Diets for weight loss and cardiovascular health in obesity

PhD thesis

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Table of contents

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Torolv you are my rock! Thank you Torolv, Helene and Sofie for always cheering me up, supporting me and for telling me: "of course you can do it!". Your eternal love means the world to me!

Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMI	Body mass index
CVD	Cardiovascular disease
CER	Continuous energy restriction
CETP	Cholesteryl ester transfer protein
EAR	Estimated Average Requirement
ER	endoplasmic reticulum
HL	Hepatic lipase
IER	Intermittent energy restriction
LDL	Low density lipoprotein
MAB	Monoclonal antibodie
MUFA	Monounsaturated fatty acids
PCSK9	Protein convertase subtilisin/kexin 9
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
SFA	Saturated fatty acids
TFEQ	Three Factor Eating Questionnaire
TG	Triglyceride
TGN	Trans Golgi network
VLDL	Very low density lipoproteins
WHO	World Health Organization

List of papers

Paper I

Sundfør TM, Svendsen M, Tonstad S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: A randomized 1-year trial. Nutr Metab Cardiovasc Dis. 2018 Jul;28(7):698-706. doi: 10.1016/j.numecd.2018.03.009.

Paper II

Sundfør TM, Tonstad S, Svendsen M. Effects of intermittent versus continuous energy restriction for weight loss on diet quality and eating behavior. A randomized trial. Eur J Clin Nutr. 2018 Dec 4. doi: 10.1038/s41430-018-0370-0.

Paper III

Sundfør TM, Svendsen M, Heggen E, Dushanov S, Klemsdal TO, Tonstad S. BMI modifies the effect of dietary fat on atherogenic lipids: a randomized clinical trial. Am J Clin Nutr. 2019 Jun 19. pii: nqz113. doi: 10.1093/ajcn/nqz113. [Epub ahead of print]

1. Introduction

1.1. Overview of obesity, cardiovascular disease, metabolic risk factors and diet

Obesity rates are at all-time high and the World Health Organization (WHO) has declared obesity the largest global chronic health problem in adults [1, 2]. Obesity is associated with reduced life expectancy and numerous comorbidities such as cardiovascular disease (CVD), type 2 diabetes, hypertension, certain cancers and sleep apnea. Obesity is an independent risk factor for CVD [3], the leading cause of death worldwide [2]. It is well established that overweight and obesity can lead to adverse metabolic effects; raised blood pressure, elevated blood lipids, increased blood glucose and insulin resistance [2]. These modifiable cardiometabolic risk factors will in turn increase the risk of CVD, mainly coronary heart disease and stroke [1].

Dietary modification is a cornerstone in the prevention and treatment of obesity, metabolic risk factors and CVD. Nutrition science has lately moved from focusing on isolated nutrients, deficiency diseases and surrogate outcomes to food pattern, diet quality, and prevention of chronic diseases. Results of multiple studies have been incorporated to formulate evidence based dietary guidance, however, controversy and some confusion still remain [5]. One of the biggest areas of discussion is about the best dietary approach for weight management, metabolic health, and prevention and treatment of CVD.

Energy restriction to achieve and maintain a healthy body weight is of paramount importance in the treatment of obesity and concomitant cardio-metabolic risk factors [6]. Dietary interventions to promote weight loss reduce the risk of CVD, but have been proved difficult for patients to sustain [3,6]. Many patients do not manage to adhere to conventional weight-loss diets, because food intake must be continually limited. Furthermore, changes in neurobiological pathways tend to favor weight regain [6]. This brings up the question of whether different forms of energy restriction may be helpful. Given that weight-loss maintenance requires long-term adherence to dietary changes [6], the overall benefit of weight loss diets depends on more than solely weight reduction. In addition diet quality must be considered. Weight loss diets may affect initial weight loss, maintenance, cardio-metabolic risk factors and diet quality differently. Equally important is the potential for diet to influence cardiometabolic risk factors regardless of weight loss [7, 8]. The macronutrient composition, food matrix and overall dietary patterns may substantially affect multiple CVD risk factors [2, 6].

CVD is currently the major cause of mortality in most Western populations. However, death rates have decreased steadily for the past 5 decades. Part of the decrease is due to lower rates of smoking, dietary changes in particular lower intakes of trans-fats, and improved socioeconomic conditions. Other unknown factors may also have contributed. Most of the decline is due to better prevention, though treatment also contributes to a major part of the decline. The causal role of low density lipoprotein (LDL)-cholesterol in the pathogenesis of atherosclerosis is well established, and clinical trials have shown that reduction in LDL-cholesterol reduces cardiovascular events [7]. Dietary fatty acids modulate LDL-cholesterol substantially [8]. Saturated fatty acids (SFAs) and trans-fatty acids increase LDL-cholesterol while polyunsaturated fatty acids (PUFAs) lower it. Nutritional guidelines generally encourage a low consumption of SFAs, restricted to less than 10% of daily energy intake [2, 8]. However, the lipid response varies and may be affected by the presence of obesity [9], and

nutritional recommendations for the general population may not always "fit" the obese segment.

1.2. Obesity, metabolic risk factors and cardiovascular disease

1.2.1 Definitions
Overweight and obesity
Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health [1, 6]. The most commonly used anthropometric tool to assess relative weight and classify obesity is the body mass index (BMI), defined as a person's weight in kilograms divided by the square of his/her height in meters (kg/m2). In adults, (age over 18 years) obesity is defined by a BMI 30 kg/m^2 or more and overweight by a BMI between 25 and 29.9 kg/m^2 [1].

BMI cannot distinguish between elevated body weight due to high levels of lean versus fat body mass, and BMI does not reflect fat distribution. Excess abdominal fat is more frequently associated with metabolic abnormalities than peripheral fat [10]. Central obesity and increase in ectopic fat (fat distributed viscerally and around internal organs) is more often related to a range of metabolic abnormalities, including decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles. These abnormalities are in turn risk factors for type 2 diabetes and CVD [2]. Measures of central obesity including waist circumference, waist-to-hip ratio and waist-to-height ratio, which more accurately describe the accumulation of intra-abdominal fat, are suggested to be more closely associated with metabolic abnormalities and CVD risk [11, 12].Both general adiposity and abdominal adiposity are associated with the risk of cardiovascular morbidity and mortality supporting the use of waist circumference or waist-to-hip ratio in addition to BMI in risk assessment [6, 10-12].

Cardiovascular disease (CVD)
CVD is an umbrella term for a number of linked pathologies including all types of diseases that affect the heart or blood vessels, commonly defined as coronary heart disease, cerebrovascular disease (stroke), peripheral vascular disease, hypertension, heart failure, rheumatic heart disease, congenital heart disease and cardiomyopathies [13].

The causes of these CVDs are multifactorial. Many of the risk factors are relate to lifestyles and can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet, obesity, physical inactivity and harmful use of alcohol [14]. Other risk factors such as hypertension, type 2 diabetes and dyslipidemia are also modifiable. The World Health Organization (WHO) has estimated that 80% of premature heart disease and stroke is preventable across the European Region [14].

CVD is a multifactorial disease and multiple risk factors may increase risk more than their sum would imply [14]. International guidelines for the prevention of CVD, recommend the estimation of an individual's total risk of CVD, to determine the extent of interventions that are needed. A number of multivariate risk models have been developed for estimating the risk of initial CVD events in apparently healthy, asymptomatic individuals based upon assessment of multiple variables. Most estimators use the variables of age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, diabetes mellitus (DM), and current smoking. Some of the models most commonly used in clinical practice are The Framingham risk score, the modified third Adult Treatment Panel (ATP III), SCORE CVD and in Norway we use the NORRISK 2 score [15]. The state of metabolic syndrome appears to confer substantial additional risk of CVD (see paragraph about metabolic syndrome).

Atherosclerosis

Atherosclerosis is the dominant pathological process causing CVD including coronary heart disease, heart failure, stroke and peripheral vascular disease. Despite the various conditions, the underlying disease development has an important common denominator; a chronic inflammatory process in the arteries wall causing plaque development on the inside of the arteries which narrows the lumen of the artery, reduces the blood flow and thereby the supply of oxygen and nutrients [16, 17]. Over time this can lead to plaque rupture, formation of thrombosis and acute vascular events as myocardial infarct and stroke [18]. Atherosclerosis is a multifactorial disease involving the interplay of genetic and environmental factors [17]. Among the risk factors are obesity, hypertension, dyslipidemia, diabetes, smoking, unhealthy diet and physical inactivity.

Sub-endothelial retention of LDL-particles is considered an important early stage of the atherosclerotic process. In intima, the LDL-particles are oxidized promoting activation of intracellular processes that lead to inflammation and endothelial dysfunction [17]. Activated endothelium allows monocytes to penetrate into the intima [18]. The monocytes can develop to macrophages which mediate the uptake of oxidized LDL resulting in formation of foam cells which accumulate into fatty streaks that build up the vessel wall [18, 19].
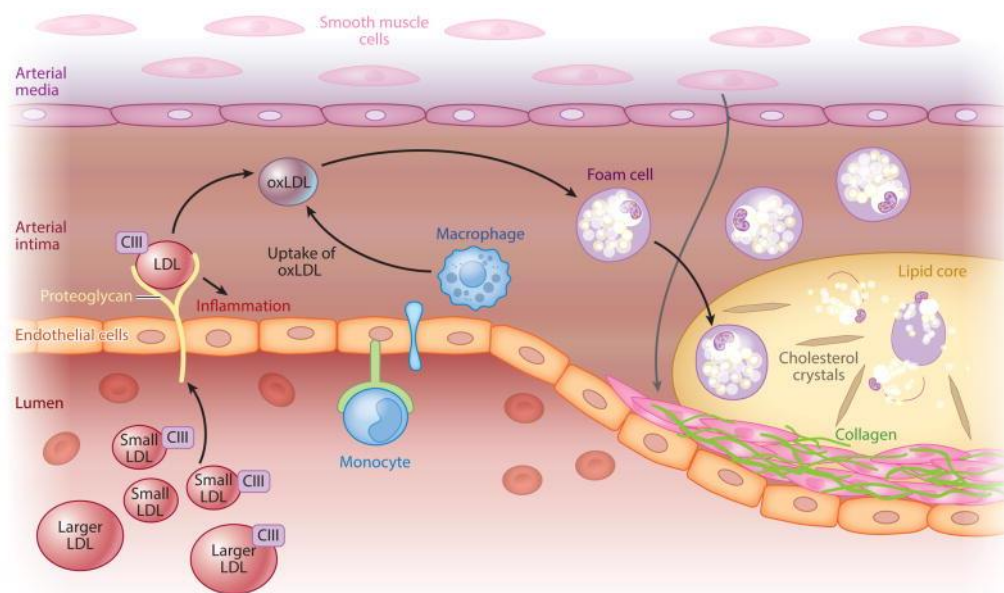
Figure 1. In the initial steps of atherogenesis. LDL-particles circulating in the blood infiltrate the endothelial layer of arteries and become oxidized. This triggers inflammatory processes and foam cell formation by responding macrophages. These lipid-laden foam cells form the core of the atherosclerotic plaque and can amplify local inflammation and promote thrombosis. Small, dense LDL is considered more atherogenic due to its longer plasma residence time, greater arterial retention, and increased susceptibility to oxidation, triggering inflammatory and thrombotic processes. Adapted from [80] with permission.

Metabolic syndrome
The term metabolic syndrome is characterized by visceral adiposity, insulin resistance, elevated blood pressure and glucose, elevated triglycerides, and low levels of high density lipoprotein (HDL)-cholesterol [20, 21]. The state of metabolic syndrome appears to confer substantial additional risk of CVD, above and beyond the individual risk factors [20, 21]. Patients with metabolic syndrome double their risk of developing CVD over the next 5 to 10 years and have a five-fold increase in risk for type 2 diabetes mellitus [20, 21]. The dramatic increase in the prevalence of obesity has led to a marked increase in metabolic syndrome and this is considered to be one of the driving forces for the ongoing CVD epidemic [20].

The common definition of metabolic syndrome is a result of the harmonization of various criteria by a group of international experts and published in Circulation in 2009 [20]. The presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome; waist circumference >94/ 80 cm (men/women), circulating levels of triglycerides (TGs) $\geq$1.7 mmol/l, HDL-cholesterol $\leq$ 1.0/1.3 (men/women), blood pressure $\geq$130/85 mmHg (or use of antihypertensive drugs) or fasting glucose$\geq$5.6 mmol/l [20, 21]. Lower cut-off points for central obesity are proposed for different ethnic groups [20, 21]. Having just one or two of these conditions is not defined as the metabolic syndrome, but the risk for CVD increases with the number of metabolic risk factors [20]

Atherogenic dyslipidemia
Atherogenic dyslipidemia, characterized primarily by elevated TGs, higher proportions of small-dense LDL-particles and decreased levels of HDL-cholesterol, is a phenotype associated with increased cardiovascular risk [22-24]. Obesity, metabolic syndrome, insulin resistance and type 2 diabetes mellitus are commonly accompanied with atherogenic dyslipidemia [22, 23]. Along with the increased prevalence of obesity and physical inactivity atherogenic dyslipidemia has emerged as an important risk factor for myocardial infarction and cardiovascular disease [22, 23].

1.2.2 Weight loss and cardiometabolic risk factors
For many overweight or obese individuals attaining a normal BMI and maintaining it over time presents a major challenge. However lesser degrees of weight loss may have salutary effects on cardio-metabolic risk and quality of life. A maintained weight loss of 5-10 % can improve and prevent many cardio-metabolic risk factors and obesity-related comorbidities [6, 25-31]. While greater improvement in risk factors may occur with greater sustained weight losses [6, 25, 26, 30] the initial goal of treatment is to achieve and hopefully maintain a minimum of 5-10% of weight loss [6, 26].

Most recommendations support the use of continuous calorie restriction with a consistent daily reduction in energy intake [6, 26]. Balanced hypocaloric diets seem to result in clinically significant weight loss regardless of which macronutrients they emphasize [6, 26]. Instructions to consume a carbohydrate restricted diet in comparison with a calorie-restricted low-fat diet, high or low in protein result in equivalent weight loss regardless of which macronutrients they emphasize [6]. This was recently confirmed in a randomized clinical trial (RCT) of 609 overweight and obese adults following either a healthy low-fat diet or a healthy low-carbohydrate diet for 12-months showing no significant difference in weight [32]. With moderate weight loss, lower-fat, higher-carbohydrate diets result in greater reduction in LDL-cholesterol, but lesser reduction in TG and lesser increases in HDL-cholesterol compared to higher-fat, lower-carbohydrate diets [6, 32].

However, even moderate weight loss is difficult to sustain and many patients find it difficult to adhere to weight-loss diets given the complex interaction between environmental, cognitive, behavioral and biological factors favoring weight regain [6, 33, 34].

1.3. Intermittent fasting

1.3.1. Definition
One of the most recent dieting trends is intermittent energy restriction (IER). IER involves cycling between extreme calorie restriction and normal eating usually according to a weekly pattern, implicating that strict adherence is only needed some days a week. The most studied IER approaches include alternate day fasting and the 5:2-diet with 2 self-selected, nonconsecutive, modified "fasting" days with extreme energy restriction and eating normal the remaining 5 days a week [35, 36]. On "fasting" days, the dieter typically reduces energy intake to about 500 kcal/day [35,36].

1.3.2. Intermittent fasting for weight loss, maintenance and cardio-metabolic risk factors
Recently, the notion that IER may improve dietary adherence and attain potentially greater benefits than continuous energy restriction (CER) on cardiometabolic risk factors has achieved attention in popular science as well as in research.

The Mail on Sunday, 2018-04-22

The fascination with IER partly arises from findings in animal studies indicating that IER may improve cardiometabolic risk factors and prevent chronic disease to similar or even greater extent than CER [37]. Results from human studies are inconsistent. Most short-term studies indicate equivalent weight loss and improvements in cardiometabolic risks with IER and CER [35-40]. However, two studies conducted in woman with overweight or obesity suggested even greater reductions in insulin and body fat with IER than with CER despite similar weight loss [41, 42]. Furthermore a variant of IER with alternating 2-wk cycles of energy restriction

and balance showed greater weight and fat loss with intermittent than CER in men with obesity [43]. Two meta-analyses summarizing the effects of IER and CER concluded that neither IER nor CER was superior to the other with respect to weight loss [35, 44]. The authors stressed the need for larger long-term trials [35, 44]. Two recent large, long-term randomized controlled trials (RCT) in obese metabolically healthy adults found that neither intermittent nor continuous calorie restriction is superior to the other with respect to weight loss, maintenance and improvements in cardiovascular risk [45, 46] (one published ahead of the study in this thesis [45], the other afterwards [46]). It is relevant to clinical practice to increase our knowledge about whether intermittent fasting is effective for weight loss and improvements in cardio-metabolic risk in particular in a high risk population with abdominal obesity and signs of increased cardio-metabolic risk.

1.4 Diet quality and eating behavior

1.4.1. Diet quality and health
Improvements in diet quality may be paramount to improve long-term health and reduce the risk of lifestyle diseases independently from benefits seen with weight loss [47, 48]. Healthful diets in line with dietary guidelines reduce the risk of chronic lifestyle-related diseases and meet requirements for essential nutrients [49, 50]. Recently published systematic reviews and meta-analysis of prospective cohort studies found that diets of highest quality were associated with lower risks of all-cause mortality, cardiovascular disease, cancer, and type 2 diabetes [51, 52]. This is also reflected in the recently published Summary Report of the EAT–Lancet Commission on healthy diets from sustainable food systems [53].

1.4.2. Diet quality in weight loss
Given that weight-loss maintenance requires long-term adherence to dietary changes [6, 25], the overall benefit of weight loss diets depends on more than solely weight reduction. If a diet is followed over time consideration of nutritional composition is important. Focus on diet quality concomitantly with weight loss may result in potentially synergistic effects on overall health [47, 48]. Most dietary plans emphasize the macronutrient composition of the diet, including the amounts or percentages of energy from protein, fat and carbohydrates. However, little published data exist on the micronutrient intakes of free-living persons following different forms of weight-loss diets. Earlier studies have shown that a variety of weight loss diets, including Atkins, Zone, LEARN, and Ornish, were associated with inadequate intakes of several micronutrients [54]. A significant proportion of individuals shifted to intakes associated with risk of inadequacy for several vitamins and minerals in the Atkins, LEARN and Ornish group. In contrast, in the Zone group no significant increases in risk of inadequacy were observed, and the proportion at risk of inadequacy significantly decreased for vitamins A, E, K, and C. Very little published data exists regarding nutritional composition in free-living subjects following an IER compared to a CER for weight loss.

1.4.3. Eating behavior and weight loss
Adherence to conventional weight-loss diets and success in weight loss and maintenance is limited over the long-term [55, 56]. For individuals who successfully lost weight, maintaining their new weight is often a lifetime challenge. Studies indicate that weight loss and maintenance is associated with improved eating behavior [57]. Eating behavior is a broad term that includes food choice and motives, meal habits, dieting and eating-related problems such as overeating and other eating disorders. Eating behavior is extremely complex and influenced by a variety of personal physiological and psychological characteristics, social, cultural, environmental and economic factors. Eating behavior and food choice depends om

multiple mechanisms like regulation of hunger and satiety, taste, learned food preferences, reward systems in the brain, knowledge, motivation, values, personality traits, cognitive processes and self-regulation. Improvements in uncontrolled eating and cognitive restraint, meaning control over food intake in order to influence body weight, seem to be key factors associated with enhanced weight loss and long-term maintenance [58-60]. Studies indicate that successful dieters improve uncontrolled eating, emotional eating and cognitive restraint assessed by the Three Factor Eating Questionnaire (TFEQ) [59, 60].

1.5 Dietary fat, lipids and cardiovascular disease

1.5.1. Dietary fat and cardiovascular disease

Dietary modification is a cornerstone in the prevention and treatment of CVD [49, 61, 62]. Dietary fatty-acid composition regulates lipids and lipoprotein metabolism and thereby potentially CVD risk. Dietary change modifies lipid concentrations within 2-3 weeks [63]. A main focus in dietary recommendations is reduction in saturated fat intake, primarily to reduce LDL-cholesterol [50, 61, 62]. The causal role of LDL-cholesterol in the pathogenesis of atherosclerosis is well established as discussed above and dietary fatty acids modulate LDL-cholesterol substantially [61, 64, 65]. Nevertheless, controversies exist on the effects of SFAs, on CVD risk [65]. The reasons for the discrepancy seem to be affected by macronutrient composition of the comparator diet. Clinical trials indicate that the replacement of some dietary SFAs with PUFAs reduces CVD risk [65, 66, 67]. The trials looked at the effect of replacing SFAs with PUFAs. Thus, it was not possible to distinguish between the benefits of reducing SFAs and increasing PUFAs. Both n-6 and n-3 polyunsaturated fatty acids are associated with lower CVD risk. Intake of industrially produced trans-fat is consistently associated with higher CVD risk. Replacement of SFA with carbohydrates, mostly refined, results in no improvement or maybe even a worsening in CVD risk [65, 67, 68]. In a recent series of systematic reviews and meta-analyses total dietary fiber or whole grains on the other side were associated with decrease in all-cause and cardiovascular related mortality and incidence of coronary heart disease, stroke incidence and type 2 diabetes, when comparing the highest dietary fiber consumers with the lowest consumers [69].

Numerous factors, including genetic and metabolic variation affect the variability of diets on lipid concentrations [9, 70-72] and reduction of SFAs may potentially affect CVD risk differently in different populations.

1.5.2. Effect of type of fat on lipid profile

Meta-analyses have concluded that SFA increase LDL- and HDL-cholesterol, while PUFAs and monounsaturated fatty acids (MUFAs) decrease LDL- and HDL-cholesterol, though MUFAs to a lesser extent [73, 74]. MUFAs and PUFAs do not increase LDL-cholesterol when added to a low-fat diet, but do increase HDL-cholesterol, but the increase in HDL-cholesterol levels is less marked than for saturated fat [75, 76]. The total cholesterol: HDL-cholesterol ratio is more favorable for MUFAs and PUFAs than SFAs [1, 2].

The effect on plasma LDL-cholesterol concentrations differs between saturated fatty acids of different chain length. Short chain SFAs (6:0 to 10:0) and long chains 18:0 have little effect on plasma cholesterol concentrations, while those with intermediate chain lengths (12:0 to 16:0) increase the cholesterol concentrations [77].

Replacing saturated fats with carbohydrates reduces LDL- and HDL-cholesterol levels, but increases triglyceride concentrations. Dietary saturated, monounsaturated, and polyunsaturated fats decreased plasma triglyceride concentrations, relative to carbohydrates, to about the same extent [73-75].

SFAs increase circulating LDL-cholesterol through suppressed LDL-receptor activity thus reducing clearance of LDL from the circulation [78]. On the other hand, replacing SFAs with PUFAs lowers LDL-cholesterol via increased LDL-receptor mediated uptake of LDL [78, 79].

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1.5.3. Choice of nutrient to replace saturated fat
Current evidence supports that different types of dietary fatty acids have divergent effects on CVD risk, and the effects depend strongly on the replacement macronutrient. It is difficult to consider the independent effect of different types of dietary fat, carbohydrates or proteins on plasma lipoprotein patterns because in order to maintain a stable body weight, if the intake of one macronutrient is increased or decreased another will be adjusted through compensatory mechanisms. The observed effect on plasma lipoprotein patterns is consequently due to the addition of one macronutrient, the reduction of another or a combination of both. If a single macronutrient is increased or decreased without compensatory adjustments, body weight will change and any the change in body weight will then have a potentially effect on plasma lipoprotein patterns.

The effects of SFAs on CVD risk factors and clinical endpoints are modulated by the nutrients that replace them [66, 80]. Replacement by PUFAs is associated with reduction in CVD risk, whereas replacement of saturated fat with monounsaturated fat does not appear to reduce risk, but the results from studies are less clear [65, 66, 81, 82]. Replacement with carbohydrates, particularly refined carbohydrates, has been associated with no improvement or a worsening in CVD risk [80]. This difference appears to be due, at least in part through effects of dietary fatty acids on atherogenic dyslipidemia. This is a growing concern regarding the segment of the population with overweight and insulin resistance. These individuals demonstrate increased sensitivity for adverse lipoprotein effects of refined carbohydrates [66, 80, 82, 83]

1.5.4. Atherogenic dyslipidemia and diet
Macronutrient composition can affect atherogenic dyslipidemia independent of weight loss [6, 83]. Carbohydrates can increase triglyceride-rich very low density lipoproteins, thereby promoting formation of small dense atherogenic LDL-particles, and reducing HDL-cholesterol, while carbohydrate restriction indicate reversing of these changes [80, 83, 84]. Carbohydrate restriction even without weight loss has been shown to reduce TGs, apolipoprotein B, total: HDL-cholesterol-ratio and increase LDL-cholesterol peak diameter, in overweight men with atherogenic dyslipidemia [84]. Unfortunately, increased intake of refined carbohydrates is precisely what appears to have happened in parallel with the obesity epidemic [85]. Given the numerous dietary changes required for obese people to lose weight, the sugar- fat seesaw illustrates how sugar intakes may adversely increase when fat is reduced [86]. In line with this, reducing dietary saturated fat can lead to increased formation of small dense LDL-particles in overweight and negatively affect CAD risk[80, 87].
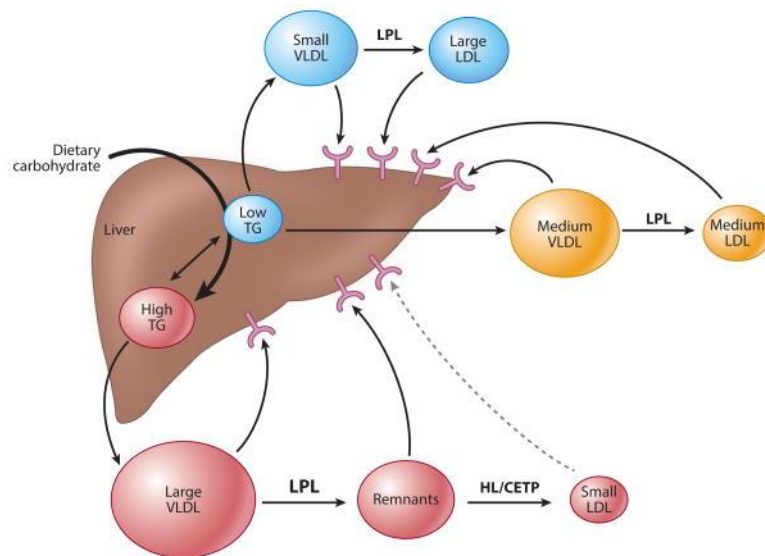
Figure 2. Dietary carbohydrate increases hepatic TG that drives the secretion of very-low-density lipoproteins (VLDLs) that are larger and TG enriched. These particles are rapidly lipolysis by lipoprotein lipase to remnant lipoproteins that are then catabolized by hepatic lipase (HL) to small, dense low-LDL-particles that are less efficiently cleared from plasma, likely due to reduced LDL-receptor affinity. Dietary saturated fat has been shown to preferentially increase plasma concentrations of larger LDL particles, likely by reducing their plasma clearance through suppression of LDL-receptor activity, although increased hepatic secretion of their precursors may also play a role. Abbreviation: CETP, cholesteryl ester transfer protein. Adapted from [80] with permission.

1.5.5. Serum lipid response in obesity

Metabolic variations seem to contribute to variability in lipid response to dietary intervention and major heterogeneity appears to arise due to obesity [70, 71]. Results of a limited number of clinical studies indicate an inverse relationship between BMI and the amount by which reduction in dietary saturated fat lowers LDL-cholesterol concentrations [70, 71, 88, 89]. A recent review and meta-analysis assessing the evidence regarding dietary replacement of SFA with unsaturated fatty acids in adults with overweight and obesity concluded that this intervention may be only marginally effective in improving lipid profiles in these populations [9]. This possible difference in lipid responses to dietary change according to body weight appears not to be well known or discussed in current dietary recommendations aiming to reduce CVD [61,62, 64, 90]. Thus limited data is available to date to understand differences in the lipid response to saturated fat between normal weight and obese populations.

1.6 PCSK9 - a novel risk factor

1.6.1. PCSK9 and cardiovascular disease risk

Protein convertase subtilisin/kexin 9 (PCSK9) plays a major regulatory role in cholesterol homeostasis, mainly by destroying LDL-receptors on the plasma membrane [91]. A high level of PCSK9 reduces LDL-receptors thus decreasing the metabolism of LDL-particles, which leads to higher LDL cholesterol concentrations in the blood [91, 92]. When PCSK9 binds to the LDL-receptor, this redirects the LDL-receptor to lysosomal degeneration. High PCSK9 levels or a gain-of-function mutation in PCSK9, will enhance the degradation of the LDL-receptors, resulting in low levels of the LDL-receptors at the cell surface and increased levels of circulating LDL-cholesterol. If levels of PCSK9 are low, cell surface LDL-receptors levels

are high and the LDL-receptors can be recycled back to the surface after delivery of LDL particles to the endosomes [91, 93].

Individuals with high levels of PCSK9 or gain-of-function mutations in PCSK9 have increased levels of plasma LDL-cholesterol and enhanced CVD risk, whereas loss-of - function is associated with low LDL-cholesterol and reduced CVD [91, 93]. Pharmacologically induced PCSK9 inhibition efficiently reduces LDL-cholesterol levels. Monoclonal antibodies (mAbs) are now the most advanced way of reducing PCSK9 activity. PCSK9 inhibitors have been demonstrated to result in substantial lowering of LDL cholesterol levels. Data from trials of anti-PCSK9 mAbs in high-risk patients indicate that they yield the expected reduction in CVD events without major adverse effects [91].
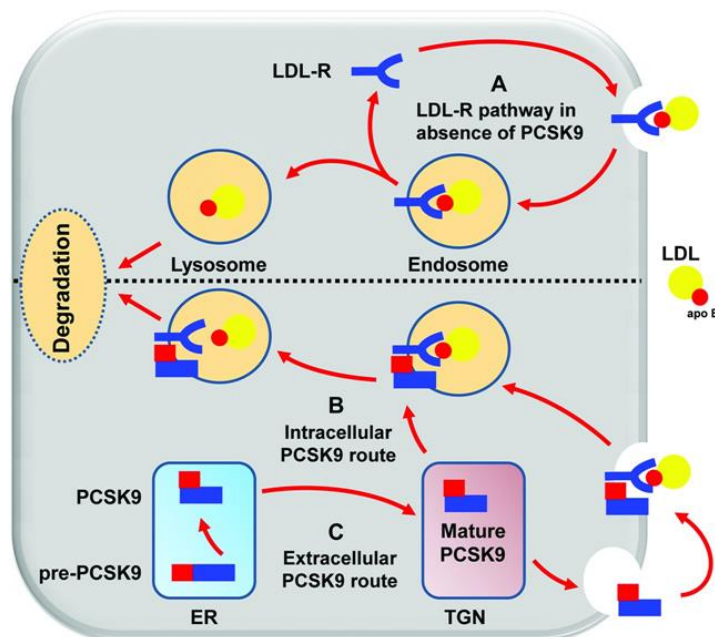
Figure 3. Theoretical model of PCSK9 role in the cholesterol homeostasis. The LDL-receptor (LDL-R) binds to apo B of LDL-particles and the complex is incorporated by receptor-mediated endocytosis. The LDL-receptor undergoes recycling to the plasma membrane, while the LDL-particle is directed toward lysosomal degradation. PCSK9 undergoes autocatalytic cleavage and is secreted in plasma, where it binds to the LDL-receptor. The LDL-receptor–PCSK9 complex is directed to lysosomal degradation in both intracellular and extracellular PCSK9 pathway. Abberivations: LDL-R; LDL-receptor, ER; endoplasmic reticulum, TGN; trans Golgi network. Adapted from [92] with permission.

1.6.2. Diet and PCSK9

PCSK9 has become a promising lipid-lowering target, but the research on diet's effects on PCSK9 is only in its initial phase. Dietary interventions appear to have varying effects on PCSK9 concentrations. Plasma PCSK9 concentrations were stable in healthy subjects assigned to a high-fat or high-protein diet for 4 weeks [94]. However, the lipid composition of high-fat meals may play a role in the regulation of PCSK9 activity, because different fatty acids may have varying effects [94, 95]. Marine n-3 polyunsaturated fatty acids and a Mediterranean style diet have been associated with low PCSK9 concentrations, whereas a high fructose diet was associated with high PCSK9 concentrations [94, 95]. The response to diet may differ in normal weight and obese subjects due to altered metabolic conditions. At this point, whether reducing dietary SFAs and subsequent beneficial effects on LDL-

cholesterol is attributable to reduced PCSK9 levels, and whether PCSK9 concentrations respond differently to SFA restriction in normal weight and obese individuals has not been clarified.

1.7. Summary

Dietary modification is essential in the prevention and treatment of obesity and CVD [6]. Moderate weight loss improves cardiometabolic risk factors, but long-term adherence to conventional weight loss diets is limited [3,6]. Therefore, to improve long-term health, accompanied with weight loss focus on qualitative dietary changes that contribute to reduced CVD risk regardless of weight loss, is of considerable importance [7, 8].

Lack of success with usual CER recommended in most obesity treatment guidelines [6, 25], have contributed to the proliferation of various diets which are commercially promoted. Most recently, different forms of IER, has achieved popularity. Whether IER is effective for weight loss, maintenance and improvements in cardiometabolic risk, and how IER versus CER affects nutritional composition and eating behavior is relevant to clinical practice. Currently larger long-term trials in order to understand the impact of IER on long-term weight loss and cardiometabolic risk factors in high risk populations is limited [35, 44], and to our knowledge the effect of IER versus CER on nutritional composition and eating behavior has not been compared in a head-to-head trial.

Given that weight loss maintenance requires long-term adherence to dietary changes [6, 25], the overall benefit of weight loss diets depends on more than solely weight reduction. If a diet is followed over time consideration of nutritional composition is important. Dietary fatty-acid composition regulates lipids and lipoprotein metabolism and thereby potentially CVD risk[49, 61, 62]. A main focus in dietary recommendations is replacement of saturated with unsaturated fat, primarily to reduce LDL-cholesterol [61-65]. However, variability in lipid responses to changes in dietary fat intake according to body weight, appears not to be discussed or considered in current dietary guidelines to reduce cardiovascular risk [61-65]. In the context of the current exploding obesity epidemic, better understanding of how obesity affects the lipid response to dietary fat and possible mechanisms are of major clinical importance.

2. Aims

The overall aim of this thesis was to examine the effect of different dietary interventions on a broad spectrum of cardiovascular risk factors in individuals at increased risk of cardiovascular disease.

Paper I (Study I: 5:2-study).

To compare the effects of IER versus CER on weight loss, maintenance and cardiometabolic risk factors after one year in men and women with abdominal obesity and at least one additional component of metabolic syndrome.

Paper II (Study I: 5:2-study).

To evaluate changes in nutritional composition and eating behavior over the course of three months among men and women randomized to IER or CER.

Paper III (Study II: The Saturated Fat and BMI Study).

To compare the effect of substitution of unsaturated fat for saturated fat for 6 weeks on serum lipids in normal weight (BMI $\leq$25 kg/m^2) and obese (BMI 30-45 kg/m^2) subjects with elevated LDL-cholesterol, and assess the effect of these changes on serum PCSK9 concentrations.

3. Ethics

The studies were approved by the local Regional Ethics Committee, and conducted according to the Declaration of Helsinki. All participants provided written informed consent before enrollment. The studies were registered at www.clinicaltrials.gov, NCT02480504 (Study 1) and NCT02589769 (Study 2).

4. Subjects and Methods

We conducted both trials at the outpatient clinic of the Preventive cardiology section, Department of endocrinology, morbid obesity and preventive medicine, Oslo University Hospital .

4.1. Study I; The 5:2–study

Study I had a randomized, parallel group controlled design. Eligible participants were men and women aged 21-70 years with abdominal obesity BMI 30-45.0 kg/m^2 and waist circumference ≥94/≥80 cm (men/women)), ≥ 1 additional metabolic syndrome component and weight stability within ≤3 kg during the last 3 months. Exclusion criteria were diabetes if treated with insulin or incretin analogues, bariatric surgery, use of anti-obesity drugs or other drugs affecting body weight, eating disorder, or psychiatric illness, or alcohol or drug abuse.

Participants were randomized in a 1:1 ratio to an IER or CER group by a computer-generated randomization list. A 6-month weight-loss phase including 10 visits with dieticians was followed by a 6-month maintenance phase without additional face-to-face counselling. Researchers and participants were not blinded to the intervention group.

The intervention diets were equally calorie restricted. Participants in the IER group were advised near-fasting (400 kcal/day for females and 600 kcal/day for males), on two non-consecutive days weekly while eating as usual the remaining five days a week. They received menus that recommended ~50 g protein/day from lean fish, chicken breast, lean white meat, fat-free yogurt, cottage cheese, egg or legumes, and vegetables to increase satiety on near-fasting days. Participants in the CER group were advised to reduce energy intake evenly on all seven days a week. The daily energy intake for participants in the CER group was based on the calculated caloric restriction two "fasting" days a week equals when the calorie restriction is evenly distributed on all 7 days of the week; calculated energy expenditure per week (TDEE x 7) minus total reduction in energy intake per week (TDEE minus 400/600 kcal [female/male] x 2)/7. They received individualized menus calculated in relation to each person's estimated energy requirements. Participants in both groups were encouraged to follow the general principles of a Mediterranean type diet, and they were instructed not to change their physical activity habits throughout the trial to avoid potential confounding. To improve compliance all participants received individualized dietary plans including educational materials and individual counselling in cognitive behavioral methods.

Dietary intake and adherence were assessed at baseline and after three months with a 7-day food record, using semi structured forms which questioned time/hour, name of the meal, type of food and amount of food. The dietary records were analyzed using a diet tool produced by The Norwegian Food Safety Authority and The Norwegian Directorate of Health [96].

Body weight, waist circumference, blood pressure and laboratory measures were obtained following a 10-h fast. Ratings of well-being, hunger and overeating were measured at three, six and 12 months with a subjective Visual Analogue Scale with a numeric rating from 1 (to a small degree) to 10 (to a very high degree). To examine changes in eating behavior, the participants completed the Norwegian version of the Three Factor Eating Questionnaire (TFEQ R-21) validated for measuring dysfunctional eating behaviors in obese individuals, at

baseline and after 3 months [97, 98]. The TFEQ R-21 consists of 21 items covering three categories; "uncontrolled eating", "cognitive restraint of eating" and "emotional eating".

In Paper I: The primary endpoint was change in body weight after 1 year. Secondary outcomes were changes in weight after 6 months and waist circumference, blood pressure, and other cardiometabolic risk factors after 6 months and 1 year.

In Paper II: The primary endpoint was change in dietary intake and eating behavior after 3 months.

4.2. Study II; The Saturated Fat and BMI Study

Study II also had a randomized, parallel group, controlled design. Inclusion criteria were men and women aged 21 to 70 years with normal BMI (≤ 25 kg/m^2) or obesity (BMI 30-45 kg/m^2) and elevated LDL cholesterol (≥ 3.0 mmol/l). Exclusion criteria were diabetes types 1 and 2, history of CVD or other atherosclerotic disease, eating disorder, secondary causes of hyperlipidemia, use of cholesterol-modifying drugs, genetic lipid disorder, gastrointestinal disorders that limit food choices, psychiatric illness, and drug or alcohol abuse.

In this study 83 men and women, stratified by BMI (normal: n=44; obese: n=39), were randomly assigned in a 1:1 ratio to follow a SFA- or PUFA-enriched diet for 6 weeks. Stratified block randomization with a fixed block size of 6 was performed. Since the trial was a dietary intervention of free-living individuals it was not feasible for participants or study personnel to be blinded, but the laboratory staff was blinded.

Study participants were randomly assigned to one of two weight maintenance diets that differed in their primary fat sources: either a PUFA-diet enriched with sunflower and rapeseed oil based margarine or a SFA-diet enriched with butter. Participants were provided with free margarine or butter at the biweekly study appointments dependent on their allocation at randomization. The diets aimed to achieve equal energy intakes and energy percentages (E%) from protein, carbohydrates (including E% from added sugar and grams of fiber) and fat, other than the differences in fatty acid composition. The goal was ~ 9 E% higher intake of SFA in the SFA-diet compared to the PUFA-diet and ~ 4 E% higher intake of PUFA in the PUFA- compared to the SFA-diet. Both diets emphasized choices of vegetables, fruits and whole grains and minimized intakes of sugar, processed meat and refined grains. The PUFA-enriched dietary group was instructed to use the sunflower and rapeseed oil based margarine or other vegetable oils low in SFA for cooking and spreads, choose low fat dairy products and lean meat and to use a minimum of 25 g standardized prepacked portions (10 g x 2.5) of sunflower and rapeseed oil based margarine daily. Participants in the SFA-enriched dietary group were recommended to choose full fat dairy products, meats and poultry without trimming off the fat, butter for cooking and spreading on breads, including a minimum of 24 g of standardized prepackaged portions (12 g x 2) of butter daily.

They were encouraged to maintain their usual level of physical activity and alcohol intake during the study. All subjects met individually face-to-face for dietary counseling at the beginning of the study and every second week thereafter, to facilitate understanding and adherence to the diet. Dietary intake and adherence were assessed at baseline and after 6 weeks using a weighed dietary record for 7 consecutive days which was analyzed using a diet tool produced by The Norwegian Food Safety Authority and The Norwegian Directorate of Health [96]. In order to assess ongoing dietary intake the dietitian questioned each participant

about consumption of the recommended portions of butter or margarine since the last visit at 2, 4 and 6 weeks and recorded the responses.

Clinical and laboratory measures were obtained at the biweekly appointments following a minimum of 10 hours of fasting.

In Paper III the primary endpoint was the change in LDL-cholesterol concentration from baseline to the mean of values at week 4 and 6 between the diet groups, with a subsequent comparison of the changes stratified according to BMI group if the interaction between BMI and change in LDL-cholesterol was statistically significant. Secondary outcomes were changes in concentrations of total- and HDL-cholesterol, TGs, apolipoprotein B and PCSK9 following the same approach as with LDL-cholesterol.

4.3. Overview of inclusion criteria, study design and participant flow

After provided written informed consent procedures and screening, the inclusion and exclusion criteria were evaluated and eligible subjects were randomized. Key features of the two randomized, parallel group, controlled design studies are summarized in **Table 1.**

Table 1. Overview of inclusion criteria and study designs

Study/ Paper	Intervention	Study design	Population	No of participants	Outcome	Duration
Study I/ Paper I & II	Comparison of two weight loss diets; IER and CER	Randomized, parallel groups	Men and woman with abdominal obesity and ≥ one additional metabolic syndrome component	Paper I, n = 112	Paper I change in -body weight, -waist circumference, -blood pressure, -lipids, -CRP, -glucose and HbA1c	12 months
				Paper II, n = 98	Paper II change in -dietary intake, -eating behavior	3 months
Study II/ Paper III	Comparison of substituting of PUFA diet for SFA diet	Randomized, parallel groups, stratified by BMI	Men and woman with normal weight (BMI ≤25 kg/m2) or obesity (BMI 30-45 kg/m2) and elevated LDL-cholesterol	n = 83	Change in -LDL-cholesterol, -other lipids, -PCSK9	6 weeks

Participants in both studies were men and women between 21 and 70 years Participant characteristics are shown in **Table 2.**

Table 2. Flow of participants, and age, sex and BMI distribution of randomized participants

	Study I; 5:2-study	Study II; The Saturated fat and BMI study
Screened, n	128	95
Randomized, n	112	83
Completed the study, n (%)	105 (94)	79 (95)
Mean age at inclusion	49±11	54±10
Women, %	50	68
Baseline BMI, kg/m^2	35.2±3.7	28.3±6.2

4.4. Statistics

Sample sizes were calculated according to study design and expected mean changes in primary outcome. The results are expressed as means ± SD and changes as means (95 % CI [lower bound, upper bound]). Significance level was assumed at $p < 0.05$. All continuous variables were checked for normality with the histogram, the Q-Q-plot and the Shapiro-Wilk test. Variables that were not normally distributed were logarithmically transformed, and parametric tests were used since normality was attained. Descriptive statistics were used to summarize baseline characteristics. Data was analyzed using IBM SPSS Statistics for Windows version 21 (SPSS Inc., Chicago, IL). Specific statistical analyses used in each of the papers are described.

Paper I: A linear mixed model, repeated measure analysis of variance (ANOVA) was used for between group comparisons. A paired sample t-test was used for within-group comparisons but these were considered secondary analyses and not primary results. We did not adjust for the primary outcome variable (body weight) at baseline, as it did not differ between groups. Analyses followed the intent-to-treat principle with the last value carried forward for dropouts, with additional complementary analyses of the per protocol population (i.e. the population that completed all 12 months). These analyses did not differ substantially, and the intent-to-treat analyses are presented.

Paper II: Analysis of covariance (ANCOVA) was used to compare changes in food intake, micro- and macronutrients and eating behavior between the treatment groups from baseline to the 3-month visit. Analyses were adjusted for baseline values (with baseline values as a covariate), and p-values represent between-group differences.

Paper III: Analyses followed the intent-to-treat principle with the last value carried forward for dropouts. ANCOVA was used to compare change between baseline and final visit (mean of week 4 and 6) for the treatment groups. Analyses were adjusted for baseline values (baseline values as a covariate), and p-values represent between-group differences from baseline to the means of weeks 4 and 6, after adjustment for baseline values. Individual analyses using a general linear model with change in LDL-, total and HDL-cholesterol, TG and apolipoprotein B as dependent variables and BMI, diet group and the product term BMI*diet group as fixed independent factors was conducted to determine if there was a significant interaction between BMI group and diet on LDL-, total and HDL-cholesterol, TG

and apolipoprotein B changes. ANCOVA, adjusted for baseline values (baseline values as covariate) was used to compare changes in macronutrients between baseline and after intervention for the treatment groups.

5. Summary of results

5.1 Study I; The 5:2–study

5.1.1 Paper I

Overall, weight loss was similar among participants in the IER versus CER group after 1 year (8.0 kg [SD 6.5] versus 9.0 kg [SD 7.1]; p = 0.6) as were changes in waist circumference (8.7 cm [SD 5.9] versus 9.6 cm [SD 6.3]; p = 1.0. Weight regain during the maintenance phase was minimal and similar between the intermittent and continuous energy restriction groups (1.1 kg [SD 3.8] versus 0.4 kg [SD 4.0]; p = 0.6. In total 63% of the participants in the IER group and 69% in the CER group achieved >5% weight loss. There were no between group differences in changes in cardiometabolic risk factors after 12 months. Within-group improvements were observed in regard to blood pressure and concentrations of HDL-cholesterol, TG and HbA1c in both groups after 12 months. No serious adverse events were reported.

Based on dietary records participants in the IER group reduced estimated energy intake by 28% (SD 18%) and participants in the CER group by 26% (SD 17%) from baseline to three months, with no between group differences (p = 0.6).

IER and CER resulted in similar weight loss, maintenance and improvements in cardiovascular risk factors after one year.

5.1.2 Paper II

Weight loss, energy intake, and macronutrient composition were similar in the IER and CER groups after 3 months. Based on results from the analyzes of the dietary records the CER compared to the IER group reported a greater increase in intake of fresh fruit and berries (45 g/day [95% CI 21, 71] vs. 2 g/day [95% CI −28, 33]; p = 0.047) and vegetables (135 g/day [95% CI 91, 179] vs. 65 g/day [95% CI 35, 96]; p = 0.010) and a greater decrease in sweets and bakery goods (−42 g/day [95% CI −57, −28] vs. −20 g/day [95% CI −37, −3]; p = 0.005). Fiber intake increased in the CER compared to the IER group (1.0 g/MJ/day [95% CI 0.8, 1.2] vs. 0.2 [95% CI 0.0, 0.4]; p < 0.001). The CER group had a greater reduction in E% from added sugar compared to the IER group (−2.2E% [95% CI −3.2, −2.2] vs. −0.1E% [95% CI −1.2, 1.0]; p = 0.049). Vitamin C intake increased more in the CER group than in the IER group (37 mg/day [95% CI 19, 56] vs. 4 mg/day [95% CI −10, 18]; p < 0.001). The IER group had a significantly greater decrease in folate, potassium magnesium intakes than the CER group (all p-values <0.014). For a substantial share of the study participants, the estimated intake of micronutrients did not meet the recommended intake for micronutrients at baseline and after 3 months in both diet groups. The proportion of participants whose estimated average daily intakes of vitamins and minerals did not meet the Estimated Average Requirement (EAR) in the Nordic Nutrition Recommendations [99] increased from baseline to 3 months and more in the IER group.

The participants in both diet groups improved eating behavior scores from baseline to 3 months, but cognitive restraint increased more in the CER than the IER group (34 [30, 39] vs. 17 [12, 22]; p=0.013).

Among men and women with abdominal obesity and ≥1 additional component of metabolic syndrome those following a CER compared to IER weight loss diet had more favorable changes in nutritional composition (in regard to intake of fruit and berries, vegetables, fiber,

sugar, and vitamin C). However, in both groups, a remarkable proportion of the study participants did not meet the EAR for micronutrients after the intervention.

5.2. Study II; The Saturated Fat and BMI Study

5.2.1 Paper III

Based on results of the dietary records, the participants achieved a difference in dietary fat intake in line with the goals for the dietary intervention. After intervention the SFA intake was 8.7 E% (7.1, 10.2) higher in the SFA than the PUFA diet group (p<0.001), and PUFA intake was 4.3 E% (3.5, 5.2) higher in the PUFA than the SFA diet group (p<0.001).

The PUFA compared to the SFA diet lowered total cholesterol, LDL-cholesterol, HDL-cholesterol and apolipoprotein B concentrations (all p-values ≤0.001). Analyses using a general linear model with change in lipid and apolipoprotein B concentrations as dependent variables, and BMI, diet group and product term BMI*diet group as fixed independent factors showed interactions between BMI*diet group in regard to changes in total cholesterol (p =0.001), LDL-cholesterol (p=0.009) and apolipoprotein B (p=0.007). For HDL-cholesterol and TG there were no significant interactions.
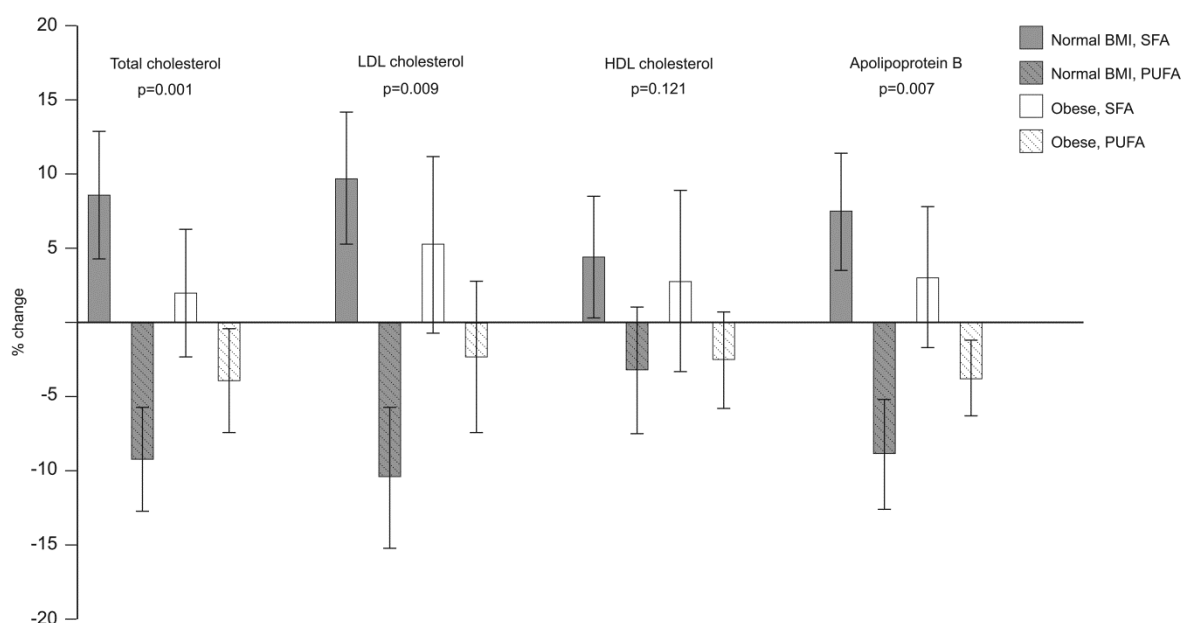
Figure 4. Mean changes (%) with 95% CI (lower bound, upper bound) in lipids from baseline to means of weeks 4 and 6 according to assignment to SFA or PUFA diet in participants with normal BMI or obesity. P-values for the interaction between BMI and diet determined by a general linear model for test of interaction (BMI*diet group), adjusted for baseline values. Post hoc comparisons showed that the respective changes in total cholesterol were 8.6% (95% CI 4.3, 12.9) in the normal weight versus 2.0% (-2.3, 6.3) in the obese participants (p=0.010) in the SFA-group, and -9.2% (-12.7,-5.7) in the normal weight versus -3.9% (-7.4, -0.4) in the obese participants (p=0.187) in the PUFA-group. LDL-cholesterol changed by 9.7% (5.3, 14.2) in the normal weight versus 5.3% (-0.7, 11.2) in the obese participants (p=0.206) in the SFA-group, and by -10.4% (-15.2,-5.7) in the normal weight versus -2.3% (-7.4, 2.8) in the obese participants (p=0.020) in the PUFA-group. Apolipoprotein B changed by 7.5% (3.5, 11.4) in the normal weight versus 3.0% (-1.7, 7.7) in the obese participants (p=0.140) in the SFA-group, and by -8.9% (-12.6,-5.2) in the normal weight versus -3.8% (-6.3,-1.2) in the obese participants (p=0.021) in the PUFA-group.

There were no significant changes from baseline to post intervention in PCSK9 concentrations between the diet groups. Furthermore changes in PCSK9 concentrations did not differ between normal weight and obese participants.

BMI modifies the effect of PUFA versus SFA with lesser improvements in atherogenic lipids in obese than normal weight individuals, possibly supporting adjustment of dietary recommendations according to BMI.

6. Discussion

I start with a brief discussion of the main results followed by methodological considerations.

6.1. Discussion of the main results

Study I; **the 5:2-study**: The overall results in the present thesis is that the 5:2 approach to IER seems to be as effective, but not superior to CER at inducing clinically significant weight loss, maintenance and improving cardiometabolic risk factors in free-living men and women with abdominal obesity at cardiovascular risk. Participants advised to follow a CER compared to the participants advised to follow an IER had more favorable changes in nutritional composition (in regard to intake of fruit and berries, vegetables, fiber, sugar, and vitamin C) and cognitive restraint, a component of eating behavior.

Study II; **the Saturated fat and BMI Study** : BMI seems to modify the effect of substituting unsaturated fat for saturated fat on circulating LDL-cholesterol, total cholesterol and apolipoprotein B concentrations, with lesser improvements in atherogenic lipids in obese than in normal weight individuals with similarly elevated LDL-cholesterol. These results may support adjusting dietary recommendations according to BMI.

The study results are thoroughly discussed in each paper. In this paragraph the results are discussed in the light of clinical implications.

6.1.1. Study I; the 5:2-study
Promising results from experimental and animal studies have shown that IER reduces body weight and improves metabolic risk factors [36]. Most previous human studies of intermittent fasting were limited to short intervention periods [34, 35, 44]. Results from short-term human studies were somewhat inconsistent. Most short-term studies indicate equivalent weight loss and improvements in cardiometabolic risks with IER and CER (34, 37, 38), while results from two studies in overweight or obese women suggested greater reductions body fat and insulin levels with IER than CER (40,41). Also a less studied IER regime, with alternated 2-wk cycles of energy restriction and balance, showed greater weight and fat loss with IER than with CER in obese men (42). In a review and meta-analysis of IER trials lasting a minimum of 6 months the author concluded that the preliminary results of the limited number of long-term studies indicated that neither IER nor CER was superior with respect to weight loss. The authors emphasized the need for larger long-term studies of 12 months or more to be conducted in order to understand the impact of IER on weight loss and long-term weight management.

Recently results from two long-term randomized controlled studies of metabolic healthy individuals have been published [45, 46] (one published ahead of the study in this thesis [45], the other afterwards [46]). Results from both of these studies indicate that IER is equivalent, but not superior to CER for weight reduction, maintenance and prevention of cardiometabolic risk factors. The authors in both studies point out that the generalizability of the findings related to cardiomatabolic risk factors to high risk populations may be limited considering the enrollment of predominantly metabolically healthy obese individuals. The participants in our trial were at high risk for adverse health conditions, given the presence of at least two

metabolic syndrome components in addition to all grades of obesity. This group remains the primary target for obesity treatment and intervention, but still less well represented in previous long-term trials comparing IER and CER [35, 44, 45-46]. To our best knowledge, our study was the first randomized, controlled, long-term study of IER operationalized as the 5:2-diet, showing that IER is as effective, but not superior to continuous energy restriction at inducing clinically significant weight loss [6], maintenance and improving cardiometabolic risk factors in men and women with abdominal obesity at cardiovascular risk. An updated meta-analysis of RCT trials summarizing the most recent evidence on the efficacy of IER versus CER on weight loss and multiple metabolic outcomes, confirmed our findings concluding that IER is as effective as CER for promoting weight loss and metabolic improvements [100]. Weight regain usually occurs with time and weight maintenance is an important component of the management of obesity. The three existing long-term RCT trials (12 months follow-up) did not find between-arms differences in weight loss maintenance when comparing IER and CER [45, 46, our 5:2-study].

The overall benefit of weight loss diets depends on more than solely weight reduction, and focus on nutritional composition concomitantly with weight loss may result in potentially synergistic effects on overall health [47, 48]. We found that weight loss, energy intake, and macronutrient composition were similar in the IER and CER groups. Despite the growing popularity of IER, studies comparing intake of micronutrients and different food groups between participants following an IER and a CER diet are generally lacking in the literature. We found that CER was associated with more favorable changes in nutritional composition in regard to intake of fruit and berries, vegetables, fiber, vitamin C and sugar compared to intermittent energy restriction. The findings of equal energy consumption in both intervention groups, but greater increase in intake of fruit, berries and vegetables, fiber and vitamin C and greater decrease in intake of sugar could indicate that subjects following a CER make more favorable food choices than subjects following an IER. This may be a consequence of the fact that the participants who followed an IER primarily were more aware of their food choices on the two weekly "fast days", while study participants who followed a CER were attentive to their food choices every day. This despite the fact that the participants in both intervention groups received the same qualitative dietary advice, and were encouraged to follow the general principles of a Mediterranean diet emphasizing more vegetables, fruits, legumes, fish, poultry, nuts, fermented dairy products, and olive oil and restricting processed meats, red meat, sweets, sugar-sweetened beverage and fruit juices. To ensure corresponding improvement in diet quality for participants following an IER it might be important to emphasize the intake of even more fruits and vegetables at the expense of sugar sweetened snack, bakery goods and beverages on the non-fasting days to weigh up the low food intake on the fasting days

It is well known that there really is no 'One Size Fits All' diet. Both IER and CER have been shown to be effective at inducing clinically significant weight loss of 5–10%, for weight-loss maintenance ≤1 y, and improving cardiometabolic risk factors in free-living men and women. This leaves us with more options for effective individualized dietary interventions in clinical practice.

6.1.2. Study II; The Saturated fat and BMI study.
We observed that the effect of replacing SFA with PUFA is dependent on BMI, with lesser improvements in LDL-cholesterol and apolipoprotein B in obese than in normal weight individuals. Our findings regarding the effect of BMI on the LDL-cholesterol response to

fatty acid composition is consistent with data from earlier dietary intervention studies indicating that subjects with increased BMI appear to demonstrate a lesser reduction in LDL-cholesterol in response to reduction in dietary SFA compared to their normal weight counterparts [71, 72, 88, 89]. However, this is the first study to our knowledge to directly compare normal weight and obese participants matched for LDL- cholesterol and excluding subjects with overweight (BMI 25-29.9 kg/m^2). This group was thought to be in-between the other two groups. Including overweight participants may impair the clarity of the results, given that one would not expect an absolute cut-off between groups, for example, between a BMI of 29.9 or 30.1 kg/m^2.

The typical obesity related dyslipidemia, atherogenic dyslipidemia, consists of increased TG, decreased HDL-cholesterol and normal or slightly increased LDL-cholesterol with increased small dense LDL [21, 22, 101]. Atherogenic dyslipidemia is a phenotype associated with increased cardiovascular risk [21-23]. Obesity, especially central obesity, is the main cause of metabolic syndrome characterized by visceral adiposity, insulin resistance, elevated blood pressure and glucose, elevated triglycerides, low levels of HDL-cholesterol [19, 20, 102]. Metabolic syndrome substantially increases the risk of CVD [19, 20, 101]. The dramatic increase in the prevalence of obesity has led to a marked increase in metabolic syndrome and this is considered to be one of the driving forces for the ongoing CVD epidemic [19].

In the current study, obese participants had significantly higher levels of TG and lower levels of HDL-cholesterol than those with normal BMI while both groups had similarly elevated LDL-cholesterol which was the lipid-related criterion for inclusion. These metabolic differences may likely affect dietary responses (24, 25). Limiting carbohydrates may be important in obese persons, as replacement of SFA with carbohydrates, especially refined carbohydrates, appears to have deleterious effects on atherogenic dyslipidemia [73]. Refined carbohydrates increase TG and small dense LDL-particles and reduce HDL-cholesterol, while carbohydrate restriction reverses these changes [83]. Moderate carbohydrate restriction and weight loss have been shown to provide equivalent but non-additive approaches to improving atherogenic dyslipidemia in men with overweight and obesity [84]. A recent meta-analyses of short- to medium-term (6 months–2 years) intake of low dietary fat compared with high dietary fat in people who are overweight or obese, was associated with lower plasma total cholesterol and LDL-cholesterol [103]. Conversely, low-fat diets were associated with a more unfavorable change in TGs, HDL-cholesterol and diastolic blood pressure compared with high-fat diets [103].

Numerous factors affect variability in lipid response to diet. Several different mechanisms have been proposed to account for the relation between BMI, adiposity and the reduced LDL-cholesterol response to dietary replacement of SFA with unsaturated fatty acids. In individuals with obesity, increased hepatic cholesterol synthesis as well as reduced cholesterol absorption could affect LDL-cholesterol concentrations, causing diminished plasma lipid response to diet [104, 105]. Furthermore the high VLDL concentrations seen with obesity could lead to increased conversion of very-low-density lipoprotein to LDL cholesterol and this production along with the storage of cholesterol by adipocytes may maintain a high plasma cholesterol concentration despite dietary changes [88].

Our secondary aim was to explore whether substitution of unsaturated fat for saturated fat affected serum PCSK9 concentrations and if the response differed between participants with normal or high BMI. We found no association between the responses in circulating LDL-cholesterol and changes in PCSK9 concentrations in normal weight or obese participants. We lacked data concerning other metabolic pathways that may characterize differences in dietary responsiveness, but our results suggest that differences in PCSK9 function may not be the

major pathway. Increased knowledge of the factors that diminish LDL-cholesterol response to dietary fat modulation in persons with obesity, will improve our understanding of the blunted lipid response to dietary interventions.

With the ongoing obesity epidemic with the pronounced atherogenic dyslipidemia the strategy of replacing total and saturated fats with mono- and poly unsaturated fat would still be recommended. However given that the effect of replacing SFA with PUFA is dependent on BMI, with lesser improvements in atherogenic lipids in obese than in normal weight individuals combined with the sugar-fat seesaw [86] the potential benefits of reducing SFA may be limited at least in the obese segment of the population. Our findings suggest that dietary advice aiming at cardiovascular risk reduction may be individualized according to BMI in addition to the lipid profile.

6.2 Methodological considerations

6.2.1 Study design
The two studies included in this thesis were designed as parallel RCT. RCT studies are known as the gold standard to determine the efficacy and safety of a treatment and whether a cause-effect relation exists [106]. In an RCT, the treatment groups in a trial are as similar as possible, except for the treatment they receive. If well-conducted, random assignment ensures that potential confounding factors are divided equally among the treatment groups, reduces bias and provides a rigorous tool to examine cause-effect relationships between an intervention and outcome.

To ensure equal distribution of important aspects as gender and BMI known as possible confounders the participants were randomized in a 1:1 ratio by a stratified sampling procedure by sex and BMI in both studies [107]. Two stratification factors, each with two values, yield four strata in both studies. In the 5:2-study (paper 1 and II) the participants were randomized using the four strata; male and BMI 30 to <35 kg/m^2, male and BMI 35 - 45 kg/m^2, female and BMI 30 to <35 kg/m^2, and female and BMI 35 - 45 kg/m^2, and in the Cholesterol-study; male and BMI <25 kg/m^2, male and BMI 30 - 45 kg/m^2, female and BMI <25 kg/m^2, and female and BMI 30 - 45 kg/m^2. Block randomization ensured balance in sample size across the intervention groups [108].

We considered a randomized crossover design for the **Saturated Fat and BMI Study** to lower the inter-individual variation in the response to dietary fat between participants [109], but due to long summer vacation seasons starting in June until the middle of August, dietary changes in the Christmas season starting already in the beginning of December and Easter dietary traditions starting in the end of March to April, the washout period is generally difficult to keep stable in Norway.

Study participants
The study populations in both studies were clearly defined including men and woman between 21 and 70 years at increased cardiovascular risk. The study participants were recruited through advertisement in newspaper and on the face-book page of Oslo University Hospital as well as from patient referrals to the Section of Preventive Cardiology, Department of Endocrinology, Morbid Obesity and Preventive Medicine. Exclusion criteria were both for

safety reasons and in order to exclude diseases, conditions and medications that could interfere with the outcome measures.

The participants in the **5:2-study** were at high risk for adverse health conditions, given the presence of at least two metabolic syndrome components in addition to all grades of obesity. This population are the primary target for obesity treatment and intervention, despite this, mainly metabolic healthy obese have been represented in the few long-term randomized controlled trials of intermittent fasting [35, 44, 45].

In the **Saturated Fat and BMI Study** only persons with elevated LDL-cholesterol were included in order to represent the most likely population to benefit from modification of dietary fat. The normal weight and obese participants were selected to be matched for elevated LDL-cholesterol as far as possible. The main benefit of dietary changes in fatty acid intakes is shown through the reduction in LDL-cholesterol. Even though the obese sample was matched for LDL-cholesterol to the normal weight sample, they had lower HDL-cholesterol and higher TGs than the normal weight sample, as would be expected given the effect of obesity on lipids. We could have selected the obese sample to match the normal weight participants in regard to HDL-cholesterol and TGs too, but that would require screening a very high number of individuals, and the final participants would not be representative of general obese populations.

Blinding
In intervention studies with whole diet approaches in free living subjects, blinding is very challenging, since the intervention usually is easily identified by both participants and researchers. In these trials, neither the researcher giving the dietary advice nor the participants were blinded given the nature of the intervention. Blinding is particularly difficult in regard to the extremely low energy intake on the "fasting days" in the **5-2 study**. In the **Saturated Fat and BMI Study** neutral packing of the margarine and butter would have been possible, but was not done in this study. We believe that the study participants anyhow would have tasted and felt the texture difference, since butter becomes very hard when it is stored in the fridge. The part of the dietary intervention concerning the selection of low fat versus full fat dairy products and lean meat versus meats and poultry without trimming off the fat, could have been possible if food for the whole period was handed out in concealed containers. This would have been very expensive and it would limit the participants' possibility to make individual food choices according to their preferences. The laboratory staff was blinded, and data entry was done by assistants who were blinded to study group. Computer generated block randomization lists were provided by an independent statistician, and a person not otherwise involved in the study administered assignment of the dietary group according to the list.

6.2.2 Generalizability
The main strength is the generalizability of the results due to high retention rates in both studies. The very low drop-out-rates of 5% in the CER group and 7% in the IER group in the 5:2-study are particularly unusual for long-term weight management trials. Most 6 to 12 months trials comparing IER versus CER generally show drop-out rates of 20% or higher [35,44, 45].

The study participants in both studies were persons that would be seen in clinical practice, including men and woman, lean and obese persons, and generally at increased cardiovascular risk. Unfortunately, men have been consistently underrepresented in randomized controlled trials of lifestyle weight loss interventions [110], although the prevalence of overweight and

obesity is similar for men (39 %) and woman (40 %) worldwide [1]. Consequently, most publications on weight loss interventions is largely based on women-dominant trials. In the **5:2-study** the proportion of men and women was equal. The **Saturated fat and BMI Study** also included both sexes, but in this trial women consisted of two-thirds of the sample.

In both studies participants had a wide age distribution, but little spread with regard to ethnicity (mostly White, 98 %). Since most of the participants were recruited through advertisements on Facebook and in the newspaper, they may have been somewhat more motivated for dietary changes than the general population.

The free living settings in both studies are useful to indicate how large dietary changes can be attained through individual counselling (dietary advice and behavior therapy) given by trained dietitians in people continuing their everyday lives. To achieve similar results the same level of follow-up from trained personnel is probably necessary.

6.2.3. Dietary assessment
A limitation in dietary intervention studies with free-living subjects is both compliance and how to make an accurate estimation of the dietary intake.

To compare the dietary intake and evaluate compliance with the dietary intervention, a 7-day weighed record were filled out for seven consecutive days, by the participant before screening and after 3 months in the **5:2-study** and before screening and between 4 and 6 weeks in the **Saturated fat and BMI study**. Dietary assessment is complex, a 7-day weighed dietary record has been regarded as the "gold standard", but studies validating weighed food records with doubly labelled water found high levels of under-reporting [111]. Despite this, 7-day weighed food records are often used and are often regarded as the most precise method for estimating food and/or nutrient intake [112]. Some previous studies have indicated that underreporting is more common among obese individuals [113-115o], anyway, we will assume that the underreporting is relatively similar in the randomized groups.

In order to assess ongoing dietary intake the **Saturated fat and BMI study** the dietitian also handed out a simplified dietary questionnaire, designed as a true or false check-list at visit 2, 4 and 6 weeks giving possibilities for feedback on the participants dietary intake during the study. The questionnaire included 9 statements covering key components of the recommended dietary pattern (fruit and vegetables, whole grains, fish, meat, dairy products and major sources of added sugars including beverages) and fat sources. The same type of questionnaire was given to participants in both dietary groups, statements regarding fat sources and fat quality being the only difference between groups. A maximum of 9 points reflected good compliance. Compliance scores were generally high as shown below:

Table 3. Compliance scores according to a simplified dietary questionnaire (scores shown are out of 9 checked items), mean ±SD values are shown.

	2 weeks (visit 3)	4 weeks (visit 4)	6 weeks (visit 5)
SFA (normal BMI, n= 23)	7.7 ± 1.5	8.3 ± 1.1	8.2 ± 1.3
SFA (obese, n= 17)	8.0 ± 0.8	8.1 ± 0.8	8.0 ± 1.5
PUFA (normal BMI, n= 20)	7.7 ± 1.1	8.1 ± 0.9	8.4 ± 0.9
PUFA (obese, n= 18)	7.9 ± 1.2	8.1 ± 1.1	8.3 ± 1.0

The 7-day dietary record is a validated method for comparing nutrient intake between groups, we chose to report results of the dietary record in the article and not the data from the simplified dietary questionnaire we used to assess ongoing dietary intake.

6.2.4. Statistical considerations
For study I; the **5-2 study** the sample size and power estimation was conducted to identify differences in weight loss which was the primary outcome, and not to identify differences in cardiometabolic factors, macro nutrients or food groups. This must be taken into consideration when viewing the data presented in paper I and paper II.

In study II; the **Saturated fat and BMI study** we based the power calculation on the expected changes in LDL-cholesterol between the diet groups. No comparable estimates regarding the treatment*BMI interaction was available. We performed a post hock comparison to ensure adequate power to investigate the treatment*BMI interaction. The power to detect the observed change between BMI categories of LDL–cholesterol across time between the two intervention groups (SFA and PUFA) was estimated by first calculating SD of the difference in LDL-cholesterol for each BMI category. This was done for each intervention group. Mean differences were calculated similarly. The power to detect a net difference in LDL-cholesterol over time was >0.99 (calculated with sampsi in STATA V14).

6.2.5. Ethical considerations
All participants were well informed before the study and provided written informed consent before enrollment. The informed consent emphasized the participant's right to withdraw from the study at any time also without giving a reason. In both studies diets in the intervention and control groups are based on nutritional recommendations in Norway to increase fruits, vegetables and whole grains and decrease sugar and processed meat intake. Since the intervention period in the **Saturated fat and BMI study** only lasted for 6 weeks there were no Institutional review board concerns regarding the increase in SFA in this population. All participants were informed of the study results at the last visit, and given nutritional guidance accordingly. None of the participants reported any concern about the increase in SFA.

7. Consequences of the findings of the thesis for clinical practice and suggestion for future research

7.1. Implications for clinical dietary treatment

7.1.1. Study I; the 5:2-study

Ideal, sustainable dietary approaches for long-term weight loss should be satiating and satisfying, meet nutritional requirements, promote loss of fat and preserve lean body mass, improve and prevent obesity-related comorbidities and cardiometabolic risk factors, enhance compliance and ensure long-term safety. The era of personalized nutrition is drawing closer, but still, adherence to the diet is essential. Clinicians must ask themselves how they can individualize dietary advices to help the patients to achieving dietary adherence. IER has been shown to be safe and effective to induce clinically significant weight loss and maintenance, and improve cardiometabolic risk factors in free-living men and women. This leaves us with more options for effective individualized dietary interventions which hopefully could improve the effectiveness of obesity treatment, resulting in better long-term adherence and sustained health benefits. An explicit focus on diet quality to favor positive changes in nutritional composition especially in regard to increased intakes of fruit, berries, and vegetables and lower sugar intakes seems to be important to ensure equally positive changes in diet quality for people following IER compared to CER.

7.1.2. Study II; the Saturated fat and BMI study

Clearly, diets high in either saturated fats or refined carbohydrates are not suitable for CVD prevention. Although intake of saturated fat should remain low, a singular focus on reduction of saturated fat can be counterproductive. The overall changes in the entire lipoprotein profile and cardiometabolic risk must be taken into account. It appear that dietary advice to reduce cardiometabolic risk in people with obesity should be tailored to the individual's wishes and capacity for weight loss and ability to make multiple dietary changes, as well as consideration of the degree of insulin resistance and atherogenic dyslipidemia. A wider range of dietary plans to lose weight may be acceptable and more emphasis may be placed on balancing the diet.

7.2. Suggestion for further research

In the future it would be of interest to investigate if it is possible to identify any specific behavioral traits or differences in BMI, or other clinical characteristics which make IER more tolerable for some individuals than others. Learning more about whether IER affect components of appetite regulation (e.g. ghrelin and other incretin concentrations) and postprandial metabolism differently from CER would be of great interest. Furthermore, evaluating hard endpoints including cardiovascular outcomes and type 2 diabetes mellitus would be preferred but is not feasible. Studies should be conducted to investigate whether the promising findings from animal studies which indicate that fasting may counteract several disease processes involved in cancer, neurological diseases as Alzheimer's and Parkinson's' and type 2 diabetes also seem to play a role in humans.

BMI seems to modify the effect of PUFA versus SFA with lesser improvements in atherogenic lipids in obese than normal weight individuals, but the mechanism explaining the

difference in response remains to be elucidated. Considering that longer intervention periods could possibly lead to other adaptive mechanisms studies with longer intervention period than 6 weeks should be conducted, though the lipid response tends to occur within this time frame. Whether weight loss reverses the observed diminished LDL-cholesterol response to dietary fat modulation in persons with obesity also requires future study.

8. Conclusion

- In men and women with abdominal obesity at high cardiovascular risk
  - IER and CER energy restriction resulted in similar weight loss, maintenance and improvements in cardiovascular risk factors after one year
  - IER was effective at inducing clinically significant weight loss of 5−10%, maintaining the weight loss for up to 1 year, and improving cardiometabolic risk factors

  These findings provide the opportunity for more options for effective individualized dietary interventions for weight loss.

- CER was associated with more favorable changes in nutritional composition (in regard to intake of fruit and berries, vegetables, fiber, vitamin C and sugar) compared to intermittent energy restriction. To ensure improvement in the overall quality of weight loss diets, focus on food choices and the adequacy of micronutrient intakes need to be emphasized.

- CER also resulted in more favorable changes in cognitive restraint, a component of eating behavior, than intermittent energy restriction. The significance of this finding may be better compliance over longer time, however this possibility needs more investigation.

- The effect of replacing SFA with PUFA was dependent on BMI, with lesser improvements in atherogenic lipids in obese than in normal weight individuals with elevated LDL-cholesterol.

- Dietary advice aiming at cardiovascular risk reduction may be individualized according to BMI in addition to the lipid profile.

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10. Appendix

Beregning av energiinntak jevn energireduksjon

Mifflins formel

Kvinner: REE (kcal) = 10×vekt (kg) + 6.25×høyde (cm) - 5×alder (år) - 161

Menn: REE (kcal) = 10×vekt (kg) + 6.25×høyde (cm) - 5×alder (år) + 5

Mifflin MD, St Jeor ST, Hill LA, et al. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr 1990; 51: 241-7.

Kvinner REE:

10 x vekt _____(kg) + (6,25 x høyde) _____(cm) – 5 x alder ____ (år) – 161 = _____kcal

Menn REE:

10 x vekt _____(kg) + 6,25 x høyde _____(cm) – 5 x alder ____ (år) + 5 = _____kcal

Aktivitetsfaktor: _____

Totalt energiforbruk pr dag:

REE _____kcal x aktivitetsfaktor _____ = _____kcal

Totalt energiforbruk per uke:

Energiforbruk pr.dag _____kcal x 7 = _____kcal

Total reduksjon i energiforbruk per uke kvinner

(Energiforbruk pr dag _____kcal – 400) x 2 = _____kcal

Total reduksjon i energiforbruk per uke menn

(Energiforbruk pr dag _____kcal – 600) x 2 = _____kcal

Gjennomsnittlig energibehov per dag:

Totalt energiforbruk pr uke _____kcal – reduksjon i energiforbruk pr uke _____kcal/ 7 = _____kcal

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Energiinntak per dag, ved jevn energireduksjon

MENY _____kcal

Slik får du suksess med 5:2-dietten, en enkel guide

Tradisjonelt har man anbefalt å spise litt færre kalorier enn man trenger hver dag for å gå ned i vekt. Men i 5:2 dietten, anbefales du heller å kutte drastisk ned på kaloriinntaket, tilnærmet faste to dager i uken, og spiser normal mengde mat resten av uken. Resultatet er at du over tid får i deg færre kalorier enn du ellers ville ha gjort og at du går ned i vekt. Fastedagene skal spres utover uken og gjennomføres fortrinnsvis på mandag og torsdag. Du kan velge andre dager, men skal ikke faste to dager på rad. På fastedagene skal kvinner innta kun 400 kalorier og menn kun 600 kalorier. Det er veldig viktig at du begrenser deg til dette inntaket de dagene du faster for å få best mulig resultat. For å bli mest mulig mett med, anbefaler vi at du spiser mye grønnsaker og matvarer som inneholder protein (ren fisk, kylling, belgfrukter og cottage cheese). Nedenfor finner du tips og enkle retter for fastedagene. De dagene du ikke «faster» skal du forsøke å følge prinsippene i middelhavsdietten, se oversikt side 2

Tips for fastedagene.

1) **Drikk mye vann.** Det er bra for alle å drikke mye vann, men det er spesielt viktig de dagene du faster. Drikk minst to liter vann. Dette demper sultfølelsen og minsker sjansen for hodepine. Du kan også drikke svart kaffe, vanlig te og urtete uten tilsatt sukker, honning eller melk. Hva med å tilsette skiver av appelsin, sitron eller agurk til vannet?

2) **Planlegg fastedagene.** Bestem deg for hvilke dager du skal faste før uken begynner og planlegg nøyaktig hva du skal spise disse dagene. Det er opp til deg om du vil fordele maten du spiser på to eller tre måltider. Her er to måter og fordele maten på for henholdsvis kvinner og menn. Det er opp til deg når du velger å innta måltidene. Mange opplever at det er best å spise hoveddelen av maten utover kvelden, men det er opp til deg.

Kvinner (400 kcal)	Kvinner (400 kcal)	Menn (600 kcal)	Menn (600 kcal)
Alternativ 1: Frokost 100 kcal Lunsj: 150 kcal Middag: 150 kcal	Alternativ 2: Frokost eller lunsj: 200 kcal Middag: 200 kcal	Alternativ 1: Frokost 100 kcal Lunsj: 250 kcal Middag: 250 kcal	Alternativ 2: Frokost eller lunsj: 300 kcal Middag: 300 kcal

3) **Unngå overspising.** Spis normalt fem dager i uken, men for å få full effekt av dietten både for vekten og helsen er det viktig å unngå overspising disse dagene og at du spiser sunt. Du anbefales å følge middelhavskostholdet, se veiledning side 2.

4) **Forberede deg mentalt.** Forberede deg og bestem deg. Vi mennesker er vanedyr. Det er viktig at du forbereder deg mentalt til den første fastedagen. Mange opplever at den første fastedagen er tøff fordi de føler seg sultne og litt uopplagte, men det går stadig lettere og etter hvert er det mange som beskriver at de faktisk føler seg ekstra opplagt og skjerpet de dagene de faster. Det er helt normalt at du føler deg sulten og det er ikke farlig å være sulten, men det kan oppleves ubehagelig. Dette er ofte forbigående og det kan hjelpe å drikke mye vann og en svart kaffe/te om du pleier å drikke kaffe og/eller te.

5) **Gjør noe.** Mange opplever at det hjelper å holde på med noe de dagene man faster enten det er et strikketøy, nedvasking av kjøkkenet, prate med noen i telefon eller noe annet. Husk at både sult og sug er forbigående.
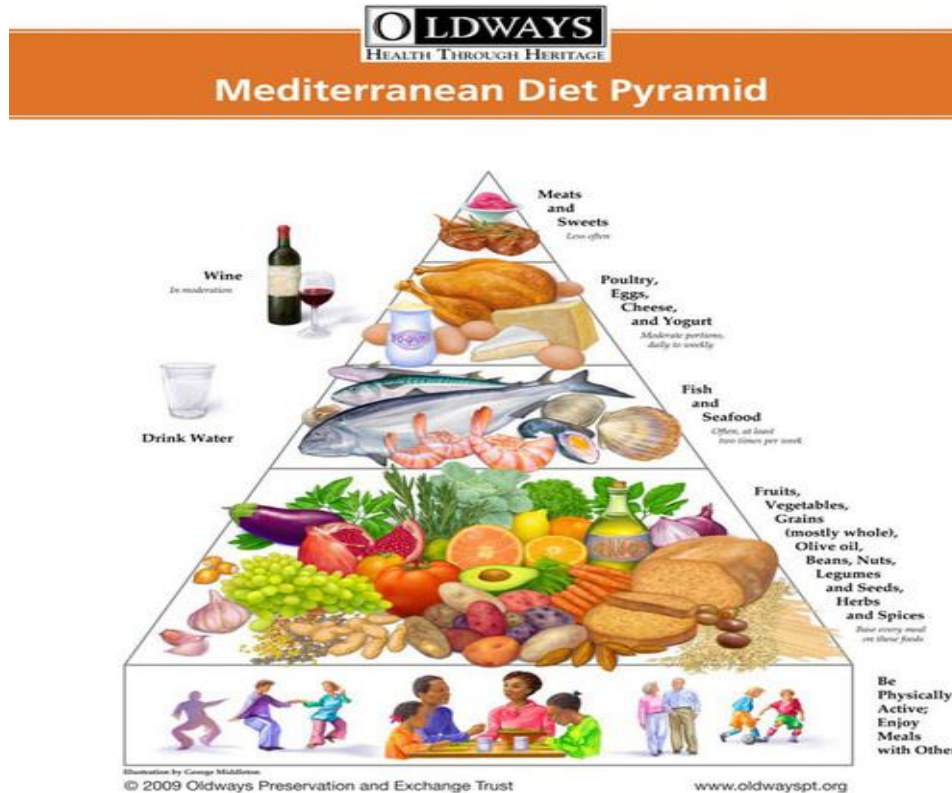
Hovedprinsippene i Middelhavsdietten.

Det er godt dokumentert at middelhavsdietten minsker risikoen for hjerte og karsykdommer og kan bidra vektnedgang. I denne studien skal du derfor forsøke å pise i tråd med kostholdsprinsippene i middelhavsdietten. Vi vil hjelpe deg med å gjøre individuelle tilpasninger, slik at det blir lettere for deg å følge kostholdsplanen. Hovedprinsippene for Middelhavsdietten er et kosthold med mye grønnsaker, frukt, grove kornprodukter, fisk, kylling, usaltede nøtter og olivenolje, moderat inntak av ost og yoghurt og begrenset inntak av oppblandede kjøttprodukter, sukker, snacks og godteri.

ANBEFALT

- Grønnsaker: Spis minimum to porsjoner (400 g) hver dag
- Frukt: Spis 2-3 porsjoner (600 g) hver dag
- Olivenolje: Velg olivenolje fremfor smør til steking, dressinger og ovnsbaking
- Fisk: Spis fisk, helst tilsvarende 3 middagsporsjoner per uke, gjerne fet fisk.
- Velg rent kjøtt og gjerne hvitt kjøtt fremfor oppblandede kjøttprodukter som pølser og kjøttdeig både som pålegg og til middager.
- Belgfrukter: Spis gjerne bønner, linser eller kikerter
- Grove kornprodukter: Spis grovt brød og knekkebrød, fullkornspasta og musli med lite sukker
- Vann som tørstedrikk

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

Fastedag kvinner 400 kalorier (100 + 150 + 150). Velg ett frokost alternativ til 100 kalorier og et kunsj/middagsalternativ til lunsj og et til middag.

Frokost: 100 kalorier

Alternativ 1

En Skyr i smalt beger (finnes i flere smaker)

Vann og kaffe/te

Alternativ 2

2 beger Yoplait 0 % (finnes i flere smaker)

Vann og kaffe/te

Alternativ 3

Ett knekkebrød (WASA Husmann eller Sport)

Mager smøreost, en porsjon 20 g eller tre skiver kylling-/kalkunpålegg
En tomat
10 skiver agurk   Vann og kaffe/te

Lunsj/middag: 150 kalorier per alternativ

Alternativ 1; salat
2 dl grønn salat (isberg, ruccola, spinat etc)
1 tomat i biter
10 cm agurk i terninger
100 g kalkun-/kyllingpålegg/ linser/ kikerter/cottage cheese eller 80 g tunfisk i vann
3 ts mager kesam med urter
Vann og kaffe/te

Alternativ 2; knekkekbrød og yoghurt
1 knekkebrød (WASA Husmann eller Sport)
Mager smøreost, en porsjon 20 g
1 tomat
10 skiver agurk
1 beger Yoplait 0 %
Vann og kaffe/te

Alternativ 3; tomatsuppe
2 dl tomatsuppe fra pose
1 kokt egg
Vann og kaffe/te

Alternativ 4; fiskesuppe
2 dl fiskesuppe fra pose
1 strimlet gulrot som koker med suppen
60 g torsk i biter trekkes i suppen
Vann
Kaffe/te

Alternativ 5; Linsesuppe (se oppskriftshefte)
2,5 dl suppe
1 ss kesam
Vann og kaffe/te

Alternativ 6; wok
150 g frossen wok blanding eller ferske grønnsaker (f.eks brokkoli, paprika, gulrot, løk)
60 g kyllingbryst, mager hvit fisk, tunfisk, kikerter, brunebønner eller magert kjøtt i strimler
1 ss soyasaus
1 ts sursøt chillisaus
Vann og kaffe/te

Alternativ 7; egg
1 stk speilegg eller kokt egg
1 tomat
10 cm agurk
1 dl salat
1 skive røkt laks eller ørret eller 4 skiver kalkun/kyllingpålegg/ren skinke
Vann og kaffe/te

Alternativ 8; ratatouille
2 dl ratatouille (se oppskriftshefte)
50 g linser, kikerter, bønner eller kylling/-kalkunbryst (pålegg eller stekt selv)
Vann og kaffe/te

200 kaloriers måltider

Alternativ 1; Skyr og frukt
En Skyr i smalt beger (finnes i flere smaker)

1 frukt i biter (eple, appelsin, kiwi)
2 ss (10 g) fiberrik kornblanding, eks Vita
Vann og kaffe/te

Alternativ 2; Yoghurt og frukt
2 beger Yoplait 0 % (finnes i flere smaker)

1 frukt i biter (ikke banan)
2 ss (10 g) fiberrik kornblanding, eks Vita
Vann og kaffe/te

Alternativ 3; knekkebrød
To knekkebrød (WASA Husmann eller Sport)

Mager smøreost, to porsjon, totalt 40 g
Eller 6 skiver kylling/kalkunpålegg
En tomat
10 skiver agurk
Vann og kaffe/te

Alternativ 4; salat
2 dl grønn salat (isberg, ruccola, spinat etc)
1 tomat i biter
10 cm agurk i terninger
130 g kalkun-/kyllingpålegg/ linser/ kikerter/cottage cheese eller 80 g tunfisk i vann
4 ts mager kesam med urter
Vann og kaffe/te

Alternativ 5; knekkebrød og yoghurt
1 knekkebrød (WASA Husmann eller Sport)
Mager smøreost, en porsjon, 20 g
1 tomat
10 skiver agurk
1 beger Yoplait 0 %
En frukt (ikke banan)
Vann og kaffe/te

Alternativ 6; tomatsuppe
2,5 dl tomatsuppe fra pose
1,5 kokt egg
Vann og kaffe/te

Alternativ 4; fiskesuppe
2,5 dl fiskesuppe fra pose
1 strimlet gulrot som koker med suppen
100 g torsk i biter trekkes i suppen
Vann og kaffe/te

Alternativ 5; Linsesuppe (se oppskriftshefte)
4 dl suppe
1 ss kesam
Vann og kaffe/te

Alternativ 6; wok
170 g frossen wok blanding eller ferske grønnsaker (f.eks brokkoli, paprika, gulrot, løk)
100 g kyllingbryst, hvit fisk, tunfisk i vann, kikerter, brunebønner eller magert kjøtt i strimler
1 ss soyasaus
1 ts sursøt chillisaus
Vann og kaffe/te

Alternativ 7; egg
2 stk kokt eller stekt egg (speilegg, omelett)
1 tomat
10 cm agurk
1 dl salat
1 skive røkt laks eller ørret eller 4 skiver kalkun/kyllingpålegg/ ren skinke
Vann og kaffe/te

Alternativ 8; ratatouille
2,5 dl ratatouille (se oppskriftshefte)
65 g linser, kikerter, bønner eller kylling/-kalkunbryst (pålegg eller stekt selv)
Vann og kaffe/te

Frokost: 100 kalorier
Alternativ 1
En Skyr i smalt beger (finnes i flere smaker)

Vann og kaffe/te

Alternativ 2
2 beger Yoplait 0 % (finnes i flere smaker)

Vann og kaffe/te

Alternativ 3
Ett knekkebrød (WASA Husmann eller Sport)

Mager smøreost, en porsjon 20 g eller 3 skiver
kylling/kalkunpålegg
En tomat
10 skiver agurk
Vann og kaffe/te

Lunsj/middag: 250 kalorier per alternativ
Alternativ 1; salat
2 dl grønn salat (isberg, ruccola, spinat etc)
2 tomat i biter
10 cm agurk i terninger
160 g kalkun-/kyllingpålegg/ linser/
kikerter/cottage cheese eller 80 g tunfisk i vann
5 ts mager kesam med urter
Vann og kaffe/te

Alternativ 2; knekkekbrød og yoghurt
2 knekkebrød (WASA Husmann eller Sport)
Mager smøreost, 2 porsjoner, totalt 40 g
2 tomat
10 skiver agurk
1 beger Yoplait 0 % eller en frukt (ikke banan)
Vann og kaffe/te

Alternativ 3;tomatsuppe
3 dl tomatsuppe fra pose
2 kokt egg
Vann og kaffe/te

Alternativ 4; fiskesuppe
3 dl fiskesuppe fra pose laget med lettmelk 0,5
% fett
1 strimlet gulrot som koker med suppen
100 g torsk i biter trekkes i suppen
Vann og kaffe/te

Alternativ 5; Linsesuppe (se oppskriftshefte)
5 dl suppe
1 ss kesam
Vann og kaffe/te

Alternativ 6; wok
200 g frossen wok blanding eller ferske
grønnsaker (f.eks brokkoli, paprika, gulrot, løk)
120 g kyllingbryst, hvit fisk, tunfisk, kikerter,
brunebønner eller magert kjøtt i strimler
1 ss soyasaus
1 ts sursøt chillisaus
Vann og kaffe/te

Alternativ 7; egg
2 stk speilegg, kokt egg eller eggerøre av 2 egg
1 tomat
10 cm agurk
1 dl salat
2 skive røkt laks eller ørret eller 8 skiver
kalkun/kyllingpålegg/ ren skinke
Vann og kaffe/te

Alternativ 8; ratatouille
3 dl ratatouille (se oppskriftshefte)
100 g linser, kikerter, bønner eller kylling/-
kalkunbryst (pålegg eller stekt selv)
Vann og kaffe/te

 300 kaloriers måltider

Alternativ 1; Skyr og frukt
En Skyr i smalt beger (finnes i flere smaker)

2 frukt i biter (eller en liten banan)
5 ss (20 g) fiberrik kornblanding, eks Vita
Vann og kaffe/te

Alternativ 2; Yoghurt og frukt
2 beger Yoplait 0 % (finnes i flere smaker)

2 frukt i biter (eller en liten banan)
5 ss (25 g) fiberrik kornblanding, eks Vita
Vann og kaffe/te

Alternativ 3; knekkebrød
Tre knekkebrød (WASA Husmann eller Sport)

Mager smøreost,3 porsjoner, totalt 60 g eller
12 skiver kylling-/kalkunpålegg
To tomater
10 skiver agurk
Vann og kaffe/te

Alternativ 4; salat
3 dl grønn salat (isberg, ruccola, spinat etc)
1 tomat i biter
10 cm agurk i terninger
200 g kalkun-/kyllingpålegg/ linser/
kikerter/cottage cheese eller 160 g pillede
reker
4 ts mager kesam med urter
Vann og kaffe/te

Alternativ 5; knekkekbrød og yoghurt
2 knekkebrød (WASA Husmann eller Sport)
Mager smøreost, to porsjoner, totalt 4 g
1 tomat
10 skiver agurk
1 beger Yoplait 0 %
En frukt (ikke banan)
Vann og kaffe/te

Alternativ 6; tomatsuppe
4 dl tomatsuppe fra pose
2 kokt egg
Vann og kaffe/te

Alternativ 4; fiskesuppe
4 dl fiskesuppe fra pose laget med lett melk
0,5 % fett
1 strimlet gulrot som koker med suppen
120 g torsk i biter trekkes i suppen
Vann og kaffe/te

Alternativ 5; Linsesuppe (se oppskriftshefte)
6 dl suppe
1 ss kesam
Vann og kaffe/te

Alternativ 6; wok
200 g frossen wok blanding eller ferske
grønnsaker (f.eks brokkoli, paprika, gulrot,
løk)
200 g kyllingbryst, mager hvit fisk, tunfisk,
kikerter, brunebønner eller magert kjøtt i
strimler
1 ss soyasaus
1 ts sursøt chillisaus
Vann og kaffe/te

Alternativ 7; egg
2 stk speilegg, kokt egg eller eggerøre av 2 egg
1 tomat
10 cm agurk
1 dl salat
2 skive røkt laks eller ørret eller 6 skiver
kalkun/kyllingpålegg/ ren skinke
1 knekkebrød (WASA Husmann eller Sport)
Vann og kaffe/te

Alternativ 8; ratatouille
2,5 dl ratatouille (se oppskriftshefte)
65 g linser, kikerter, bønner eller kylling/-
kalkunbryst (pålegg eller stekt fillet)
Vann og kaffe/te

Jevn energireduksjon.

Du er nå med i en vektreduksjonsstudie der du vil få tett oppfølging gjennom ett år. I denne studien vil vi forsøke å hjelpe deg med å innarbeide et opplegg som passer for nettopp deg og din kropp. Vi vet at det er krevende å gjøre omlegginger i kostholdet, men vi vil støtte deg og oppmuntre deg i prosessen. Du vil få gode tips og en individualisert kostholdsplan som øker dine sjanser for å gå ned i vekt og bli der. Nedenfor finner du noen generelle tips og din kostholdsplan som er tilpasset din vekt og ditt energibehov.

Drikk mye vann. Det er bra for alle å drikke mye vann, men det er spesielt viktig når du skal gå ned i vekt siden det bidrar til å dempe sultfølelsen noe. For å få en friskere smak på vannet kan du gjerne tilsette noen skiver appelsin, sitron, lime eller agurk til vannet?

Planlegg dagene dine. Det er en forutsetning for å klare å gjøre sunne og gode matvalg at du planlegger måltidene dine både med hensyn på når og hva du skal spise. Du bør ta utgangspunkt i din kostholdsplan, men det er opp til deg om du ønsker å slå sammen noen av måltidene eller stokke litt om på tidspunktene slik at du f.eks spiser en tidlig middag og heller forskyver litt av lunsjen til en litt større kveldsmat. Du må finne en rytme som passer for deg og ditt liv og vi hjelper deg gjerne.

Unngå overspising. Jobb bevisst med å trene deg på å unngå overspising og ukontrollert spising. Dersom dette er utfordrende for deg bør du bruke litt ekstra tid på øvelsen om sult og sug som du vil få utdelt etter hvert, spør gjerne om å få denne tidligere dersom du merker at dette er en av dine utfordringer.

Forberede deg mentalt. Forberede deg og bestem deg. Vi mennesker er vanedyr og det er utfordrende å gjøre endringer i kostholdet. Det tar lang tid å innarbeide nye vaner og når du skal legge om kostholdet og gå ned i vekt er det en forutsetning for å lykkes at du er fokusert og jobber med dette hver dag. Vi er her for å støtte deg! Fortell hva du syns er vanskelig, så prøver vi sammen å finne gode løsninger.

Rydd i skap og kjøleskap

For de fleste er det flere årsaker til at man spiser mer enn man ønsker, men felles for de fleste av oss er det at tilgjengeligheten er en viktig faktor. Dersom man vet at det ligger sjokolade (særlig en åpnet pakke), havrekjeks eller en middagsrest i skapet ender vi ofte opp med å spise litt ekstra. Ta en titt i ditt kjøleskap og dine skap; sørg for at du har tilgang på fristende frukt og grønnsaker og rydd unna fristelser som er vanskelig å motstå.

Få nok søvn. Søvnunderskudd er vist å trigge spising.

Ikke alle, men mange tyr til mat når man føler seg trøtt og uopplagt. Dette er en ond sirkel og beste medisin er å passe på at man får nok søvn. Studier har vist at særlig lysten på sukker og andre raske karbohydrater øker ved søvnunderskudd. For å dempe søtsuget er det derfor viktig å sove nok.
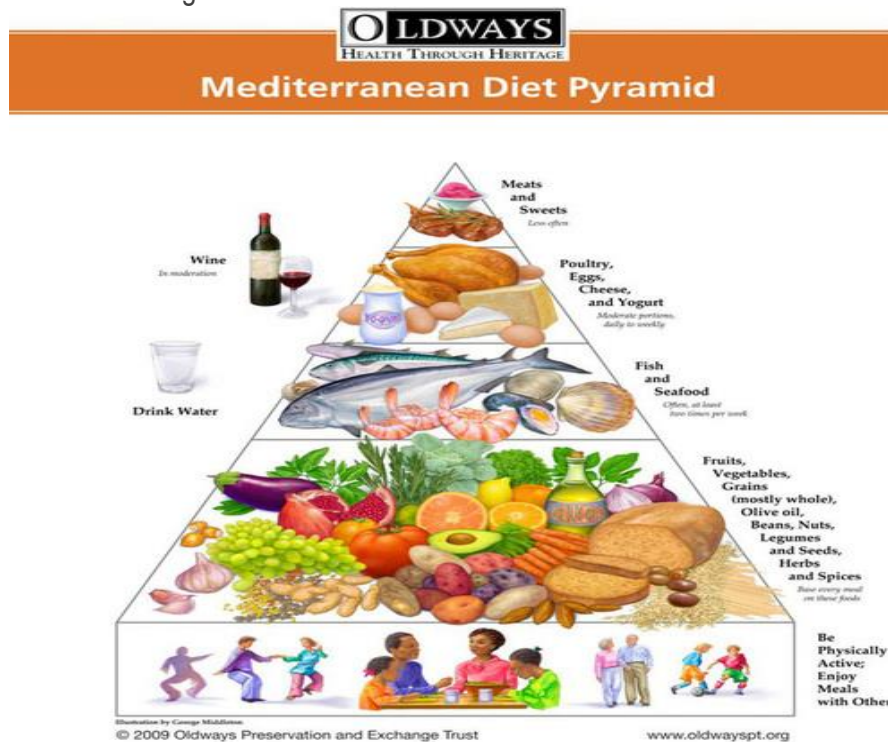
Det er godt dokumentert at middelhavskostholdet minsker risikoen for hjerte- og karsykdommer og kan bidra vektnedgang. Du bør ta utgangspunkt i hovedprinsippene i middelhavskostholdet når du setter sammen ditt kosthold. Hovedprinsippene for Middelhavsdietten er et kosthold med mye grønnsaker, frukt, grove kornprodukter, fisk, kylling, usaltede nøtter og olivenolje, moderat inntak av ost og yoghurt og begrenset inntak av oppblandede kjøttprodukter, sukker, snacks og godteri. Vi kan hjelpe deg med å gjøre individuelle tilpasninger, slik at det blir lettere for deg å følge kostholdsplanen.

ANBEFALT

- Grønnsaker: Spis minimum to porsjoner (400 g) hver dag
- Frukt: Spis 2-3 porsjoner (600 g) hver dag
- Olivenolje: Velg olivenolje fremfor smør til steking, dressinger og ovnsbaking
- Fisk: Spis fisk, helst tilsvarende 3 middagsporsjoner per uke, gjerne fet fisk.
- Velg rent kjøtt og gjerne hvitt kjøtt fremfor oppblandede kjøttprodukter som pølser og kjøttdeig både som pålegg og til middager.
- Belgfrukter: Spis gjerne bønner, linser eller kikerter
- Grove kornprodukter: Spis grovt brød og knekkebrød, fullkornspasta og musli med lite sukker
- Vann som tørstedrikk

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

Dagsmeny 1500 kalorier

Denne måltidsplanen er tilpasset din utgangsvekt og ditt energibehov og ved å følge denne måltidsplanen kan du gå ned mellom 0,5 og 1,0 kg per uke. Du finner ulike alternativer for både frokost, lunsj og mellommåltider som har tilsvarende kalori- og næringsinnhold slik at du selv kan velge det du foretrekker.

Dersom du f.eks ønsker en litt mindre frokost og en litt større lunsj kan du selvfølgelig «spare» f.eks. et knekkebrød fra frokosten og legge det til lunsjmåltidet ditt, dette vil ikke påvirke vektnedgangen. Men husk at dersom du legger til noe som ikke står på dagsmenyen eller spiser et ekstra stort måltid en dag, må du kutte ned på noe annet for å oppnå forventet vektreduksjon (se bytteliste for å vite hvor mange kalorier det er ulik matvarer).

Frokost (300 kalorier)

Alternativ 1:

- 1 skive grovt brød med minimum 75 % fullkorn, bruk brødskalaen
- Tynt lag myk lett/vanlig margarin hvis ønskelig og pålegg, se påleggsalternativer* nedenfor
- tomat, agurk, paprika, salat etc til pynt
- vann
- kaffe/ te

Alternativ 2:

- 2 grove knekkebrød med minimum 75 % fullkorn bruk brødskalaen
- Tynt myk lett/vanlig margarin hvis ønskelig og pålegg, se påleggsalternativer* nedenfor
- tomat, agurk, paprika, salat etc.til pynt
- vann
- kaffe/ te

Alternativ 3:

- Havregrøt kokt av 1 dl havregryn
- 2 dl vann og 1 dl melk
- 1 ss lettsyltetøy, en halv banan, 1 dl friske bær eller 1 strøken ss rosiner
- vann
- kaffe/ te

Alternativ 4:

- 50 gram kornblanding med mye fullkorn og lite sukker f.eks Vita kornblanding
- 1,5 – 2 dl yoghurt naturell, yoghurt med mindre fett og sukker eller melk
- vann
- kaffe/ te

Alternativ 5:

- 1 skiver grovt brød
- Omelett av 1 egg, 2 skiver skinke, finhakket purre og paprika, 2 ss (20 g) ost
- tomat, agurk, paprika, salat til pynt
- vann
- kaffe/te

Alternativ 6:

- 2 speilegg
- 1 dl hvite bønner i tomatsaus
- tomat, agurk, paprika, salat til pynt
- vann
- kaffe/te

*Pålegg (listen er ikke uttømmende, les varedeklarasjonen og finn dine favoritter):

- Ost, gjerne mager ost med færre kalorier og bruk bare ett lag
- Kjøttpålegg av hvitt kjøtt som kalkun og kyllingpålegg eller rent kjøttpålegg med maks 4 % fett som kokt skinke, hamburgerrygg, roastbiff etc.

- Lett syltetøy (mer bær, mindre sukker) og hjemmelaget rørte bær
- Fiske pålegg og skaldyr: røkt eller gravet laks eller makrell, makrell i tomat, tunfisk, sild, sardiner, reker, krabbe, crabstics (hvis majones ett tynt lag lettmajones)
- Majonessalater med maks 10 % fett
- Avokado
- Egg (maks 7 egg per uke totalt)

NB: Husk at mengden pålegg er vel så viktig som typen, bruk et «lag», tilsvarende en f.eks en ferdigskåret osteskive eller en porsjonspakning makrell i tomat per brødskive.

Lunsj (350)

Alternativ 1:

- Så mye salat, tomat, agurk, paprika, purre , løk og gulrot i strimler som du ønsker.
- 100 g rensede reker/ 100 g tunfisk i gele eller vann/ 100 g kylling/ 100 g cottage cheese/ 120 g bønner eller kikerter
- Dressing av olivenolje eller olivenoljebasert dressing (se oppskriftshefte)
- ½ (liten) avokado eller 6 oliven
- Vann, kaffe/te

Alternativ 2:

- En stor tallerken suppe uten fløte med grønnsaker, fisk og/eller kylling
- En skive ekstra grovt brød
- Vann, kaffe/te

Alternativ 3:

- 2 tynne skiver grovt brød med minimum 75 % fullkorn, bruk brødskalaen
- Tynt lag myk lett/vanlig margarin hvis ønskelig og pålegg, se påleggsalternativer*
- tomat, agurk, paprika, salat til pynt
- vann, kaffe/ te

Alternativ 4:

- 3 grove knekkebrød med minimum 75 % fullkorn bruk brødskalaen
- Tynt lag lett/vanlig margarin hvis ønskelig og pålegg, se påleggsalternativer*
- tomat, agurk, paprika, salat til pynt
- vann, kaffe/ te

Alternativ 5

- Varmmat med ren fisk eller rent hvitt kjøtt (150g) og grønnsaker eller salat
- Vann
- Kaffe/ te

Alternativ 6

- Yoghurt naturell, yoghurt eller Skyr med mindre sukker eller cottage cheese 2 dl
- En håndfull bær eller frukt i biter
- 2 ss hakkede nøtter eller fiberrik kornblanding
- Vann, kaffe/te

Mellommåltider x 2, velg ett alternativ (75 kalorier) dersom du ønsker det kan du slå sammen to små mellommåltider til ett større mellommåltid (75 kalorier x 2), dette kan også spares til kvelden.

1. Fri mengde rå gulrøtter, agurk, stangselleri eller andre grønnsaker unntatt oliven, avokado, mais og erter
2. 1 frukt
3. 1 yoghurt uten sukker Yoplait 0,0 eller 1 dl naturell yoghurt
4. En liten håndfull usaltede nøtter (10 - 15 g)

Middag (500):

Følg tallerkenmodellen: Fyll minimum 1/3, helst 1/2 tallerkenen med grønnsaker, 1/3 med ris, pasta, belgfrukter eller potet og 1/3 med kjøtt fisk eller fugl

Mer konkret kan du spise:
- Grønnsaker i fri mengde, varier mellom råkost, salater, wok, ovnsbakte og dampede grønnsaker
- 1 mellomstor poteter, 40 g (ukokt) pasta eller ris eller 140 g ferdig kokte eller hermetisk linser, bønner eller kikerter(tilsvarer 45 g ukokte, tørre linser, bønner, kikerter)
- 150 g fisk, fugl eller magert kjøtt (tilsvarer ca 1 kyllingfillet). Velg i hovedsak fisk, kylling eller kalkun og noe rent kjøtt. Alle typer fisk, unntatt kavringpanert fisk som fiskepinner og kylling eller kalkun uten skinn er gode valg. Hvis du ønsker kjøtt velg indre, ytre fillet, mørbra, steik, koteletter fra kotelettkammen, karbonadedeig og skjer alltid bort synlig fett. Unngå oppblandede kjøttprodukter som pølser, kjøttdeig, familiedeig, medisterdeig og kjøtt som er mer marmorert med fett som for eksempel nakke koteletter, bacon, flesk, entrecôte, og lammekoteletter som inneholder mye fett som kan øke kolesterolet.

Til steking **bør du velge olivenolje, rapsolje eller flytende VITA margarin, bruk maks 1 liten ss fett per pers.**

Saus og dressing:

- **Saus**: Litt god ekstra virgin olivenolje f.eks på grønnsakene, salaten, potetene, pastaen, fisken eller kyllingen, gjerne sammen med litt friske urter gir deilig smak og kan på mange måter erstatte sausen. Du kan varier med hjemmelagede tomatsauser (se oppskrift på tomatsaus, Sofrito i oppskriftsheftet) eller eventuelt tomatsaus fra glass, soyasaus og chillisaus i wok eller sauser laget med jevning eller fra pose. Velg posesauser med maksimalt 2 gram fett per 100 gram ferdig tilbredt saus, les på pakken.
- **Alternativ 2, dressing**: dressing av 1 ss olivenolje gjerne tilsatt litt balsamikoeddik, rødvinseddik eller sitron og litt sennep eller urter + salt og pepper, 2 ss pesto eller en dressing basert på

Kesam, skyr, gresk yoghurt eller ekstra lettrømme. Du lager enkelt en god og smakfull dressing ved å tilsette hvitløk, friske urter, salt og pepper og eventuelt et par dråper sitron eller du kan bruke ferdig kryddermiks fra Knorr.

Snakcs (Maks 1 – 2 ganger per uke), (250 kalorier per porsjon)

1. 50 g nøtter (helst usaltede) husk eller potetgull på mengden

2. 50 g sjokolade, gjerne mørk

3. 75 g popcorn

Alkohol hvis du ønsker og pleier å drikke alkohol (totalt 600 kalorier) maksimalt 6 glass rød eller hvit vin (tilsvarer 750 ml altså en flaske) per uke, fordeles utover uken.

I tillegg kan du drikke saft/brus uten sukker

Lykke til med investeringen i egen helse. Tine☺

tinsun@ous-hf.no

Dagsmeny 2000 kalorier

Denne måltidsplanen er tilpasset din utgangsvekt og ditt energibehov og ved å følge denne måltidsplanen kan du gå ned mellom 0,5 og 1,0 kg per uke. Du finner ulike alternativer for både frokost, lunsj og mellommåltider som har tilsvarende kalori- og næringsinnhold slik at du selv kan velge det du foretrekker.

Dersom du f.eks ønsker en litt mindre frokost og en litt større lunsj kan du selvfølgelig «spare» f.eks. et knekkebrød fra frokosten og legge det til lunsjmåltidet ditt, dette vil ikke påvirke vektnedgangen. Men husk at dersom du legger til noe som ikke står på dagsmenyen eller spiser et ekstra stort måltid en dag, må du kutte ned på noe annet for å oppnå forventet vektreduksjon (se byttelisten for å vite hvor mye kalorier det er i en del ulik matvarer).

Frokost (350 - 400)

Alternativ 1:

- 2 skiver grovt brød med minimum 75 % fullkorn, bruk brødskalaen (se nedenfor)
- Tynt lag lett/vanlig myk margarin hvis ønskelig og pålegg, se påleggsalternativer* nedenfor
- tomat, agurk, paprika, salat i fri mengde
- vann, kaffe/ te

Alternativ 2:

- 3 grove knekkebrød med lett/vanlig myk margarin og pålegg*
- tomat, agurk, paprika, salt etc i fri mengde
- 1 frukt
- Vann, kaffe/ te

Alternativ 3:

- Havregrøt kokt av 1,5 dl havregryn 3 dl vann og 1,5 dl melk
- 2 ss lettsyltetøy, en banan, 1,5 dl friske bær eller 2 ss rosiner
- Vann, kaffe/ te

Alternativ 4:

- 60 gram kornblanding med mye fullkorn og lite sukker f.eks Vita kornblanding
- 2 – 2,5 dl yoghurt naturell, yoghurt med mindre fett og sukker eller melk
- Vann, kaffe/ te

Alternativ 5:

- 1 skiver grovt brød
- Tynt lag lettmargarin hvis ønskelig
- Omelett av 2 egg, 2 skiver skinke, finhakket purre og paprika, 2 ss (20 g) revet ost, 2 skiver kalkun/kylling skinke
- tomat, agurk, paprika, salat til pynt
- vann, kaffe/te

Alternativ 5:

- 2 stk speilegg
- 2 dl hvite bønner i tomatsaus
- tomat, agurk, paprika, salat til pynt
- vann, kaffe/te

*Pålegg (listen er ikke uttømmende, les varedeklarasjonen og finn dine favoritter):

- Ost, gjerne mager ost, bruk bare ett lag
- Kjøttpålegg av hvitt kjøtt som kalkun og kyllingpålegg eller rent kjøttpålegg med maks 4 % fett som kokt skinke, hamburgerrygg, roastbiff etc
- Lett syltetøy (mer bær, mindre sukker) og hjemmelaget rørte bær
- Fiske pålegg og skaldyr: røkt eller gravet laks eller makrell, makrell i tomat, tunfisk, sild, sardiner, reker, krabbe, crabstics (hvis majones ett tynt lag lettmajones)
- Majonessalater med maks 10 % fett
- Avokado
- Egg (maks 7 egg per uke totalt)

NB: Husk at mengden pålegg er vel så viktig som typen, bruk et «lag», tilsvarende en f.eks en ferdigskåret osteskive eller en porsjonspakning makrell i tomat per brødskive.

Lunsj (500)

Alternativ 1:

- Så mye salat, tomat, agurk, salat, purre. løk og gulrot i strimler som du ønsker.
- 150 g rensede reker/ 150 tunfisk/ 150 g ren kylling eller ren skinke/ 150 g cottage cheese/ 150 g bønner eller kikerter
- Dressing av olivenolje eller olivenoljebasert dressing (se oppskriftshefte)
- ½ avokado, 6 oliven
- 1 skive ekstra grovt brød
- Vann, kaffe/te

Alternativ 2:

- En tallerken suppe med grønnsaker, fisk og/eller kylling
- 2 tynne ekstra grovt brød eller ett grovt rundstykke
- Vann, kaffe/te

Alternativ 3:

- 2 skiver grovt brød + 1 knekkebrød med minimum 75 % fullkorn, bruk brødskalaen
- Tynt lag lett/vanlig myk margarin hvis ønskelig og pålegg, se påleggsalternativer* nedenfor
- Tomat, agurk, paprika, salat til pynt
- Vann, kaffe/te

Alternativ 4:

- 4 grove knekkebrød
- Tynt lag lett/vanlig myk margarin hvis ønskelig og pålegg, se påleggsalternativer* nedenfor
- tomat, agurk, paprika, salt til pynt
- Vann, kaffe/te

Alternativ 5

- Varmmat med ren fisk eller rent kjøtt (200g) og grønnsaker eller salat
- Vann, kaffe/te

Alternativ 6

- Yoghurt naturell, yoghurt eller Skyr med mindre sukker eller cottage cheese 3 dl
- En stor håndfull bær eller frukt i biter
- 3 ss hakkede nøtter eller fiberrik musli
- Vann, kaffe/te

Mellommåltider x 2, velg ett alternativ (75 kalorier) dersom du ønsker det kan du slå sammen to små mellommåltider til ett større mellommåltid (75 kalorier x 2), dette kan også spares til kvelden.

1. Fri mengde rå gulrøtter, agurk, stangselleri eller andre grønnsaker unntatt oliven, avokado, mais og erter
2. 1 frukt
3. 1 yoghurt uten sukker Yoplait 0,0 eller naturell
4. En liten håndfull usaltede nøtter 10-15 g

Middag (700):

Følg tallerkenmodellen: Fyll minimum 1/3, helst 1/2 tallerkenen med grønnsaker, 1/3 med ris, pasta eller potet og 1/3 med kjøtt fisk eller fugl

Mer konkret kan du spise:
- Grønnsaker i fri mengde, varier mellom råkost, salater, wok, ovnsbakte og dampede grønnsaker
- 2 middels store poteter eller 60 g (ukokt) fullkornspasta eller ris, kikerter, bønner, linser 200 g ferdig kokt eller hermetisk, tilsvarer 60 g ukokte/ tørre kikerter, bønner, linser.
– 200 g porsjon fisk, fugl eller magert kjøtt (tilsvarer 1,5 kylling filleter) Velg i hovedsak fisk, kylling eller kalkun og noe rent kjøtt. Alle typer fisk, unntatt kavringpanert fisk som fiskepinner og kylling eller kalkun uten skinn er gode valg. Hvis du ønsker kjøtt velg indre, ytre fillet, mørbra, steik, koteletter fra kotlettkammen, karbonadedeig og skjer alltid bort synlig fett. Unngå oppblandede kjøttprodukter som pølser, kjøttdeig, familiedeig, medisterdeig og kjøtt som er mer marmorert med fett som for eksempel nakke koteletter, bacon, flesk, entrecôte, og lammekoteletter som inneholder mye fett som kan øke kolesterolet.

Til steking **bør du velge olivenolje, rapsolje eller flytende VITA margarin, bruk mals 1 liten ss fett per pers**

Saus eller dressing:

- **Saus**: Litt god ekstra virgin olivenolje f.eks på grønnsakene, salaten, potetene, pastaen, fisken eller kyllingen, gjerne sammen med litt friske urter gir deilig smak og kan på mange måter erstatte sausen. Du kan varier med hjemmelagede tomatsauser (se oppskrift på tomatsaus, Sofrito i oppskriftsheftet) eller eventuelt tomatsaus fra glass, soyasaus og chillisaus i wok eller sauser laget med jevning eller fra pose. Velg posesauser med maksimalt 2 gram fett per 100 gram ferdig tilbredt saus, les på pakken.

- **Alternativ 2, dressing**: dressing av 1 ss olivenolje gjerne tilsatt litt balsamikoeddik, rødvinseddik eller sitron og litt sennep eller urter + salt og pepper, 2 ss pesto eller en dressing basert på Kesam, skyr, gresk yoghurt eller ekstra lettrømme. Du lager enkelt en god og smakfull dressing ved å tilsette hvitløk, friske urter, salt og pepper og eventuelt et par dråper sitron eller du kan bruke ferdig kryddermiks fra Knorr.
-

Snakcs (Maks 2 ganger per uke eller dobbel porsjon en dag), (250 kalorier per porsjon)

1. 50 g nøtter (helst usaltede) eller potetgull, husk på mengden

2. 50 g sjokolade, gjerne mørk

3. 75 g popcorn

Alkohol hvis du ønsker og pleier å drikke alkohol (totalt 650 kalorier):

maksimalt 7 glass rød eller hvit vin (tilsvarer 875 ml) per uke, fordeles utover uken.

I tillegg kan du drikke saft/brus uten sukker

Lykke til med investeringen i egen helse. Tine☺

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Dagsmeny 2500 kalorier

Denne måltidsplanen er tilpasset din utgangsvekt og ditt energibehov og ved å følge denne måltidsplanen kan du gå ned mellom 0,5 og 1,0 kg per uke. Du finner ulike alternativer for både frokost, lunsj og mellommåltider som har tilsvarende kalori- og næringsinnhold slik at du selv kan velge det du foretrekker.

Dersom du f.eks ønsker en litt mindre frokost og en litt større lunsj kan du selvfølgelig «spare» f.eks. et knekkebrød fra frokosten og legge det til lunsjmåltidet ditt, dette vil ikke påvirke vektnedgangen. Men husk at dersom du legger til noe som ikke står på dagsmenyen eller spiser et ekstra stort måltid en dag, må du kutte ned på noe annet for å oppnå forventet vektreduksjon (se bytteliste bakerst i dokumentet for å vite hvor mye kalorier det er i en del ulik matvarer).

Frokost (400)

Alternativ 1:

- 2 skiver grovt brød med minimum 75 % fullkorn, bruk brødskalaen (4/4 skravert)
- Tynt lag lett/vanlig myk margarin hvis ønskelig og pålegg, se påleggsalternativer* nedenfor
- tomat, agurk, paprika, salat i fri mengde
- vann,kaffe/ te

Alternativ 2:

- 3 grove knekkebrød med lett/vanlig myk margarin og pålegg*
- tomat, agurk, paprika, salt etc i fri mengde
- 1 frukt
- Vann, kaffe/ te

Alternativ 3:

- Havregrøt kokt av 2 dl havregryn 4 dl vann og 2 dl melk
- 2 ss lettsyltetøy, en banan, 1,5 dl friske bær eller 2 ss rosiner
- Vann, kaffe/ te

Alternativ 4:

- 70 gram kornblanding med mye fullkorn og lite sukker f.eks Vita kornblanding
- 2 – 2,5 dl yoghurt naturell, yoghurt med mindre fett og sukker eller melk
- Vann, kaffe/ te

Alternativ 5:

- 1 skiver grovt brød
- Tynt lag lettmargarin hvis ønskelig
- Omelett av 2 egg, finhakket purre og paprika, 2 ss (20 g) revet ost, 2 skiver kalkun/kylling skinke
- tomat, agurk, paprika, salat til pynt
- vann, kaffe/te

Alternativ 5:

- 1 skiver grovt brød
- 2 stk speilegg
- 1 dl hvite bønner i tomatsaus (eller 2,5 dl bønner i tomatsaus og dropp brødet)
- tomat, agurk, paprika, salat til pynt
- vann, kaffe/te

*Pålegg (listen er ikke uttømmende, les varedeklarasjonen og finn dine favoritter):

- Ost, gjerne mager
- Kjøttpålegg av hvitt kjøtt som kalkun og kyllingpålegg eller rent kjøttpålegg med maks 4 % fett som kokt skinke, hamburgerrygg, roastbiff etc
- Lett syltetøy (mer bær, mindre sukker) og hjemmelaget rørte bær
- Fiske pålegg og skaldyr: røkt eller gravet laks eller makrell, makrell i tomat, tunfisk, sild, sardiner, reker, krabbe, crabstics (hvis majones ett tynt lag lettmajones)
- Majonessalater med maks 10 % fett
- Avokado
- Egg (maks 7 egg per uke totalt)

NB: Husk at mengden pålegg er vel så viktig som typen, bruk et «lag», tilsvarende en f.eks en ferdigskåret osteskive eller en porsjonspakning makrell i tomat per brødskive.

Lunsj (600)

Alternativ 1:

- Så mye salat, tomat, agurk, salat, purre og gulrot i strimler som du ønsker.
- 200 g rensede reker/ 200 tunfisk/ 200 g kylling eller ren skinke/ 200 g cottage cheese/ 200 g bønner eller kikerter
- Dressing av olivenolje eller olivenoljebasert dressing (se oppskriftshefte)
- ½ avokado, 8 oliven
- 1 skive ekstra grovt brød
- Vann, kaffe/te

Alternativ 2:

- To tallerkener med suppe med grønnsaker, fisk og/eller kylling
- 1 skiver ekstra grovt brød (eller en tallerken suppe og to brødskiver)
- Vann
- Kaffe/te

Alternativ 3:

- 2-3 skiver grovt brød med minimum 75 % fullkorn, bruk brødskalaen (se nedenfor)
- Tynt lag lett/vanlig myk margarin hvis ønskelig og pålegg, se påleggsalternativer* nedenfor
- tomat, agurk, paprika, salat til pynt
- vann, kaffe/te

Alternativ 4:

- 4-5 grove knekkebrød med lettmargarin og pålegg*
- tomat, agurk, paprika, salt til pynt
- 1 glass skummet, ekstra lett melk eller juice
- Vann, kaffe/te

Alternativ 5

- Varmmat med ren fisk eller rent hvitt kjøtt (250g) og grønnsaker eller salat
- 1 potet eller 2 ss fullkornsris/pasta
- Vann, kaffe/te

Alternativ 6

- Yoghurt naturell, yoghurt eller Skyr med mindre sukker eller cottage cheese 3 dl
- To håndfuller bær eller frukt i biter
- 5 ss hakkede nøtter eller fiberrik musli
- Vann, kaffe/te

Mellommåltider x 2, velg ett alternativ (150 kalorier) dersom du ønsker det kan du slå sammen to små mellommåltider til ett større mellommåltid (150 kalorier x 2), dette kan også spares til kvelden.

1. Fri mengde rå gulrøtter, agurk, stangselleri eller andre grønnsaker unntatt oliven, avokado, mais og erter
2. 2 frukt
3. 1 yoghurt
4. En håndfull usaltede nøtter 25 - 30 g

Middag (700): dette tilsvarer egentlig to små porsjoner til middag, dersom du pleier å spise mindre er det ingen grunn til å øke inntaket.

Følg tallerkenmodellen: Fyll minimum 1/3, helst 1/2 tallerkenen med grønnsaker, 1/3 med ris, pasta eller potet og 1/3 med kjøtt fisk eller fugl

Mer konkret kan du spise:
- Grønnsaker i fri mengde, varier mellom råkost, salater, wok, ovnsbakte og dampede grønnsaker
- 2-3 middels store poteter eller 70 g (ukokt) fullkornspasta eller ris, kikerter, bønner, linser 250 g ferdig kokt eller hermetisk, tilsvarer 100 g ukokte/ tørre kikerter, bønner, linser.   -
- 250 porsjon fisk, fugl eller magert kjøtt (tilsvarer 2 kyllingfilleter). Velg i hovedsak fisk, kylling eller kalkun og noe rent kjøtt. Alle typer fisk, unntatt kavringpanert fisk som fiskepinner og kylling eller kalkun uten skinn er gode valg. Hvis du ønsker kjøtt velg indre, ytre fillet, mørbra, steik, koteletter fra kotlettkammen, karbonadedeig og skjer alltid bort synlig fett. Unngå oppblandede kjøttprodukter som pølser, kjøttdeig, familiedeig, medisterdeig og kjøtt som er mer marmorert med fett som for eksempel nakke koteletter, bacon, flesk, entrecôte, og lammekoteletter som inneholder mye fett som kan øke kolesterolet. NB, dersom du velger oppblandede kjøttprodukter f.eks pølser tilsvarer dette kun 2 grillpølser!!!

Til steking **bør du velge olivenolje elelr alternativt rapsolje eller Vita flytende margarin**

Saus eller dressing:

- **Saus**: Litt god ekstra virgin olivenolje f.eks på grønnsakene, salaten, potetene, pastaen, fisken eller kyllingen, gjerne sammen med litt friske urter gir deilig smak og kan på mange måter erstatte sausen. Du kan varier med hjemmelagede tomatsauser (se oppskrift på tomatsaus, Sofrito i oppskriftsheftet) eller eventuelt tomatsaus fra glass, soyasaus og chillisaus i wok eller sauser laget med jevning eller fra pose. Velg posesauser med maksimalt 2 gram fett per 100 gram ferdig tilbredt saus, les på pakken.

- **Alternativ 2, dressing**: dressing av 1 ss olivenolje gjerne tilsatt litt balsamikoeddik, rødvinseddik eller sitron og litt sennep eller urter + salt og pepper, 2 ss pesto eller en dressing basert på Kesam, skyr, gresk yoghurt eller ekstra lettrømme. Du lager enkelt en god og smakfull dressing ved å tilsette hvitløk, friske urter, salt og pepper og eventuelt et par dråper sitron eller du kan bruke ferdig kryddermiks fra Knorr.

Snakcs (Maks 1-2 ganger per uke), (550 - 650 kalorier per porsjon)

1. 100 g nøtter, gjerne usaltede eller potetgull husk på mengden

2. 100 g sjokolade, gjerne mørk

3. 125 g popcorn

Alkohol hvis du ønsker og pleier å drikke alkohol (totalt 650 kalorier, tilsvarer i snitt 90 kalorier per dag):

maksimalt 7 glass rød eller hvit vin (tilsvarer 875 ml) per uke, fordeles utover uken.

I tillegg kan du drikke saft/brus uten sukker

Lykke til med investeringen i egen helse. Tine☺

tinsun@ous-hf.no

11. Papers I-III