A randomized trial analyzing the effect of a diet rich in SFA or PUFA on the lipid profile of subjects with normal-weight and subjects with obesity and elevated LDL-cholesterol

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Summary

Background: People with elevated cholesterol have an increased risk for developing cardiovascular disease (CVD). Lipid modifying diets, which reduces the intake of saturated fatty acids (SFA) and increases the intake of polyunsaturated fatty acids (PUFA) reduces the cholesterol and affects the risk for developing CVD. There are gaps in research about whether subjects with normal-weight (NW) and subjects with obesity (OB) respond differently to lipid-modifying diets.

Objective: To investigate if there are differences in the changes in the lipid profile between weight stable, non-statin treated NW (BMI < 25 kg/m^2) and subjects with OB (BMI 30-45 kg/m^2) with elevated low-density lipoprotein cholesterol (LDL-C) eating a diet enriched with either SFA from butter or PUFA from soft margarine for six weeks.

Method: A total of 71 men and women aged 18-70 years were randomized to one of the two diets. 23 NW and 14 OB were randomized to the SFA diet and 20 NW and 14 OB were randomized to the PUFA diet group. Butter and soft margarine was handed out to the participants, enough to supply them with a minimum portion of 24 grams butter and 25 grams soft margarine each day. The dietary intake was registered with a weighed seven days food registration at baseline and at the end of the study period. Measurements of the lipid profile, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and Apolipoprotein B (Apo B) were measured at the screening, randomization visit and after four and six weeks.

Results: The baseline values for TC and LDL-C for all the participants in the study were 6.5 mmol/L and 4.4 mmol/L. There was a significant between group difference in the mean change in TC after six weeks between NW and OB subjects in the SFA diet group (TC NW 7.1 mmol/l (SD 1.0) and TC OB 6.4 mmol/L (SD 1.3)), with a greater increase in TC for the NW (difference 0.4 mmol/L, 95 % CI 0.0,0.8, p= 0.04). In an adjusted linear regression analysis there was a significant effect for the variable "diet group" (all $p \leq 0.001$) and a trend for an effect of the interaction variable between BMI and diet group on the change in TC, LDL-C and Apo B. For the NW in the SFA diet group there were significant within group changes with an increase in TC, LDL-C, HDL-C and Apo B. For the OB subjects in the SFA diet group there were no significant changes. For both the NW and OB subjects in the PUFA diet group there were significant within group changes with a reduction in TC, LDL-C and Apo B. Significant changes in the diet after six weeks were attained according to the planned dietary intervention, with a different in 9.1 E% from SFA and 4.2 E% from PUFA between the NW and 10.2 E% from SFA and 5.4 E% from PUFA between the OB subjects in the two diet groups.

Conclusions: For the subjects that increased their intake of SFA it was a difference in the response in TC between NW and OB. For NW subjects with elevated LDL-C increasing their intake of SFA (19.6 E%) lead to a significant increase in TC, LDL-C, HDL-C and Apo B while increasing the intake of PUFA (9.9 E%) gave beneficial changes in TC, LDL-C, Apo B and TG. For the OB subjects with elevated LDL-C, an increased intake of SFA (20.4 E%) did not significant change the lipid profile, while increasing the intake of PUFA (10.1 E% lead to a reduction in TC, LDL-C and Apo B. A failure to include enough participants with obesity reduced the strength of these conclusions.

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Abbreviations

Apo B	Apolipoprotein B
ALAT	Alanine aminotransferase
BMI	Body Mass Index
BP	Blood pressure
CHD	Coronary heart disease
CRF	Case Report Form
CRP	C-reactive protein
CVD	Cardiovascular disease
EI/REE	Energy intake/resting energy expenditure
HDL-C	High-density lipoprotein cholesterol
kg	kilograms
LDL-C	Low-density lipoprotein Cholesterol
MetS	Metabolic Syndrome
MUFA	Mono Unsaturated Fatty Acid
NW	Subjects with normal-weight
OB	Subjects with obesity
PAL	Physical activity level
PUFA	Polyunsaturated Fatty Acid
RCT	Randomized Clinical Trial
SD	Standard Deviation
SFA	Saturated fatty acid
TC	Total cholesterol
TG	Triglycerides
TSH	Thyroid-Stimulating Hormone
VSMCs	Vascular smooth muscle cells
WHO	World Health Organization

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1 Introduction

1.1 Cardiovascular disease

Diet is important for the prevention and treatment of cardiovascular disease (CVD). The World Health Organization (WHO) defines CVD as “disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions” (1). CVD is the reason for 31 % of all global deaths, and it is a big health- and economic burden worldwide. Risk factors for CVD include elevated blood pressure (BP), glucose, lipid profile and overweight and obesity (1). Modifiable risk factors for the development of CVD are the use of tobacco, unhealthy diet and physical inactivity. WHO estimates that it is possible to prevent 80 % of premature heart attacks and strokes (1, 2). Elevated low-density lipoprotein cholesterol (LDL-C) levels are central in the developing of CVD and are used as an important risk factor for predicting the risk of the development of CVD (3-5).

1.1.1 Coronary heart disease

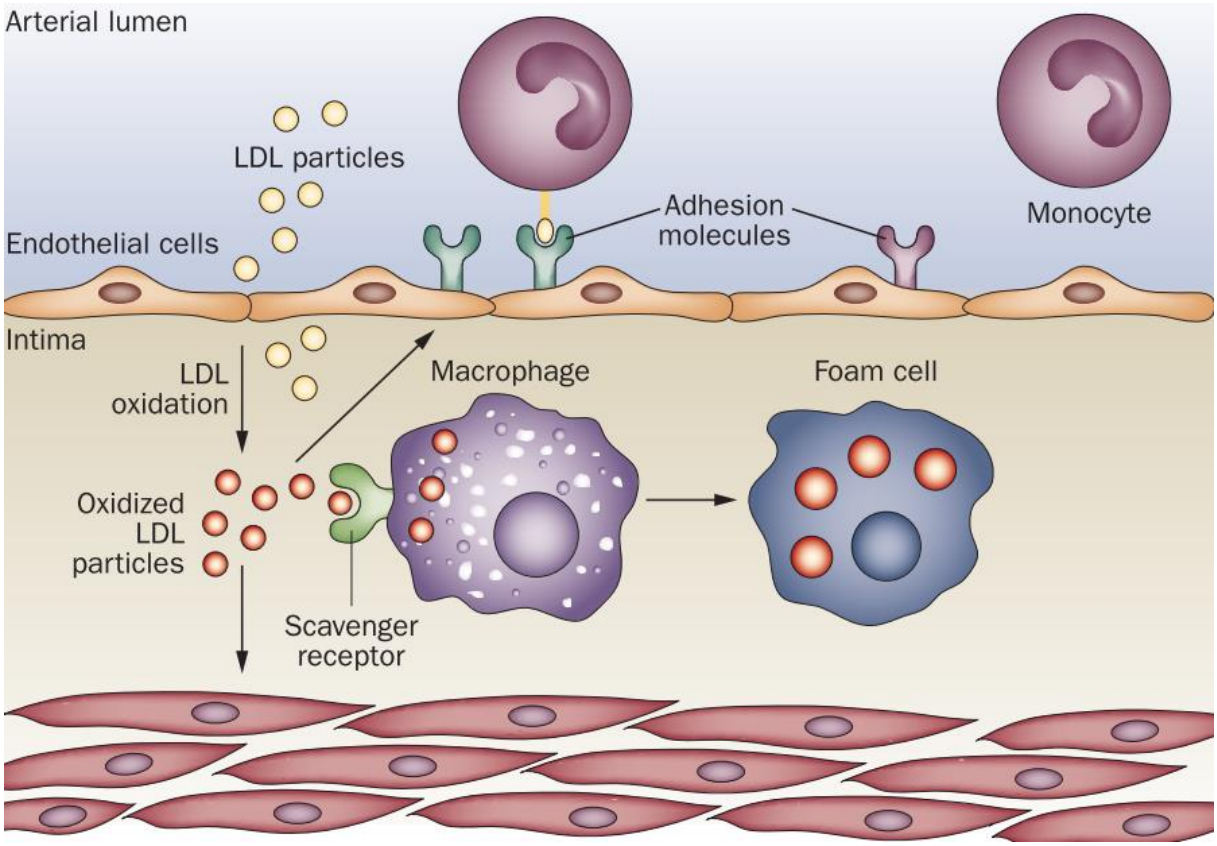
Coronary heart disease (CHD) constitutes of diseases of the blood vessels supplying the muscle of the heart. An acute event like heart attack are often caused by a blockage in the blood vessel that prevents the blood flow to the heart and deprives the affected part of the heart muscle of oxygen. The blockage mainly constitutes of a build-up of fat deposits in the blood vessel, the process called atherosclerosis (5, 6).

1.1.2 Atherosclerosis

Atherosclerosis is an inflammatory condition were cholesterol and cholesterol-esters are accumulating in the blood vessel walls in medium and large arteries. Hypercholesterolemia, high BP or free radicals from tobacco use can damage the endothelia cells. Endothelial dysfunction is an initial step in the atherosclerotic process (5, 7, 8). LDL-C can promote the atherosclerotic process through activation of intracellular processes that lead to inflammation (8). Inflammation leads to the recruitment of white blood cells like monocytes, which can adhere to the arterial wall. The Monocytes can develop to Macrophages that can engulf oxidized LDL-C and develop to lipid rich foam cells, which build up in the blood vessel wall

(5). Vascular smooth muscle cells (VSMCs) start to migrate to the intima of the blood vessel wall where they proliferate and form a vascular lesion, which can develop to an atherosclerotic plaque. The plaques contain foam cells, extracellular matrix produced by the proliferating VSMCs, matrix metalloproteinases and inflammatory factors (8). The atherosclerotic plaques can lead to CVDs like angina, infarctions or thrombosis (7).

Figure 1.1 The atherosclerotic process



The atherosclerotic process where LDL-C adheres to the blood vessel wall and is being oxidized within the intima of the blood vessel. Oxidized LDL-C particles can be engulfed by macrophages, which develop to lipid rich foam cell, an important step in the atherosclerotic process. A request is sent to the authors of "Obesity, inflammation, and atherosclerosis" 2009 (9) asking for permission to use the illustration.

The characteristics of small dense LDL-C particles accelerate the atherosclerotic process by causing endothelial dysfunction and increasing inflammation. Because of their small size, small LDL-C particles penetrate the blood vessel wall easier than larger and more buoyant LDL-C particles. Their greater affinity for the glycoproteins of the blood vessel wall increases their probability of being trapped and engulfed by macrophages, forming foam cells. They also have greater tendency for being oxidized, which drives the inflammation process further (10).

1.1.3 Lipid profile

In an assessment for the prediction for the risk of developing CVDs the lipid profile, including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) is important to evaluate (2, 4). Lipoproteins transport water-insoluble cholesterol and triglycerides in the blood (11). TC is a measurement of all the cholesterol in the blood, including LDL-C and HDL-C. LDL-C is a commonly used marker for the risk of developing CVD (12). The LDL-C particle can differentiate in size and atherogenity. The small dense particles are showed to be more atherogenic than the larger ones (5). Apolipoprotein B (Apo B) is a protein on the atherogenic lipoprotein particles. Normally, more than 90 % of the plasma Apo B is associated with the LDL-C particle. The concentration of Apo B can be measured and it is considered as a better assessment of the risk for CVD than LDL-C, because it measures the number of atherogenic particles (10, 13-16). HDL-C has a capacity for transporting cholesterol from the peripheral tissues, including the arterial wall, to the liver (17). Low concentrations of HDL-C (lower than 1.0 mmol/L for men and 1.3 mmol/L for women) is considered as an individual risk factor for CVD and is a part of the Metabolic Syndrome (MetS) criteria (18). Research suggests that it is the efficacy of reverse cholesterol transport that is central for the beneficial effects of HDL-C (5). HDL-C particles are heterogeneous, and the role of each subclass of HDL-C particles remains unclear (14). TG is a measurement of the lipids in the blood. A level >1.7 mmol/L is associated with higher risk for developing CVD and is a part of MetS criteria (10, 18, 19).

Another useful marker for assessing CVD risk is non HDL-C. Non HDL-C gives an estimate of the cholesterol content of atherogenic Apo B-containing lipoproteins. The calculation is based on TC and HDL-C. Non HDL-C can give a good measurement of atherogenic lipoproteins and is considered a better risk predictor than LDL-C (14-16).

1.2 Obesity

There is a rise in the development of overweight and obesity in the world, and this is a large public health challenge. The increase is often referred to as an obesity epidemic (19). WHO estimates that in the European Region 30-70 % of the population have overweight and 10-30 % have obesity (20). Atherogenic dyslipidemia is often present in subjects with obesity and especially abdominal obesity, and this increases the risk for developing CVD(s) (14).

Some food patterns are associated with weight gain, like diets rich in fat and sugar, and low in fiber. Dietary patterns with a large intake of fast food, which often has high energy density and large portion sizes, are associated with an increased risk of obesity (19).

1.2.1 BMI and abdominal obesity

BMI is commonly used in clinical practice and research, and is a way to calculate body fatness based on weight and height of the patient. It is calculated by the formula "weight in kg/(height in meters)^2. It was developed to estimate the risk for diseases and is often used to correlate the weight at population level with the risk for health problems. The different BMI categories are based on the effect excessive body fat has on disease and death (21, 22). BMI is an easy measurement to calculate, but it has some weaknesses; it does not give information about the body composition and fat distribution, or the muscle mass of the patient. How the body fat is distributed is an important risk factor for developing obesity related disease and health risk (22, 23). Because precise measurements of visceral and abdominal fat are expensive, waist circumference is frequently used in clinical practice as an alternative measurement for abdominal fat mass. It is a cheap, fast and feasible measurement. An increased waist circumference is an independent risk factor for CVD, Diabetes Mellitus and increased mortality, and it is one of the diagnosis criteria of MetS (18, 19, 22). Waist circumference measurements can be challenging to perform and can be methodologically difficult as it varies which anatomical site that is being used. Adiposity in women can increase the variability in the measurement. This variety does not seem to affect risk prediction for the waist circumference measurement (23). There is also variability in the measurements of hip circumference, but this measurement is less technical challenging and has less variability with increased obesity in women than waist circumference. Hip circumference is uncertain to use alone as a risk factor for health predictions. It is more common to use hip circumference to

calculate the hip-waist ratio that is a useful predictor for health risk, like the risk for developing CVD (23).

Table 1.1 WHO classification of BMI categories (21):

BMI	Nutritional status
<18.5 kg/m^2	Underweight
18.5-24.9 kg/m^2	Normal-weight
25.0-29.9 kg/m^2	Pre-obesity (overweight)
30.0-34.9 kg/m^2	Obesity, class I
35.0-39.9 kg/m^2	Obesity class II
>40 kg/m^2	Obesity class III

1.2.2 Metabolic syndrome

Metabolic Syndrome (MetS) is a cluster of risk factors associated with increased risk of developing type 2 diabetes and CVDs (19). The MetS is a cluster of atherothrombotic abnormalities, and the risk for developing CVDs or type 2 diabetes increases when several of the risk factors occur at the same time. These atherothrombotic abnormalities are often present concurrent with abdominal obesity (14). The MetS has several definitions, and by the National Cholesterol Education Program Adult Treatment Panel III 2001 definition it is constituted of three or more of the following criteria (18):

- Central obesity: Waist circumference > 102 cm for males and > 88 cm for females.
- Triglycerides > 1.7 mmol/L
- HDL-C < 1.0 mmol/L for males and < 1.3 for females
- Blood pressure > 130/85 mmol/L or using blood pressure medication
- Fasting plasma glucose > 6.1 mmol/L

1.3 Healthy diets

The lipid profile can be influenced by lifestyle changes like eating a healthy diet, exercise and weight loss (16, 24). Studies have shown that if you replace saturated fatty acids (SFA) with unsaturated fatty acids (FA) it will improve the lipid profile by having a lowering effect on the TC and the LDL-C. It will also improve the LDL-C:HDL-C ratio and reduce the risk for CVD (24-31). The Norwegian nutrition guidelines recommends reducing the intake of SFA to less than 10 % of the total energy intake (E%) to prevent development of CVD. They recommend to reduce the intake of SFA from full-fat dairy products, hard margarine, butter, processed- and red meat (24). The effect of the dietary changes is partial through the different effects of the dietary fatty acids on the regulation of LDL-receptors expression and activity on the cells (3, 31). Dietary changes that can reduce the TG concentration are an increased intake of n-3 FA, reduced intake of sugar and avoiding excessive intakes of alcohol (16, 32, 33). A weight reduction of 5-10 % can have a beneficial effect on the lipid profile for subjects with obesity (16).

1.3.1 Dietary fatty acids and other nutrients effects on the lipid profile

There are several types of SFAs, having different LDL-C raising effects. Lauric (12:0), myristic (14:0) and palmitic (16:0) acids have a well-documented cholesterol rising effect, while stearic acid (18:0) is considered to have a neutral effect on LDL-C (31). SFA elevates plasma LDL-C by increasing the formation of LDL-C in the plasma and simultaneously decreasing the LDL-C turnover. Both increased intake of SFA and PUFA leads to an increase in the cholesterol synthesis, so the FA`s different effects on the LDL-C is likely through other mechanism than the production of cholesterol. PUFA increases the LDL-receptor number on the hepatocytes and the LDL-C turnover (31). It seems like PUFAs have a better effect as a substitute for SFAs than MUFAs or carbohydrates, with a greater effect on the reduction of LDL and CVD (28, 34).

The different contents of the individual SFAs and unsaturated FAs in food have different cardiovascular effects. However, the effect of specific types of food on CVD cannot be predicted exclusively by their content of FAs (28, 34). Food consists of more than just FAs, and the other nutrients can affect the food effects on the lipid profile and the risk for developing CVD (34). This seems to be especially relevant for dairy products and nuts.

Studies have shown that different types of dairy products, which can have a high content of SFA, have different effects on the lipid profile (35-39). Nuts on the other hand are a good source for MUFA and PUFA, and contain numbers of other additional nutrients that can have cardio protective effects and have showed lipid-lowering effects (40-42).

Research has shown that plant sterols, β-glucans and red yeast rice can have a cholesterol lowering effect. A study with a plant sterol containing soft margarine showed a cholesterol lowering effect with a dose of 25 grams margarine for four weeks (43). B-glucan is a type of soluble dietary fiber from oat products, which can have a cholesterol lowering effects at dosages ≥ 3 grams oat β-glucan per day (44). Red yeast rice has shown to have a TC and LDL-C lowering effect (45), but long-term controlled studies are needed to investigate the safety of the use of red yeast rice in patients with dyslipidemia.

1.3.2 Norwegian dietary recommendations

WHOs dietary recommendations for prevention of CVDs include eating fruit and vegetables, fish, whole grain products, lean meats and pulses and restrict the intake of salt, fat and sugar (2). This recommendation has many common features with the Mediterranean diet, which have shown to have a cardio-protective effect. Central in the Mediterranean diet are olive oil, nuts and other sources for unsaturated fat (29). The Norwegian dietary recommendations are in line with WHOs cardio protective advice and share many features with the Mediterranean diet. The Norwegian dietary recommendations are appropriate to follow for children, adults and elderly, and for people with increased risk for sickness, like people with overweight or high BP (46). The Norwegian dietary recommendations constitute off 12 advices on diet and physical activity and are summarized in Table 1.2. New Norwegian guidelines for the prevention of CVDs were published in august 2017 and consolidate the already existing nutritional guidelines. The new guidelines focus on substituting SFA with PUFA, reduce the intake of refined carbohydrates and sugar and increase the intake of wholegrain products, vegetables and fruit (47). There are also published Norwegian nutrients recommendations, and they are listed in Table 1.3. To investigate the dietary intake in the Norwegian population, The University of Oslo carried out the NORKOST 3 investigation in collaboration with "Mattilsynet" and "Helsedirektoratet" in 2010-11. The result of the NORKOST 3 nutrition investigation was that for the participants with an average BMI of 25.5 kg/m^2 the intake of

SFAs were above the recommendations. Intake of carbohydrates was below the recommended value, while for the other macro nutrients the recommendations were followed (48).

Table 1.2 The Norwegian dietary recommendations, freely translated to English from the "Helsedirektoratets" webpage (46).

1. Have a diet with variability and a lot of vegetables, fruit and berries, wholegrain products and fish, and limited amounts of processed meat, red meat, salt and sugar.
2. Maintain a good balance between the amount of energy you ingest through food and beverages, and how much you use through physical activity.
3. Eat at least five portions of vegetables, fruit and berries each day.
4. Eat wholegrain products each day.
5. Eat fish for dinner two to three times each week. Use fish as spreads as well.
6. Choose lean meat and lean meat products. Limit the amount of processed meat and red meat.
7. Use fat-reduced dairy products as a part of the usual diet.
8. Choose cooking oil, liquid margarine and soft margarine at the expense of hard margarine and butter.
9. Choose food with a low salt content, and limit the use of salt in cooking and as an additive on the food.
10. Avoid food and beverages with a high content of sugar for everyday use.
11. Choose water as a beverage for thirst.
12. Be physical active for at least 30 minutes each day.

Table 1.3 The Norwegian nutrient recommendations (24).

Total fat intake between 25-40 E%, of which • **SFA <10 E%** • **MUFA 10-20 E%** • **PUFA 5-10 E% (n-3 FA 1 E%)**
Protein from 10 to 20 E%
Carbohydrates from 45-60 E%, of which • **Added sugar <10 E%** • **Dietary fiber at least 25-35 grams each day**

1.3.3 Dietary studies and CVD

In experimental studies like Oslo Diet and Antismoking Study and Finnish mental hospital study, it has been observed that replacing SFA with PUFA reduces the CVD incident (49, 50). In a follow-up study of the Oslo Diet and Antismoking Study, a prolonged benefit of the intervention was found several years after the end of the study (51). In the PREDIMED study, they found that eating a Mediterranean diet, which is rich in unsaturated FA, reduced the incidence of major cardiovascular events with 30 % in subjects with increased cardiovascular risk (52). The systematic review and meta-analysis of randomized controlled trials (RCTs) by Mozaffarian et al. (53) and the review of Kromhout et al. (29) consolidate the evidences for replacing SFA with unsaturated FAs reduces the risk for CVD in subjects with normal-weight, and we have never had as solid documentation for this as we have today (25-29, 49-51, 53).

However, there is some uncertainty around how the intake of dietary SFA affects the risk of developing CVD (54, 55). The meta-analysis of epidemiologic studies by Siri-Tarino et al (55) published in 2010 did not find an association between the intake of SFA and increased risk of CVD, and this has got a lot of attention. Meta-analysis constitutes of studies that can have large differences in the study design, the dietary interventions and the participant characteristics. When combining studies with large methodological differences and quality in the designs, the variability in the findings can reduce the statistical power. This can make it more difficult to find the real effects (56). In an article published later in 2010 Siri-Tarino et al. writes that the lack of association between SFA and CVD observed in several epidemiologic studies can be explained by the negative effect of replacing SFA with carbohydrates, in particular refined carbohydrates and added sugar (30). Other factors than which nutrient SFA is replaced with may also determine which effect the changes in diet will have on the lipid profile. Factors like age, gender, baseline cholesterol levels, types of food and body weight may have an influence of the effects of decreasing the intake of SFA (25, 34, 36, 37, 39, 57), and lately especially BMI as a measurement of body weight has got much attention as an important factor.

1.3.4 Dietary interventions studies with subjects with obesity

The obtained changes in the lipid profile and risk reduction for CVD when substituting SFA with PUFA (26, 49, 50), seems to be impaired in people with obesity (BMI > 30 kg/m^2) and individuals with Mets (25, 27, 58-60). Mukuddem et al completed a study with subjects with an average BMI of 35 kg/m^2. They obtained no changes in the lipid profile between an intervention diet with nuts compared to a control diet with no nuts (58). In another study called the SYSDIET study, the participants with an average BMI > 30 kg/m^2 reduced their intake of SFA in a "Healthy diet" group compared to a "Control" group (27). They observed non-significant changes in the LDL- C, TC, HDL-C, Apo B and TG during the 18-24 weeks long study (27).

There seems to be an inverse connection between high BMI categories and the response in the lipid profile after interventions that changes the content of SFA, cholesterol and PUFA in the diet (25, 27, 58-60). There are hypothesis that the greater the BMI category the more blunted effects in the lipid profile seems to be. The suggested inverse connection between BMI and the response in lipids in the blood may be due to factors like genetics, insulin resistance, a greater rate of hepatic cholesterol synthesis and increased inflammation in subjects with obesity. Hormones (growth hormone, thyroid hormone, and cortisol) and gut microbiota are also suggested mechanism that may influence the changed lipid response in subjects with obesity to dietary interventions (25). It seems like the LDL-receptor (LDL-R) mediated uptake of LDL-C from the blood is reduced in people with obesity and that it is not positively affected in the same way as in subjects normal-weight when substituting SFA with PUFA (25). People with obesity often have a greater endogenous FA flux in the blood due to release of FA from the adipose tissue. This may lead to an increased FA exposure of the liver even when the intake of SFA in the diet is reduced (59). There are limited data available to explain the differences in lipid response that are observed in some studies after altering the intake of SFA in subjects with obesity and normal-weight.

2 Aims and hypothesis

There is currently little knowledge on whether dietary changes in the intake of SFA and PUFA affects subjects with normal weight and subjects with obesity differently. The intention of the "Cholesterol Study" was to investigate the changes in TC, LDL-C, HDL-C, TG and Apo B between weight stable, non-statin treated subjects with normal-weight (BMI < 25 kg/m^2) and subjects with obesity (BMI 30-45 kg/m^2) eating a diet enrich with either SFA or PUFA.

2.1 Hypothesis

H0: There are no differences in the response in total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and Apo B when subjects with normal-weight and people with obesity and an elevated LDL-cholesterol eat a diet enrich with either saturated fatty acids or polyunsaturated fatty acids.

HA: There are differences in the response in total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and Apo B when subjects with normal-weight and people with obesity and an elevated LDL-cholesterol eat a diet enrich with either saturated fatty acids or polyunsaturated fatty acids.

3 Method

The “Cholesterol Study” was a paralleled design intervention study performed at Oslo University Hospital, Norway. Because of the nature of the study, it was an open intervention, and neither the participants nor the nutritionists were blinded. The nutritionists involved with the study were two students completing their master degree in clinical nutrition in the University of Oslo (hereafter termed nutritionists). They were supervised by two experienced nutritionists and by doctors who work at the Section for Preventive Cardiology at Oslo University Hospital where the study took place. Participants for the study population for this thesis were enrolled in the study from January 2017 to May 2017. The data collection period was divided in two, one period from the end of January to the middle of April 2017, and the second from the end of April to the beginning of July 2017. The “Cholesterol Study” is still ongoing due to an inability to recruit enough participants in the first enrollment period, and it is planned to end in December 2017.

3.1 Study population

Men and women in the age from 21 to 70 years were recruited to participate in the “Cholesterol Study”. They were recruited through advertisements in the newspaper, through Oslo University Hospital Norway`s official webpage and Facebook page, with posters and from previous clinical trials in the Section for Preventive Cardiology. People that were interested in participation contacted the study staff by e-mail or telephone. They were interviewed over the phone by the nutritionists using a standardized telephone interview form, see Attachment 1. The purpose of the telephone interview was to give information to those who were interested in participating in the study about what participation would entail, and to make sure that they met the inclusion criteria and did not have any of the exclusion criteria. An appointment for a screening visit was made with eligible participants.

3.1.1 Inclusion criteria

The inclusion criteria were that the subjects had to have elevated LDL-C (>3.0 mmol/L) and be either normal-weight (BMI <25 kg/m^2) or have obesity (BMI 30-45 kg/m^2). They had to be able to meet at the Section for Preventive Cardiology at Oslo University Hospital five times during eight weeks, be willing to take fasting blood samples and measure BP four times, to

keep a food diary and to be willing eat either of the two intervention diets. They had to have been weight stable for the last three months, defined as no greater variation than plus or minus five kg.

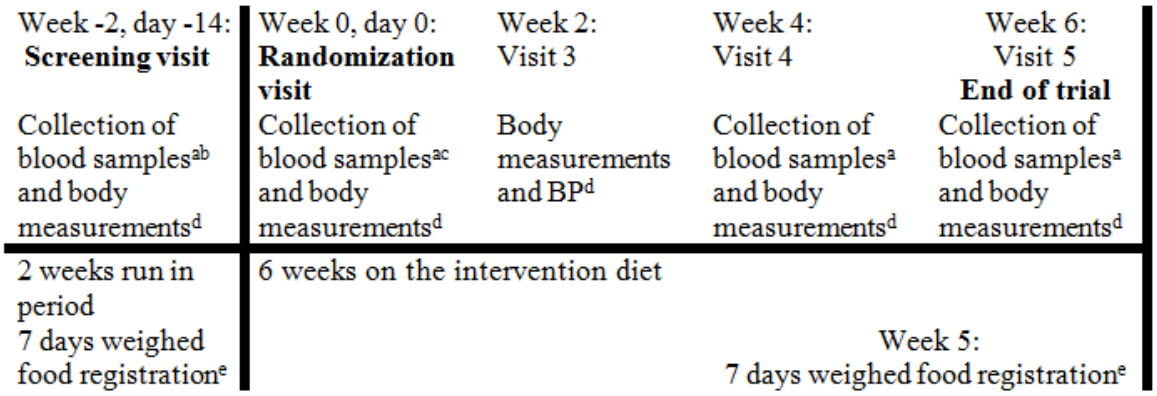
3.1.2 Exclusion criteria

The exclusion criteria included having Type 1 or Type 2 Diabetes, taking lipid-modifying medications, had a previous cardiovascular event (infarctions, stroke, Transient Ischemic Attack, angina pectoris, or other atherosclerotic diseases) or having a genetic lipid disorder. Subjects were not suitable for participating in the study if they were pregnant or were breastfeeding, if they abused medications or alcohol, had a severe eating disorder, gastrointestinal diseases or any other severe disease, had allergies or intolerances against the intervention food products or had a severe psychological disorder that would affect the individual's ability to complete the study.

3.2 Study design

The study started with a screening visit (week -2). The screening visit lasted for a total of one to one and a half hour and included a doctor appointment, a meeting with one of the two study nurses and an appointment with a nutritionist. A clinical examination and a record of the medical history of each participant were completed and fasting blood samples, a BP measurement and body measurements were collected (Figure 3.1). The blood samples collected at the screening visit included Thyroid-Stimulating Hormone (TSH), plasma-creatinine and alanine aminotransferase (ALAT) to make sure the participants did not have other medical reason for their elevated LDL-C, like a liver-, kidney- or metabolic disorder. An elevated value was not an exclusion criterion, but a doctor made individual evaluations whether the subjects were suited to participate in the study or not.

Figure 3.1 Timeline for the study and the measurements taken during the study period



BP; Blood pressure

[a]: Fasting blood samples: Lipids (total-cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, Apo lipoprotein B), glucose, HbA1c, and C-reactive protein. Only small amounts of water were allowed, in addition to the subject's normal medication if they were taking any.

[b]: Thyroid-Stimulating Hormone (TSH), plasma-creatinine and alanine aminotransferase (ALAT) were measured.

[c]: TSH, plasma-creatinine and ALAT were measured again in the individuals that had elevated values at the screening visit.

[d]: Hip circumference, waist circumference, weight

[e]: The food registration form were handed out and explained

At the screening visit, the participants were encouraged to maintain a stable weight during the whole study period. The nutritionist evaluated the participants` weight development at each visit and gave individual advice to each participant to maintain a stable weight. They were also instructed to keep their physical activity level stable and to report any changes in physical activity or medication use. At each visit after the randomization visit, it was registered if they experienced any unwanted events or side effects of the food intervention. Smoking status was recorded at the beginning and the end of the study. The participants were instructed to maintain their usual alcohol intake. The screening visit was followed by a two weeks run in period. In the run in period, the participants ate their usual diets and completed a seven days weighed food registration to provide a dietary baseline. The randomization visit

lasted for approximately one hour and visit 3, 4, and 5 for 30 minutes to one hour. All the visits included a meeting with a study nurse for the blood sample collection and BP- and pulse-measurement, except from visit 3 where no blood samples were drawn and the nutritionist measured the BP and pulse.

Portions of butter or margarine were handed out at the randomization visit, visit 3 and 4. Visit 5 (week 6) was the last visit and marked the end of the study period. The participants were offered to have the blood sample results from the screening visit, randomization visit and visit 4 reviewed with the nutritionist at visit 5. More dietary advice was given and a follow up appointment with the nutritionist and/or a doctor was scheduled if the participants wanted it. The participants who did not want a follow up appointment with the nutritionist or the doctor were advised to follow up their cholesterol levels with their general practitioner. It was the same nutritionist who met the participants at every visit, unless sickness or other unforeseen events made that impossible.

3.3 Randomization

A blind randomization was performed based on BMI category and on the strata gender (male/female). A computer generated block randomization list provided by an independent statistician was used for the randomization. A person independent from the study divided the randomization list and put one randomization number in separate envelopes. The envelopes were divided in four groups based on gender and BMI category:

- Females with BMI < 25 kg/m^2
- Females with BMI 30-45 kg/m^2
- Males with BMI < 25 kg/m^2
- Males with BMI 30-45 kg/m^2

The envelope with the randomization number and intervention group was kept in each participant Case Report Form (CRF).

3.4 Primary outcome

The primary outcome was to compare the change in the lipid profile (TC, LDL-C, HDL-C, TG and Apo B) from baseline to week 6 between normal-weight and the participants with obesity in the SFA diet group and in the PUFA diet group.

The fasting blood samples were taken at the screening visit, the randomization visit, visit 4 and 5 by two experienced study nurses. The participants had fasted for at least 10 hours and the blood samples were taken between 07.30 and 12.00 in the morning. The blood samples were taken from a vein in the arm. After the blood samples were collected, the samples rested for 30 minutes before they were centrifuged in a cooling centrifuge for 15 minutes with 200 x g (Hettich universal 32R, yearly quality controlled and given calibration certification). After centrifugation the samples were sent to the lab for analysis. TC, LDL-C, HDL-C, TG and Apo B were measured with methods from Roche Diagnostic. The uncertainty levels in the analysis of the blood samples are reported with variation coefficients in percentages: TC 2.5 %, LDL-C 3.5 %, HDL-C 4 %, TG 4 % and Apo B 4 % (61).

3.5 Secondary outcomes

Because changes in body weight can affect the lipid profile, we wanted to investigate if the participants were weight stable during the study period. Since changes in the intake of SFA and PUFA were the dietary interventions, analyzing the nutrition differences were central to see if we reached our goals for the dietary intervention. The secondary outcomes were changes in the diet, body weight, waist circumference and hip circumference from baseline to week 6 between normal-weight participants and those with obesity in the SFA diet group and the normal-weight and participants with obesity in the PUFA diet group.

Two seven days food registrations were used to calculate the energy- and nutrient intake, the qualitative mean changes in the nutrition intake from baseline to the end of the study within the groups and to compare between group differences. Body weight was measured without heavy clothes and shoes, on a "Seca Unitronic" scale (seca gmbh & co. kg, 22089 Hamburg, Germany, last calibrated 24.06.2016). A doctor measured the subject's height at the screening visit with a stadiometer attached to the wall for the BMI calculation. BMI was calculated by the formula: weight (kg)/height (meters) ^{2} (21). Standardized procedures were developed for the waist and hip circumference measurements. The same nutritionist measured waist and hip

circumference at each visit, unless sickness or other unforeseen events occurred, which happened less than five times. To make sure that both the nutritionist used the same method for measuring waist and hip circumference, a training session was conducted before the start of the study. The waist circumference was measured at the midpoint between the lowest rib and the top of the hipbone. For those individuals where this point was hard to find it was measured at the widest point close to the umbilicus. The measurement tape was horizontal and untwisted against the subject's skin, tight but without putting any pressure on the abdomen. The subjects were standing, relaxed and were instructed to breathe out when the measurement were taken. The hip circumference was measured at the widest part below the hip bone and over the buttocks with a horizontal and untwisted measurement tape against the subject's skin. The subjects were standing, relaxed and were instructed to breathe out when the measurement was taken.

3.6 Post Hoc

One additional cardiometabolic risk factor, Non HDL-C, was calculated from the TC and HDL-C measured in the blood. The equation used for the calculations was (62):

- Non HDL-C = TC – HDL-C

3.7 Study interventions

The two intervention diets were based on the Norwegian nutrition recommendations; with the exception that one of the group should eat full-fat products and have a high SFA intake, and the other group should eat low-fat products and have a high PUFA intake. The aim for the two diet groups was to have the same intake in energy percentage (E%) from carbohydrates, fiber, protein and fat, but with a difference in the E% intake from SFA, MUFA and PUFA, see Table 3.1. Both groups were advised to reduce the intake of sugar, sodas with sugar, sweet snacks, refined carbohydrate and processed meat, see Table 3.2. They were advised to eat whole grain products, fish and lots of fruit, berries and vegetables.

Table 3.1 The planned differences in E% intake from SFA, MUFA and PUFA aimed for between the two diet groups.

Dietary nutrient	Planned difference in E%
SFA	≥ 9 E%, highest intake in the SFA diet group compared to the PUFA diet group
MUFA	≥ 5 E%, highest intake in the PUFA diet group compared to the SFA diet group
PUFA	≥ 4 E%, highest intake in the PUFA diet group compared to the SFA diet group

E%, energy intake in percentage; SFA, Saturated fatty acids; MUFA, Monounsaturated fatty acids; PUFA, Polyunsaturated fatty acids

Table 3.2 The recommended food items in the two diet groups.

SFA diet group	PUFA diet group
Choose the minimum portion of 24 gram butter each day ("Tine Meierismør")	Choose the minimum portion of 25 gram margarine each day ("Vita Hjertego´ margarine")
Choose butter as spread, for baking, frying and other types of cooking	Choose margarine as spread and margarine or rapeseed oil for baking, frying and other types of cooking
Choose sour cream based dressings	Choose oil based dressings
Choose full fat dairy products (milk, cheese, sour cream, yoghurt)	Choose fat reduced fat dairy products (milk, cheese, sour cream, yoghurt)
Increase the intake of fruit, berries and vegetables, at least 5 portions per day	Increase the intake of fruit, berries and vegetables, at least 5 portions per day
Choose wholegrain products (bread, crisp bread, cereals, pasta, and rice) instead of refined carbohydrates (regular pasta, white rice, sweet cereals, buns etc.)	Choose wholegrain products (bread, crisp bread, cereals, pasta, and rice) instead of refined carbohydrates (regular pasta, white rice, sweet cereals, buns etc.)
Choose fish and fish products	Choose fish and fish products
Choose red meat and poultry with fat and avoid processed meat products (bacon, fast food, sausages, hamburgers, fries, etc.)	Choose read meat and poultry with the fat trimmed of and avoid processed meat products (bacon, fast food, sausages, hamburgers, fries etc.)
Limit the intake of sugar rich food (soda, snacks, cakes, chocolate, candy, ice-cream etc.) to maximum 1-2 portions per week	Limit the intake of sugar rich food (soda, snacks, cakes, chocolate, candy, ice-cream etc.) to maximum 1-2 portions per week
Limit the intake of margarine, unsalted nuts (almonds, hazelnut, walnut), peanut butter, avocado, olive oil, rapeseed oil, mayonnaise and mayonnaise based products, seeds, olives, pesto etc.	Choose margarine, unsalted nuts (almonds, hazelnut, walnut), peanut butter, avocado, olive oil, rapeseed oil, mayonnaise and mayonnaise based products, seeds, olives, pesto etc.
Snack list for both groups: Fruit salad, berries, smoothies, vegetables with sour cream dip	

3.7.1 Minimum portions of butter or margarine

Butter or margarine was handed out to the participants, enough to supply them with a minimum intake of 24 grams butter or 25 grams margarine each day until the next visit. 24 grams butter equals two small sachets of "Tine Meierismør" (12 grams in one sachet) and 25 grams margarine equals two and a half sachets of "Vita Hjertego´" (10 grams in one sachet). The butter and margarine was sponsored by "Tine" and "Mills" and were handed out to the participants free of charge. The minimum portion of butter was handed out to secure the intake of SFA in the SFA diet group each day. To the PUFA diet group, margarine was handed out to ensure an intake of MUFA and PUFA, see Table 3.3 for the nutrient composition for the butter and margarine that was handed out. The SFA E% in 24 grams butter and 25 grams margarine is 64.2 E% and 19.9 E%, which gives a 44.3 E% difference from SFA in the two diet groups. The minimum portions functioned as a measurement of compliance to the diets, and as a daily reminder to the participants about the food intervention. In the Norwegian diet, there is a tradition for bread meals (48), so the butter or margarine could be used as spread on bread and crisp bread. For those participants who ate little or no bread, advice was given to use it in porridges, melt it over potatoes, wholegrain pasta or rice, vegetables or put it in their portions of sauce etc. The participants were instructed to make sure no other people in their household ate from their minimum portions and preferably put the butter or margarine in a separate box in the fridge. If the participants were unable to finish all the minimum portions, they were instructed to bring the remaining portions to the next visit so the amount could be registered. If the participants forgot to bring any leftovers to the visit, they sent an email to tell about the amount that was not eaten or they told the amount over the telephone. If the participants had missed one visit and had emptied all the sachets handed out at earlier visits, they were instructed to weigh butter or margarine to make sure they had eaten the minimum amount each day.

No calories recommendations were calculated because the participants were free-living subjects with ad libitum food consumption. The participants in both diet groups were advised to reduce their calorie intake from sugar rich food and processed minced meat, and this should be replaced with calories from an increased fat intake from SFAs or PUFAs accordant to their diet group.

Table 3.3 Nutrient composition of 100 grams of butter and margarine

	Butter ("Tine Meierismør")	**Margarine (Vita Hjertego´)**
Kilojoule/calories	3051/742	2598/632
Total fat g	82	70
SFA g	53	14
Trans fat g	2	0
MUFA g	19	27
PUFA g	2	25
n-3 FA g	0.4	2.6
n-6 FA g	1.4	21
Cholesterol mg	231	0
Carbohydrates g	0.5	0.3
Added sugar	0	0
Fiber	0	0
Protein g	0.5	0.2
Salt g	1.3	0.8

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; FA, fatty acids.

Nutrition information from "Kostholdsplanleggeren": https://www.kostholdsplanleggeren.no/comparefoods/?profileId=53&slot0Id=08.005&slot1Id=08.228 (1.8.2017)

3.8 Seven days weighed food registration/diary

A weighed food registration was completed for seven days at baseline; between the screening visit and randomization visit (period 1), and in the end of the study between visit 4 and visit 5 (period 2). If the participants for any reason had registered fewer than seven days, the number of days registered were used for the analysis. If they had registered more than seven days, the first seven days that were registered were used for the analysis. The participants could use their own scale or borrow one from the Section for Preventive Cardiology. They were instructed to eat as usual in period 1, but to weigh what they ate and drank and register it in the standardized food diary handed out at the screening visit. If they did not have the opportunity to weigh the food, they were instructed to estimate the amount as accurate as possible in household measures (i.e deciliters, pieces, tablespoons, teaspoons etc.). They were instructed to be accurate when they reported what type of food or drink they had consumed (brand, fat percentages etc.), how it was prepared (boiled, fried etc.) and the amount and type of fat used for cooking, as spread or as dressings. A new registration form was handed out at

visit 4 and they were instructed to write down what they ate and drank in period 2 to give information about their changes in the diet after randomization to one of the two diets.

The seven days food registrations were plotted in an online program called "Kostholdsplanleggeren", a tool for analyzing food intake developed by "Helsedirektoratet" and "Mattilsynet" which is public available (63). The nutrition information in this program is based on the Norwegian food composition table "Matvaretabellen" (64) and "Kostholdsplanleggeren" is updated from "Matvaretabellen" once a year. If the amount of food registered was not given in grams, but in "pieces", "tablespoons", "teaspoons", "portions", "slices" etc., the standard amounts in "Kostholdsplanleggeren" were used. The diaries were thoroughly reviewed by the nutritionist and the participant in collaboration, the diary from period 1 at the randomization visit and the diary from period 2 at visit 5. If any lack of details were detected when the diaries were plotted in "Kostholdsplanleggeren", the nutritionist asked the participants about those details at later visits, by email or over the phone. Water, tea and other drinks without energy content were not registered in the food diaries. The coffee intake was plotted as either filtrated-coffee or instant coffee due to lack of other coffee types (capsule coffee, cafetière, coffee from espresso machines) in the "Kostholdsplanleggeren" database.

About 15 to 30 minutes were used to review each diary at the randomization visit and at visit 5. Between one to three hours were used to plot each diary in "Kostholdsplanleggeren". An addition of 15 to 30 minutes was later used to revise the plotted data in "Kostholdsplanleggeren". If a registered food item in a diary was not a part of the "Kostholdsplanleggeren" database, the nutritionist entered information of the nutrition content of the food item in the database. If the nutrition content was not available, a similar food item from the database was chosen. If a participant had registered a recipe in the food diary for a dish, the recipe was entered in the database and the amount of that dish eaten was registered.

For the analysis of the food intake, 138 food diaries were plotted in "Kostholdsplanleggeren": 71 for period 1 and 67 for period 2. Four participants dropped out of the study and did for that reason not register their food intake in period 2. A total of 389 new food items were entered in the "Kostholdsplanleggeren" database, and a total of 246 food recipes were registered.

3.9 Assessment of underreporting

An EI/REE (energy intake/resting energy expenditure) ratio was calculated to produce a PAL (physical activity level) value to investigate the occurrence of underreporting of the food intake. The EI/RMR ratio was calculated by dividing the registered energy intake (in calories) on the REE. Mifflin's formula was used to calculate the REE for both subjects with normal-weight and the subjects with obesity at baseline and visit 5. Mifflin's formula was used to calculate the REE for all the participants because it is the formula that is recommended to use in people with BMI > 30 kg/m^2 (65). Estimating TEE (total energy expenditure) with the factorial approach (TEE= BMR x PAL) (66) is calculated with BMR instead of REE. In both international (65) and Norwegian (67) literature, it is normal to use REE for the TEE calculation instead of BMR because of the difficulties of estimating the basal values. The Mifflin equation used for the calculation was (68):

REE (kcal) = 9.99 x weight + 6.25 x height (cm) – 4.92 x age + 166 x gender – 161
(gender: Male =1, female = 0)

3.10 Dietary counselling

At the randomization visit, the participants were informed about which diet group they were randomized to, either the SFA or PUFA diet group. Each participant was given individual advice on how to eat according to their assigned diet group based on their normal food preferences. The individual advice was based on the seven days food registration and the participants were asked how they wanted to implement the different fat sources in their diet. A presentation about cholesterol and food was discussed with the participants, see Attachment 2 and 3, and they were educated in sources of different types of FA. Margarine, unsalted nuts, avocado, olive oil and rapeseed oil etc. replaced the reduced amounts of calories in the fat reduced food items and increased the intake of MUFA and PUFA in the PUFA diet groups. They were given a list with food items they were advised to choose, and the list could be used as a shopping list, see Attachment 4 and 5. The participants were educated in how to read food labels to get information about the content and nutrition composition in the food items to make food choices according to their diet group. The dietary counselling was individualized to each participant's personal preferences, existing habits and needs, but some topics were discussed in a less or greater extent in both diet groups. Emphasized topics were:

1. Increase the intake of fruit, berries and vegetables, aiming for at least five portions each day.
2. Choose wholegrain bread, crisp bread, pasta and rice which contain more fiber, micronutrients and phytochemicals than white bread, crisp bread, pasta and rice.
3. Reduce the intake of processed minced meat, sausage-products and bacon for the advantage of unprocessed meat, poultry and fish products for dinner and as sandwich filling.
4. Reduce the intake of sugar-rich food, cakes, beverages and snacks to reduce the intake of sugar, calories and fat from these types of food items and choose fruit, berries and vegetables as snacks instead to increase the intake of fiber, vitamins and antioxidants.

Wholegrain bread was emphasized as a good source of dietary fiber. The participants in both diet groups were explained a bread scale (Figure 3.2), the visual tool "Brødskala`n". "Brødskala`n" is a volunteer labeling system used in Norway. The scale is divided in four categories (white bread, semi-dark bread, dark bread and whole grain) based on the breads content of whole grain, wholemeal and bran. The participants were encouraged to choose bread with a "full circle" in the "Brødskala`n". These types of breads are in the "whole grain" category, which has a whole grain content of 75-100 %.

Figure 3.2 "Brødskala`n" (The Bread Scale)

Published with permission from "opplysningskontoret for brød og korn".
http://www.matportalen.no/merking/tema/merking_av_mat/bruk_brodskalan (1.08.2017)

Coffee intake and brewing method was not discussed with the participants by the nutritionist during the study. It was discussed after the end of the study if the participants reported a high intake of coffee made with an unfavorable brewing method and they still had cholesterol levels above the recommendations.

The subjects could not take any lipid lowering food supplements like plant sterols (i.e Vita Proaktiv margarine), β-glucan products (i.e Betaglucare oat hearts) or red yeast rice during the study period. The subjects were requested to terminate any use of such kind of supplements during the telephone interview, and this instruction was repeated and affirmed at the screening visit. Fish oil or vegetable oil supplements were allowed.

3.11 Compliance measurements

Compliance to the diets was investigated with the seven day weighted food registration, with dietary questionnaires and by calculating the percentage intake of the minimum portions of butter and margarine. The dietary questionnaire was handed out at visit 3, 4 and 5, see Attachment 6 and 7. The dietary questionnaire where check lists were the participants could check off "true" or "untrue" for different statements, which described their diet for the last two weeks. The dietary questionnaire focused on the participants` food choices. The same type of dietary questionnaire was given to both groups, with different fat sources and fat quality being the only difference. They could score a maximum of nine points, which reflected a good compliance to the diet. Intake of the minimum portions of butter or margarine was recorded at visit 3, 4 and 5, and a percentage was calculated and registered. A score of 100 % meant that all the minimum portions were eaten and that the participants had good compliance. Less than 100 %, but more than 50 % was partial compliance and less than 50 % meant poor compliance to the intake of minimum portions of butter or margarine. The intake of the minimum portions of butter or margarine was recorded in the same manner in both groups.

For three of the four drop outs, no compliance measurements were registered because they dropped out right after the randomization visit. For the one subject that dropped out after visit 3, compliance measurements were registered at visit 3.

3.12 Sample size and statistical analyses

IBM Statistical Package for the Social Science (SPSS) version 23 was used for all the statistical tests presented in this thesis.

3.12.1 Power calculation

The sample size was calculated based on the change in LDL-C after eating a diet with nine E% difference in the intake of SFA for the subjects with normal-weight in the SFA diet group and the normal-weight PUFA diet group. With nine E% difference in SFA intake the expected difference in LDL-C was 0.4-0.5 mmol/L in the normal-weight sample (57) and this is also in line with a previous study perform by the Section for Preventive Cardiology at Oslo University Hospital (69). For the sample with the subjects with obesity, the expected difference in LDL-C was estimated as <0.1 mmol/L based on previous data (27). With the estimated between group difference of 0.4 mmol/L and a standard deviation (SD) of the difference of 0.65 mmol/L, 37 subjects were required for each groups with β of 0.8 and alpha set at 0.05 (Sample power version 3). A total of 42 normal-weight subjects and 42 subjects with obesity were planned to be included in the study to make up for dropouts.

3.12.2 Examination of data

The data was proofread by checking 10 % of the observations and it was checked for outliers. All continuous variables were checked for normality in SPSS by looking at the histogram, the Q-Q plot and the Kolmogrov-Smirnov test and Shapiro-Wilk test. The descriptive data for continuous variables are presented with means and SD for the normal distributed variables and were analyzed with parametric tests (Paired-Samples T Test and Independent-Sample T Test). The not normal distributed continuous variables are presented with median and 25-75th percentiles. They were analyzed with non-parametric tests (Wilcoxon`s Signed Rank Test and Mann-Whitney U Test). The categorical data are presented as numbers and percentages and are analyzed with Fisher`s Exact Test. Linear regression analysis were used to analyze the primary outcomes. Dummy variables were created to analyze the effect of diet group and the interaction between BMI and diet group in the linear regression analysis. A linear regression analyze preformed with the values for the last visit as the independent variable, adjusted for the baseline values, did not give very different results than using the difference in the variables from baseline to six weeks as the independent variable (data not shown).

3.12.3 Missing data

The statistical analysis followed the "intention-to-treat" and "per protocol" (last value carried forward) principles, which means that the data for all the randomized participants was analyzed. If a participant dropped out, the last registered data from the visits before the participant left the study were registered for the remaining scheduled visits. If any values for a variable were missing or the participants had been unable to meet at one visit, the last registered value for the variable was used.

3.13 Ethical aspects

The participants in the "Cholesterol Study" were over 18 years old, and thereby legally capable and they volunteered to participate in the study. The participants and their doctor at the screening visit signed a written consent form, see Attachment 8. They were informed that they could withdraw from the study at any time during the study period without giving any reasons or without any consequences. The participants were given verbal information about the study from a nutritionist during the telephone interview, they were sent written information in the mail after the telephone interview and were given verbal and written information again at the screening visit by a doctor and a nutritionist. The participants were given a medical examination by a doctor at the screening visit, and were followed up during and after the study. All the participants were offered a consultation with the doctor and a nutritionist after the end of the study. If they wanted, the participants with obesity were given counselling about weight reduction and those with BMI >34.9 kg/m^2 were offered to participate in a weight reduction group at the Section for Preventive Cardiology at Oslo University Hospital.

The study protocol for this project was approved by the National Committees for Research Ethics in Norway (2014/1786 REK sør-øst D) and registered in Clinicaltrials.gov 16.06.2015 (registration number NCT02589769). The principles of the Helsinki Declaration were followed (70). The personal data were treated with confidentiality and were locked up, and the study staff was under professional secrecy. The hospital`s guidelines were followed for storage of the data on a server in a file marked "sensitive" with restricted access. Collected data were only used as described in the purpose of the study in the protocol.

3.14 Literature search

A literature search in the PubMed database was performed to collect relevant literature for the work in this thesis. The titles were read first, and the abstract were read for those articles that were suitable for the focus of the master thesis. Only articles with available full text were included in this thesis.

The main literature search was performed the 09.10.2017 in the PubMed database with the search words “cholesterol” AND “dietary saturated fatty acids”. This search resulted in 803 articles when these filters were activated: “Clinical trial”, “review”, “full text”, “10 years” and “humans”.

Additional searches in PubMed were also performed, and articles from the study protocol and articles recommended by the supervisors are included in this master thesis.

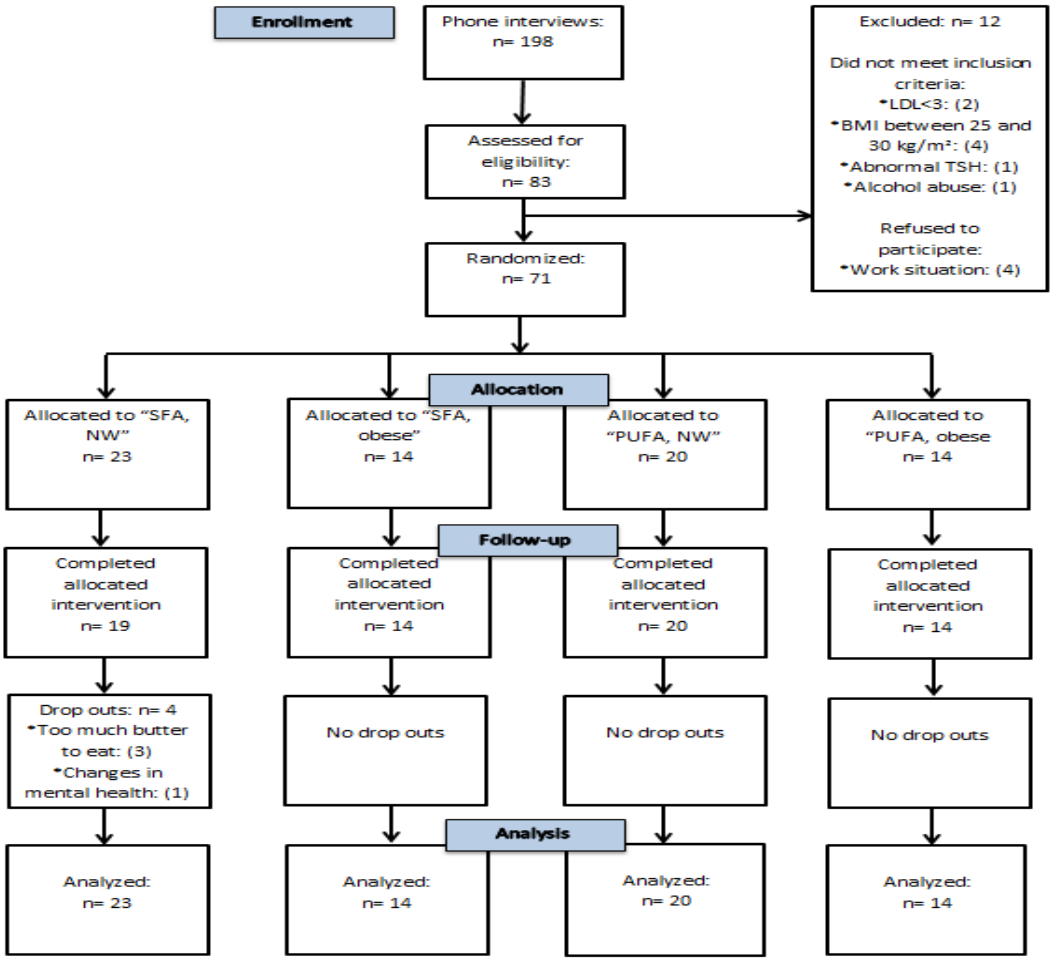
4 Results

The results will be presented with the baseline results first, then the primary outcome. Secondary outcomes and the post hoc results will be presented after the main results.

4.1 Participant characteristics

After conducting 198 phone interviews, 83 persons were assed for eligibility. After the medical examination at the screening visit, 71 subjects met the inclusion criteria and had none of the exclusion criteria. They were randomized to either of the two diet groups. This was 13 subjects less than calculated in the power calculation. We failed to recruit as many participants with obesity as planned (Figure 4.1). Four participants dropped out during the study, all were subjects with normal-weight in the SFA diet group. This gives a drop out score of 5.6 %.

Figure 4.1 Flowchart of the participants



Abbreviations: LDL-C, low density lipoprotein cholesterol; TSH, Thyroid-Stimulating Hormone; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; NW, normal-weight

The normal-weight and the subjects with obesity were randomized in separate groups based on different BMI. There is a difference in anthropometric measurements, like waist circumference, between subjects with normal-weight and with obesity. Furthermore, obesity is associated with changes in the lipid profile and hypertension. For this reason, we compared the baseline values for subjects with normal-weight in the SFA diet group with the PUFA diet group and subjects with obesity in the SFA diet group with the PUFA diet group. There was no significant differences in the anthropometric measurements (Table 4.1) or biochemical values at baseline (Table 4.2).

The baseline values for the subjects with normal-weight were compared with the subjects with obesity in the SFA diet group and the baseline values for normal-weight with the subjects with obesity in the PUFA diet group in some chosen variables; the primary outcomes (the lipid profile) and for socioeconomic variables (gender, education and smoking status). The subjects with normal-weight in both the SFA and PUFA diet group had significant higher HDL-C values than the subjects with obesity in the SFA and PUFA diet group at baseline (Table 4.2). For HDL-C, the normal-weight females in both diet groups had significantly higher HDL-C than the females with obesity. There were no significant differences in the HDL-C between the males. The normal-weight in the SFA diet group had significantly lower TG than the subjects with obesity. It was no significant differences in TC, LDL-C, Apo B (Table 4.2) or the socioeconomic variables (Table 4.1) at baseline between normal-weight and the subjects with obesity in the SFA diet group and normal-weight and subjects with obesity in the PUFA diet group.

Table 4.1 Baseline characteristics of the anthropometric measurements, BP and pulse of the participants after randomization to the diet groups

(Mean values and standard deviations; numbers and percentages)

	SFA, NW (n=23)	**SFA, Obese (n=14)**	**PUFA, NW (n=20)**	**PUFA, Obese (n=14)**	**All subjects (n=71)**
Female (%)	16 (69.6%)	10 (71.4%)	13 (65.0%)	10 (71.4 %)	49 (69.0 %)
Age (years)‡	56.7 (10.8)	50.9 (8.6)	52.4 (13.4)	55.7 (8.3)	54.2 (10.8)
Smokers	2 (8.7%)	0 (0%)	1 (5.0%)	3 (21.4%)	6 (8.5%)
Elementary school, n (%)	1 (4.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (1.4 %)
Secondary school, n (%)	2 (8.7 %)	3 (21.4%)	3 (15.0%)	5 (35.7%)	13 (18.3 %)
University, n (%)	20 (87.0%)	11 (78.6%)	17 (85.0%)	9 (64.3%)	57 (80.3)
Body weight (kg)	67.3 (7.1)	102.0 (13.1)	69.4 (9.3)	93.9 (14.5)	80.0 (18.2)
BMI (kg/m^2)	23.2 (1.5)	34.8 (3.4)	23.6 (1.6)	33.0 (3.9)	27.6 (5.8)
WC (cm)	85.4 (7.3)	112.3 (6.3)	84.9 (7.5)	105.9 (10.9)	94.6 (14.3)
Females	83.9 (7.1)	110.5 (6.5)	82.7 (7.9)	106.6 (11.2)	93.6 (14.9)
Males	88.9 (6.9)	116.9 (2.2)	88.9 (5.2)	104.3 (11.8)	96.8 (13.1)
HC (cm)	93.5 (5.6)	117.1 (8.2)	94.3 (5.2)	111.9 (7.8)	102.0 (12.1)
Females	93.7 (6.0)	118.1 (8.0)	92.8 (5.1)	113.8 (6.8)	102.5 (12.9)
Males	93.1 (5.1)	114.8 (9.6)	97.0 (4.4)	107.1 (9.2)	100.8 (10.4)
Waist/hip ratio	0.9 (0.1)	1.0 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Females	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Males	1.0 (0.1)	1.0 (0.1)	0.9 (0.1)	1.0 (0.0)	1.0 (0.1)
Systolic BP (mmHg)	121.2 (15.9)	124.6 (11.2)	117.8 (12.5)	122.8 (11.7)	121.2 (13.3)
Diastolic BP (mmHg)	79.7(9.0)	83.0 (8.9)	76.9 (6.6)	81.1 (7.9)	79.8 (8.3)
Heart rate/minute	65.2 (9.6)	67.8 (9.0)	62.0 (11.3)	65.9 (5.7)	64.9 (9.4)
Hypertensive medication	1.0 (4.3 %)	2.0 (14.3%)	1.0 (5.0 %)	4.0 (28.6 %)	8 (11.3 %)

Abbreviations: SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; NW, normal-weight; BMI, body mass index; WC, waist circumference, HC, hip circumference; BP, blood pressure.

Table 4.2 Baseline characteristics of the lipid profile and other laboratory values (Mean values and standard deviations; medians and 25-75th percentiles; *= significant, p <0.05, **= significant, p <0.01)

	SFA, NW (n=23)	SFA, Obese (n=14)	PUFA, NW (n=20)	PUFA, Obese (n=14)	All subjects (n=71)
Lipid profile					
TC (mmol/L)	6.6 (1.0)	6.3 (1.3)	6.6 (0.7)	6.3 (0.6)	6.5 (0.9)
LDL-C (mmol/L)	4.4 (0.8)	4.4 (1.0)	4.5 (0.7)	4.3 (0.7)	4.4 (0.8)
HDL-C (mmol/L)	1.9 (0.6)	1.3 (0.3)	1.8 (0.4)	1.4 (0.4)	1.6 (0.5)
Females	2.1 (0.5)	1.5 (0.3)	1.9 (0.4)	1.3 (0.4)	1.8 (0.5)
Males	1.6 (0.5)	1.0 (0.1)	1.4 (0.2)	1.5 (0.4)	1.4 (0.4)
TG (mmol/L) ‡	0.9 (0.7-1.3)	1.7 (1.4-2.7)	1.0 (0.8-1.4)	1.5 (1.2-2.0)	1.2 (0.8-1.7)
Non HDL-C (mmol/L)	4.7 (0.9)	5.0 (1.2)	4.8 (0.7)	4.9 (0.7)	4.8 (0.9)
Laboratory values					
Apo B (gram/L)	1.2 (0.2)	1.3 (0.3)	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)
Glucose (mmol/L)	5.1 (0.5)	5.6 (0.6)	5.4 (0.6)	5.7 (0.4)	5.4 (0.6)
HbA1c (%)	5.2 (0.3) [a]	5.5 (0.5)	5.2 (0.3)	5.4 (0.4)	5.3 (0.4) [a]
CRP (mg/L) ‡	0.7 (0.6-1.3)	2.5 (1.2-4.6)	0.7 (0.6-1.2)	2.3 (1.3-3.9)	1.1 (0.6-2.4)

Abbreviations: SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; NW, normal-weight; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; Apo B, Apolipoprotein B; HbA1c, glycated hemoglobin (A1c); CRP, C-reactive protein.
‡: Mann-Whitney U Test was used for not normally distributed variables. Presented with Median and 25-75th percentile
[a] Missing for one subject because of wrong material for the blood analysis.

4.2 Dietary intake at baseline

We compared the subjects with normal-weight in the SFA diet group with normal-weight in the PUFA diet group and the subjects with obesity in the SFA diet group with subjects with obesity in the PUFA diet group. There were no significant differences at baseline, except for sugar intake (E%) (Table 4.3), which was significantly higher for the normal-weight in the PUFA diet group than for the normal-weight in the SFA diet group (mean 2.6, SD 1.1).

One normal-weight subject in the SFA diet group reported no use of supplements during the telephone interview, but had registered 3 grams Vita Proactive Margarine each day during the run in period. The participant was instructed to stop eating the Vita Proactive Margarine at the randomization visit. One normal-weight subject in the PUFA diet group had eaten 20 grams of β-glucans two times a week during the whole study period. This was first discovered at the last visit in week 6.

Table 4.3 Dietary intake at baseline, registered in a seven days food registration.

(Mean values and standard deviations; medians and 25-75th percentiles)

	SFA, NW (n=23)	PUFA, NW (n=20)	SFA, obese (n=14)	PUFA, obese (n=14)	All subjects (n=71)
Kilojoule (kJ)	8242 (2339)	8753 (2355)	9477 (3393)	9126 (1955)	8803.7 (2507.5)
Kilocalories	1957 (568)	2089 (561)	2264 (810)	2181 (471)	2098.7 (602.9)
EI/REE [a] (PAL)	1.3 (0.3)	1.3 (0.3)	1.2 (0.4)	1.2 (0.2)	1.3 (0.3)
Fat (E%)	40.5 (10.5)	39.7 (4.0)	40.4 (4.2)	42.6 (9.4)	40.7 (7.7)
SFA (E%)	15.7 (6.9)	14.3 (2.5)	15.0 (2.0)	15.9 (2.2)	15.2 (4.3)
Trans fat (E%) ‡	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.3)	0.0 (0.0-0.0)
MUFA (E%)	13.9 (3.3)	13.4 (3.0)	13.5 (2.6)	14.3 (4.9)	13.8 (3.4)
PUFA (E%)	6.0 (1.9)	5.8 (1.6)	6.2 (2.3)	5.8 (2.5)	5.9 (2.0)
n-3 (gram)	2.9 (1.3)	2.9 (1.6)	3.0 (1.4)	2.8 (1.6)	2.9 (1.4)
n-6 (gram)	9.4 (3.5)	9.4 (3.5)	12.2 (7.0)	11.1 (6.8)	10.3 (5.1)
Cholesterol (mg)	307.8 (229.3)	271.5 (96.7)	304.0 (131.2)	351.4 (113.8)	305.4 (159.4)
Carbohydrates (E%)	41.9 (9.9)	42.8 (3.9)	40.4 (4.3)	40.1 (9.8)	41.5 (7.6)
Sugar (E%)	5.6 (2.9)	8.2 (4.2)*	6.2 (4.2)	7.1 (3.1)	6.7 (3.7)
Fiber (g)	23.6 (6.6)	22.1 (6.4)	24.8 (7.2)	24.2 (7.6)	23.6 (6.8)
Protein (E%)	17.6 (3.0)	17.4 (2.3)	19.3 (3.3)	17.6 (2.7)	17.9 (2.8)
Alcohol (gram)	11.7 (11.2)	10.9 (6.6)	9.6 (16.3)	10.3 (11.8)	10.8 (11.3)
Number of days [b] (n) ‡	7.0 (7.0-7.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)

Abbreviations: SFA, saturated fatty acids; NW, normal-weight; PUFA, polyunsaturated fatty acids; EI, energy intake; REE, resting energy expenditure; PAL, physical activity level; MUFA, monounsaturated fatty acids

*p<0.05: NW SFA v. NW PUFA and obese SFA v. obese PUFA; Independent-Sample T Test was used for normally distributed variables.

[a]: EI/REE (Calculated with Mifflin's formula)

[b]: number of days registered in the seven days food registration.

‡ Mann-Whitney U Test was used for not normally distributed variables. Presented with median and 25-75th percentile

4.3 Primary outcome: Changes in the lipid profile from baseline to the end of the study

4.3.1 Between group differences and within group changes in the lipid profile

The change in TC was significantly different between the subjects with normal-weight in the SFA diet group and the subjects with obesity in the SFA diet group, with an increase in TC in the normal-weight and no change in the subjects with obesity after the dietary intervention with increased SFA intake. There were no between group differences between the normal-weight and subjects with obesity in the PUFA diet group.

From baseline to the end of the study, the normal-weight in the SFA diet group had a significant within group increase in TC, LDL-C, HDL-C and Apo B of 7.6%, 9.1%, 5.3% and 8.3 % respectively (Table 4.4). The subjects with obesity in the SFA diet group had no significant changes in the lipid profile from baseline to six weeks. Both the normal weight and subjects with obesity in the PUFA diet group had a significant reduction in TC, LDL-C and Apo B of 12.1 %, 13.3 and 7.7 % (normal-weight) and 7.9%, 7.0 % and 7.7% (obese). The normal-weight in the PUFA diet group had a significant reduction in TG from baseline to six weeks of 21.4 %.

4.3.2 Linear regression

In the adjusted linear regression analysis, there were a trend of an effect of the interaction between “BMI x diet group” on the difference in TC, LDL-C and Apo B from baseline to six weeks (Table 4.6). “Diet group” was significant in the adjusted analysis for the difference in TC, LDL-C and Apo B. For the difference in TC, LDL-C and Apo B there were also performed a linear regression analysis with the variable “weight change” to investigate the effect of the weight reduction from baseline to six weeks in the PUFA group. There were no significant effects of the variable “weight change” in the analysis (data not shown

Table 4.4 The within group changes in the lipid profile from baseline to six weeks and the between group difference in the lipid profile between normal-weight and subjects with obesity in the two dietary intervention groups.

(Mean values and standard deviations; *= significant, p <0.05; **= significant, p < 0.01)

	6 weeks		**Within group change**		**Between groups difference NW SFA v. obese SFA and NW PUFA v. obese PUFA**	
	Mean	**SD**	**Mean change (SD)**	**P1†**	**Mean difference 95% CI**	**P2‡**
TC (mmol/L)						
SFA, NW	7.1	(1.0)	0.5 (0.6)	<0.001**	0.4 (0.0, 0.8)	0.04*
SFA, obese	6.4	(1.3)	0.1 (0.5)	0.40		
PUFA, NW	5.8	(0.8)	-0.8 (0.7)	<0.001**	-0.2 (-0.6, 0.2)	0.22
PUFA, obese	5.8	(0.7)	-0.5 (0.4)	<0.001**		
LDL-C (mmol/L)						
SFA, NW	4.8	(0.9)	0.4 (0.4)	<0.001**	0.2 (-0.2, 0.5)	0.30
SFA, obese	4.6	(1.1)	0.2 (0.6)	0.15		
PUFA, NW	3.8	(0.7)	-0.6 (0.5)	<0.001**	-0.3 (-0.7, 0.0)	0.07
PUFA, obese	4.0	(0.7)	-0.3 (0.4)	0.02*		
HDL-C (mmol/L)						
SFA, NW	2.0	(0.6)	0.1 (0.2)	0.04*	0.0 (-0.1, 0.2)	0.52
SFA, obese	1.4	(0.3)	0.1 (0.2)	0.31		
PUFA, NW	1.7	(0.4)	-0.1 (0.2)	0.15	-0.0 (-0.2, 0.1)	0.67
PUFA, obese	1.3	(0.4)	-0.0 (0.1)	0.17		
Apo B (gram/L)						
SFA, NW	1.3	(0.2)	0.1 (0.1)	0.002*	0.1 (-0.0, 0.1)	0.14
SFA, obese	1.3	(0.3)	0.0 (0.1)	0.41		
PUFA, NW	1.1	(0.2)	-0.1 (0.1)	<0.001**	-0.1 (-0.1, 0.0)	0.13
PUFA, obese	1.2	(0.2)	-0.1 (0.1)	<0.001**		
TG (mmol/L)						
SFA, NW	0.9 (0.7-1.4)			0.62§		0.08§‖
SFA, obese	1.6 (1.1-2.0)			0.06§		
PUFA, NW	0.8 (0.7-1.3)			0.006**§		0.52§‖
PUFA, obese	1.5 (0.9-1.8)			0.16§		

Abbreviations: SFA, saturated fatty acids; NW, normal-weight; PUFA, polyunsaturated fatty acids; TC, total cholesterol, LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Apo B, Apolipoprotein B; TG, triglycerides.

P1†: Baseline v. end of study: Paired-Sample T Test.

§ Baseline v. end of study; Wilcoxon`s Signed Rank Test was used for not normally distributed variables. Presented with median and 25-75th percentiles

P2‡: Between group changes, SFA NW v. SFA obese and PUFA NW v. PUFA obese: Independent-Sample T Test.

§‖: Between group changes; Mann-Whitney U Test was used for not normally distributed variables. Presented with median and 25-75th percentile.

Table 4.5 The between group changes between normal weight in the SFA diet group and normal-weight in the PUFA diet group and the subjects with obesity in the two diet groups after six weeks on the intervention diet

	6 weeks		**Between group differences NW v. NW and obese v. obese**	
	Mean	**SD**	**Mean difference 95 % CI**	**P†**
TC (mmol/L)				
SFA, NW	7.1	(1.0)	1.3 (0.9, 1.7)	<0.001*
PUFA, NW	5.8	(0.8)		
SFA, obese	6.4	(1.3)	0.6 (0.3, 1.0)	0.001*
PUFA, obese	5.8	(0.7)		
LDL-C (mmol/L)				
SFA, NW	4.8	(0.9)	1.0 (0.7, 1.3)	<0.001*
PUFA, NW	3.8	(0.7)		
SFA, obese	4.6	(1.1)	0.5 (0.1, 1.0)	0.010*
PUFA, obese	4.0	(0.7)		
HDL-C (mmol/L)				
SFA, NW	2.0	(0.6)	0.2 (0.0, 0.3)	0.013*
PUFA, NW	1.7	(0.4)		
SFA, obese	1.4	(0.3)	0.1 (-0.0, 0.2)	0.11
PUFA, obese	1.3	(0.4)		
Apo B (g/L)				
SFA, NW	1.3	(0.2)	0.2 (0.1, 0.3)	<0.001*
PUFA, NW	1.1	(0.2)		
SFA, obese	1.3	(0.3)	0.1 (0.0, 0.2)	0.005*
PUFA, obese	1.2	(0.2)		
TG (mmol/L)				
SFA, NW	0.9 (0.7-1.4)			0.06§
PUFA, NW	0.8 (0.7-1.3)			
SFA, obese	1.6 (1.1-2.0)			0.51§
PUFA, obese	1.5 (0.9-1.8)			

Abbreviations: SFA, saturated fatty acids; NW, normal-weight; PUFA, polyunsaturated fatty acids; TC, total cholesterol, LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Apo B, Apolipoprotein B; TG, triglycerides

P†: Between group changes, NW SFA v. NW PUFA and obese SFA v. obese PUFA

§: Between group changes; Mann-Whitney U Test was used for not normally distributed variables. Presented with median and 25-75th percentile

Table 4.6 Analysis of the interaction between dietary group and BMI with a multiple regression.

(95 % confides interval; *= significant, p <0.05, ** = significant, p < 0.01)

TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein cholesterol;

Variable	Unadjusted effect	95 % CI	P1† value	Adjusted effect [a]	95 % CI	P2† value
TC change (mmol/L) [b]						
BMI	-0.0	-0.0, 0.0	0.64	0.0	-0.0, 0.1	0.032
Diet group‡	1.0	0.8, 1.3	<0.001**	2.6	1.3, 3.9	<0.001**
BMI x diet group	0.0	0.0, 0.0	<0.001**	-0.1	-0.1, -0.0	0.013
LDL-C change (mmol/L) [b]						
BMI	0.0	-0.0, 0.0	0.92	0.0	-0.0, 0.1	0.11
Diet group‡	0.8	0.6, 1.0	<0.001**	1.9	0.8, 3.1	0.001**
BMI x diet group	0.0	0.0, 0.0	<0.001**	-0.0	-0.1, -0.0	0.044
HDL-C change (mmol/L)						
BMI	-0.0	-0.0, 0.0	0.51	0.0	-0.0, 0.0	0.62
Diet group	0.1	0.1, 0.2	0.003**	0.4	-0.0, 0.9	0.07
BMI x diet group	0.0	0.0, 0.0	0.015*	-0.0	-0.0, 0.0	0.21
Apo B change (gram/L) [b]						
BMI	-0.0	-0.0, 0.0	0.78	0.0	-0.0, 0.0	0.20
Diet group‡	0.2	0.1, 0.2	<0.001**	0.4	0.2, 0.7	0.001**
BMI x diet group	0.0	0.0, 0.0	<0.001**	-0.0	-0.0, 0.0	0.044
TG change (mmol/L)						
BMI	0.0	-0.0, 0.0	1.00	0.0	-0.0, 0.1	0.28
Diet group‡	0.1	-0.2, 0.3	0.66	1.0	-0.3, 2.3	0.14
BMI x diet group	0.0	-0.0, 0.0	0.90	-0.0	-0.1, 0.0	0.15

Abbreviations: TG, triglycerides; Apo B, Apolipoprotein B.

[a]: Adjusted for all BMI, diet group and BMI x diet group in a linear regression analysis.

[b]:Also analyzed for the effect of weight reduction from baseline to six weeks, not statistical significant (data not shown).

‡SFA diet group compared to PUFA diet group.

P1†: Unadjusted effect; Linear Regression.

P2†: Adjusted for BMI, diet group and BMI x diet group; Linear regression.

4.4 Secondary outcomes: Changes in diet composition, body weight, hip and waist circumference from baseline to six weeks

4.4.1 Between group dietary changes during the study

The change in the intake of n-6 FA was significantly different between the subjects with normal-weight and the subjects with obesity in the SFA diet group from baseline to six weeks. The subjects with obesity had a significantly greater reduction (mean -3.6, SD 1.6) in the intake of n-6 FA (g) compared to the subjects with normal-weight. There were no significant between group changes in the other dietary variables from baseline to 6 weeks.

4.4.2 Within group dietary changes during the study

For the intake of SFA (E%), PUFA (E%), trans fat (E%) cholesterol (mg), n-3 FA (grams) and n-6 FA (grams) the changes in the intake were as expected according to the planned dietary intervention (Table 4.7).In energy intake (kJ), there was a significant reduction for the subjects with normal-weight in the PUFA diet group. The subjects with obesity in the PUFA diet group had a change in the intake of MUFA (E%) and protein intake (E%), with a significant increase. There were no significant within group changes in EI/REE ratio for any of the groups from baseline to the end of the study.

In the other dietary variables analyzed, the subjects with normal-weight in the SFA diet group had a significant reduction in the total carbohydrate (E%) intake (Table 4.8). The subjects with normal-weight and those with obesity in the PUFA diet group and the normal-weight in the SFA diet group had a significant reduction in the sugar intake (E%).

Table 4.7 Dietary values of the intake of energy, different fat acids and cholesterol at the end of the study registered in a seven days food registration and their changes during the study. (Mean values and standard deviations; medians and 25-75th percentiles; *= significant; p <0.05** = significant, p < 0.01)

	6 weeks		**Within group change**		**Between groups change NW SFA v. obese SFA and NW PUFA v. obese PUFA**	
	Mean	**SD**	**Mean (SD)**	**P1†**	**Mean difference 95% CI**	**P2‡**
Energy (kJ)						
SFA, NW	8656	(1935)	416 (1652)	0.24	535 (-526, 1596)	0.31
SFA, obese	9357	(2787)	-120 (1456)	0.76		
PUFA, NW	8037	(1996)	-716 (1481)	0.04*	-91 (-1143, 961)	0.86
PUFA, obese	8500	(1345)	-625 (1483)	0.14		
EI/REE [a] (PAL)						
SFA, NW	1.4	(0.3)	0.1 (0.2)	0.148	0.1 (-0.1, 0.2)	0.25
SFA, obese	1.2	(0.3)	-0.0 (0.2)	0.809		
PUFA, NW	1.2	(0.2)	-0.1 (0.2)	0.058	-0.0 (-0.2, 0.1)	0.54
PUFA, obese	1.2	(0.3)	-0.1 (0.2)	0.355		
Fat (E%)						
SFA, NW	45.1	(8.3)	4.6 (8.3)	0.015*	1.0 (-4.1, 6.0)	0.70
SFA, obese	44.0	(5.7)	3.6 (5.3)	0.02*		
PUFA, NW	41.2	(4.7)	1.5 (4.3)	0.15	1.4 (-1.9, 4.7)	0.40
PUFA, obese	42.7	(9.3)	0.1 (5.1)	0.96		
SFA (E%)						
SFA, NW	19.6	(5.3)	4.0 (5.5)	0.002**	-1.4 (-4.6, 1.8)	0.38
SFA, obese	20.4	(2.7)	5.4 (2.5)	<0.001**		
PUFA, NW	10.5	(2.2)	-3.8 (3.3)	<0.001**	1.9 (-0.2, 4.1)	0.08
PUFA, obese	10.2	(1.5)	-5.7 (2.6)	<0.001**		
Trans fat (E%)						
SFA, NW	0.0 (0.0-1.0)			0.020*§		0.61§‖
SFA, obese	0.5 (0.0-1.0)			0.01*§		
PUFA, NW	0.0 (0.0-0.0)			0.16§		0.59§‖
PUFA, obese	0.0 (0.0-0.3)			0.08§		
MUFA (E%)						
SFA, NW	13.8	(2.6)	-0.1 (3.2)	0.85	0.2 (-1.8, 2.3)	0.83
SFA, obese	13.1	(2.6)	-0.4 (2.6)	0.62		
PUFA, NW	15.1	(2.8)	1.7 (4.4)	0.10	-0.1 (-2.8, 2.6)	0.95
PUFA, obese	16.1	(4.7)	1.8 (2.7)	0.03*		
PUFA (E%)						
SFA, NW	5.7	(1.8)	-0.3 (1.9)	0.46	1.2 (-0.3, 2.7)	0.12
SFA, obese	4.7	(1.2)	-1.5 (2.6)	0.047*		
PUFA, NW	9.9	(2.0)	4.1 (2.8)	<0.001**	-0.3 (-2.1, 1.5)	0.77
PUFA, obese	10.1	(2.2)	4.4 (2.2)	<0.001**		
n-3 (g)						
SFA, NW	3.0	(1.2)	0.1 (1.4)	0.66	0.6 (-0.4, 1.6)	0.24
SFA, obese	2.6	(1.2)	-0.4 (1.5)	0.29		
PUFA, NW	4.0	(1.7)	1.1 (1.6)	0.008**	-0.1 (-1.2, 1.0)	0.87
PUFA, obese	4.0	(1.2)	1.2 (1.6)	0.01*		
n-6 (g)						
SFA, NW	8.6	(2.8)	-0.8 (3.6)	0.32	3.6	0.033*

SFA, obese	7.8	(2.9)	-4.4 (6.2)	0.021*	(0.3, 6.9)	
PUFA, NW	15.5	(5.8)	6.0 (4.9)	<0.001**	1.3 (-1.8, 4.3)	0.40
PUFA, obese	15.8	(5.8)	4.8 (3.3)	<0.001**		
Cholesterol (mg)						
SFA, NW	359.9	(207.0)	52.1 (121.5)	0.052	-6.0 (-81.6, 69.6)	0.87
SFA, obese	362.1	(125.0)	58.1 (86.8)	0.03*		
PUFA, NW	218.4	(83.0)	-53.1 (90.8)	0.02*	41.6 (-27.9, 109.1)	0.22
PUFA, obese	256.6	(99.1)	-94.7 (100.9)	0.004**		

Abbreviations: CI, confidence interval; SFA, saturated fatty acids; NW, normal-weight; PUFA, polyunsaturated fatty acids; EI, energy intake, REE, resting energy expenditure; PAL, physical activity level; MUFA, monounsaturated fatty acids

P1†: Baseline v. end of study; Paired-Sample T Test.

§ Baseline v. end of study; Wilcoxon`s Signed Rank Test was used for not normally distributed variables. Presented with median and 25-75th percentile.

P2‡: Between group changes, SFA NW v. SFA obese and PUFA NW v. PUFA obese; Independent-Sample T test.

§‖: Between group changes; Mann-Whitney U Test was used for not normally distributed variables. Presented with median and 25-75th percentile.

[a]: EI/REE (Calculated with Mifflin's formula).

Table 4.8 Dietary values of the intake of carbohydrates, sugar, protein and fiber at the end of the study registered in a seven days food registration and their changes during the study. (Mean values and standard deviations; *= significant, p <0.05; p <0.05** = significant, p < 0.01)

	6 weeks		**Within group change**		**Between groups change NW SFA v. obese SFA and NW PUFA v. obese PUFA**	
	Mean	**SD**	**Mean change (SD)**	**P1†**	**Mean difference 95%CI**	**P2‡**
Carbohydrates (E%)						
SFA, NW	37.7	(9.0)	-4.2 (8.1)	0.02*	-1.8 (-6.6, 3.1)	0.46
SFA, obese	38.0	(5.1)	-2.4 (4.9)	0.09		
PUFA, NW	41.1	(5.4)	-1.8 (5.0)	0.14	-0.0 (-3.6, 3.5)	0.98
PUFA, obese	38.4	(8.5)	-1.7 (5.0)	0.22		
Sugar (E%)						
SFA, NW	4.6	(2.9)	-1.0 (1.8)	0.02*	0.5 (-1.3, 2.3)	0.58
SFA, obese	4.7	(3.3)	-1.5 (3.7)	0.15		
PUFA, NW	4.8	(2.3)	-3.4 (3.3)	<0.001**	-0.8 (-3.2, 1.5)	0.48
PUFA, obese	4.5	(2.9)	-2.6 (3.3)	0.01*		
Protein (E%)						
SFA, NW	17.2	(3.0)	-0.4 (2.6)	0.44	0.8 (-1.1, 2.6)	0.40
SFA, obese	18.1	(2.8)	-1.2 (2.8)	0.13		
PUFA, NW	17.9	(2.3)	0.5 (2.5)	0.38	-1.0 (-2.7, 0.7)	0.24
PUFA, obese	19.1	(4.2)	1.5 (2.2)	0.03*		
Fiber (gram)						
SFA, NW	24.3	(6.0)	0.6 (6.1)	0.63	1.2 (-3.4, 5.7)	0.61
SFA, obese	24.3	(6.9)	-0.5 (7.2)	0.79		
PUFA, NW	24.5	(6.8)	2.4 (6.8)	0.13	-0.0 (-5.2, 5.2)	1.00
PUFA, obese	26.6	(8.3)	2.4 (8.0)	0.27		
Alcohol (gram)						
SFA, NW	11.9	(12.8)	0.2 (5.8)	0.86	1.4 (-3.9, 6.6)	0.60
SFA, obese	8.5	(11.8)	-1.1 (9.9)	0.676		
PUFA, NW	8.9	(10.7)	-2.0 (7.8)	0.264	-1.2 (-6.2, 3.8)	0.63
PUFA, obese	9.5	(12.8)	-0.8 (5.6)	0.549		

Abbreviations: CI, confidence interval; SFA, saturated fatty acids; NW, normal-weight; PUFA, polyunsaturated fatty acids

P1†: Baseline v. end of study; Paired-Sample T Test.

P2‡: Between group changes, SFA NW v. SFA obese and PUFA NW v. PUFA obese; Independent-Sample T test.

4.4.3 Between group changes and within group changes in body weight, waist and hip circumference

The change in waist circumference was significantly different between the subjects with normal-weight and the subjects with obesity in the SFA diet group from baseline to six weeks (Table 4.9). The normal-weight subjects had a significantly higher increase compared to the subjects with obesity in the SFA diet group. The normal-weight in the SFA diet group had a significant within group change with an increase in the waist circumference (cm). The participants in the PUFA diet group had a significant reduction in body weight (kg) from baseline to the end of the study. There was no significant difference in the weight reduction between the normal-weight and the subjects with obesity in the PUFA diet group.

Table 4.9 Anthropometric values at the end of the study and their changes through the study. (Mean values and standard deviations; medians and 25-75th percentiles; *= significant, p <0.05; **= significant, p < 0.01)

	6 weeks		**Within group change**		**Between groups change NW SFA v. obese SFA and NW PUFA v. obese PUFA**	
	Mean	**SD**	**Mean change (SD)**	**P1†**	**Mean difference 95% CI**	**P2‡**
Body weight (kg)						
SFA, NW	67.2	(7.2)	-0.1 (0.8)	0.56	0.4 (-0.4, 1.2)	0.34
SFA, obese	101.5	(13.4)	-0.5 (1.6)	0.28		
PUFA, NW	68.3	(9.1)	-1.1 (1.2)	0.001**	0.0 (-0.9, 0.9)	1.00
PUFA, obese	92.8	(13.8)	-1.1 (1.4)	0.01*		
WC, cm						
SFA, NW	86.7	(7.6)	1.2 (2.4)	0.02*	1.7 (0.0, 3.3)	0.045*
SFA, obese	111.9	(5.7)	-0.4 (2.4)	0.51		
PUFA, NW	84.1	(7.3)	-0.8 (2.6)	0.21	-0.8 (-2.5, 1.0)	0.37
PUFA, obese	105.9	(10.5)	0.0 (2.3)	0.96		
HC, cm						
SFA, NW	93.6	(5.4)	0.1 (2.5)	0.90	1.1 (-0.6, 2.8)	0.18
SFA, obese	116.1	(8.3)	-1.0 (2.2)	0.11		
PUFA, NW	93.4	(5.7)	-0.9 (2.3)	0.10	-1.0 (-2.5, 0.5)	0.17
PUFA, obese	112.0	(7.7)	0.1 (1.7)	0.76		

Abbreviations: CI, confidence interval; SFA, saturated fatty acids; NW, normal-weight; PUFA, polyunsaturated fatty acids; WC, waist circumference; HC, hip circumference

P1†: Baseline v. end of study: Paired-Sample T Test.

P2‡: Between group changes, SFA NW v. SFA obese and PUFA NW v. PUFA obese: Independent-Sample T Test.

4.5 Post hoc analysis

4.5.1 Within group and between group changes in non HDL-C

For non HDL-C there was a significant increase in the normal-weight SFA diet group (Table 4.10), and there was a between group difference between the normal-weight and the subjects with obesity with a greater increase for the normal-weight. Both the normal-weight and the subjects with obesity in the PUFA diet group had a significant reduction in non HDL-C, and there were no between group differences.

Table 4.10 Non HDL-C at six weeks and their changes through the study. (Mean values and standard deviations; *= significant, p <0.05; ; **= significant, p < 0.01)

	6 weeks		**Within group change**		**Between groups differences NW SFA v. obese SFA and NW PUFA v. obese PUFA**	
	Mean	**SD**	**Mean change (SD)**	**P1†**	**Mean difference (95 % CI)**	**P2‡**
Non HDL-C (mmol/L)						
SFA, NW	5.1	(1.0)	0.4 (0.5)	0.001**	0.4 (0.0, 0.7)	0.04*
SFA, obese	5.1	(1.2)	0.1 (0.5)	0.59		
PUFA, NW	4.1	(0.8)	-0.7 (0.5)	<0.001**	-0.2 (-0.5, 0.1)	0.16
PUFA, obese	4.4	(0.8)	-0.5 (0.3)	<0.001**		
PUFA, obese	0.4	(0.3)	-0.2 (0.3)	0.08		

Abbreviations: NW, normal-weight; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; CI, confidence interval.

P1†: Baseline v. end of study: Paired-Sample T Test.

P2‡: Between group changes, SFA NW v. SFA obese and PUFA NW v. PUFA obese: Independent-Sample T Test.

4.6 Compliance

There were no between group differences in either of the groups in any of the compliance measurements. The subjects with obesity in the PUFA diet group had a significantly higher intake of the minimum portions of margarine at the end of the study compared with visit 3 (Table 4.11). Both the normal-weight and the subjects with obesity in the PUFA diet group had a significant higher score in the dietary questionnaire at visit 5 compared to visit 3.

Table 4.11 Compliance measured as percentage intake of the minimum portions of butter or margarine and with a questionnaire at visit3, 4 and the end of the study.
(Median and 25-75th percentiles, *= significant, p <0.05)

	Visit 3 2 weeks		**Visit 4 4 weeks**		**Visit 5 6 weeks**		**Within group change**	**Between groups change NW SFA v. obese SFA and NW PUFA v. obese PUFA**
	Median	27-75th percentile	Median	27-75th percentile	Median	27-75th percentile	**P1†**	**P2‡**
Minimum portions (%)								
SFA, NW, n=20	100.0	(100.0-100.00)[a]	100.0	(100.0-100.00)[a]	100.0	(100.0-100.00)[a]	0.66	0.74
SFA, obese, n=14	100.0	(100.0-100.00)	100.0	(100.0-100.00)	100.0	(100.0-100.00)	0.317	
PUFA, NW, n=20	100.0	(94.6-100.0)	100.0	(87.8-100.0)	100.0	(100.0-100.0)	0.05*	0.55
PUFA, obese, n=14	100.0	(98.6-100.0)	100.0	(94.6-100.0)	100.0	(100.0-100.0)	0.29	
Dietary questionnaire §								
SFA, NW, n=20	8.0	(7.0-9.0)	9.0	(8.0-9.0)	9.0[c]	(7.2-9.0)	0.17	0.82
SFA, obese, n=14	8.0	(7.0-9.0)	8.0	(7.8-9.0)	8.0[d]	(7.9-9.0)	0.73	
PUFA, NW, n=20	8.0	(7.0-8.8)	8.0	(7.6-9.0)	9.0[b]	(8.0-9.0)	0.003*	0.89
PUFA, obese, n=14	8.0	(7.0-9.0)	8.5	(7.0-9.0)	9.0[b]	(8.0-9.0)	0.04*	

Abbreviations: NW, normal-weight; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; CI, confidence interval.

P1† Within group changes from week 3 to week 6; Wilcoxon`s Signed Rank Test.

P2‡ Between group changes from week 3 to week 6, SFA NW v. SFA obese and PUFA NW v. PUFA obese; Mann-Whitney U Test.

§The dietary questionnaire was not handed out to 11 of the participants at the last visit.

[a]: 3 missing (3 drop outs after visit 2, no minimum portions registered)

[b]: 3 missing

[c]: 7 missing

[d]: 4 missing

4.7 Physical activity level

There were no significant differences between the normal-weight and the subjects with obesity in the two dietary intervention groups at visit 3, p = 1.00, visit 4, p = 0.16, or visit 5, p = 0.248, analyzed with Fisher`s Exact Test. When comparing the normal-weight with the subjects with obesity in the SFA diet group, there were no significant differences at visit 3, p = 1.00, visit 4, p = 0.15, or visit 5, p = 1.00, in the self-reported activity level. In the PUFA

diet group there were no significant differences at visit 3, p = 1.00, visit 4, p = 0.15, or visit 5, p = 0.37, between the normal-weight and the subjects with obesity.

4.8 Side effects and changes in smoking habits

It was reported 11side effects at visit 3, two at visit 4 and five at visit 5 in the two dietary groups during the study (Table 4.12). The participants related very few of the side effects to the dietary intervention.

One normal-weight subject in the SFA diet group reported changes in smoking status from 0-5 cigarettes per day at the screening visit to smoking "a bit more" at visit 5. There were no significant differences in changes in smoking status between the groups (data not shown).

Table 4.12 Side effects that the participants reported during the study and which they related to the dietary intervention.

Visit	Diet intervention group and BMI category	Relation to the intervention diet [a]	Side effect reported by the participants
3	SFA, NW	"Likely"	"Mild nausea"
3	SFA, NW	"Likely"	"Waked up by a pain in the right side of abdomen (gall bladder pain?)"
3	SFA, obese	"Most likely"	"Ache in the left kidney"
3	PUFA, NW	"Most likely"	"Nausea and a "heavier" feeling of satiety (uncomfortable to eat more fat than usual)" and "stomach pain".
3	PUFA, NW	"Most likely"	"Frequently toilet visits (extreme amounts twice a day)"
5	SFA, NW	"Likely"	"Neck pain"
5	SFA, NW	"Likely"	"More frequently toilet visits and more fluid feces"
5	SFA, obese	"Most likely"	"Forgetful"
5	SFA, obese	"Likely"	"Bloated and reduced frequency of emptying of the bowel".
5	PUFA, NW	"Likely"	"It takes longer time to go to the toilet

Abbreviations: NW, normal-weight; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids.

[a]: The participants were asked if the related the reported side effects with the changes in the diets with the three options "most likely", "likely" or "not likely".

5 Discussion

5.1 Method

5.1.1 Participant characteristics at baseline

The participants were randomized to either of the two diet groups. The statistical analysis showed that there were no significant differences between the normal-weight in the two diet groups or between the subjects with obesity in the two diet groups at baseline.

Both diet groups had the same number of visits scheduled, so neither of the groups were given more nutritional advice than the other. They were given the same amounts and types of written information. Written information is important because studies has shown that much of the verbal advice given is forgotten or misunderstood (71).

5.1.2 Blinding

When doing research, it is optimal with blinding of the researcher and participants. This is difficult to carry out in practice in studies were nutritional advice is given. The nutritionists that were in charge of both implementing the intervention and interpreting the results in this study were not blinded. They knew which dietary intervention group each participant was randomized to and this was necessary to carry out the nutrition guidance and handing out the minimum portions of either butter or margarine. The participations knew which group they were in because they needed to know which food choices they had to make to eat according to their diet group. Blinding could have been possible if food for the whole study period was handed out in concealed containers. This would be expensive and it could be a bigger burden for the participants because they had to eat the food that was handed out and they could not have made individual food choices according to their preferences. An advantage with the open intervention is that its shows how big dietary changes people can manage to attain in their everyday life.

To avoid changes in the behavior because of the changes or lack of changes in the lipid profile during the intervention period, the participants and the nutritionist did not see any blood results during the intervention period. The blood results were first reviewed at visit 5

when the last blood sample was taken and the study had ended. The dietary interventions were defined and materials for both diet groups were developed in advance of the study. The nutritionists were objective and followed the pre-defined guidelines for the study and dietary intervention. Nutritionist, doctors and nurses with experience in nutrition research supervised the two nutritionist responsible for implementing the dietary intervention. The technicians who analyzed the blood results had no information about the intervention allocation.

5.1.3 Measurements errors

There are some factors that can affect the accuracy of the blood sample measurements (61). Pre-analytic factors like biological (age and gender) and behavioral factors (exercise and diet), and analytic factors can affect the results of the blood samples (13). In this study it was defined that the participants needed to fast 10 hours before the blood samples were collected. There was no standardization of how long they should have fasted, meaning that some participants could have been fasting for example 10 hours and others for 16 hours. In the written information sent to the participants after the telephone interview it was stated that they should avoid alcohol 24 hours before the collection of blood samples. However, we cannot be sure if all the participants followed this instruction. This is examples of behavioral factors that can influence the results of the blood results. To reduce the effects of the analytic sources of errors, the blood samples were drawn and handled by two experienced study nurses and the blood samples were analyzed by the laboratory at Oslo University Hospital following protocol. LDL-C can be analyzed directly as done in this study or be calculated by Friedewald`s formula. The calculation of LDL-C from Friedewald`s formula is based on the measurement of plasma TG, TC and HDL-C and was primarily developed for research. Direct analyses of LDL-C have the benefit that fasting is not necessary before the blood sample is collected. It is recommended that LDL-C should be measured several times before clinical decision making because analytic and biological variability can cause measurement errors that affects the result of the test. To reduce biological and analytical variability, blood samples could have been collected two times at subsequent days at baseline and at the last visit (13). The mean of the two days could have been used to reduce the effect of the measurements errors of the tests on the results. This would have added cost to the study as well as an increased burden for the participants as they must have met at the hospital two more times and had two more blood samples collected. In addition, the results were analyzed at group level,

and the advice of two serial samples are recommended before decision making in the clinical setting for individuals (13).

5.1.4 Dietary data collection

A normal challenge when doing nutrition research is to make an accurate record of the nutrition intake. Every method for registration of dietary intake has different strengths and weaknesses (72, 73). A food registration has the strength that it is a prospective method, it is not dependent on the subject's ability to remember what they have eaten before, and it is less prone to recall bias than for example a food frequency questionnaire or a 24 hour recall. Because the subjects weighed what they had eaten, it is an accurate method. However, it can be a strain on the subjects to register what they eat several days in a row, and this can affect what people eat. Studies have shown that food registration is prone to measurements errors like wrong registration of the amount eaten, that people forget to record some of the food intake or that they change their diet during the registration period (74, 75). It can be difficult to make accurate registrations if you eat in a cafeteria or in a restaurant because you may have to make some assumptions about the food content and amounts eaten. Pleasing bias can also occur, that the participants eat healthier in the period trying to please the nutritionist or they report food consumption to follow what they perceive as socially desirable (75). To reduce pleasing bias, the intervention diets and nutrition advice were not discussed with the participants at the screening visit.

A seven days weighed food registration provides detailed information about the food intake, but is vulnerable for seasonal fluctuations in the food intake such as for Christmas, Easter and summer holidays. However, it was a suitable method for this study because with one registration at baseline and one at the end of the study it can reveal short time changes in the food intake in a detailed manner. This was desirable for this study with a food intervention where qualitative data on the nutrition intake was essential. Seven days of registration was chosen because it gives information about the food intake for an entire week, and possible variations in the food intake from weekdays and weekends are included. Seven days increases the burden of the participants compared to four days, but increases the information of food consumed once or twice a week (75). The importance of participants eating as close to their normal diet as possible at baseline registration was emphasized, and they were instructed to try not to be affected by the registration of their food intake.

Underreporting

To assess the degree of underreporting present in this study, a PAL value was calculated based on the reported energy intake and estimated resting energy expenditure. Several factors can affect the degree of underreporting when people register their nutritional intake. It has been shown that individuals with obesity have a tendency to underestimate and underreport what they eat (19). Low socioeconomic status and economy can also increase underreporting, but on the other hand can high knowledge of health topics can also lead to increased underreporting (72, 74). Efforts to maintain weight stability can also lead to underreporting (72, 74). There was no significant difference in education level or smoking status between any of the groups at baseline, see (Table 4.1). An EI/REE ratio was calculated to produce a PAL value as a way to investigate the degree of underreporting. There were no significant differences between the groups in the PAL value at baseline and no within group changes from baseline to the end of the study or between group differences at the end of the study.

When a registration of the physical activity level has been made, it can be compared with a calculated PAL value and be used for evaluating the degree of underreporting. No registration of the physical activity level was made in this study; only changes in the participant's physical activity level were registered. If the physical activity level was registered with a heart rate monitoring or a physical activity level questionnaire, an estimate of the physical activity level could be calculated for each participant. Alternatively, an average PAL value of 1.55 can be used. A PAL value of 1.55 represents a sedentary level of physical activity level (72). The normal-weight in the SFA diet group had the highest estimated PAL value at the end of the study of 1.4. The normal-weight and the subjects with obesity in the PUFA diet group and the subjects with obesity in the SFA diet group all had an estimated PAL value of 1.2 at the end of the study. This shows that there is underreporting in our sample. This is a problem because it underestimates the energy intake and the intake of macro nutrients, and it is often food groups of certain types of foods that are not registered, like food that are perceived unhealthy (75). There were no significant within group changes in the PAL value from baseline to the end of the study nor between group changes (Table 4.7), which is a strength because it means that the degree of underreporting remained consistent throughout the study period.

5.1.5 Compliance

Registrations of compliance were done in the same manner in both diet groups and for both BMI categories. Registration of the intake of minimum portions of butter or margarine gave a quantitative measurement of compliance to the dietary intervention. There were no significant between group differences in the intake of the minimum portions or in the questionnaires. The questionnaires were a self-reported measurement and can be influenced by pleasing bias like any other method for registration of the dietary intake (74, 75). The questionnaire could have be analyzed as nine separate variables instead of one total score to give a better understanding of the changes in the diet.

5.1.6 Statistics

71 participants were enrolled in the study. This was 13 less than estimated in the power calculation to be sufficient to detect a difference in the LDL-C of 0.4-0.5 mmol/L between the subjects with normal-weight in the two diet groups with more than nine E% difference in the SFA intake. The calculation included potential dropouts. Only 28 participants with obesity were enrolled in the study, this was nine participants less (if there were no dropouts) than estimated in the power calculation as necessary to get significant results. This may have affected the results because the strength in the study was weakened. There may have been too few participants with obesity to detect the true differences in the lipid profile after the dietary intervention, and precaution in interpretation of the results is needed.

For the baseline analyses preformed for HDL-C, hip and waist circumference, males and females were analyzed separately. The variables for the males were not normally distributed, but they were analyzed as normally distributed variables because of a small n. It was assumed that if there were more male participants, the variables would have been normally distributed.

The four normal-weight participants in the SFA diet group that dropped out from the study are included in the analysis according to the intention to treat and last value carried forward principle. The blood results from the randomization visit are being used for visit 5, so no blood result after consuming butter are registered for the four participants that dropped out during the study period. The observed effect for the subjects with normal-weight in the SFA diet group might have been greater if the four drop outs had the same development in the lipid profile as the other subjects with normal-weight in the SFA diet group.

The power calculation was performed on changes in the LDL-. The statistical power might have been too weak to detect the changes in other variables analyzed in this thesis.

The regression analysis is not adjusted for multiple analyses. In this type of adjustments, the significant level is set lower than 0.05 to correct for the multiple analyses preformed. Preforming many analyses increases the chance that you reject the H0 when it is true, inducing type I error (76). This means that some of the significant results in this study can have occurred only by chance.

5.1.7 Weaknesses

There was no control group in this study because both the SFA and PUFA diet group were instructed to make large changes in their diets during the study period. The changes in the diet were both regarding to the fat quality and the intake of wholegrain products, fruit, berries and vegetables, the intake of sugar rich beverages, cakes etc. according to the Norwegian dietary advices (24). Butter is often used as a negative control in dietary intervention studies (77), and the dietary intervention in this study was with butter and margarine. However, advices to change several other food sources to SFA than only butter were given.

In the run in period, the participants ate their habitual diets. If the participants had a run in period were they ate both butter and margarine in equal amounts it would give a more similar baseline diet and maybe an easier transition to the intervention diets. However, there were no significant differences in the fat intake at baseline between the normal-weight in the SFA diet group and the normal-weight in the PUFA group or between the subjects with obesity in the two diet groups, and the dropout rate was low (5.6 %). This indicates that the transmission to the intervention diet was feasible.

5.1.8 Strengths

This was a randomized intervention study, with a low dropout rate. The participants met for the scheduled visits and had good compliance to the intervention diets. They met the same nutritionist each time, and it was the same nutritionists who performed the body measurements at each visit. Butter and margarine was handed out to the participants free of charge. The planned difference in SFA intake between the SFA diet group and PUFA diet

group was achieved. The participants reported few side effects and adverse events, and the participants linked few of the side effects reported to the intervention diets.

5.2 Results

5.2.1 Primary outcomes

We found a significant between group difference in TC between the normal-weight and participants with obesity in the SFA diet group. The normal-weight had a greater mean change from baseline to six weeks. In the literature search conducted for this master thesis, no intervention studies that have analyzed if there is a difference in the lipid profile response in normal-weight and participants with obesity were identified. Many of the studies identified in the literature search had participants with a mean BMI in the overweight category (BMI from 25.0-29.9 kg/m^2) (26, 35, 37, 41, 78-89).

A study by Raziani et al from 2016, with participants with ≥ 2 MetS risk factors and BMI between 28.6-29.3 kg/m^2, analyzed the effect of increasing the SFA intake from regular-fat cheese on LDL-C. The participants were randomized to one of three intervention groups with regular-fat cheese, reduced-fat cheese or a carbohydrate control with no cheese for 12 weeks. There were no significant between group differences in LDL-C after 12 weeks between the participants who ate regular-fat cheese and reduced-fat cheese or the carbohydrate control (37). This is similar to our findings, were an increased intake of SFA had no LDL-C increasing effects after six weeks for the subjects with obesity. The regular-fat cheese group had an intake of SFA of 14.2 E% and the reduced-fat cheese group had a significantly lower intake of SFA of 11.4 E% (37). The difference was only 2.8 E%, and this might be too small to cause a between group change in the LDL-C. The SFA intake was 5.2 E% higher in the group that ate regular-fat cheese compared to the carbohydrate control. However, the regular-fat cheese group also increased their intake of MUFA compared to the carbohydrate control group. The authors suggest that the higher intake of MUFA might be a part of the explanation why they did not see an effect of increasing the intake of SFA (37). A possible explanation could be that subjects with overweight and features of MetS do not respond to an increased intake of SFA, similar to what we also found for subjects with obesity in our study.

Most studies identified in the literature search compare the difference in LDL-C after substituting SFA with PUFA. The study by Denke et al investigated individual cholesterol variation and showed that margarine intake, compared to butter intake, lowered LDL-C. The study was a two period crossover trial lasting for 5 weeks. Even though heavier individuals had higher LDL-C at baseline, they found that they had less response in the LDL-C after the dietary change. They raised the hypothesis that the larger endogenous pool of FA in adipose tissue of subjects with obesity can have an effect on the responsiveness to dietary changes (59). If this is true, this can be a part of the reason why the normal-weight had an increase in the LDL-C compared to the participants with obesity in the SFA diet group. The linear regression analysis preformed showed significant effects for the variable "diet group" and a trend for an effect of the interaction between BMI and diet group for the changes in TC, LDL-C and Apo B from baseline to the end of the study. This shows that diet group had an effect on the changes in TC, LDL-C and Apo B, and that it is a trend that indicates that there can be an effect of the interaction between diet group and BMI for the effect in TC, LDL-C and Apo B.

We found an augmentation in TC, LDL-C, HDL-C and Apo B from baseline to the end of the study after an increased intake of SFA for the subjects with normal-weight in the SFA diet group. Based on previous studies and the nutritional guidelines recommending substituting SFA for PUFA these results were as expected (24, 77, 90-92). For the participants with obesity in the SFA diet group there was a blunted effect of the dietary changes; they did not have any significant within group changes in the lipid profile. This is in accordance with some of the findings in the randomized study with a crossover design and two 3-week dietary interventions by Kralova Lesna et al in 2013 (93). They showed significant changes in TC and LDL-C but not in TG or HDL-C in the participants that increased their intake of SFA. A reason for the difference in the findings can be that they handed out all the food to the participants and they had an intake of 29 E% from SFA and 3 E% from PUFA, which was a 8.6 E% higher intake from SFA and 1.7 E% lower from PUFA than the participants in our study attained. All the participants were women, and they had a lower BMI 31.6 kg/m^2 (93) compared to the BMI of 34.8 kg/m^2 for the participants with obesity in the SFA diet group in our study. Gender can influence the changes in the lipid profile after changing the dietary intake of SFA and PUFA (57). The failure to include enough participants with obesity in the

"Cholesterol Study" may also have affected the results for the participants with obesity in the SFA diet group.

There were no between group differences between the subjects with normal-weight and the subjects with obesity in the PUFA diet group. Based on previous studies and the nutritional guidelines recommending substituting SFA for PUFA, it was expected that the normal-weight would have a reduction in the lipid profile after six weeks eating a diet with reduced SFA intake and increase PUFA intake (24, 57, 91, 92, 94, 95). Both the normal-weight and participants with obesity had significant within group reductions in TC, LDL-C and Apo B of 12.1 %, 13.3 and 7.7 % (normal-weight) and 7.9%, 7.0 % and 7.7% (obese). The normal-weight in the PUFA diet group had a significant reduction in TG from baseline to six weeks of 21.4 %. The changes for the participants with obesity in the PUFA diet group are in line with the within group changes for the participants increasing their PUFA intake in the study by Kralova Lesna et al (93) described in the previous section, except for HDL-C. The participants reduced their TC, LDL-C and HDL-C after three weeks of increased PUFA intake, while the participants with obesity in our study reduced TC and LDL-C, but had no significant changes in their HDL-C. Reasons for the differences in HDL-C response might be that we were not able to include enough participants with obesity in our study, and may not have had sufficient power to detect changes in HDL-C. The intake of fatty acids were different in the two studies, with a 1.7 % higher intake of SFA and 14.9 % lower intake of PUFA in our study (93).

In the LIPGENE Dietary Intervention Study, they found no changes in TC or LDL-C after 12 weeks with a reduction in the SFA intake of participants with obesity and MetS (60). Reasons of the different result can be that they reduced SFA intake with 8 E%, but had no changes in the PUFA intake in the three intervention diets compared to a SFA rich diet with 16 E% from SFA, 12 E% from MUFA and 6 E% from PUFA. The diet interventions in the LIPGENE study was a combination of a food exchange model and some study food that was handed out, with mainly a change in the intake of MUFA. MUFA may have a smaller effect on the LDL-C when substituting SFA compared to when SFA are replaced by PUFA (4).

When comparing the SFA diet group with the PUFA diet group in our study, there was a significant between group difference for both the subjects with normal-weight and the

subjects with obesity. The PUFA diet groups had a reduction in the TC, LDL-C and Apo B compared to the subjects in the SFA diet group.

Within group changes in LDL-C

The difference attained in the intake of SFA between the normal-weight in the SFA diet group and the normal-weight in the PUFA diet group was 9.1 E% at the end of the study. A difference of nine E% in the intake from SFA was used in the power calculation to achieve an expected difference of 0.4-0.5 mmol/L in the LDL-C. The power calculation were based on a meta-analysis were they estimated that when 10 E% from SFA were replaced with PUFA, the LDL-C concentration was reduced with 0.47 mmol/L (57). The difference in LDL-C at the end of the study for the normal-weight in the SFA diet group and the normal-weight in the PUFA diet group was 0.9 mmol/L (95 % CI 0.5-1.4, $p < 0.001$), which is almost double the reduction that was calculated in the meta-analysis. In the Meta-analysis, 27 studies were included and original articles published between 1970 and 1991 were selected. For 24 of the studies LDL-C could be calculated. Some of the studies had crossover design and some had a parallel design. Reasons for this difference in effect on the LDL-C can be that Friedewald`s equation was used for the calculation of LDL in seven of the studies. The calculation was based on the reported mean concentrations of TC, HDL-C and TG and includes the total accumulated measurement errors of all three variables (13), while in the "Cholesterol Study" LDL-C was analyzed directly. In 16 of the studies, the participants were only men, while in our study it was most women who participated. Gender may influence the magnitude in the lipid profile response (57).The age range was almost the same in the meta analysis as in the "Cholesterol Study", from just below 20 years to older than 70 years. Neither the weight nor the BMI of the participants included in the meta-analysis were given, and there are indications that body weight can influence the effect of cholesterol-lowering diets (25). There was a large difference in the number of days the intervention periods, 42 days in the "Cholesterol Study" while it varied from 14-91 days in the studies included in the meta-analysis (57). 14 days may be too short to attain a difference in the LDL-C because it is little time to achieve changes dietary habits and adhere to the dietary intervention. 91 days on the other hand may be too long and lead to fatigue and decreased compliance.

For the participants with obesity, the attained difference in the intake of SFA between the SFA diet group and PUFA diet group was 10.2 E% at the end of the study, also reaching the

goal of nine E% difference in the SFA intake planned. There was a not significant difference in the LDL-C at the end of the study of 0.6 mmol/L between the participants with obesity in the SFA diet group and the participants with obesity in the PUFA diet group (95 % CI -0.1, 1.3, p = 0.090). A sample size smaller than estimated in the power calculation reduces the strength of this analysis. The power calculation was based on the SYSDIET study where they found no significant difference in the LDL-C after participants with an average BMI of 31.6 kg/m^2 had eaten a "Healthy" diet or a "Control" diet for 18-24 weeks (27). In the SYSDIET study, the primary endpoint was insulin sensitivity and glucose tolerance, and the use of lipid lowering medications was allowed. A sub group analysis without statin users gave similar results as with statin users included in the analysis. Baseline LDL-C in the SYSDIET study was 3.2 mmol/L, while it was higher in our study (4.4 mmol/L, obese SFA diet group and 4.3 mmol/L, obese PUFA diet group). Because people with higher cholesterol levels have better potential for reduction (96), the participants in the SYSDIET study may have had a smaller potential for reduction. In the SYSDIET study, LDL- C was calculated using Friedewald`s equation and was based on the reported mean concentrations of TC, HDL-C and TG and includes the total accumulated measurement errors of all three (13). The dietary changes attained in the SYSDIET study was a difference of 4.3 E% in the intake of SFA at the end of the study and 2.1 E% from PUFA between the "Healthy" diet group and the "Control" group, a smaller dietary difference than in the "Cholesterol Study". 200 participants were randomized in the SYSDIET study and there was a dropout rate of 27 %, much higher compared to 5.6 % in the "Cholesterol Study". Age and gender of the participants in the two studies were similar, and the advice given to the PUFA diet group were similar to the "Healthy" diet group in the SYSDIET study. Despite some methodological differences, both studies resulted in non-significant differences in LDL-C between the two dietary intervention groups, but the "Cholesterol Study" did not have enough participants with obesity included which may have affected the results.

One normal-weight subject reported to eat 3 grams Vita Proactive soft margarine each day during the intervention period. This amount may have been too small to have an effect on the cholesterol, as 3 grams only constitutes 12 % of the amount that gave cholesterol-lowering effects in a study performed by Heggen et al (43). One normal-weight subject in the PUFA diet group had a intake of 20 grams β-glucans two times a week during the whole study period. This is more likely to have an effect on the cholesterol. However, the intake was constant both before the study started and throughout the study period.

Studies have shown that the SFA from different sources of dairy products may affect the LDL-C differently (35, 39). Especially butter and cheese may have different effects (36). Nuts are rich in MUFA, PUFA and other nutrients that can have a lipid lowering effect (40-42). However, it is beyond the scope of this master thesis to investigate this further.

Within group changes in TC and Apo B

The subjects with normal-weight and the subjects with obesity in the PUFA diet group had significant within group changes with reductions in TC and Apo B from baseline to the end of the study. The meta-analysis from Mensik et al showed that changes in TC mirrored the changes of LDL-C after replacing SFA with PUFA (57), which are in concordance with our findings. The main reason for this relation is that the changes in TC are mainly constituted by the changes in LDL-C. The attained reduction in Apo B shows that the reduction in TC and LDL-C is concurrent with a smaller concentration of the atherogenic lipoprotein particles.

The subjects with normal-weight in the SFA diet group had a significant within group change with an increase in TC and Apo B from baseline to six weeks. The increase in TC is in line with findings in previous studies with normal-weight participants that increased their intake of SFA and with the nutritional guidelines recommending reducing the intake of SFA (24, 77, 90-92). The changes in Apo B paralleled the changes in LDL-C for the normal-weight participants in the SFA diet group, also seen in the study by Tonstad et al (69).

Within group changes in HDL-C

The subjects with normal-weight in the SFA diet group had a significant within group change in HDL-C from baseline to the end of the study (Table 4.4). The normal-weight in the SFA diet group had a significant within group change with an increase in the waist circumference of 1.2 cm from baseline to the end of the study, and a significant increase (1.7 cm) compared to participants with obesity in the SFA diet group. The subjects with normal-weight in the SFA diet group had a significant increase in HDL-C, but this may had been even greater if they did not have the increase in the waist circumference. The normal-weight in the SFA diet group had a significant reduction in the carbohydrate intake in E% during the study and a significant increase of the intake of fat in E%. Replacing carbohydrates with fat raises HDL-C (57), and this can be a part of the reason why this group had significant within group increase in the HDL-C.

The participants in the PUFA diet group did not have any significant changes in the HDL-C. If the intake of SFA is reduced and the intake of PUFA concurrently is increased, this may lead to only small changes in the HDL-C (57).

Within group changes in TG

The subjects with normal-weight in the PUFA group had a 21.4 % reduction in TG from baseline to the end of the study. This may be explained by a significantly higher intake of n-3 FA at six weeks compared to the beginning of the study, because long chain fatty acids (eicosapentaenoic acid and docosahexaenoic acid) have showed to lower TG (12, 16, 32, 97). The normal-weight in the PUFA diet group started higher in TG; 1.4 mmol/L compared to the normal-weight in the SFA diet group (1.1 mmol/L), although this difference was not significant it may have given a greater potential for reduction. They had a weight reduction of 1.1 kg, the same as the participants with obesity in the PUFA diet group. In percentage, the normal-weight had a weight reduction of 1.6 % and the participants with obesity reduced their weight with1.2 %. However, this weight reduction might be too small to cause the reduction in TG, as a weight loss of 5-10 % may be needed to reduce TG with 25 % (16). The intake of carbohydrates, especially sugar, and alcohol has effects on the concentration of TG in the blood (16). A reduction in the sugar intake from baseline to six weeks can have influenced the changes in the TG values. There were no significant changes in the alcohol intake. All these factors can have contributed to the observed reduction in TG for the normal-weight participants in the PUFA diet group.

5.2.2 Secondary outcomes

Dietary intake

There were no significant differences at baseline, except for a significantly higher sugar intake (E%) for the normal-weight in the PUFA diet group compared to the normal-weight in the SFA diet group. The participants started with a baseline intake of SFA between 14.3-15.9 E% which is 1.3-2.9 E% higher than in the NORKOST 3 investigations where the average intake was 13 E% (48). The dietary intake at baseline for the participants in the "Cholesterol Study" was close to the intake of the participants in the NORKOST 3 investigation for PUFA (E%), protein (E%), sugar (E%) and fiber (grams). The intake of SFA (E%), fat (E%), MUFA

(E%) and alcohol (grams) were higher for the participants in the "Cholesterol Study" compared to the NORKOST 3 data. The intake of PUFA (E%) and carbohydrates (E%) were lower compared to the NORKOST 3 data. For the normal-weight subjects, the energy intake was lower and for the participants with obesity it was similar to the NORKOST 3 data (48). In both the NORKOST 3 data and for the participants in the "Cholesterol Study" the intake of SFA (E%) was higher than the recommendations and the intake of carbohydrates was lower than the recommendations (24). The intake of fiber was just below 25 grams/day for the participants in the "Cholesterol Study". This means that the dietary intake at baseline in the "Cholesterol Study" is quite similar to the intake in NORKOST 3, and follows the Norwegian dietary recommendations except for the intake of SFA, carbohydrates and fiber (24, 48).

Based on the seven days food registrations, the compliance to the diets was satisfactory. After the dietary intervention period, the PUFA diet group had an average intake of 10.5 E% (normal-weight) and 10.2 E% (obese) from SFA. This is just above the Norwegian recommendations for SFA intake, which recommends limiting the intake of SFA to less than 10 E% (24). The subjects reduced their intake of SFA with 3.8 E% (normal-weight) and 5.7 E% (obese) from baseline to the end of the study. This was achieved with dietary guidance from a nutritionist every other week and a close follow up. That they did not achieve a greater reduction in SFA when participating in this study, were they were instructed to avoid sources of SFA and choose low fat food items, shows how difficult it can be to avoid SFA in the diet.

Changes in body weight

The participants in the study were given individual advice for weight stability, were weighed every other week and were closely followed up. The participants in the PUFA diet group lost 1.1kg during this six-week long study. They were advice to choose low fat product and to increase the calorie intake from food items rich in PUFA. Despite this focus on weight stability, both the normal-weight and participants with obesity the PUFA diet group lost weight during the study period, which can indicate that it may be easier to lose weight when eating a diet rich in PUFA than SFA.

The weight reduction of 1.1 kg during the study may have affected the response in the lipid profile. In percentage, the 1.1 kg weight reduction constitutes a weight reduction of 1.6 % for the normal-weight and 1.2 % for the participants with obesity in the PUFA diet group. It has been estimated that a weight loss over 5 % has an effect on the lipid profile (3, 12, 16). The

effect of weight reduction was statistically analyzed in the linear regression analysis, and was not significant (data not shown).

5.2.3 Post hoc analysis

Non HDL-cholesterol

Non HDL- C was calculated as an additional marker for the risk of CVD, and it is suggested to be a better marker for predicting CVD risk than LDL-C (14-16). There was a significant between group difference between the normal-weight and participants with obesity in the SFA diet group for non HDL-C at the end of the study (Table 4.10). For the normal-weight in the SFA diet group there was a significant increase in the non HDL-C. For both the normal-weight and the participants with obesity in the PUFA diet group there was a significant reduction in non HDL-C. The attained reduction in non HDL-C for all the participants in the PUFA diet group was similar to the reduction in non HDL-C found in the SYSDIET study. The observed change in non HDL-C in the SYSDIET study was estimated to give a 10 % reduction in the CVD risk in the Healthy diet group (27).

6 Implications

There is limited data available to explain the differences in lipid response between people with obesity and normal-weight that are observed in some studies after altering the intake of SFA. It is important to determine if there is a difference in the response, because if this is the case different nutritional recommendations for people with normal-weight and people with obesity should be developed. In this study, we investigated the effect of changes in the diet on multiple biomarkers. Studies on how diet affects CVD are important conduct, as biomarkers are only associated with CVD and are not perfect for predictions of CVD. However, it is a strength to analyze multiple biomarkers compared to one single biomarker alone.

7 Conclusions

Currently, there are gaps in research on whether people with normal-weight and people with obesity respond differently to lipid-modifying diets. The intention of the "Cholesterol Study" was to investigate the changes in lipid profile between weight stable, non-statin treated subjects with normal-weight (BMI < 25 kg/m^2) and subjects with obesity (BMI 30-45 kg/m^2) eating a diet with either SFA or PUFA.

For the subjects that increased their intake of SFA there was a difference in the response in TC between normal-weight and the subjects with obesity. For normal-weight subjects with elevated LDL-C increasing the intake of SFA to 19.6 E% lead to a significant increase in TC, LDL-C, HDL-C and Apo B while increasing the intake of PUFA to 9.9 E% gave beneficial changes in TC, LDL-C, Apo B and TG. For the subjects with obesity and elevated LDL-C, increasing the intake of SFA to 20.4 E% did not significant change the lipid profile, while increasing the intake of PUFA to 10.1 E% lead to a reduction in TC, LDL-C and Apo B. This means that for participants with obesity, eating PUFA were beneficial for the lipid profile while SFA were neutral. The reduction in the lipid profile is associated with a risk reduction for the development of CVD. A failure to include enough participants with obesity reduced the strength of these conclusions. More clinical research on humans is needed, especially because of the expected future rise in obesity.

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9 Attachments

Attachment 1 "Telephone interview form"

TELEFONINTERVJU kolesterol-studien

Navn: _____

Fødselsdato, helst personnumer:_____

Alder (21 – 70 år) _____

Adresse(Oslo og omegn) :_____

E-post:_____

Telefon nr:_____Mob.nr:_____

Høyde:_____Vekt: _____ BMI <25 kg/m^2 eller BMI 30-45 kg/m^2	**JA**	NEI
Stabil vekt (mindre enn 3 kg endring i vekt) i løpet av siste 3 måneder	**JA**	NEI
Har du høyt kolesterol, LDL > 3,0	**JA**	NEI
Har du diabetes (type 1 eller 2)	JA	**NEI**
Har du hatt hjerte- eller karsykdom (hjerteinfarkt, utblokking, slag, TIA, eller angina)	JA	**NEI**
Bruker du kolesterolmedisin:	JA	**NEI**

Lipitor (atorvastatin), Pravastatin, Crestor (rosuvastatin), Simvastatin, Ezetrol (ezetimib), PCSK9-hemmere

Psykisk sykdom

Pågående bruk av antidepressive medikamenter (må vurderes individuelt)	JA	**NEI**
Tidligere eller nåværende alvorlig psykiatrisk sykdom	JA	**NEI**

Annet

Alvorlig sykdom	JA	**NEI**
Gastrointestinal sykdom, allergi eller intoleranse for en rekke matvarer	JA	**NEI**
Gravid, ammende eller planlagt graviditet i løpet av de nærmeste 6 mnd	JA	**NEI**
Misbruk av alkohol eller medikamenter	JA	**NEI**

Studien innebærer at du er:

Villig til å møte opp fastende ved avdelingen 5 ganger i løpet av 8 mnd	**JA**	NEI
Villig til å registre kosthold 1 uke x 2, ta fastende blodprøve og BT 5 ganger	**JA**	NEI
Villig til å spise begge dietter (mettet fett og umettet fett)	**JA**	NEI

.

Medikamenter:_____

Kosttilskudd som senker kolesterolet, i tilfelle hva_____

Er det OK for deg å møte fastende til visittene?	**JA**	NEI
Planlegger du en lengre ferie i studieperioden?	JA	**NEI**

Attachment 2 "Presentation about cholesterol and food - PUFA", reviewed with the participants after the randomization.

Næringstabell

Mettet fett

- Det er mye mettet fett i:
  - fete meieriprodukter (fete oster, fløte, rømme, creme fraiche, lett-rømme, smør og H-melk)
  - hard margarin (Melange)
  - fett kjøtt og oppblandede kjøttprodukter
  - kaker, kjeks, sjokolade og mange typer snacks

Umettet fett

- Finnes i:
  - Myk/flytende margarin og matoljer
  - Fet fisk
  - Nøtter, mandler, frø, korn
  - Avocado og oliven
  - Majonesbaserte pålegg, pesto
  - Oljebaserte leverposteier og dressinger

Tips

- Jo mykere margarinen og smøret er ved kjøleskaptemperatur, desto mer umettet fett inneholder de.

Magre meieriprodukter

- Det er like mye av de viktige næringsstoffene i magre som i fete melkeprodukter, men mindre mettet fett.
- Velg skummet melk, lett melk (0,5%/0,7%) og yoghurt.
- Matlagingsprodukter (fløte og rømme), med under eller lik 10g fett/100 g matvare.
- Ost med under eller lik 20 g fett/100 g matvare.

Tips

- Velger du 1 skive mager ost i stedet for 1 skive helfet ost reduserer du inntaket av mettet fett. Tar du 2 skiver mager ost har du like mye mettetfett som i 1 skive helfet ost.
- For å få tilsvarende mengde fett totalt, bruk for eksempel litt ekstra Vita Hjertego` eller majones baserte produkter på brødskiva, eller litt ekstra olivenolje på salaten.

“

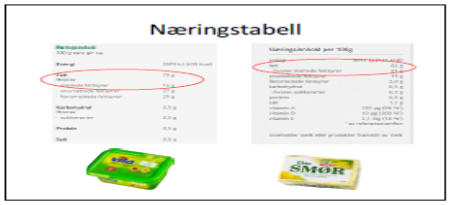
Dressinger

- Hvis du lager dressingen selv bør du bruke olje, eddik, majones (helst lettmajones), avokado, Drømmelett/lettrømme 10 % og Kesam som basis.
- Ellers bør velge industrifremstilte dressinger som har soyaolje først i listen over ingredienser, f.eks. thousand island - gjerne lett-thousand island.
- Bruk gjerne pesto og guacamole.

Snacks

- Mange typer snacks inneholder mye mettet fett og sukker samt lite næringsstoffer.
- Når det gjelder potetgull er typen stekt i peanøttolje (eks. Sørlandschips) bedre enn annet potetgull.
- Velg nøtter, popcorn, oliven og saltstenger fremfor potetgull, og mørk sjokolade fremfor lys.
- Saftis og sorbet inneholder ikke fett.
- Yoghurtis og lettis har ca 3% fett.
- Sjokolade fylt med nøtter, marsipan, gele eller skum er bedre enn ren sjokolade, fordi det inneholder mindre mettet fett.

Attachment 3 "Presentation about cholesterol and food - SFA", reviewed with the participants after the randomization.



Mettet fett

- Det er mye mettet fett i:
  - fete meieriprodukter (fete oster, fløte, rømme, creme fraiche, lett-rømme, smør og H-melk)
  - hard margarin (Melange)
  - fett kjøtt
  - Unngå disse kildene til mettet fett
    - oppblandede kjøttprodukter
    - kaker, kjeks, sjokolade og mange typer snacks

Mettet fett

- Finnes hovedsakelig i matvarer fra dyreriket, men plantefett fra palmeolje, kakao og kokos (vegetabilsk fett), inneholder også mye mettet fett.

Kjøttprodukter

- Ikke skjær bort synlig fett.
- Eksempler:
  - Fjærkre med skinnet på
  - Entrecôte, kotelett, lam med fettrand og kjøttdeig
- Velg bort magre kjøttprodukter.

Attachment 4 "Kostliste -PUFA" Handed out after the randomization.

Kostliste umettet fett

- velg varene til venstre

(OBS! Denne listen er ikke utfyllende pga av stadige endringer i produkter, men et forslag til hva du kan velge)

Dine varer: magre produkter	Helfete produkter
Daglig minimumsporsjon: 2,5 pakke (25 g) Vita Hjertego'	
MATLAGINSPRODUKTER • Mager vanilje Kesam 0,9% • Kesam Mager 1% • Q Drømmelett 5% • Kesam: lime 6,5%, vanilje 7,4%, jordbær og rabarbra 6,4% • Kesam Orginal 8% • Lettrømme 10% • Vita Hjertego Mat 15% • Crème Fraiche 10% • Lett matfløte 10% • Kaffefløte 10%	MATLAGINSPRODUKTER • Lettrømme 18% • Lett Cremè Fraiche 18% • Cremè Fraiche 35% • Seterrømme 35% • Matfløte 20% • Kremfløte 38%
OST < 20% fett • Prim Original 8% • Smøre ost 10-17% • Mager tube ost 6-8% • Synnøve Lett Gulost 16% • Synnøve Ekstra Lett Gulost 10% • Lettere Norvegia 16 % • Jarlsberg Lettere 16 % • Lett brunost 16% • Mozarella 17% • Gammalost 1% • Pultost 1% • Mager Cottage Cheese 2% • Cottage Cheese 4,3% • Prim Lettere 4% • Philadelphia light 11%	OST > 20% fett • Fetaost 21-29% • Philadelphia Original 23,5% • Synnøve Norsk Gulost 26% • Norvegia Original 27% • Jarlsberg Original 27% • Tine Kremost Original 27% • Brunost 27-36% • Parmesan 27% • Brie 32% • Gräddost 38%
MELK • Skummetmelk • Lettmelk (0.5 /0.7 %)	MELK • Lettmelk 1,2 %, 1,0% • Helmelk
YOGHURT Alle yoghurt-typer, men anbefaler sukker	YOGHURT Alle yoghurt-typer, men anbefaler sukker

reduserte typer • Yoghurt naturell • Dobbel 0% • Tine Fyldig • Zero • Skyr	reduserte typer • Yoghurt naturell • Dobbel 0% • Tine Fyldig • Zero • Skyr
PÅLEGG • Vita Hjertego` ovnsbakt leverpostei • Gilde og` og mager leverpostei • Stabburet Kyllingpostei • Kjøttpålegg <6% fett • Makrell i tomat • Fiskekaker/burger – velg varianter med minst mettet fett • Kaviar, alle typer • Ansjos, sild • Lett majones • Reke-, Italiensk-, Egg-, Rødbete-majonesbaserte salater • Peanøttsmør, nøttesmør	PÅLEGG • Ovnsbakt leverpostei (de originale typene) • Kokt skinke • Kalkun krydderskinke skivet (Prior) • Ribberull/servelat/sylte • Makrell i tomat • Fiskekaker/burger • Kaviar, alle typer • Ansjos, sild • Ekte majones • Ekte Remulade
KJØTTPRODUKTER • Karbonadedeig • Svinefilet uten fett • Storfekjøtt med lite fett • Kylling/kalkun uten skinn • Viltkjøtt Begrens inntaket av bearbeidet kjøtt • Ferdiglagde kjøttkaker og hamburger • Pølser (helst magre varianter) • Spekeskinke	KJØTTPRODUKTER • Kjøttdeig • Svinekotelett • Entrecote • Kylling/Kalkun med skinn • Viltkjøtt Begrens inntaket av bearbeidet kjøtt • Ferdig lagde kjøttkaker og hamburger • Pølser og bacon • Spekeskinke
FISKEPRODUKTER Velg de med høyest fiskeinnhold • Rene fileter • Ferdige fiskeprodukter med minst 60% fisk	FISKEPRODUKTER Velg de med høyest fiskeinnhold • Rene fileter • Ferdige fiskeprodukter med minst 60% fisk

Attachment 5 "Kostliste -SFA" Handed out after the randomization.

Kostliste mettet fett

-velg varene til høyre

(OBS! Denne listen er ikke utfyllende pga av stadige endringer i produkter, men et forslag til hva du kan velge)

Magre produkter	Dine varer : Helfete produkter
	Daglig minimumsporsjon: 2 pakker (24 g) Tine Meierismør
OST < 20% fett • Smøre ost 10-17% • Mager tube ost 6-8% • Synnøve Lett Gulost 16% • Synnøve Ekstra Lett Gulost 10% • Lettere Norvegia 16 % • Jarlsberg Lettere 16 % • Lett brunost 16% • Mozarella 17% • Gammalost 1% • Pultost 1% • Mager Cottage Cheese 2% • Cottage Cheese 4,3% • Prim Lettere 4% • Prim Original 8% • Philadelpiha light 11%	OST > 20% fett • Fetaost 21-29% • Philadelpiha Original 23,5% • Synnøve Norsk Gulost 26% • Norvegia Original 27% • Jarlsberg Original 27% • Tine Kremost Original 27% • Brunost 27-36% • Parmesan 27% • Brie 32% • Gräddost 38%
MELK • Skummetmelk • Lettmelk (0.5 /0.7 %)	MELK • Lettmelk 1,2 %, 1,0% • Helmelk
YOGHURT Alle yoghurt-typer, men anbefaler sukker reduserte typer • Yoghurt naturell • Dobbel 0% • Tine Fyldig • Zero • Skyr	YOGHURT Alle yoghurt-typer, men anbefaler sukker reduserte typer • Yoghurt naturell • Dobbel 0% • Tine Fyldig • Zero • Skyr
PÅLEGG • Vita Hjertego` ovnsbakt leverpostei • Gilde og` og mager leverpostei • Stabburet Kyllingpostei • Kjøttpålegg <6% fett • Makrell i tomat	PÅLEGG • Ovnsbakt leverpostei (de originale typene) • Kokt skinke • Kalkun krydderskinke skivet (Prior) • Ribberull/servelat/sylte

• Fiskekaker/burger – velg varianter med minst mettet fett • Kaviar, alle typer • Ansjos, sild • Lett majones • Reke-, Italiensk-, Egg-, Rødbete-majonesbaserte salater • Peanøttsmør, nøttesmør	• Makrell i tomat • Fiskekaker/burger • Kaviar, alle typer • Ansjos, sild • Ekte majones • Ekte Remulade
KJØTTPRODUKTER • Karbonadedeig • Svinefilet uten fett • Storfekjøtt med lite fett • Kylling/kalkun uten skinn • Viltkjøtt Begrens inntaket av bearbeidet kjøtt • Ferdiglagde kjøttkaker og hamburger • Pølser (helst magre varianter) • Spekeskinke	KJØTTPRODUKTER • Kjøttdeig • Svinekotelett • Entrecote • Kylling/Kalkun med skinn • Viltkjøtt Begrens inntaket av bearbeidet kjøtt • Ferdig lagde kjøttkaker og hamburger • Pølser og bacon • Spekeskinke
FISKEPRODUKTER Velg de med høyest fiskeinnhold • Rene fileter • Ferdige fiskeprodukter med minst 60% fisk	FISKEPRODUKTER Velg de med høyest fiskeinnhold • Rene fileter • Ferdige fiskeprodukter med minst 60% fisk

Attachment 6 "Dietary questionnaire – PUFA"

Test deg selv!

Er ditt kosthold i tråd med anbefalingene?

Hvordan stemmer følgende utsagn med ditt kosthold de siste 2ukene?	Sant	Usant
Jeg spiser minst fem porsjoner grønnsaker, frukt og bær hver dag (en porsjon tilsvarer en god håndfull).		
Jeg spiser fullkorn/ grove kornprodukter og fremfor fine (brød, knekkebrød, pasta, ris, kornblanding, lefser etc).		
Jeg spiser magre meieriprodukter daglig (kesam, yoghurt m/ lite fett og sukker, mager melk etc.).		
Jeg spiser fisk til middag og som pålegg tilsvarende to til tre middagsporsjoner i uken.		
Jeg velger magert kjøtt og begrenser inntaket av bearbeidet kjøtt som pølser, kjøttdeig, familiedeig).		
Jeg velger oliven- og rapsolje, flytende margarin og myk margarin, fremfor hard margarin og smør.		
Jeg spiser minimum 2,5 porsjonspakker Vita Hjertego` margarin per dag.		
Jeg unngår mat og drikke med mye sukker til hverdags (brus og saft med sukker, nektar, iste, sportsdrikk, godteri, kaker, sjokolade, is osv.).		
Jeg velger vann som tørstedrikk.		

Hva må jeg jobbe videre med!

Attachment 7 "Dietary questionnaire – SFA"

Test deg selv!

Er ditt kosthold i tråd med anbefalingene?

Hvordan stemmer følgende utsagn med ditt kosthold de siste 2 ukene?	Sant	Usant
Jeg spiser minst fem porsjoner grønnsaker, frukt og bær hver dag (en porsjon tilsvarer en god håndfull).		
Jeg spiser fullkorn/ grove kornprodukter og fremfor fine (brød, knekkebrød, pasta, ris, kornblanding, lefser etc).		
Jeg spiser helfete meieriprodukter daglig (seterrømme, lettrømme 18 %, helfete oster, yoghurt m/ lite sukker, helmelk etc.).		
Jeg spiser fisk til middag og som pålegg tilsvarende to til tre middagsporsjoner i uken.		
Jeg begrenser inntaket av bearbeidet kjøtt (som pølser og ferdiglagde kjøttprodukter), men skjærer ikke bort fettet på kjøttet.		
Jeg velger smør til steking, baking og annen matlaging.		
Jeg spiser minimum 2 porsjonspakker Tine meierismør per dag.		
Jeg unngår mat og drikke med mye sukker til hverdags (brus og saft med sukker, nektar, iste, sportsdrikk, godteri, kaker, sjokolade, is osv.).		
Jeg velger vann som tørstedrikk.		

Hva må jeg jobbe videre med!

_____

_____

_____

_____

_____

Attachment 8 "Consent form"

Forespørsel om deltakelse i en klinisk studie

Endring i kolesterol ved å redusere mettet fett i kostholdet hos normalvektige og overvektige personer

Bakgrunn og hensikt
Dette er en forespørsel til deg om å delta i en forskningsstudie som undersøker om effekten av mettet fett i kosten er avhengig av kroppsvekt. Hensikten med studien er å undersøke effekten av redusert mengde mettet fett (i hovedsak fett fra fete kjøttprodukter og fete meieriprodukter) som behandling ved høyt kolesterol hos henholdsvis normalvektige og overvektige personer. Vi vil finne ut om normalvektige og overvektige personer oppnår den samme kolesterolreduksjon ved å redusere mettet fett i kostholdet og erstatte det med umettet fett. Vi vil undersøke effekten av dietten ved å måle ditt kolesterolnivå og andre parametere i blodet som viser risiko for hjerte- og karsykdom. Du blir spurt om å delta i studien fordi du har forhøyet kolesterol (LDL kolseterol lik eller over 3,0 mmol/l) og er enten normalvektig (kroppsmasseindeks under 25) eller overvektig (kroppsmasseindeks 30-45). LDL kolesterol er den delen av totalkolesterolet som kan avleire seg i blodåreveggen slik at passasjen blir trangere, og etterhvert kan dette utvikle seg til hjerte- og karsykdom.

Studien vil kunne bidra til presisering av kostråd for personer med forhøyet LDL kolesterol. Studien finansieres av Nasjonalforeningen for folkehelsen og Oslo Universitetssykehus.

Hva innebærer studien?
84 forsøkspersoner i Oslo og omegn vil delta i studien ved Seksjon for preventiv kardiologi, Oslo Universitetssykehus. Dersom det etter første besøk viser seg at du er aktuell for deltakelse i studien, vil du bli tilfeldig valgt til **enten** diett 1 eller diett 2 (beskrevet nedenfor) som du skal følge i 6 uker. Begge diettgruppene skal følge et sunt middelhavskosthold, med unntak av at man skal spise ulike typer fett.

Dietten du skal følge vil bli tilpasset dine behov og matpreferanser i samtale med klinisk ernæringsfysiolog. Fysisk aktivitet skal være uforandret i perioden du deltar i studiene.

Diett 1: Middelhavsdiett der du spiser 5 grønnsaker og/eller frukt daglig, grovt brød og knekkebrød bakt på sammalt mel, fisk, fettredusert melk og/eller surmelk, fettredusert ost, yoghurt og ekstra lettrømme eller kesam. Du skal spise Vita margarin på brødskivene og bruke oljer i matlagingen samt spise ca 30 g nøtter daglig (fortrinnsvis usaltede). Du vil kunne spise rødt kjøtt og fjærfe uten skinn eller fett. Inntaket av sukker og oppblandede kjøttprodukter (pølser, hamburger, salami) reduseres kraftig.

Diett 2: Middelhavsdiett der du spiser 5 grønnsaker og/eller frukt daglig, grovt brød og knekkebrød bakt på sammalt mel, fisk, vanlig (ikke fettredusert) melk og/eller surmelk og vanlig (ikke fettredusert) ost, yoghurt og rømme. Du vil bli anbefalt bruk av smør i matlagingen og på brødskivene. Rødt kjøtt og fjærfe spises uten at du fjerner skinn eller fett. Inntaket av sukker og oppblandede kjøttprodukter (pølser, hamburger, salami) reduseres kraftig.

Studien vil innebære 5 besøk ved avdelingen i løpet av en periode på 8 uker. Konsultasjonene vil vare fra 1 til 2 timer hver gang. I tillegg skal du registrere kostholdet ditt i syv dager ved oppstart og avslutning av studien. En oversikt over hvilke undersøkelser, prøver og aktiviteter som skjer på hvert besøk, finner du på side 4. Hvis du bestemmer deg for ikke å delta, vil du

få den behandlingen du normalt ville fått ved avdelingen. Legen vil forklare deg om de ulike behandlingstilbudene og informere om mulige fordeler og ulemper med disse.

Studiedeltakerens ansvar
Du må komme til avtalte studiebesøk og følge dietten så godt du kan. På hvert besøk må du informere ernæringsfysiologen om eventuelle symptomer, sykdommer og ubehag du har hatt. Du må fortelle om eventuelle medisiner du har tatt, også kosttilskudd og vitaminer.

Du må registrere ditt inntak av mat og drikke i èn uke ved oppstart og èn uke ved avslutning. Du må møte fastende på 4 av totalt 5 besøk (dvs. ikke spise eller drikke på 10 timer, unntatt vann). Du kan ta dine eventuelle medisiner som vanlig selv om du møter fastende.

Mulige fordeler, ulemper og bivirkninger
For deltagere i studien vil alle prøver, undersøkelser og veiledning være gratis, og du vil få ekstra tett oppfølging av ernæringsfysiolog gjennom faste studiebesøk. Oppfølgingen hos ernæringsfysiologen vil kunne inspirere og motivere deg til å gjøre flere gunstige kostholdsendringer med positive helseeffekter. Reiseutgifter i forbindelse med studiebesøkene blir ikke dekket.

Kostholdsplanen i begge gruppene baserer seg på middelhavskostholdet med mye grønnsaker, frukt og kornvarer, men mindre rødt kjøtt, bearbeidet kjøtt og søtt. Middelhavskostholdet kan redusere forekomsten hjerte- og karsykdom selv om LDL kolesterol ikke endres. Gruppen som følger diett 1 vil sannsynligvis få en reduksjon i LDL kolesterolet, mens ved diett 2 venter man ingen endring i LDL kolesterolet. Disse sannsynlighetene er basert på gjennomsnitt i hele gruppen, og dine verdier kan vise oppgang, nedgang eller ingen endring i LDL kolesterol.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplyningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Listen som kan koble ditt navn til koden, vil kun bli oppbevart på sykehuset og bare personell med ansvar for studien har tilgang til denne. Alle registrerte opplysninger vil bli lagret i fem år. Det vil ikke være mulig å identifisere deg når resultatene fra studien publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke deg fra studien uten at det får konsekvenser for din videre behandling. Du må undertegne samtykkeerklæringen dersom du ønsker å delta, og du vil få med deg en kopi hjem.

Dersom du senere ønsker å trekke deg fra studien, har spørsmål til studien eller om dine rettigheter, ta kontakt med:

Overlege Serena Tonstad tlf. 22 11 79 39 eller klinisk ernæringsfysiolog Tine Sundfør tlf. 22 11 90 24.

Kapittel A - utdypende forklaring om hva studien innebærer

Kriterier for å delta

For å kunne delta i studien må du være mellom 21 til 70 år. I tillegg må du ha en kroppsmasseindeks (KMI) enten lik eller under 25 kg/m^2 eller mellom 30-45 kg/m^2. (Beregning av KMI: vekt i kg/ (høyde i m) ^{2})

Du kan ikke ha diabetes, tidligere hjerte- og karsykdom (hjerteinfarkt, angina, blokking, bypassoperasjon, hjerneslag, kortvarig hjerneslag "TIA" eller annen karsykdom. Du kan ikke ha spiseforstyrrelse eller være vegetarianer. Ditt forhøyede LDL kolesterol må ikke være et resultat av en annen sykdom eller ha en klar arvelig årsak. Du må ikke bruke medisiner som senker kolesterolet (statiner som Simvastatin, Atorvastatin/ Lipitor eller lignende). Ta kontakt dersom du er usikker. Tarmsykdom eller allergi mot matvarer slik at du ikke kan gjennomføre diettene i studien, vil også hindre deg fra å kunne delta. Du kan ikke ha aktiv alvorlig psykisk sykdom eller stoff- eller alkoholavhengighet.

Bakgrunnsinformasjon om studien

Kostholdsendringer for å redusere LDL kolesterol har vært undersøkt i mange studier, men man har ikke tidligere stadfestet om normalvektige personer og overvektige personer får den samme kolesterolreduksjon av å redusere det mettede fettet i kosten. I denne studien ønsker vi å sammenlikne effekten av å redusere animalsk fett (og øke plante- og fiskefettet) hos personer med normal vekt og personer med overvekt. Om overvektige personer får en reduksjon i LDL kolesterol ved å spise mindre animalsk fett sammenliknet med normalvektige personer, er ikke fullt ut kartlagt. Vi vil også undersøke om et stoff i blodet ("PCSK9") som vanligvis øker LDL kolesterolet, blir redusert ved reduksjon av mettet fett.

De ulike diettene

Kostholdet vil bli tilpasset dine matpreferanser og behov uansett hvilken av diettene du skal følge. Begge gruppene vil bli inspirert og oppfordret til å spise mer frukt og grønnsaker, fisk og grove kornprodukter og må kutte ut mest mulig av oppblandede kjøttprodukter som pølser, hamburgere og lunsjkaker og søtsaker som sjokolade, is, kaker, brus og sukkerholdig saft. Begge diettene vil være energibalanserte. Det vil si at du ikke skal gå opp eller ned i vekt i løpet av studieperioden. Du vil bli bedt om å veie og skrive ned alt det du spiser i 7 dager før du får vite hvilken diett du skal følge og etter at du har fulgt dietten i 5 uker.

Hvis du kommer i diettgruppe 1, gruppen som skal redusere inntaket av mettet fett, vil du få tips og råd om hvilke matvarer du kan erstatte fete kjøttprodukter og fete meieriprodukter med. Du vil bli oppfordret til å spise mer usaltede nøtter og bruke mer olje og Vita margarin. Du vil *ikke* bli tvunget til å spise noen matvarer som du ikke liker. Ernæringsfysiologen vil gi deg informasjon om hvilke meieriprodukter som har lite fett, og hvordan du kan få kjøtt- og kylling til på smake selv om du fjerner de fete delene.

Kommer du i diettgruppe 2, gruppen som ikke skal redusere inntaket av mettet fett, vil du bli oppfordret til å velge de fete meieriproduktene slik som ost, fløte, smør og rømme. Du vil også kunne spise skinnet på kyllingen og eventuelt fettranden på entrecôten.

Mulige ubehag, bivirkninger og risiko

Man regner ikke med at korttidsforandring i kosten over 6 uker vil ha noen langvarige effekter på helsen. Endring av kostsammensetning kan medføre ubehag i mage og tarm. Ubehaget er

som regel lett og forbigående. Du er fri til å trekke deg fra studien når du måtte ønske. Hvis du trekker deg fra studien, vil du få tilbud om ordinær behandling for forhøyet kolesterol ved Seksjon for Preventiv Kardiologi.

Ubehag i forbindelse med studieprosedyrer

Blodprøven krever nålestikk, og du kan oppleve følgende ubehag: Smerter, blåmerker, svimmelhet og noen få kan besvime.

Studiedeltagerens ansvar

Legene ved Seksjon for Preventiv Kardiologi vil avgjøre om du fyller kravene for å delta. Visse medisiner og medisinske tilstander kan utelukke din mulighet til å delta. Du må komme til avtalte visitter og undersøkelser og gjøre kostregistreringer og kostholdsendringer som avtalt. Dersom en annen lege vil gi deg nye medisiner mens du deltar i studien, må du informere om at du deltar i en forskningsstudie. Vennligst kontakt studiepersonalet før du starter på ny medisin hvis mulig.

Informer studieansvarlig umiddelbart dersom du får en skade eller har symptomer eller plager. Det er viktig at du rapporterer alle symptomer og bivirkninger umiddelbart gjennom hele studien, uansett om du tror det skyldes deltagelsen eller ikke.

Avbrutt studiedeltagelse

Legen eller studieansvarlig kan stoppe din deltagelse i studien hvis:

1. Du ikke følger opp studieprotokollen som avtalt.
2. Du får en alvorlig sykdom.
3. Studielegen mener at deltagelse i studien ikke er til ditt beste.
4. Du blir gravid, planlegger å bli gravid eller ammer under studieperioden.

Informasjon til kvinner

Graviditet og amming vil kunne påvirke de undersøkelsene vi gjør i studien, og derfor må kvinner i fruktbar alder bruke prevensjon godkjent av studielegen. Hvis du tror du er gravid, må studieansvarlig informeres så snart som mulig.

Oversikt over studiebesøkene

Visitt/besøk nr.	1 Uke minus 2	2 Uke 0 Randomisering	3 Uke 2	4 Uke 4	5 Uke 6
Informert samtykke	x				
Gjennomgang av kriteriene for å delta	x				
Legeundersøkelse	x				
Måling av vekt, livvidde, blodtrykk og puls	x	x	x	x	x
Gjennomgang av ditt vanlige kosthold	x				
Kostveiledning v/ klinisk ernæringsfysiolog		x	x	x	x
Kostholdsregistrering	x				x
Rutineblodprøver tas fastende (kolesterolverdier, diabetesrelaterte prøver)	x	x		x	x
Blodprøve til måling av "PCSK9"	x	x		x	x
Gjennomgang av symptomer eller ubehag	x	x	x	x	x
Gjennomgang av medisinbruk og kosttilskudd	x	x	x	x	x

Kapittel B – Ytterligere informasjon om personvern, biobank, økonomi og forsikring

Personvern
Det er en forutsetning for å delta, at du sier ja til insynsrett i gjeldende relevante journalopplysninger som er nødvendige å kunne kontrollere at studieopplysningene stemmer overens med tilsvarende opplysninger i din journal. All informasjon vil bli behandlet konfidensielt. Fastlegen din blir vanligvis informert om din deltagelse hvis du ikke har noe i mot det. Personlige opplysninger om deg som kan være sensitive (for eksempel sykehistorie og medisinbruk), vil bli samlet inn og behandlet, men kun til forskningsformål i forbindelse med studien. Du vil ikke bli referert til ved navn eller bli identifisert i noen publikasjon, så dataene kan ikke spores tilbake til deg. Oslo universitetssykehus er databehandlingsansvarlig for studien.

Forskningsbiobank
Blod- og urinprøvene som blir tatt, vil bli lagret i en forskningsbiobank. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet inngår i biobanken. Oslo Universitetssykehus ved prosjektleder Serena Tonstad er ansvarshavende for forskningsbiobanken. Biobanken planlegges å vare til 2020. Etter dette vil materialet bli destruert etter interne retningslinjer.

Innsynsrett og oppbevaring av materialet
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, vil det ikke samles inn flere opplysninger eller mer materiale. Opplysninger som allerede er registrert, vil ikke bli slettet dersom opplysningene allerede har inngått i analyse.

Finansiering
Denne studien er finansiert ved hjelp av midler fra Seksjon for preventiv kardiologi, Oslo Universitetssykehus og Nasjonalforeningen for Folkehelsen.

Forsikring
Vi forventer ikke at du skal få noen helseproblemer ved å delta i denne studien, men dersom din helse allikevel skulle forverres som et resultat av deltagelse, vil du kunne få erstatning. Du må ikke bevise at det var noen sin skyld. Dersom det viser seg at problemene oppstod som følge av studien, vil du få erstatning. Du er forsikret i henhold til Oslo universitetssykehus sine egne forsikringer.

Informasjon om resultatet av studien
Du har rett til å få informasjon om resultatet av studien. Legen i studien vil kunne fortelle deg dette når resultatene er klare.

Samtykke for deltagelse i studien

Jeg er villig til å delta i studien

(Signert og datert av deltager)

Deltagers navn med blokkbokstaver

Deltagers fødselsdato

Bekreftelse på at informasjon er gitt deltageren i studien

Jeg bekrefter å ha gitt skriftlig og muntlig informasjon om studien

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(Signert og datert av lege)

Attachment 9 "Dietary intervention information – PUFA" Handed out after the randomization.

Kolesterolstudien

Hjertevennlig kosthold.

Hovedformålet ned studien er å undersøke effekten av ulike typer fett på kolesterol hos personer med ulik vekt (KMI≤25 kg/m²og 30-45 kg/m²).

Du er med i gruppen som skal spise et hjertevennlig kosthold med umettet fett i form av minst 2 ½ porsjonspakke (25 gram) Vita margarin per dag, magre meieriprodukter og fett-reduserte kjøttprodukter. Kostholdet er basert på et typisk nordisk kosthold, med mye grove kornprodukter, fisk, fjærfe, grønnsaker, frukt og bær.

-Første mål er å komme i gang med å spise 2 ½ porsjonspakke (25 gram) Vita margarin per dag.

- Deretter fokuserer du på å velge magre meieriprodukter og fett- reduserte kjøttprodukter.

KILDER TIL UMETT FETT
- Spis dagens minimumsdose 25 g Vita margarin hver dag!
- Matlaging: Velg Vita margarin, olivenolje eller rapsolje til steking, dressinger og ovnsbaking.
- På brødskiva/knekkebrød bruk Vita margarin.
- Avokado er en god kilde til sunt fett.
- Spis gjerne usaltede nøtter som valnøtter, mandler og hasselnøtter som snacks.

Synlig fett skal skjæres vekk fra kjøttstykkene og skinnet skal fjernes fra kylling og liknende. Velg karbonadedeig fremfor kjøttdeig og unngå å spise bearbeidet kjøttprodukter. Velg fettredusert melk, ost, yoghurt og liknende- se kostlisten for mer informasjon.

Planlegging av matinnkjøpene og måltidene er viktig for å oppnå de ønskede endringene. Planlegg frokosten dagen i forveien og lag matpakke til lunsjen så kan du lettere følge kostrådene.

Varedeklarasjonen gir nyttig informasjon om hva en matvare inneholder. Ingrediensene er satt opp i fallende rekkefølge, den det er mest av står først i innholdslisten. Dette gjør det lettere for deg å sammenligne produkter. På baksiden av varen er det en næringsinnhold-tabell. Denne kan også brukes til å sammenlikne ulike produkter.

Næringsinnhold	Per 100g
Energi (kJ/kcal)	1869/488
Fett	29g
Hvorav mettede fettsyrer	19g
Karbohydrat	36g
Hvoravsukkerarter	31g
Protein	11g
Salt	0,7g

Næringsinnhold	Per 100g
Energi (kJ/kcal)	2560/620
Fett	50 g
Hvorav mettede fettsyrer	9 g
Enumettede fettsyrer	**23 g**
Flerumettede fettsyrer	**17 g**
Karbohydrat	14 g
Hvoravsukkerarter	9 g
Kostfiber	8 g
Protein	24 g
Salt	0,6 g

Hovedprinsippene i et hjertevennlig kosthold

Det er godt dokumentert at med mye grove kornprodukter, fisk, fjærfe, grønnsaker, frukt og bær minsker risikoen for hjerte og karsykdommer. I denne studien skal du derfor forsøke å spise i tråd med kostrådene. Vi vil hjelpe deg med å gjøre individuelle tilpasninger, slik at det blir lettere for deg å følge kostholdsplanen.

SPIS

- Grove kornprodukter
- Fiskefileter og fiskeprodukter med høyest mulig innhold av fisk
- Kylling, kalkun og andre fjærfe fileter eller produkter
- Grønnsaker, frukt og bær

BEGRENS

−Rødt kjøtt og bruk minimalt med bearbeidede kjøttprodukter som pølser, bacon og kjøttdeig
−Ferdigmat og halvfabrikata
−Raffinerte kornprodukter som loff og kneip, vanlig pasta, boller, polert ris og søte kornblandinger
−Godteri, snacks og kaker til maksimalt en til to ganger i uken.
−Brus og saft med sukker

Hva med snacks? Selv om man spiser sunt er det plass til å kose seg med noe godteri eller snacks en gang i blant. Man må bare passe på mengden og hyppigheten da godterier og snacks ofte inneholder en kombinasjon av mye kalorier, mettet fett, sukker og salt som er ugunstig for helsen i store mengder. Ha minst mulig godterier og snacks tilgjengelig, det kan være lurt å rydde i skuffer og skap. Noen ganger føler man et søtsug eller et behov for snacks når man egentlig er sulten og kroppen trenger et skikkelig måltid. Det er også vanlig å få lyst på noe søtt etter middag, og skjer dette med deg kan du titte i oppskriftsheftet vårt for å finne sunne, søte fristelser som bremser søtsuget, smaker deilig og øker inntaket av sunne frukter og bær.

Forberede deg mentalt og bestem deg. Vi mennesker er vanedyr. Det er viktig at du forbereder deg mentalt på en livsstilsendring. Det kan være vanskelig å endre kostholdet over natten, derfor er det viktig at du setter deg mål, planlegger og bygger gode rutiner fra starten av. I tillegg til å være motivert må du også ha tro på at du kan gjennomføre endringene. Motivasjon og mestringsevne er viktig for livsstilsendring. Støtte og positiv oppmuntring fra de rundt deg kan gjøre det lettere å nå de målene du har satt deg.

Attachment 10 "Dietary intervention information – SFA" Handed out after the randomization.

Kolesterol-studien

Hovedformålet med studien er å undersøke effekten av ulike typer fett på kolesterol hos personer med ulik vekt (KMI≤25 kg/m²og 30-45 kg/m²).

Du er med i gruppen som skal spise et hjertevennlig kosthold samtidig som du skal innta mettet fett i form av minst 2 porsjonspakker (24 gram) Tine meierismør per dag, helfete meieriprodukter og kjøttprodukter. Kostholdet er basert på et typisk nordisk kosthold, med mye grove kornprodukter, fisk, fjærfe, grønnsaker, frukt og bær.

-Første mål er å komme i gang med å spise 2 ½ porsjonspakke (24 gram) Tine meierismør per dag.

- Deretter fokuserer du på å velge helfete meieriprodukter og kjøttprodukter.

KILDER TIL METT FETT

-Spis dagens minimumsdose 24 g smør hver dag!
-Matlaging: Velg smør til steking, ovnsbaking, sauser, supper og baking.
-På brødskiva/knekkebrød bruk smør.
-Rødt kjøtt og fjærfe spises uten at skinn eller fett fjernes.
-Helfete meieriprodukter (se kostlisten).

Velg kjøttdeig, helfete meieriprodukter og unngå å spise bearbeidet kjøttprodukter - se kostlisten for mer informasjon.

Planlegging av matinnkjøpene og måltidene er viktig for å oppnå de ønskede endringene. Planlegg frokosten dagen i forveien og lag matpakke til lunsjen så kan du lettere følge kostrådene.

Varedeklarasjonen gir nyttig informasjon om hva en matvare inneholder. Ingrediensene er satt opp i fallende rekkefølge, den det er mest av står først i innholdslisten. Dette gjør det lettere for deg å sammenligne produkter. På baksiden av varen er det en næringsinnhold-tabell. Denne kan også brukes til å sammenlikne ulike produkter.

Næringsinnhold	Per 100g
Energi (kJ/kcal)	1869/488
Fett	29g
Hvorav mettede fettsyrer	19g
Karbohydrat	36g
Hvoravsukkerarter	31g
Protein	11g
Salt	0,7g

Næringsinnhold	Per 100g
Energi (kJ/kcal)	2560/620
Fett	50 g
Hvorav mettede fettsyrer	9 g
Enumettede fettsyrer	**23 g**
Flerumettede fettsyrer	**17 g**
Karbohydrat	14 g
Hvoravsukkerarter	9 g
Kostfiber	8 g
Protein	24 g
Salt	0,6 g

Hovedprinsippene i et hjertevennlig kosthold

Det er godt dokumentert at med mye grove kornprodukter, fisk, fjærfe, grønnsaker, frukt og bær minsker risikoen for hjerte og karsykdommer. I denne studien skal du derfor forsøke å spise i tråd med kostrådene. Vi vil hjelpe deg med å gjøre individuelle tilpasninger, slik at det blir lettere for deg å følge kostholdsplanen.

SPIS

- Grove kornprodukter
- Fiskefileter og fiskeprodukter med høyest mulig innhold av fisk
- Kylling, kalkun og andre fjærfe fileter eller produkter
- Grønnsaker, frukt og bær
-

BEGRENS

-Rødt kjøtt og bruk minimalt med bearbeidede kjøttprodukter som pølser, bacon og kjøttdeig
-Ferdigmat og halvfabrikata
-Raffinerte kornprodukter som loff og kneip, vanlig pasta, boller, polert ris og søte kornblandinger
-Godteri, snacks og kaker til maksimalt en til to ganger i uken.
-Brus og saft med sukker

Hva med snacks? Selv om man spiser sunt er det plass til å kose seg med noe godteri eller snacks en gang i blant. Man må bare passe på mengden og hyppigheten da godterier og snacks ofte inneholder en kombinasjon av mye kalorier, mettet fett, sukker og salt som er ugunstig for helsen i store mengder. Ha minst mulig godterier og snacks tilgjengelig, det kan være lurt å rydde i skuffer og skap. Noen ganger føler man et søtsug eller et behov for snacks når man egentlig er sulten og kroppen trenger et skikkelig måltid. Det er også vanlig å få lyst på noe søtt etter middag, og skjer dette med deg kan du titte i oppskriftsheftet vårt for å finne sunne, søte fristelser som bremser søtsuget, smaker deilig og øker inntaket av sunne frukter og bær.

Forberede deg mentalt og bestem deg. Vi mennesker er vanedyr. Det er viktig at du forbereder deg mentalt på en livsstilsendring. Det kan være vanskelig å endre kostholdet over natten, derfor er det viktig at du setter deg mål, planlegger og bygger gode rutiner fra starten av. I tillegg til å være motivert må du også ha tro på at du kan gjennomføre endringene. Motivasjon og mestringsevne er viktig for livsstilsendring. Støtte og positiv oppmuntring fra de rundt deg kan gjøre det lettere å nå de målene du har satt deg.

Attachment 11 "Ethical approval from the National Committees for Research Ethics in Norway".

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Gjøril Bergva	22845529	11.09.2015	2014/1786 REK sør-øst D
			Deres dato:	Deres referanse:
			19.06.2015	

Vår referanse må oppgis ved alle henvendelser

Serena Tonstad
Oslo universitetssykehus HF

2014/1786 Har reduksjon i mettet fett samme kolesterolsenkende effekt hos personer med fedme som normalvektige?

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Serena Tonstad

Vi viser til prosjektendring, mottatt 19.06.2015, i forbindelse med ovennevnte prosjekt. Prosjektendringen ble behandlet i komiteens møte 19.08.2015.

Prosjektleders prosjektbeskrivelse
Hjerte- og karsykdom øker i takt med fedmeepidemien hos visse grupper. Dietter med mer fett enn anbefalt er populære, men kan øke kolesterolet. Målsetningen er å forstå om personer med fedme får like betydningsfull reduksjon i kolesterolverdi som normalvektige ved å bytte mettet med umettet fett. Menn og kvinner 21-70 år med enten kroppsmasseindeks (KMI) < 25 kg/m2 (normalvekt) eller KMI 30-45 (fedme) og forhøyet LDL kolesterol randomiseres til intervensjon (bytte av mettet med umettet fett) eller kontrollkosthold i 8 uker. Begge grupper unngår raffinerte karbohydrater. Endepunkter: lipider, insulinresistens, inflammasjon. Analyse: Intention to treat. Styrke: 42 i hver gruppe. Prosjektet vil bidra til presisering av kostråd for personer med fedme, et omdiskutert tema i ukepressen og faglitteraturen. Hvis andelen mettet fett i kostholdet har mindre å si for risiko hos personer med fedme, vil variasjon i kostrådene kunne utvides og individuelle preferanser tas i betraktning.

Saksgang
Søknad om forhåndsgodkjenning av forskningsprosjekt ble første gang behandlet i møtet 22.10.2014. Komiteen skrev følgende i sitt brev av 11.11.2014:

Hovedformålet med prosjektet er å undersøke om det å bytte mettet med umettet fett har effekt på LDL kolesterol hos overvektige og normalvektige. Det skal ikke undersøkes om en eventuell endring i LDL påvirker pasientens sykdom eller helse. I motsetning til sykelig overvekt, som er en behandlingskrevende tilstand, er forhøyet kolesterol en risikofaktor for kardiovaskulær sykdom og ikke i seg selv uttrykk for helse eller sykdom. Komiteen vurderer derfor at prosjektet, slik det er presentert i søknad og protokoll, ikke vil frembringe ny kunnskap om helse og sykdom som sådan.

Prosjektet faller derfor utenfor REKs mandat etter helseforskningsloven, som forutsetter at formålet med prosjektet er å skaffe til veie ny kunnskap om helse og sykdom.

Prosjektendring
I søknad om prosjektendring innsendt 19.06.2015 blir det opplyst om at det er behov for å opprette en spesifikk forskningsbiobank i forbindelse med prosjektet. Prosjektleder ber om en fornyet vurdering av prosjektet.

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

Vurdering
Komiteen erkjenner at den første vurderingen av forskningsprosjektet, slik den fremkommer i brev datert 11.11.2014, er for streng. Etter en fornyet vurdering av søknaden har komiteen kommet til at prosjektet kan frembringe ny kunnskap om sykdom og helse, og komiteen har ingen innvendinger til at prosjektet gjennomføres som beskrevet i søknad og protokoll.

I prosjektendringen oppgis det at det skal opprettes en forskningsbiobank i forbindelse med prosjektet. Komiteen har ingen innvendinger mot at det opprettes en spesifikk forskningsbiobank, men ber om at navn på biobanken og ansvarshavende sendes komiteen til orientering.

Vedtak
Med hjemmel i helseforskningsloven § 9 jf. 33 godkjenner komiteen at prosjektet gjennomføres.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Komiteen godkjenner opprettelse av en spesifikk forskningsbiobank, i tråd med det som er oppgitt i endringssøknaden. Biobankregisteret vil få kopi av dette brev. Hvis forskningsbiobanken opphører, nedlegges eller overtas av andre, skal det søkes REK om tillatelse, jf. helseforskningsloven § 30.

Tillatelsen gjelder til 31.12.2017. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2022. Forskningsfilen skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren».

Dersom det skal gjøres vesentlige endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Prosjektet skal sende sluttmelding på eget skjema, senest et halvt år etter prosjektslutt.

Klageadgang
REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Gjøril Bergva
Rådgiver

Kopi til: kaabir@ous-hf.no
Biobankregisteret ved Nina Hovland: nina.hovland@fhi.no
Oslo universitetssykehus HF ved øverste administrative ledelse: oushfdlgodkjenning@ous-hf.no

Attachment 12 "Advertisement for the study"

Oslo universitetssykehus

HAR DU HØYT KOLESTEROL OG VIL VÆRE MED I EN STUDIE DER VI UNDERSØKER HVORDAN KOLESTEROLET PÅVIRKES AV ULIKE TYPER FETT?

Vi søker etter personer som ønsker å være med i en studie ved Oslo Universitetssykehus, Ullevål, Seksjon for preventiv kardiologi. Vi vil undersøke hvordan kolesterolet og helsen vår påvirkes av om vi spiser vanlig meierismør, helfet ost og fett kjøtt eller VITA margarin, mager ost og kjøtt uten fett.

I studien vil du bli tilfeldig trukket ut til å være i èn av to grupper.
- Gruppen som skal spise meierismør, helfet ost og fete kjøttprodukter, eller
- gruppen som skal spise VITA margarin, nøtter, mager ost og kjøtt uten fett.

Begge gruppene skal for øvrig spise som vanlig og anbefales et kosthold med mye frukt og grønnsaker, grove kornprodukter og fisk og lite sukker, snacks og bearbeidede kjøttprodukter.

Du kan delta i studien hvis du:
- er mellom 21 og 70 år,
- har normalvekt (KMI ≤ 25 kg/m^2) eller fedme (KMI 30-45 kg/m^2) og stabil vekt siste 3 måneder
- forhøyet kolesterol (LDL kolesterol ≥ 3.0 mmol/l)
- bor i Oslo eller omegn og har mulighet til å møte opp på avdelingen annenhver uke i 6 uker, totalt 5 ganger. Konsultasjonen varer mellom 0,5 og 1,5 timer hver gang.

Du passer ikke inn i studien hvis du:
- hvis du har diabetes type 1 eller 2
- har hatt hjerte- eller karsykdom
- bruker medisiner for å senke kolesterolet (statiner eller PCSK9 hemmer)
- har allergi mot melkeprodukter inkludert smør og ost

Blodprøver, undersøkelser og veiledning og som inngår i studien er helt gratis og du vil få utdelt gratis smør eller Vita margarin. (Reiseutgifter i forbindelse med studiebesøkene blir **ikke** dekket.) Studien krever at du møter opp totalt 5 ganger i løpet av 6 uker.

Hvis du er interessert i å delta, send e-post til studieansvarlig, klinisk ernæringsfysiolog Tine Sundfør tinsun@ous-hf.no eller sms til 924 32 168. I e-posten/sms må du oppgi følgende: **navn, adresse, mobiltelefon nr., fødselsdato, vekt, høyde, eventuelle faste medisiner og dersom du har målt ditt kolesterol (HDL-, LDL- og total kolesterol) er det flott om du oppgir dette.**

Vi går etter "førstemann til mølla prinsippet", så ta gjerne kontakt allerede nå.

Studien finansieres av Nasjonalforeningen for folkehelsen og Oslo universitetssykehus.