live bacteria (yogurt) and heat-treated whole milk yogurt with inactivated bacteria (heat-treated yogurt)) and two non-fermented dairy products (whole milk (milk) and chemically acidified whole milk (acidified milk)) on liver fat (primary outcome) and metabolic risk markers in males with abdominal obesity. We hypothesized that consumption of fermented yogurt products would lead to reductions in liver fat and improvements in metabolic risk markers compared to non-fermented milk products.

## 2. Materials & methods

This study was a parallel randomized controlled trial with four arms, comprising a 4-week standardization lead-in period, and a 16-week active intervention period (Fig. 1). The study was conducted in accordance with Good Clinical Practice and the study protocol complied with the relevant sections of the Declaration of Helsinki. The study was approved by the Scientific Ethics Committee of the Capital Region of Denmark (# H-20059243) and was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (# NCT04755530). The study was conducted from February 2021 to June 2022 at the Department of Nutrition, Exercise and Sports at the University of Copenhagen, Denmark.

### 2.1. Study products

During the standardization lead-in period, subjects were instructed to consume 400 g/day of whole milk as part of their habitual diet, while refraining from other dairy products except from maximum 1 dL milk and 25 g butter daily. The standardization period was followed by a 16-week intervention period, where subjects were randomized in a 1:1:1:1 ratio to one of four dairy product groups. Each subject was randomized individually using a computer generated list and informed of the allocation by study staff. The randomization was stratified for age (30–50 years/51–70 years) and BMI (28.0–32.9 kg/m<sup>2</sup>/33.0–45.0 kg/m<sup>2</sup>). The four dairy products were 1) whole milk (milk); 2) whole milk yogurt with live bacteria (yogurt); 3) heat-treated whole milk yogurt (heat-treated yogurt) where the heat treatment inactivated the live bacteria; 4) chemically acidified whole milk (acidified milk) which was acidified by lactic acid and did not contain any bacteria. All study products were of plain neutral flavor. Table 1 describes the macronutrient content of the dairy products and a more detailed characterization has been published elsewhere [33].

During the intervention period, subjects were instructed to consume 400 g/day of the allocated dairy product as part of their habitual diet, while refraining from other dairy products except from maximum 1 dL milk and 25 g butter daily. Subjects were not blinded to the milk and yogurt since these products were provided in original packaging and because of the obvious difference in taste and viscosity between milk and yogurt. The heat-treated yogurt and acidified milk were provided in identical packaging and had similar taste and viscosity; thus, subjects were blinded to these dairy products. Study staff were similarly blinded as the participants. The four dairy products were supplied to the subjects free of charge every week at the study site.

### 2.2. Subjects

Males with abdominal obesity were recruited by advertisement through different media sources. Prior to screening, subjects were informed about the study design as well as inclusion and exclusion criteria. Subjects provided written informed consent before initiation of any study-related procedures. Eligibility was identified at screening, where subjects met the inclusion criteria if they were 30–70 years old, had a BMI 28.0–45.0 kg/m<sup>2</sup>, and waist circumference  $\geq 102$  cm.

Exclusion criteria included body weight changes  $\pm 5\%$  within the past three months; any diets, allergies or intolerances interfering with the study protocol (e.g. lactose intolerance); contraindications related to MRI such as having a pacemaker, claustrophobia or body weight  $> 160$  kg; history or diagnosis of diabetes, heart, liver, kidney disease, or eating disorders; diagnosis of cancer within the past 5 years (except treated localized basal cell skin cancer); use of drugs that were likely to affect study outcomes (judged by the investigators); blood donation within the past month or planning to donate blood during the study; participation in other clinical trials during the study; unwillingness to give informed consent or follow the study protocol and instructions given by the study staff.

### 2.3. Visits during the study period

The study comprised 24 visits; 1 screening visit, 2 study visits (at baseline and end of intervention), and 2 MRI visits (at baseline and end of intervention) (Fig. 1). In addition, once a week (19 visits) during the whole study period, the subjects visited the study site to pick up the study products, be weighed, and to deliver a product consumption diary for measurement of compliance.

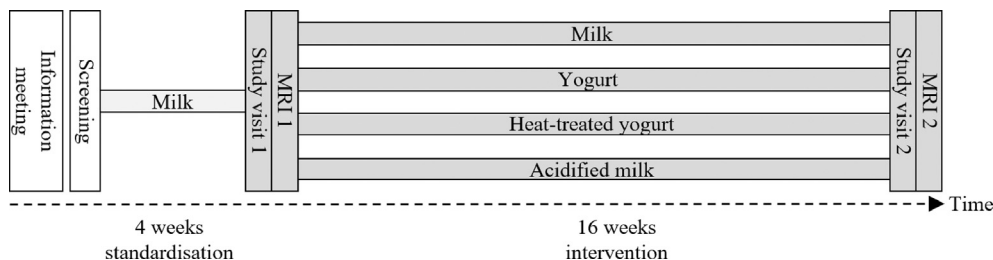


Fig. 1. Study design.

Table 1

Macronutrient content of the dairy products pr. 100 g.

	Milk	Yogurt	Heat-treated yogurt	Acidified milk
Protein (g/100 g product)	3.4	3.6	3.8	3.8
Fat (g/100 g product)	3.5	3.5	3.5	3.5
Carbohydrate (g/100 g product)	4.6	3.5	6.3	5.8

#### 2.4. Study visits

Prior to the study visits, subjects were instructed to 1) fast from 10 pm the night before except from 500 mL water; 2) refrain from vigorous physical activity and alcohol consumption for 48 h prior to the study visit; 3) arrive at the study site with the least physically active way possible. Upon arrival at the study site, subjects were asked to empty their bladder and the measurements were conducted with subjects wearing light clothing. The anthropometric measurements were obtained twice and the average was used for analyses.

Body weight was measured to the nearest 0.1 kg on a calibrated scale. Height was measured to the nearest 0.5 cm on a stadiometer. BMI was calculated using the formula: body weight (kg)/height (m)<sup>2</sup>. Sagittal abdominal diameter was measured to the nearest 0.5 cm with an abdominal caliper at the highest point at the abdomen with subjects lying down. Waist circumference (mid-way between the lower rib and iliac crest) and hip circumference (widest point between hip and buttocks) were measured to the nearest 0.5 cm with a non-elastic measuring tape while subjects were standing with their weight distributed evenly on both feet. Body composition (i.e., fat mass and fat free mass) was determined by whole-body DXA scan. Blood pressure was measured three times using an automated oscillometric device after resting for 5–10 min, and the average was used for analysis.

Fasting blood samples were collected from the antecubital vein after resting for 5–10 min. The fasting blood samples were analyzed for glucose, insulin, C-peptide, HbA1c, total cholesterol, LDL, HDL, triglycerides, ALT, AST, GGT, CRP, IL-6, and TNF- $\alpha$ . All parameters were determined by routine laboratory analysis using standardized protocols.

Dietary intake was assessed by a 3-day weighed dietary registration, which was performed before the standardization period, before the intervention period and at the last week of the intervention period. The dietary registrations were self-reported on paper and nutritional analysis was performed using the diet analysis software Dankost Pro (Matilda FoodTech AB, Malmö, Sweden), which links to the national food database (Frida.food.dk, Danish National Food institute). The validity of the dietary registrations was evaluated based on the Goldberg cut off method by using values of variation suggested by Black [34], and invalid registrations were removed from analyses.

Habitual dairy intake was assessed from the dietary registrations before the standardization period and was categorized into 5

subcategories comprising 1) Milk (all milk types); 2) Butter (butters and margarines); 3) Cheese (i.e. solid and semi solid cheeses); 4) Other fermented dairy (e.g., yogurt, skyr, sour cream); 5) Other dairy (e.g. spreadable cheeses, cream, ice cream).

#### 2.5. Magnetic resonance imaging and spectroscopy

Most MRI scans (146 of 162, corresponding to 90 %) were conducted at the Department of Radiology at Copenhagen University Hospital Herlev using a 3.0T Ingenia MRI system (Philips Medical Systems, Best, the Netherlands). Due to a fire accident in April 2022, the final MRI scans (16 of 162, corresponding to 10 %) were conducted at the Danish Research Centre for Magnetic Resonance at Hvidovre Hospital using a 3.0T Achieva (Philips Medical Systems, Best, the Netherlands) with identical scanning protocols. Consequently, 16 subjects had their pre and post intervention MRIs conducted at different devices. This was adjusted for in the statistical analyses. MRI included multi echo (5 echoes 45, 60, 75, 90, and 105 ms) single voxel (20×20 × 20 mm<sup>3</sup>) spectroscopy (PRESS) for measuring liver fat, and the chemical shift encoding-based water-fat imaging (mDixon) for pancreatic fat, visceral adipose tissue, and subcutaneous adipose tissue.

#### 2.6. Statistical analysis

The sample size was determined based on the primary outcome, which was the difference in liver fat after consumption of yogurt and milk during 16-weeks. The study was designed to have 19 completers in each group to detect a difference of 2.8 % with a SD of 3 % in liver fat at the 5 % level of significance with 80 % power. The difference in liver fat was based on results from Chen et al. [25], knowledge on change in liver fat [35,36], and previous results from iso-caloric studies [37]. Expecting 20 % dropout, 25 subjects were included in each group, summing up to a total of 100 included subjects.

Data were analyzed using linear mixed models with a group (four intervention groups) × time (pre/post) interaction and adjustment for subject id as random effect. Moreover, when using data from MRI (i.e., liver fat, pancreatic fat, visceral adipose tissue, and subcutaneous adipose tissue), adjustment for site of the scan was applied. From these models, P-values for the main effects of time, group, and group × time interaction were obtained. If needed, analyses of changes within groups and differences in changes between groups were performed by post-hoc analyses. Simple linear

regression models were used to determine differences in variables assessed only at one time point such as habitual dairy intake, protocol compliance, and baseline characteristics of completers and dropouts. Chi<sup>2</sup> tests were used to determine differences in dropout rates and occurrences of adverse events between groups.

Visual inspections of quantile-quantile plots and residual plots were used to assess assumptions of normality and homogeneity of variance for all models. Variables were log-transformed in the case of non-normality and the estimates in these cases are expressed as percent change from baseline. In order to log-transform variables with observations of 0 i.e., in subcategories of habitual dairy intake, we added +1 g/day on all observations. Normally distributed variables are presented as mean  $\pm$  SD and non-normally distributed variables are presented as median (quartile 1; quartile 3). The models were fitted using 1) complete case data comprising all subjects completing the intervention (primary analyses); 2) available case data comprising all available observations (supplemental analyses); 3) per protocol data comprising completing subjects with product compliance  $\geq 90$  %, body weight change during intervention less than  $\pm 5$  %, and absence of diabetes at baseline (supplemental analyses). For nutrition information data, per protocol analysis included completing subjects with dietary registrations considered valid by the Goldberg cut off method [34]. P-values  $< 0.05$  were considered statistically significant. Statistical analyses were carried out using R version 4.2.1 including R extension packages tidyverse, lme4, and emmeans.

### 3. Results

From a total of 446 subjects who responded to the advertisement, 100 subjects were included in the study (Fig. 2).

The subjects who initiated the 4-week standardization period had an average age of 58 (range 30–70) years, a BMI of 32.8 (SD 3.5) kg/m<sup>2</sup>, and a waist circumference of 116 (SD 8.8) cm. A total of 10 subjects dropped out during the standardization period, resulting in 90 subjects initiating the 16-week intervention period (Fig. 2). Their baseline characteristics are presented in Table 2. No differences in age and anthropometric measurements were detected between subjects who dropped out during the standardization period and those who initiated the intervention.

A total of 10 subjects dropped out during the intervention period, resulting in 80 subjects completing the intervention (Fig. 2). Subjects who dropped out during the intervention were younger ( $P = 0.015$ ) and heavier ( $P = 0.034$ ) than subjects who completed the intervention. No difference was detected between the number of subjects dropping out from the four groups ( $P = 0.584$ ). A total of 47 mild to moderate adverse events were reported during the intervention (gastrointestinal = 16, infection [including COVID-19 and symptoms related to the COVID-19 vaccine] = 23, body aches = 7, other = 1), none of which was related to the study products, and no differences were detected between the four groups. Moreover, 1 serious adverse event was reported just after inclusion, before initiating the standardization period; hence, this subject did not consume any of the study products and did not participate in the study.

Compliance with the assigned product consumption (400 g/day) was 96 % (83 % for subjects dropping out during the intervention and 97 % for subjects completing the intervention) and no differences were detected between groups (all  $P > 0.05$ ). The mean (SD) body weight changes during the intervention were  $-0.0$  (2.5) %,  $-0.7$  (2.0) %,  $-0.1$  (1.8) %, and  $-0.2$  (1.7) % for the groups consuming milk, yogurt, heat-treated yogurt, and acidified milk, respectively, with no differences between them (all  $P > 0.05$ ).

A total of 14 subjects were excluded from the per protocol analyses of which 7 were due to a study product compliance  $< 90$  % (4, 1

and 2 from the groups consuming milk, yogurt, and heat-treated yogurt, respectively), 2 were due to body weight change exceeding  $\pm 5$  % during the intervention (1 each from the groups consuming milk and heat-treated yogurt) and 5 were due to (unknowingly) having blood samples at baseline indicating a diagnosis of diabetes (fasting blood glucose  $\geq 7$  mmol/L and HbA1c  $\geq 48$  mmol/mol) which was an exclusion criterion (3 and 2 from the groups consuming yogurt and acidified milk, respectively).

The median (quartile 1; quartile 3) habitual dairy intake before the standardization period of all subjects who completed the study was 372 (228; 570) g/day, and no differences were detected between groups, whether for total dairy or dairy subcategories (all  $P > 0.05$ ) (Table 3).

The mean (SD) total energy intakes pre and post intervention for all completing subjects were 2360 (590) kcal/day and 2320 (591) kcal/day, respectively, with no differences within or between groups (all  $P > 0.05$ ) (Table 4). Further, the mean (SD) macronutrient composition as percent of total calories (E %) pre intervention was 17.0 (3.2) E %, 36.9 (5.3) E %, and 44.0 (6.7) E % for protein, fat, and carbohydrate, respectively. Protein and fat intake did not change in the four groups during the intervention but carbohydrate intake was reduced by  $-4.6$  (95 % CI  $-8.2$ ;  $-1.0$ ) % in the group consuming yogurt ( $P = 0.013$ ), and a difference in change in carbohydrate intake was detected between the groups consuming yogurt and heat-treated yogurt ( $-7.1$  (95 % CI  $-13.4$ ;  $-0.8$ ) %,  $P = 0.020$ , Table 4).

The effects of the intervention in anthropometry and body composition, blood pressure, glucose metabolism, lipid profile, liver enzymes, and inflammatory markers in all completing subjects are presented in Table 5 and Supplemental Table 1. No effects of the intervention or differences between groups were detected in anthropometry or body composition including liver fat. Moreover, no effects were detected in inflammatory markers. Main effects of time were detected in blood pressure (i.e. systolic and diastolic pressure) (decrease;  $P < 0.001$ ), insulin (decrease;  $P < 0.001$ ), C-peptide (decrease;  $P = 0.040$ ), HOMA-IR (decrease;  $P < 0.001$ ), total cholesterol (decrease;  $P = 0.016$ ), LDL (decrease;  $P = 0.033$ ), HDL (decrease;  $P = 0.006$ ), and ALT (decrease;  $P = 0.019$ ). Interactions between group and time failed to reach significance (Supplemental Table 1). Results were largely similar in available case and per protocol analyses (Supplemental Tables 1–3).

### 4. Discussion

We evaluated the effect of consumption of fermented yogurt products compared to non-fermented milk products as part of a habitual diet on liver fat and metabolic risk markers in males with abdominal obesity during 16 weeks intervention. In contrast to our hypothesis, our findings showed no superior favorable health effects of consuming fermented yogurt products as compared to non-fermented milk products. In fact, our findings indicate that all intervention products had largely similar effects on a variety of health outcomes; they did not affect anthropometry, body composition, fat distribution and ectopic fat deposition, and inflammatory markers but they did favorably affect blood pressure, glucose metabolism, lipid profile, and liver enzymes.

Only a small number of randomized intervention studies have investigated the effects of fermented dairy products during body weight stability [25–28,30–32]. Overall, these studies yielded inconsistent results reporting some favorable [25–28], some neutral, and some unfavorable [30–32] effects. The contrasting results could be due to a difference between studies in habitual dairy intake prior to initiation of the intervention (e.g., between studies conducted in Asian and Northern European populations). A study by Chen et al. [25] found that yogurt was more efficacious

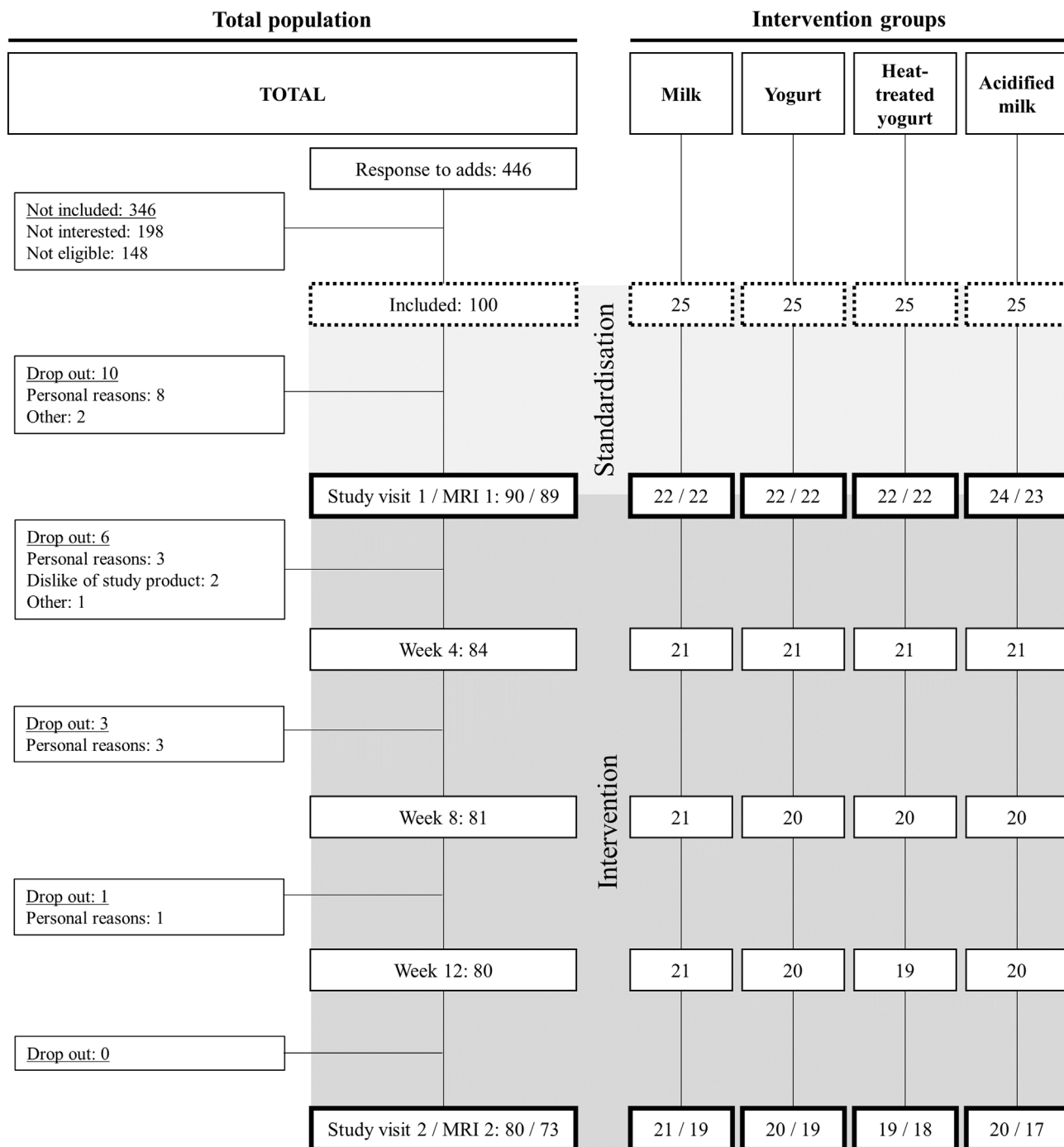


Fig. 2. Flow chart.

Table 2  
Baseline characteristics for subjects initiating the intervention.

	Milk (n = 22)	Yogurt (n = 22)	Heat-treated yogurt (n = 22)	Acidified milk (n = 24)
Age (years)	55 (51; 60)	58 (50; 66)	60 (51; 64)	60 (53; 65)
Height (meter)	1.83 ± 0.08	1.80 ± 0.09	1.79 ± 0.07	1.82 ± 0.08
Body weight (kg)	108 ± 13.5	105 ± 14.2	103 ± 13.8	109 ± 14.3
Body mass index (kg/m <sup>2</sup> )	32.3 ± 3.4	32.3 ± 3.4	32.3 ± 4.1	32.7 ± 3.1
Waist circumference (cm)	116 ± 8.8	115 ± 8.4	114 ± 8.7	117 ± 8.5
Body fat (DXA, %)	36.2 ± 4.4	35.3 ± 3.9	37.7 ± 4.9	37.5 ± 5.3
Liver fat (MRI, %)	6.8 (4.0; 12.4)	5.9 (2.8; 18.4)	6.0 (4.3; 10.2)	6.5 (2.7; 14.7)

Data are presented as mean ± standard deviation for variables that are normally distributed and as median (quartile 1; quartile 3) for variables that are non-normally distributed; Missing data from MRI from 1 subject in the group consuming acidified milk.

**Table 3**  
Habitual dairy intake (pre standardisation period).

	Milk (n = 17)	Yogurt (n = 11)	Heat-treated yogurt (n = 15)	Acidified milk (n = 9)
Overall habitual dairy (g)	493 (362; 653)	377 (233; 709)	331 (247; 418)	329 (121; 516)
Milk (g)	325 (69.3; 500)	192 (134; 546)	167 (67.4; 325)	83.3 (31.2; 138)
Butter (g)	9.2 (6.6; 17.7)	5.7 (2.8; 13.0)	9.1 (4.0; 10.7)	4.8 (1.3; 15.1)
Cheese (g)	23.0 (0.0; 34.3)	38.3 (20.2; 59.9)	30.5 (20.2; 60.7)	23.3 (0.0; 32.3)
Other fermented dairy (g)	46.7 (4.7; 213.3)	0.0 (0.0; 71.8)	4.4 (0.0; 45.6)	17.8 (2.2; 238)
Other dairy (g)	16.4 (0.0; 61.7)	23.7 (3.6; 56.7)	14.5 (0.0; 44.9)	8.3 (6.6; 28.6)

Per protocol data presented as median (quartile 1; quartile 3). Data were analysed using linear regression.

**Table 4**  
Dietary intake (i.e., energy and macronutrients) (pre and post intervention).

	Milk		Yogurt		Heat-treated yogurt		Acidified milk	
	Pre (n = 16)	Post (n = 16)	Pre (n = 13)	Post (n = 11)	Pre (n = 15)	Post (n = 14)	Pre (n = 11)	Post (n = 12)
Energy (kcal/day)	2530 ± 642	2540 ± 666	2390 ± 658	2220 ± 637	2310 ± 539	2270 ± 536	2230 ± 513	2210 ± 472
Protein (E %)	16.5 ± 2.5	16.8 ± 4.3	16.4 ± 1.6	16.6 ± 2.3	17.5 ± 3.5	16.3 ± 1.9	17.9 ± 4.8	16.7 ± 3.7
Fat (E %)	36.9 ± 6.5	38.0 ± 7.5	38.0 ± 5.9	39.6 ± 6.7	37.1 ± 3.8	34.9 ± 4.8	35.5 ± 4.9	38.3 ± 8.7
Carbohydrate (E %) <sup>a</sup>	45.3 ± 7.2	43.0 ± 10.4	43.8 ± 6.62	41.2 ± 5.82	43.0 ± 5.4	45.7 ± 5.6	43.5 ± 8.2	43.2 ± 10.3

Per protocol data presented as mean ± standard deviation. Data were analysed using linear mixed models with a fixed group × time interaction and adjustment for subject id as random effect.

<sup>a</sup> Difference in change between the group consuming yogurt and the group consuming heat-treated yogurt ( $P = 0.020$ ); <sup>2</sup>Change from pre to post intervention within group ( $P < 0.05$ ).

than milk in improving insulin resistance and liver fat. In that study, subjects were asked to refrain from all dairy products during the 8 weeks leading up to the intervention, whereas in our study, subjects were instructed to consume 400 g/day of milk during the 4 weeks leading up to the intervention period. Due to this difference, subjects in the study by Chen et al. [25] increased their dairy intake from none to 220 mL/day when initiation the intervention, whereas in our study subjects did not increase their intake of dairy (which remained steady at 400 g/day) but only switched the type of product. Other studies have used a standardization period, where subjects were instructed to refrain from yogurt and other fermented products (but no instructions for non-fermented dairy products) prior to initiation of the intervention, and found some favorable but mostly neutral effects of yogurt consumption [27,30].

Furthermore, the habitual intake of dairy products varies considerably across the world both in type and amount [38,39]. This could relate to the generally favorable effects reported from studies conducted in countries with lower habitual dairy intakes, e.g., China [25] and Iran [27], and the more neutral effects seen in studies conducted in countries with higher habitual dairy intakes, e.g., Australia [26,30], USA [31,32], and Denmark (current study). One study deviating from this general pattern is that by Hove et al. [28] from Denmark, comparing the consumption of 300 mL of fermented milk with 300 mL of acidified milk. The investigators reported favorable effects in fasting glucose after consumption of fermented milk. A reason for this could be the use of acidified milk as a control product. In our study, similar effects on glucose homeostasis were observed across all intervention products; however, a trend was apparent for neutral and even slight unfavorable effects on insulin and HOMA-IR in the group consuming acidified milk compared to the other groups. Hence, it can be speculated that acidified milk does not induce the same favorable effects in glucose metabolism as compared to other dairy products. Using acidified milk as a control condition is thus likely to reveal an apparent favorable effect of fermented milk [28].

Differences in the study population could also contribute to the contrasting results between different studies. Even the subjects in the study by Hove et al. [28] also were from Denmark, they had diabetes, resulting in them metabolically differing from the subjects

in our study who did not have diabetes. Moreover, sex and ethnicity could also influence the response to the dairy intervention. For instance, studies have shown that Asians are metabolically compromised at lower BMI values than Europeans and that females and males differ profoundly in the impact of metabolic risk markers [40,41]. Subjects in the study by Chen et al. [25] were Chinese females with obesity, NAFLD, and MetS, which are likely more metabolically compromised than the males from Denmark in our study.

Findings from our study indicate improvement in some metabolic risk markers (i.e., blood pressure, glucose metabolism, lipid profile, and liver enzymes) by the consumption of all intervention products. This is consistent with findings from many epidemiological studies indicating that the consumption of all dairy (both fermented and non-fermented dairy products) are linked to lower risk of MetS and type 2 diabetes [16,22,42–44]. Potential mechanisms have been proposed to relate to various nutrients such as calcium, protein, and fat, all of which are of high abundance in all the intervention products in our study. Calcium has antihypertensive properties by modifying intracellular calcium availability in vascular smooth muscle cells as well as modifying vascular volume via the renin-angiotensin-aldosterone system [45]. Calcium intake has also been linked to improvements in the lipid profile by binding to fatty acids and bile acids in the gut. The subsequent increased fecal lipid excretion and inhibition of fat absorption have been proposed to be partly responsible for the improvements in the HDL:LDL ratio [46]. The major dairy proteins (i.e., casein and whey proteins) also have antihypertensive properties via the renin-angiotensin-aldosterone system [47]. Furthermore, bioactive components of whey protein such as branched-chain amino acids (leucine, isoleucine, and valine) can improve glucose metabolism possibly through activation of the mammalian target of rapamycin (mTOR) [48,49]. Dairy fats containing medium-chain and odd-chain saturated fatty acids, branched-chain fatty acids, and natural trans-fatty acids have also been proposed to exert health beneficial effects such as decreasing liver fat and improving insulin sensitivity by inhibiting de novo lipogenesis and stimulating fat oxidation [50,51].

Our study has both strengths and limitations. Subjects had high compliance with consumption of the intervention products and managed to keep their total energy intake and body weight stable,

**Table 5**  
Effects of the 16-week intervention (400 g/day of either milk, yogurt, heat-treated yogurt, and acidified milk) on various health factors (complete case analyses).

	Milk (n = 21)		Yogurt (n = 20)		Heat-treated yogurt (n = 19)		Acidified milk (n = 20)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
<b>Body anthropometry and composition</b>								
Body weight (kg)	108 ± 13.8	108 ± 14.4	104 ± 14.7	104 ± 14.5	99.8 ± 10.2	99.7 ± 9.8	107 ± 13.8	107 ± 13.2
WC (cm)	116 ± 8.9	116 ± 9.7	115 ± 8.7	114 ± 8.7	112 ± 7.0	112 ± 7.2	117 ± 8.8	116 ± 8.2
HC (cm)	112 ± 6.4	112 ± 6.8	110 ± 7.9	110 ± 7.5	109 ± 4.4	109 ± 5.0	112 ± 7.0	111 ± 6.5
SAD (cm)	26.6 ± 2.9	26.6 ± 3.4	27.1 ± 3.6	26.6 ± 2.5	25.7 ± 1.9	25.8 ± 1.7	26.9 ± 2.6	26.7 ± 2.0
Body fat (DXA, %)	36.2 ± 4.5	35.9 ± 4.6	35.2 ± 4.1	35.4 ± 4.1	37.0 ± 4.9	36.7 ± 4.6	37.3 ± 5.5	36.9 ± 5.4
VAT (MRI, cm <sup>3</sup> )	245 ± 89.8	236 ± 85.7	271 ± 116	266 ± 101	270 ± 94.5	262 ± 96.6	269 ± 104	266 ± 98.1
SAT (MRI, cm <sup>3</sup> )	309 ± 81.7	298 ± 80.5	301 ± 104	297 ± 103	280 ± 95.9	275 ± 96.3	300 ± 117	302 ± 111
Liver fat (MRI, %)	6.5 (3.5; 12.0)	4.9 (2.7; 11.4)	6.3 (2.9; 21.7)	10.2 (2.7; 17.0)	6.0 (3.8; 10.2)	6.2 (2.4; 10.7)	3.9 (1.0; 15.0)	4.5 (1.5; 9.0)
Pancreas fat (MRI, %)	6.5 (4.0; 12.0)	8.3 (5.9; 12.7)	6.6 (4.1; 12.2)	6.8 (3.6; 13.0)	8.1 (4.7; 12.5)	8.2 (5.0; 9.3)	9.0 (5.2; 15.0)	7.0 (4.4; 13.5)
<b>Blood pressure</b>								
Systolic (mmHg) <sup>a</sup>	130 ± 15.5 <sup>d</sup>	125 ± 13.6 <sup>d</sup>	130 ± 16.6 <sup>c</sup>	123 ± 14.2 <sup>c</sup>	135 ± 17.0 <sup>c</sup>	128 ± 11.7 <sup>c</sup>	128 ± 9.5	127 ± 9.8
Diastolic (mmHg) <sup>a</sup>	87.2 ± 10.6 <sup>d</sup>	84.4 ± 8.6 <sup>d</sup>	86.8 ± 10.6 <sup>c</sup>	82.9 ± 9.5 <sup>c</sup>	88.6 ± 7.4 <sup>d</sup>	85.1 ± 6.2 <sup>d</sup>	86.3 ± 7.3	84.5 ± 8.0
<b>Glucose metabolism</b>								
Glucose (mmol/L)	6.0 (5.7; 6.2)	6.0 (5.7; 6.2)	6.1 (5.6; 6.8)	6.3 (5.8; 7.1)	6.0 (5.6; 6.2)	5.9 (5.3; 6.3)	6.1 (5.6; 7.0)	6.0 (5.3; 6.7)
Insulin (pmol/L) <sup>a</sup>	73.6 (38.4; 97.4) <sup>c</sup>	43.5 (22.0; 82.0) <sup>c</sup>	98.2 (32.8; 117)	84.5 (53.9; 133)	63.7 (36.2; 111) <sup>d</sup>	46.6 (32.7; 73.7) <sup>d</sup>	107 (71.5; 155)	119 (38.3; 170)
C-peptide (pmol/L) <sup>b</sup>	728 (655; 933) <sup>d</sup>	672 (616; 741) <sup>d</sup>	874 (676; 1132)	869 (694; 1093)	907 (586; 1026)	728 (612; 892)	1074 (759; 1380)	1081 (701; 1314)
HbA1C (mmol/mol)	38.6 (38.2; 40.1)	39.2 (38.2; 40.4)	42.6 (38.7; 47.1)	42.0 (39.3; 46.0)	40.0 (37.3; 43.6)	40.3 (37.0; 43.0)	41.0 (37.3; 42.8)	40.7 (38.6; 43.4)
HOMA-IR <sup>a</sup>	3.3 (1.7; 4.4) <sup>c</sup>	2.0 (1.0; 3.5) <sup>c</sup>	4.0 (2.2; 6.2)	3.7 (2.4; 7.0)	2.9 (1.7; 4.6)	2.1 (1.3; 3.1)	5.4 (2.8; 7.4)	5.5 (1.8; 8.5)
<b>Lipid profile</b>								
Cholesterol (mmol/L) <sup>b</sup>	4.8 ± 1.0	4.9 ± 1.0	4.8 ± 1.1	4.8 ± 1.0	5.2 ± 0.8 <sup>d</sup>	4.9 ± 1.0 <sup>d</sup>	4.6 ± 0.6 <sup>c</sup>	4.3 ± 0.6 <sup>c</sup>
LDL (mmol/L) <sup>b</sup>	3.1 ± 0.7	3.2 ± 0.7	3.1 ± 1.0	3.1 ± 0.9	3.3 ± 0.7	3.2 ± 0.7	3.1 ± 0.5 <sup>d</sup>	2.8 ± 0.5 <sup>d</sup>
HDL (mmol/L) <sup>a</sup>	1.1 ± 0.2	1.1 ± 0.3	1.2 ± 0.3 <sup>d</sup>	1.2 ± 0.3 <sup>d</sup>	1.2 ± 0.3	1.2 ± 0.4	1.1 ± 0.1 <sup>c</sup>	1.0 ± 0.2 <sup>c</sup>
Triglyceride (mmol/L)	1.2 (1.0; 2.1)	1.3 (0.9; 1.6)	1.0 (0.9; 1.7)	1.1 (0.8; 1.6)	1.5 (1.1; 1.9)	1.3 (1.0; 1.5)	1.4 (0.9; 1.8)	1.2 (1.0; 1.7)
<b>Liver enzymes</b>								
AST (U/L)	24.0 (21.0; 29.0)	23.0 (18.8; 26.8)	27.5 (24.5; 32.3)	26.5 (21.8; 33.3)	27.0 (25.0; 27.5)	25.0 (20.5; 28.0)	25.0 (19.5; 29.5)	23.5 (19.0; 30.8)
ALT (U/L) <sup>b</sup>	27.4 (21.7; 40.4)	23.6 (18.0; 33.7)	30.9 (25.7; 44.8) <sup>d</sup>	28.2 (23.2; 41.0) <sup>d</sup>	28.8 (20.6; 35.8)	27.2 (20.2; 32.1)	27.1 (22.5; 34.7)	25.5 (22.3; 34.8)
GGT (U/L)	27.0 (23.0; 41.0)	27.5 (22.8; 34.3)	35.0 (25.5; 57.5)	35.0 (23.5; 54.8)	38.0 (27.5; 47.0)	39.0 (23.5; 51.5)	32.0 (21.8; 48.5)	31.5 (23.0; 53.5)
<b>Inflammatory markers</b>								
CRP (mg/L)	1.2 (1.1; 5.9)	1.5 (1.0; 2.9)	1.2 (0.6; 3.5)	1.7 (0.8; 2.6)	1.4 (0.9; 2.4)	1.4 (0.8; 2.1)	1.5 (0.9; 4.1)	1.9 (0.8; 2.5)
Il-6 (pg/mL)	2.0 (1.4; 4.1)	1.9 (1.4; 3.5)	1.7 (1.4; 3.1)	1.5 (1.2; 2.1)	1.9 (1.4; 2.2)	2.0 (1.6; 2.8)	1.9 (1.5; 2.4)	2.0 (1.4; 3.1)
TNFα (pg/mL)	0.7 (0.7; 0.8)	0.8 (0.6; 0.9)	0.8 (0.6; 0.9)	0.8 (0.6; 0.9)	0.7 (0.6; 0.8)	0.6 (0.6; 0.8)	0.8 (0.7; 1.0)	0.8 (0.7; 0.9)

Complete case data presented as mean ± standard deviation for normally distributed variables and as median (quartile 1; quartile 3) for non-normally distributed variables. Data were analysed using linear mixed models with a fixed group × time interaction and adjustment for subject id as random effect. Missing data from MRI from 2, 1, 1 and 3 in the group consuming milk, yogurt, heat-treated yogurt, and acidified yogurt, respectively. WC, Waist circumference; HC, Hip circumference; SAD, Sagittal abdominal diameter; VAT, Visceral adipose tissue; SAT, Subcutaneous adipose tissue.

<sup>a</sup> Main effect of time (P < 0.01).

<sup>b</sup> Main effect of time (P < 0.05).

<sup>c</sup> Change from pre to post intervention within group (P < 0.01).

<sup>d</sup> Change from pre to post intervention within group (P < 0.05).

suggesting that they succeeded in reducing their energy intake from non-dairy foods to compensate for the energy consumed with the intervention products. This may have been facilitated by the 4-week standardization lead-in period that provided the same amount of energy from milk as that from the four intervention products during the subsequent 16-week intervention. Although not directly addressed by our study, these results indicate that males with overweight or obesity can self-regulate their diet and include full-fat dairy products without changes in energy balance and body weight, and experience modest improvement in metabolic risk markers.

When evaluating the effects of specific foods or nutrients, particularly during body weight stability, addition of a food or nutrient will inevitably require another is subtracted, to keep total energy intake constant. Therefore, we cannot exclude the possibility that the beneficial effects observed in this study might have been mediated by the reduction of non-dairy foods that compensated for the energy consumed with the intervention products, rather than by the addition of dairy foods. Our MRI assessment of abdominal fat distribution and ectopic fat accumulation are limited by the fire accident at Herlev Hospital resulting in some missing data as well as possible bias from shifting to another hospital and MRI device in about 10 % of the completing subjects. Nonetheless, this was accounted for in the statistical analysis. The per protocol analyses consisted of 16, 16, 16 and 18 subjects in each group, which

is somewhat fewer than the calculated required sample size. However, the results from the per protocol analysis were nearly identical to those from the complete cases and the available cases analyses (both with more subjects than the per protocol analysis), so we feel confident about their interpretation. Still, the generalizability of our study is limited since only males with abdominal obesity from Copenhagen, Denmark (metropolitan area) were included. There are known sex differences in liver fat, glucose homeostasis and lipid metabolism [52–54]. Recruiting females too, or only females, would be logistically and scientifically more cumbersome because of the possibility of menopause within our age range (30–70 years), and the need to schedule metabolic assessments in the same phase of the menstrual cycle in premenopausal woman. Clearly, larger intervention trials including both females and males in various ages and ethnic groups are needed to draw more generalized conclusions.

## 5. Conclusion

Findings from our study do not confirm that fermented yogurt products are superior in reducing liver fat and improving metabolic risk markers compared to non-fermented milk products. In fact, all intervention products (both fermented yogurt products and non-fermented milk products) did not affect liver fat and caused largely similar modest favorable changes in some metabolic risk



markers. Nevertheless, evidence from randomized intervention studies is largely inconsistent due to variability in study design. More and larger intervention trials will be needed to conduct a more comprehensive evaluation and thereby provide a better understanding of the effects of fermented dairy products on health.

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### Author contribution

**Karoline Sandby:** Conceptualization, methodology, funding acquisition, investigation, formal analysis, visualization, writing – original draft, writing – review & editing; **Faidon Magkos:** Conceptualization, methodology, funding acquisition, supervision, formal analysis, visualization, writing – original draft, writing – review & editing; **Elizaveta Chabanova:** Investigation, writing – review & editing; **Esben T Petersen:** Investigation, writing – review & editing; **Thure Krarup:** Supervision, writing – review & editing; **Hanne C Bertram:** Conceptualization, methodology, funding acquisition, writing – review & editing; **Karsten Kristiansen:** Conceptualization, methodology, funding acquisition, writing – review & editing; **Nina RW Geiker:** Conceptualization, methodology, funding acquisition, supervision, project administration, formal analysis, visualization, writing – original draft, writing – review & editing.

### Conflict of interest

FM has received grants from Arla Foods A/S. TK has received grants from Arla Foods amba and Danish Dairy Research Foundation. HCB has received grants from Danish Dairy Research Foundation. NG has received grants from the Danish Agricultural and Food Council. All other authors report no conflict of interest.

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### Appendix A. Supplementary data

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