The effect of dietary and smoking cessation advice on changes in risk factors for cardiovascular disease among women and men aged 18-39 years with a familial risk of coronary heart disease: a randomised trial

Master thesis by
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May 2012
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Printing: Copy Cat®
Introductory remark

I would like to dedicate this thesis to my darling parents who have been nothing but supportive of me and my studies abroad ever since I was a teenager.

The road to completing this master thesis has been long and intensive but worthwhile. I would like to thank my primary supervisor Mette Svendsen for your positive attitude and encouragement throughout this entire year. I have learned a lot and am forever grateful for this opportunity.

Kjetil, I would like to sincerely thank you for allowing me to pop in unannounced with questions. I have very much enjoyed our discussions. Like Mette, your positive attitude and encouragement have been invaluable throughout this year.

Morten Valberg – thank you for being my kind and helpful mathematical aid.

To Trine Næss Henriksen, Ingunn Molven, Thea Amalie Martinsen Bergvatn and the others at the study hall – thank you for all our talks, lunches and for your company during late study nights.

Lise Bergengen and Eli Heggen – you’re both such helpful and kind individuals. Thank you for providing me with information with regards to the method and design of the trial. Your help has been invaluable.

Finally, I want to thank my boyfriend Jacob for his proof-reading.

May 2012

Clarissa Anna Maria Alexandra Liljander
Abstract

Background: Coronary heart disease (CHD) is a major cause of death both in Norway and in the world. Current Norwegian guidelines advocate that health care resources target individuals with an increased risk of said disease such as primary relatives of subjects with premature CHD (men before the age of 55 years and women before the age of 65 years). There is limited data on interventions that target young adults with an increased risk of CHD aged below 40 years of age.

Aim: To assess the effects of one time dietary advice and intensive smoking cessation aid in young individuals with increased risk of premature CHD after 16 weeks. The primary aim was to detect a difference in change overtime in pre-selected cardiovascular risk factors (total-, LDL- and HDL-cholesterol, triglycerides, blood pressure, weight and waist-to-hip ratio) between randomised groups. The secondary aims were to assess the within group changes in these cardiovascular risk factors and to assess the association between group allocation and smoking cessation.

Method: The study was a randomised trial designed to test a simple intervention given once at baseline with no follow-up visit in between randomisation and the final visit. The intervention group received personalised dietary counseling based on a food frequency questionnaire at baseline from a registered dietitian. Subjects in the control group answered the food frequency questionnaire but did not receive any dietary advice during the trial. The smoking cessation intervention was administered by a physician. Smokers in the intervention group received intense smoking cessation aid including the use of pharmacotherapy and recurrent telephone contact. The control group received only routine smoking cessation advice. Smoking status was self-reported and smoking cessation confirmed by measured exhaled carbon monoxide (CO) levels.

Results: A total of 161 men and women with a mean age of 31 (SD: 6) years were included in the study out of which 149 subjects completed the trial. The mean duration for participation in the trial was 20 weeks. No difference in change overtime in any of the cardiovascular risk factors was seen between the intervention- and the control group. In the intervention group, there was a reduction in systolic blood pressure (SBP) by -4.50 mmHg (95% CI: -6.36; -2.63) and diastolic blood pressure by -2.50 mmHg (95% CI: -4.38; -0.69). There was also a
reduction in SBP in the control group by -2.5 (95% CI: -4.38; -0.69) and an increase in HDL-cholesterol by 0.05 mmol/l (95% CI: 0.01; 0.08). At baseline the prevalence of smoking was 16% and 30% in the intervention and the control group, respectively (P=0.88). At the end of the trial six subjects in the intervention group and six subjects in the control group reported having quit smoking, which was confirmed by CO measurements. Group allocation was not associated with smoking cessation (P=0.86).

**Conclusion:** The results of the trial indicate that dietary advice given once and intense smoking cessation aid was insufficient to significantly improve cardiovascular risk factors in young adults with increased risk of premature CHD after 20 weeks compared to controls.
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Glosses

*Angina pectoris* – a symptom of underlying CHD caused by inadequate blood supply to the myocardium

*External validity* - refers to the generalisability of a study

*Family tree* – a flow-chart illustrating the family history of disease including parents, siblings, children and their offspring

*Ischemic heart disease* – a generic term for cardiac disease caused by inadequate blood supply to the myocardium

*Myocardial infarction* - occurs when an embolus abruptly clogs the coronary arteries causing tissue hypoxia in the myocardium, also known as a heart attack

*NORRISK* = Norwegian risk model for cardiovascular mortality

*Regression to the mean* = a statistical phenomenon where an observed change in outcome is due to biological variation
Abbreviations

1839-S = “18 to 39” study

ADA = American Dietetic Association

AHA = American Heart Association

ApoB = Apolipoprotein B

BMI = Body Mass Index

CARDIA = Coronary Artery Risk Development in Young Adults

CHD = Coronary heart disease

CHO = Carbohydrates

CI = Confidence interval

CM = Chylomicrons

cm = Centimeters

CO = Carbon monoxide

CVD = Cardiovascular disease

DASH = Dietary Approaches to Stop Hypertension

DBP = Diastolic blood pressure

DHA = Dokosahexanoic acid

EPA = Eicosapentanoic acid

EPIC = European Prospective Investigation into Cancer and Nutrition

FFQ = Food Frequency Questionnaire

HDL = High density lipoprotein
HDL-2 = HDL subfraction 2
HDL-3 = HDL subfraction 3
HDL-C = HDL-cholesterol
IDF = International Diabetes Federation
IDL = Intermediate density lipoprotein
IHID = Ischemic heart disease
ITT = Intention to treat
LDL = Low density lipoprotein
LDL-C = LDL-cholesterol
LOCF = Last observation carried forward
Log = Logarithm
Lp(a) = Lipoprotein A
MetS = Metabolic syndrome
Max = Maximum
MI = Multiple imputation
Min = Minimum
MUFA = Monounsaturated fatty acids
PREDIMED = PREvención con DIeta MEDiterránea
PUFA = Polyunsaturated fatty acids
RTM = Regression to the mean
SBP = Systolic blood pressure
SD = Standard deviation

SFA = Saturated fatty acids

TC = Total cholesterol

TFA = Trans fatty acids

TG = Triglycerides

VLDL = Very low density lipoprotein

WHI = Women’s Health Initiative

WHR = Waist to hip ratio

WHO = World Health Organization
1 Background

1.1 Coronary heart disease (CHD)

Coronary heart disease (CHD), also known as coronary artery disease, is a subgroup of the umbrella term cardiovascular disease (CVD). CHD is defined by the World Health Organization (WHO) as disease of the blood vessels supplying the heart with oxygen and blood (1). An acute CHD event incorporates the diagnoses angina pectoris and myocardial infarction (2).

CHD contribute to the majority of deaths caused by CVD in the world (3;4). In the year of 2010 CVD accounted for roughly 35 percent of total deaths in Norway in all ages (5) with CHD as the central subgroup (6). Although there has been a positive trend in cardiovascular related mortality and morbidity from an epidemiological viewpoint CHD continues to be a central cause of death in Norway (6).

Prevention of CHD should commence at an early age (7) since future risk is attributable to the modifiable cardiovascular risk factors (8-10). Non-modifiable risk factors, such as family history, cannot be modified by choice and consequently the adjustment of diet, physical activity level and tobacco use is essential for primary prevention. Furthermore, according to the European Heart Network and WHO a vast majority of premature deaths from CHD could be prevented through favorable changes in these three modifiable risk factors (1;3;11).

1.1.1 Risk factors for CHD

Genetics

A family history of parental premature CHD is an independent non-modifiable risk factor in first-degree relatives (12;13). Furthermore, family history of CHD has been linked with a clustering of other independent cardiovascular risk factors (14;15) which may further predispose relatives to an increased risk. Genetic disorders in lipoprotein metabolism (such as familial hypercholesterolemia) also predisposes individuals to an increased risk of CHD due to increased concentrations of atherogenic LDL-cholesterol (LDL-C) (16) caused by abnormalities in the regulators of cholesterol homeostasis (17).
Gender

Although the incidence of CVD is equal irrespective of gender (18) women develop CHD later in life compared with men. This difference has been attributed to a genetic advantage since women have more favorable levels of endogenous estrogen and favorable levels of high density lipoprotein cholesterol (HDL-C) (19).

Age

Advancing age is a risk factor for CVD (18) and consequently for CHD since increasing age augments and prolongs an individual’s exposure to modifiable risk factors.

Elevated blood pressure

A systolic blood pressure (SBP) below 120 mmHg and a diastolic blood pressure (DBP) below 80 mmHg is defined as optimal (20) while a SBP of ≥140 mmHg and a DBP of ≥90 mmHg is defined as hypertension. Hypertension is associated with CHD and an increased risk of CHD events (21) due to its hardening of the arteries. Hypertension is often clustered together with other cardiovascular risk factors such as obesity (22). Although blood pressure increases with age (23) and genetics may predispose to hypertension (24) it is influenced by diet (25;26) and physical activity (27).

Cholesterol

Although cholesterol has important structural- and metabolic functions in the body (28), a dysfunctional cholesterol homeostasis is believed to be an integral part in the inflammatory progression that is the origin of CHD (29). Cholesterol homeostasis is regulated through the action of different lipoproteins, as is shown in Figure 1. The different classes of lipoproteins are chylomicrons (CM), very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). In the clinic, their corresponding levels in blood are measured as TG, LDL-C and HDL-C. Total cholesterol (TC) is an overall measurement including all the lipoprotein classes.

The cholesterol homeostasis is facilitated by the main protein constituents of lipoproteins known as apolipoproteins. Apolipoproteins control lipoprotein metabolism by allowing them
to be recognised by different cell-specific receptors and by facilitating their uptake of TG from other lipoproteins (30;31).

**Figure 1. The pathway of lipoprotein metabolism.**

*a*) Dietary fat is absorbed in the intestine and transported as exogenous TAG by chylomicrons to the liver. APOC2 facilitates the uptake of TAG rendering energy available for peripheral tissue by activating LPL (31). Receptors on the liver facilitate hepatic uptake of chylomicron remnants where APOE is the mediator of remnant clearance.  
*b*) VLDL transports endogenous TAG from the liver to the peripheral tissue. Once VLDL becomes a remnant, it may either undergo hepatic uptake or convert into LDL. Excess cholesterol is returned to the liver either directly by reverse cholesterol transport mediated by LCAT or indirectly by transfer from HDL-C onto LDL or VLDL mediated by cholesterol ester transfer protein (30).

**Abbreviations:** TAG (triacylglycerol), CE (Cholesterol esters), PL (Phospholipids), LPL (Lipoprotein lipase), FA (peripheral tissue), APOE/-C2 (Apolipoproteins), LCAT (lecithin-cholesterol acyltransferase), HDL (High Density Lipoprotein), VLDL (Very Low Density Lipoprotein), LDL (Low Density Lipoprotein), LRP (LDL-R-related protein), LDL-R (LDL-receptor).

*This figure was originally published in (32). Permission to reprint it in this master thesis was obtained from Elsevier Limited.*

**Total cholesterol and LDL-cholesterol**

It is believed that the circulating levels of VLDL, IDL and LDL are integrated in the development and progression of CHD (29;33). Since TC incorporates all atherogenic lipoproteins; lowering of both TC and LDL-C concentrations in blood are associated with a CHD risk reduction (34;35). Elevated levels of circulating TC (37-39) as well as of LDL-C (36) have been associated with an increase in CHD events.
LDL is the primary cholesterol carrier and distributor of cholesterol in the blood (30). It is often referred to as the “bad cholesterol” (18) since LDL is believed to facilitate the development of CHD by being prone to oxidation, which may promote inflammatory processes inside of the coronary arteries. Nevertheless, the exact mechanism is still not fully understood (29). Due to LDL’s proposed atherogenic properties it has become the foremost risk factor in preventive strategies (40). For instance a 1 mmol/l reduction in LDL-C sustained for five years could alone reduce the incidence of cardiovascular events by 23% (34). It has been suggested that reductions in LDL-C are beneficial even at very low baseline concentrations (41).

**HDL-cholesterol**

HDL-C is alleged to be an important risk factor for CHD (40;42) although recent research (43) has suggested that its protective effect is dependent on the absence of apolipoprotein C-III. HDL is commonly called the “good” cholesterol (18) due to its involvement in reverse cholesterol transport from peripheral tissue to the liver. In addition HDL is believed to have antioxidant effects (29) and carries the enzyme paraoxonase and apolipoprotein AI which have been shown in vitro to render cells unable to oxidize LDL (44). Although there are several sub fractions of HDL, it is HDL-3 and HDL-2 that are the most abundant (45).

**Triglycerides**

Elevated TG concentrations have been associated with obesity and overweight, excess alcohol intake and very-high carbohydrate diets (46). Although TG is a marker of the circulating levels of atherogenic CM, VLDL and their remnants the American Heart Association (AHA) recently published a statement (46) concluding that TG is not straightforwardly atherogenic but nevertheless an important biomarker of cardiovascular risk.

**Other potential CHD risk factors**

Some of the other potentially important markers to estimate CHD risk are apolipoproteins and lipoprotein (a) (Lp(a)) (40).

Apolipoprotein B (apoB) is the main protein constituent of IDL, VLDL and LDL and is consequently regarded as a potential cardiovascular risk marker (40).
Lpa(a) is another potential risk marker for CHD (47;48) and the European Atherosclerosis Society recommends that Lp(a) is assessed once in individuals with a family history of CVD (40). Although it is to most extent determined by genetics, cholesterol-lowering drug treatment may induce a reduction in Lp(a) levels (48).

The TC/HDL-C ratio is another potential predictor of CHD risk (19). A TC/HDL-C ratio of less than five has been suggested by the Norwegian Guidelines for Primary Prevention of CVD as a satisfactory ratio in both men and women (49).

**Overweight and obesity**

Overweight and obesity are caused by a chronic energy intake exceeding metabolic requirements and both are associated with an increased cardiovascular risk (22). Furthermore, although obesity has been associated with hypertension and high serum cholesterol (50) a weight loss can induce favorable reductions in both (51-53). To which extent overweight and obesity affect cardiovascular risk can be estimated by Body Mass Index (BMI), abdominal obesity or waist-to-hip ratio (WHR). A WHR of > 90 centimeters (cm) in men and > 85 cm in women is defined by the WHO as a ratio that substantially increases the risk of metabolic complications. Nevertheless WHO regard all three as equally important risk factors to predict cardiovascular risk (54).

**Metabolic syndrome**

The metabolic syndrome (MetS) is a syndrome characterised by a clustering of cardiovascular risk factors and consequently cardiovascular risk (50). The syndrome was first defined by WHO (55) although the most recent definitions are the ones proposed by the International Diabetes Federation (IDF) (56) and the American Heart Association (AHA) (57). The definitions are very similar and both include the cardiovascular risk factors blood pressure, triglycerides (TG), HDL-C, glucose and abdominal obesity. The IDF defines abdominal obesity as an independent risk factor while the AHA defines all risk factors as equal. Furthermore, IDF has cut-off values for abdominal obesity that are specifically suited for use in European populations. At present there are no specific guidelines for which definition of the metabolic syndrome is the most appropriate for use in the Norwegian population (49).
Diet

*Dietary cholesterol*

Dietary cholesterol is abundant in animal foods such as eggs and shrimp. Although higher intakes of dietary cholesterol has been associated with increased serum cholesterol levels WHO concludes that the effect in itself is negligible when compared with other more important dietary risk factors (22). Nevertheless, dietary cholesterol intake is generally recommended to be limited since there is an individual response.

*Total fat intake*

Dietary fat is categorised as saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and trans fatty acids (TFA) (30). Total fat intake in itself is unlikely to be directly linked to CHD (58;59) but rather it is the fatty acid composition of a diet that influence cardiovascular risk and risk factors. A restriction in total fat intake is a means to limit dietary intake of TFA and SFA which both increase TC and LDL-C. However a natural consequence of a reduction in fat intake is that HDL-cholesterol levels are lowered (60) and moderate fat diets may therefore induce more favorable effects on blood cholesterol levels if SFA and TFA are substituted with other fatty acids instead of reduced (61;62).

*Saturated fat*

Although SFA intake affects blood cholesterol levels adversely (63) the direct link between SFA and CHD is still a controversial subject (59). Not all SFA promote an adverse increase in TC and LDL-C (58) although the SFA that do are widespread in the western diet (30). Consequently there is a general recommendation to limit dietary intake of all SFA (3;22;64) since non respondence to changes in SFA intake is rare (65).

*Trans fatty acids*

TFA, particularly those with an industrial origin (58), are known to increase LDL-C, lower HDL-C (22) and increase cardiovascular risk (58;59).
Monounsaturated fat

MUFA appear to have more of a neutral effect on CHD risk than a protective one (58;66). Nevertheless substitution of SFA for MUFA may elicit favorable reductions in LDL-C and increases in HDL-C (58).

Polyunsaturated fat

PUFA is a frequently promoted substitute for SFA since it is known to reduce CHD risk when replacing SFA in the diet (58;59;67). In addition it induces a beneficial reduction in TC (68) and consequently LDL-C without adversely affecting TG levels (60). The two main subgroups of PUFA nevertheless differ in their observed effect on CHD risk.

The two subgroups of PUFA are omega-3 fatty acids and omega-6 fatty acids which are believed to be anti-atherogenic (66). Omega-3 is mainly found in fatty fish while omega-6 is abundant in vegetable fats. According to the Food and Agriculture Organization, intake of the omega -3 fatty acids eicosapentaenoic- (EPA) and docosahexaenoic acid (DHA) may aid in the prevention of CHD (58). In contrast the Norwegian Directorate of health state that there is convincing evidence that EPA and DHA reduce CHD mortality (69) and that an intake of at least 200 grams of fatty fish per week is recommend due to its richness in EPA and DHA.

Fish is also an effective method for reducing elevated TG levels (70).

Omega-6 fatty acids have recently been challenged to increase CHD risk (71). Nevertheless current guidelines recommend that at least five percent of omega-6 fatty acids are incorporated into the diet (72) although a lower intake is not necessarily harmful (73).

Carbohydrates

Many dietary guidelines advocate that 50 to 60 percent of the energy intake should come from carbohydrates (CHO) (64;74;75) mainly constituting of whole grain, vegetables, legumes and fruit. CHO may however exert a negative, TG increasing effect in diets where the CHO intake exceeds 60% of the daily energy intake (19).

Fruits, vegetables and berries

According to the WHO there is convincing evidence that fruits, vegetables and berries reduce the risk of CVD (76). Furthermore, in the EPIC-Heart study each portion of fruit was
associated with a four percent risk reduction of ischemic heart disease (IHD) (77). The exact mechanisms behind the reduced risk is unknown but fruits, vegetables and berries are rich in phytochemicals; potent antioxidants that may reduce oxidative stress and therefore potentially also inhibit oxidation of LDL (69). In addition they are abundant in potassium (22), a nutrient associated with blood pressure lowering effects. Although simply increasing fruit and vegetable intakes have negligible effects on blood pressure in non-hypertensive subjects (25) an increased intake does induce beneficial reductions in hypertensive subjects (25;26).

**Fiber**

Cohort studies link total fiber intake from fruits and cereals with a reduced CHD risk (78) and soluble fibers appear to be effective in reducing TC and LDL-C levels according to the American Dietetic Association (ADA) (79), although their conclusion is limited to studies evaluating the effects of added oats and psyllium. Whole grain may have cardio protective attributes (69;80) despite its negligible effects on blood lipids (81).

**Plant sterols**

Plant sterols (phytosterols) can exert a TC- (79) and LDL-C lowering effect that appears to be the most pronounced in individuals with high baseline concentrations (82).

**Nuts**

Incorporating nuts into the diet may induce small to moderate reductions in TC and LDL-C (79). According to the recent Norwegian dietary guidelines 140 grams of nuts each week reduces CHD risk (69). In contrast the WHO (76) and the ADA (79) make less absolute conclusions, simply suggesting a probable cardiovascular benefit.

**Alcohol intake**

The relationship between total cardiovascular mortality and alcohol intake is j-shaped (83) and abuse may induce hypertriglyceridemia (46), which is associated with unfavorable concentrations of atherogenic lipoproteins.
**Tobacco**

Tobacco is not only the leading cause of premature death in the world but is also associated with an increased risk of CHD (84;85), especially among individuals younger than 50 years of age. In addition to a direct increased morbidity and mortality risk, tobacco smoke also increases risk indirectly by inducing distress of the cells lining the arteries (7) and by reducing circulating HDL-C levels (86;87). Although smoking cessation produces beneficial increases in HDL-C and reduction in CHD risk regardless of previous smoking habits (84;87), termination is difficult and cause withdrawal symptoms in quitters (88).

Through the use of tobacco individuals are exposed to the addictive drug nicotine. Nicotine is a drug that induces a pharmacotherapeutic dependence through its actions on the reward system of the brain. Nicotine is rapidly absorbed and transported via the airway system into the circulatory system where it is subsequently conveyed to the brain. Once having diffused into the brain, nicotine binds to nicotinic acetylcholine receptors which promote the release of neurotransmitters and dopamine that mediate an additive response in combination with various pleasurable cognitive effects (89). Abstinence of nicotine consequently causes a reduction in the release of dopamine and induces withdrawals symptoms such as irritability, increased appetite and a craving for more tobacco.

Approved smoking cessation aids in Norway are nicotine replacement therapy, Varenicline and Bupropion (49). Nicotine replacement therapy reduces withdrawal symptoms by maintaining nicotine induced stimulatory effects. Varenicline suppresses nicotine stimulation by inhibiting its uptake from nicotinic acetylcholine receptors (88) and Bupropion is an anti-depressant nicotine receptor antagonist (90). The National Guidelines for Prevention of CVD recommend that a smoking cessation intervention should be offered to any patient who is motivated to quit smoking. Furthermore that the intervention should consist of information with regards to pharmacotherapy, local smoking cessation aid self-help resources and follow-up visits (49).

**Physical activity**

Physical activity reduces blood pressure (27) and increases HDL-C (91). Physical inactivity is an independent risk factor for CHD (18).
1.1.2 Pathogenesis of CHD

Atherosclerosis is a multi-factorial, inflammatory disease with a complex underlying pathogenesis (18;92) that is accountable for all CHD events and deaths (18). The progression of atherosclerosis is initiated and facilitated already during the first decades of life (93;94) by the presence of the different cardiovascular risk factors (95;96).

Although the exact pathogenesis of atherosclerosis is uncertain (29) endothelial dysfunction may be involved in the initial steps of its development since the homeostasis of the vascular wall is maintained by the endothelium (92;97). The endothelium regulates necessary various mechanisms, such as vascular tone and permeability, by producing vasodilating eicosanoids and peptides as well as the potent antioxidant nitric oxide (97;98). However, if the endothelium becomes exposed to aggravating stimuli such as elevated blood cholesterol levels (99) its vasodilating properties may become inhibited (97). Inhibition of normal endothelial function may promote compensatory responses such as an increase in endothelial permeability (97) and mediate the expression of adhesion molecules (such as VCAM-1) (100) that attract leukocytes (mainly monocytes and T-leukocytes) (100;101) to migrate into the intima. Once inside the intima, monocytes can differentiate into macrophages and commence ingesting any present sub endothelial atherogenic lipoproteins (29) and thereby facilitate the formation of “foam cells” and initial stages of atherosclerotic lesions (93).

Accumulation of leukocytes inside of the intima is suggested to be the foundation of a continuous inflammatory state where different cytokines, enzymes and growth factors promote the migration of smooth muscle cells into the intima. Ultimately this advances the formation of a weak fibrous plaque with a lipid core filled with pro-thrombotic debris (100;101). Clinical manifestations of atherosclerosis occur once the plaque ruptures and the circulation becomes exposed to its contents, which may induce the formation of a thrombus that can occlude an artery and cause acute CHD complications. Likewise, a plaque may also cause an acute event if it grows thick enough to occlude the arterial lumen and restrict blood flow to the heart.
1.2 Prevention of CHD by risk factor modification

According to recent European guidelines on CVD prevention in clinical practice “dietary modification should form the basis for CVD prevention” (7). Although risk factor modification is an essential factor in the primary prevention of CHD there is, to the knowledge of this master student, only two available randomised primary prevention trials in an outpatient care setting with a primary aim to assess the effects of lifestyle advice on hard coronary endpoints in subjects without pre-existing CHD (102;103).

The Oslo Study Diet and Antismoking Trial

In the Oslo Study Diet and Antismoking Trial, a five year primary prevention trial, Hjermann et al (102) executed an intervention with the primary aim to reduce the incidence of CHD. Subjects were normotensive hypercholesterolemic men aged 40-49 years with a high risk of CHD. The men were randomised to an intervention and a control group. The intervention group received general heart-friendly food based advice including advices to choose lean meats, skimmed fat milk, fatty fish and vegetable oils for food preparation. Anti-smoking advice was given to smokers in the intervention group. It was not stated in the original trial if the control group received any diet or anti-smoking advice. Follow-up visits were scheduled for every six months in the intervention subjects and for every twelve months for controls. At the end of the five year period, the incidence of fatal- and non-fatal clinical coronary events was 47% lower in the intervention group compared with the control group. After an additional three and a half years (104) the difference in incidence of total coronary events remained significant between the two groups in spite of counseling having ceased at the five year mark and the majority of smokers having reversed back to their previous smoking status. However, after 23 years of follow-up there was no longer a significant difference in IHD mortality between the groups (105).

Multiple Risk Factor Intervention Trial (MRFIT)

In the MRFIT study (103) men aged 35 to 57 years with an increased risk of CHD, but with no previous clinical evidence of it, were recruited and randomised to “special” or usual care for treatment of their cardiovascular risk factors. The special care group received intense smoking cessation aid and nutritional counseling modified to achieve lifelong behavioral changes in cooking, grocery shopping and eating patterns. The intervention intended to reduce
SFA and dietary cholesterol intake and to increase PUFA intake modestly. Controls received no intervention programme but nevertheless usual care. Subjects in the intervention group were seen at least every four months while the controls were monitored on a yearly basis. After approximately seven years there were significant differences in CHD risk factors between the treatment groups but no apparent benefit for the intervention group with regards to CHD mortality. However, when Gump et al (106) compared compliers to the yearly attendances with non-compliers he concluded that there was a significant benefit for the special intervention group with regards to cardiovascular mortality. Furthermore, that poor adherence to follow-up visits was on overall associated with unfavorable effects or cardiovascular risk regardless of group allocation.

**Primary prevention of CHD in women**

Previously mentioned trials have only included men. Since men develop CHD approximately ten years before women do (18) trials involving men require less resources and time to achieve enough clinical endpoints to detect a significant treatment difference. Although there are no randomised trials including only women with CHD as the primary endpoint, the Women’s Health Initiative (WHI) aimed to reduce the overall incidence of common non-communicable diseases (107) which also included CVD. Howard et al (108) assessed the effects of the WHI dietary modification trial on CHD risk by including data for all of the 48 835 randomised postmenopausal women aged 50 to 79 years. Although the dietary trial in itself did not primarily intend to prevent incidence of CHD the dietary intervention included several heart-friendly food components; a reduced fat intake, an increased intake of fruits, vegetables and grains. If randomised to the intervention group, women were given dietary advice during 18 group sessions for the first year where they were counseled to reduce their fat intake below 20 energy percent of their total calorie intake. No specific dietary advice with respect to fat quality or dietary cholesterol intake was given. Counseling continued subsequently every quarter of each year for intervention subjects while control subjects only received health related materials once and no active intervention programme. Intention to treat (ITT) analysis revealed significant differences in change in the major CHD dietary components; SFA, PUFA, dietary cholesterol, fiber, fruits and vegetable intake, nuts and grains. Nevertheless, in spite of this Howard found no significant difference in CHD incidences regardless of exclusion or inclusion of women with baseline CVD (3.4%).
Additional analyses however suggested a trend for a reduction in CHD risk for women who had the lowest intake of SFA and the highest intake of fruits and vegetables. Howard concluded that the intervention might have been inadequate to reduce CVD risk and that the intervention diet might have produced better results if aimed at a younger population.

1.2.1 Primary prevention in young adults with an elevated risk of premature CHD

Young adults (aged <40 years) have a low absolute risk of CHD and are consequently underrepresented in clinical trials (109). However, young adults may even so present with a clustering of cardiovascular risk factors that may go unnoticed by the health care system until clinical manifestations are evident at an older age. Especially young adults with a family history of CHD who might have a higher prevalence of other risk factors as well.

There is currently only one trial available that has assessed the effects of lifestyle intervention in adults aged below 40 years with a familial risk of premature CHD (110). In this randomised lifestyle trial Tonstad et al recruited CHD free young adults with suboptimal lipid profiles. Adults randomised to intervention received personalised dietary advices and one to four group counseling sessions focusing on the different aspects of a heart-friendly diet (fat, fruits and vegetables, physical exercise and motivation). In addition, intervention subjects received anti-smoking advice, intensive smoking cessation aid including follow-up visits at the clinic and pharmacotherapy aid. Controls received brief routine lifestyle advices. After a mean duration of eight months the intervention group achieved significantly different reductions in LDL-C, intake of SFA and intake of dietary cholesterol compared with the controls. Furthermore, while nine smokers quit smoking in the intervention group none did in the control group. In addition the intervention group had significantly lower concentrations of markers of endothelial stress than did the controls.
2 Aim, hypotheses and assignments

2.1 The “18 to 39” study (1839-S)

The “18 to 39” study (1839-S) is an ongoing study at Preventive Cardiology, Oslo University Hospital. The study is an extension of the predecessor trial published by Tonstad et al in the year of 2005 (110). The aim of the 1839-S is to compare the effects of one time individually specified life style advice by a physician and a registered dietitian versus routine advice on established risk factors for CHD (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio, weight, blood pressure and smoking status) after 16 weeks in men and women in the ages of 18 to 39 with increased risk of premature CHD.

There exists no study protocol for the 1839-S. As a consequence all information presented in this thesis, with regards to aim, method and design, was based on the recollection of information.

2.2 Aim of the master thesis

This master thesis is based on the 1839-S participants recruited in the 1839-S so far. The pre-specified aim of this thesis was:

- To compare the effects of one time dietary counseling and smoking cessation aid versus routine smoking cessation advice and no dietary counseling on established risk factors for CHD (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio, weight, blood pressure and smoking status) after 16 weeks in men and women in the ages of 18 to 39 with an increased risk of premature CHD.
2.2.1 **Hypotheses**

*Primary hypothesis*

H0: There are no significant differences in change in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio, weight or blood pressure between the intervention- and the control group.

H1: There are significant differences in change in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio, weight or blood pressure between the intervention- and the control group.

*Secondary hypotheses*

- H0: There are no significant changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio, weight or blood pressure at the end of the trial within the intervention- or the control group.

H1: There are significant changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio, weight or blood pressure within the intervention group only.

- H0: Intense smoking cessation aid given by a physician is not a more effective treatment than is routine smoking advice in reducing the number of subjects smoking ≥1 cigarette/day over a duration of 16 weeks.

H1: Intense smoking cessation aid given by a physician is a more effective treatment than is routine smoking advice in reducing the number of subjects smoking ≥1 cigarette/day over a duration of 16 weeks.
2.3 **Assignments of the master student**

- Attended and observed both baseline and follow-up appointments for one control subject and one intervention subject in the 1839-S study sample.

- Designed and created the database used to store the data from the 1839-S.

- Retrieved all available data for the subjects of the 1839-S from paper- and electronic medical journals.

- Called Fürst laboratory to track down any missing laboratory data.

- Imputed all the data from the medical journals into the database.

- Searched the non-electronical archives of Preventive Cardiology to track down the exact number of subjects that had been eligible for the 1839-S, had declined to participate or had agreed to participate.

- Searched the non-electronical archives of Preventive Cardiology to track down the screening lipid profiles of the randomised subjects.

- Used the available Food Frequency Questionnaires to create an additional variable in the database.

- Manually calculated all date and age differences for each subject.

- Imputed the database into a SPSS file and performed all statistical analyses.
3 Subjects, method and design

The reporting of the methodological design and the handling of data in this thesis is in accordance with the CONSORT checklist for reporting parallel group randomised trials (111).

3.1 Subjects

3.1.1 Recruitment of subjects

Subjects were recruited between the dates of 01.01.2003 to 31.03.2011. The main recruitment approach was by screening of first-degree relatives of patients with premature CHD admitted to the Oslo University Hospital. Additional subjects were recruited by the medical staff at Preventive Cardiology or through referrals from general practitioners.

Subjects recruited by their own primary relative

Screening of patients with premature CHD in a hospital setting has previously been implemented at Preventive Cardiology as a means to establish contact with primary relatives (14;110). Consequently, the procedure was also employed for the recruitment of subjects for the 1839-S.

All men and women with established premature CHD (defined as men <55 years of age and women <65 years of age) admitted to the cardiology ward at Oslo University Hospital were routinely offered a follow-up visit at Preventive Cardiology. At the end of the visit patients were asked if they were willing to contact their primary relatives (siblings and/or children) for a CHD risk factor measurement.

Every patient who agreed to contact their primary relatives was given an envelope including a letter (appendix 1), a simple questionnaire (appendix 2) and a laboratory referral form for each sibling or child. The letter requested the relative to obtain a blood test from their district health care centre and to send the complete questionnaire back to the clinic. The blood test was forwarded to Fürst laboratory for analysis. Primary relatives who did fulfill the eligibility criteria for the 1839-S were offered to participate in the study.
Subjects recruited by physicians in the Health South-East region

Young adults who were referred to Preventive Cardiology by general practitioners in the Health South-East region were automatically screened for eligibility. Eligibility to the 1839-S was assessed based on the information obtained from the referral as well as from the patient at the initial visit.

Subjects recruited by the medical staff at Preventive Cardiology

Current patients at Preventive Cardiology, and relatives of the medical staff, that were confirmed by screening to be eligible were approached with an offer to participate in the 1839-S.

The invitation

Subjects who had been contacted by their own relatives, and were eligible to partake in the study, were invited per mail to participate. The formal invitation consisted of:

- Their assessed lipid profile
- A date and time for a health examination at Preventive Cardiology
- An invitation to participate in the 1839-S and information regarding participation (appendix 3)
- A food-frequency questionnaire (FFQ) to be filled in before the appointment (appendix 4)

Additional subjects referred by general practitioners and medical staff were offered to participate during their initial visit at Preventive Cardiology.

Informed consent

Participants received oral and written information about the study and its objective. They were told that participation was voluntary and that withdrawal from the study was allowed at any point in time without it affecting any future medical or personal treatment at the hospital. Subjects who wished to participate in the study signed a written consent form at the initial visit.
3.1.2 Eligibility criteria for participation in the 1839-S

The desired study population consisted of men and women living within traveling distance from Oslo University Hospital who met the following inclusion, but not exclusion, criteria:

Inclusion criteria:

- Men and women aged 18 to 39 years
- TC >5.2 mmol/l including one/several of the following:
  1) TG >1.5 mmol/l with a TC/HDL cholesterol ratio of ≥4
  2) or HDL-cholesterol <1 mmol/l (men) or <1.2 mmol/l (women)
  3) or apoB >1.5 g/l
  4) or Lp(a) >80th percentile

Subjects who did not meet the above inclusion criteria but had a hyperlipidemia defined as TC >6.0 mmol/l and LDL-C >4.0 mmol/l were also considered eligible.

- An additional inclusion criteria was that all subjects must have at least one first degree relative (parent or sibling) with established premature CHD (men <55 years of age and women <65 years of age). Subjects were also eligible if they had at least one first degree relative with familial hyperlipidemia (including familial hypercholesterolemia or familial combined hyperlipidemia).

Subjects referred by general practitioners were only included if their referral clearly stated that the primary relative(s) were diagnosed with premature CHD or familial hyperlipidemia (including familial hypercholesterolemia or familial combined hyperlipidemia).

Exclusion criteria:

- TC >8 mmol/l
- Evidence of secondary hyperlipidemia due to endocrine, liver or kidney disorder
- Grade II obesity (BMI ≥35 kg/m²)
- Subjects with type II diabetes if on drugs or insulin
- Hypertension treated with drugs or requiring drug treatment
- Known atherosclerotic disease
- High short-term risk for atherosclerotic disease that in the judgment of the study physician warranted use of cholesterol-lowering drugs
- Pregnancy
3.2 **Method**

3.2.1 **Measurements**

All measurements were recorded at the initial and the follow-up visit.

**Anthropometrics**

The subject was allowed to wear light clothing defined as jeans and t-shirt while having his/her anthropometrics taken. However, shoes, jackets, jumpers or heavy sweaters were not allowed. Moreover, the subject had to empty his/her pockets.

Weight was measured to the nearest 0.5 kilograms on a mechanical column scale model named *Seca700*, *Seca, Lysaker, Norway*. The scale was calibrated on a yearly basis. Height was taken manually during the initial visit. The subject had to stand straight against the door with head, back and heels touching the door. The subject’s current height was measured to the nearest 0.1 cm using a manual height meter named *SECA Bodymeter 208, Seca, Lysaker, Norway*. The study physician calculated the BMI of the subject manually at each visit using the fundamental formula; weight in kilograms divided by the height in meters squared.

Waist- and hip circumference was measured using a regular measuring tape held horizontal around the waist and hip. The measuring was done in accordance with WHO standard (54); the reading of the measuring tape was done when the tape was snug but not causing compression and waist was measured between the lower rib margin and the iliac crest, at the end of a normal expiration. In subjects with a very large waist, waist circumference was measured at the widest point of the waist. Hip girth was measured at the maximum circumference of the buttocks. The subject’s current waist- and hip circumferences were measured to the nearest 0.1 cm.

**Blood pressure**

The subject’s blood pressure was measured using a sphygmomanometer from *WelchAllyn, New York, USA*. The registration was done on the subject’s right arm. During the blood pressure measurement the subject sat still in a chair in a relaxed position with both feet on the floor and arms comfortably on the arms of the chair. Blood pressure was taken twice if the first measured value was above 135 mmHg for SBP and/or 95 mmHg for DBP.
Biochemical parameters

Blood samples were drawn in the morning between 8:00 and 10:00 AM at the initial- and the follow-up visit. The subject was required to be in a fasted state defined as complete abstinence from any food or beverage except water during the last twelve hours with the exception of consumption of any type of alcohol which was not allowed within the last 24 hours. Smoking was not permitted on the day on the visit.

The subject sat down for a few minutes before the blood was collected by the study nurse. Subsequently to being drawn from the subject the blood was centrifuged for 15 minutes at the speed of 3600 rpm and then brought to the lab for immediate analysis.

The Clinical Chemistry department of Oslo University Hospital ran all of the analyses during the trial. The methods of analyses that are relevant to the results of this master thesis are described as follows:

- Serum TC, HDL cholesterol and TG were measured by enzymatic-colorimetric methods using kits from Roche Diagnostics. The analyses were performed using the machine Cobas Integra 800 from the same company.

- TC/HDL cholesterol ratio was calculated by the simple equation of dividing the two values with each other.

- LDL cholesterol was calculated using the Friedewald formula where an estimation of plasma LDL concentration is approximately given when serum TG are below 4.50 mmol/l (112):

  Friedewald formula: TC − HDL-C − TG/5 expressed in mmol/l

- ApoB was measured using an immunoturbidimetric method with a kit from Roche Diagnostics using the analyzing machine Hitachi 912 from the same company.

- Lp(a) was analysed with a turbidimetric method. The machine Cobas 501 was used.

- Serum glucose was analyzed with photometric analysis. An enzymatic method with hexokinase was used.
Lipid profiles obtained during the screening procedure had been analysed at Fürst laboratory. All lipids (TC, HDL, LDL and TG) were analysed using kits from Roche Diagnostics and the machine Cobras Integra 800 until 07.09.2009 when Fürst started using kits from Siemens Healthcare Diagnostics and the machine Advia 2400 instead.

**Smoking status**

Smoking and snuff habits were self-reported and recorded as daily, weekly or monthly quantities. Moreover, it was recorded if the current smoker was motivated to quit smoking during the trial.

In self-reported smokers carbon monoxide (CO) levels in the lungs were measured with a breath test using the Smokerlyzer Breath Carbon Monoxide Monitor from Bedfont Scientific Ltd. CO was measured in a single exhaled breath into a mouthpiece. The threshold for abstinence of smoking at follow-up was set by the master student as a CO-measurement of less than three parts per million (ppm) (113).

**Dietary intake and perceived body weight satisfaction**

The results of the Food Frequency Questionnaires (FFQ) were not used in this thesis with the exception of body weight perception.

All of the subjects in the 1839-S had to register their habitual food intake using the FFQ at both baseline and the final visit. The initial FFQ was supposed to describe the subject’s habitual food intake during the previous year and assess their degree of body weight satisfaction. The second was meant to reflect any dietary changes made between visit one and visit two. FFQ were reviewed by the registered dietitian (RD) together with each subject during both visits. The RD used the FFQ to personalise the dietary advices given.
3.3 Design of the trial

The 1839-S was a randomised trial consisting of two visits with a 16 weeks duration in between visits. The design of the entire trial from recruitment to analysis is seen in Figure 2.

Figure 2. Flow diagram of the progress through the phases of the 1839-S trial (enrolment, intervention allocation, follow-up, and data analysis). Adapted from (111) with permission from main author Moher, D.
3.3.1 Randomisation and blinding

Subjects were randomised during the initial visit to receive either intervention or routine (control) treatment. The randomisation allocation process was administered by the study physician and took place after baseline measurements but before any smoking cessation aid or dietary advice was given.

The randomisation approach used to assign the subjects to the intervention or control group was simple randomisation. The procedure was as follows: the subject was asked to pull a folded note out of a standard envelope that contained 200 notes. The notes were folded and had the letter “I” for intervention or “K” for control written inside of them with a ratio of 1:1. The subject was allocated to the group corresponding to the letter on the note which he/she had drawn.

Blinding

Due to the nature of the trial the medical staff (physician and dietitian) and subjects could not be blinded to the allocation sequence when treatment was given. The only medical staff kept blinded during the whole trial was the laboratory staff and the study nurse. The data analyst (master student) was not blinded to the allocation of the subjects.

Siblings and allocation adjustments

Siblings were allocated to the same group if the study physician suspected that they might influence each other if they were randomised to different groups. This was to make certain they would not affect each other during the intervention period. A total of three pairs of siblings were included in the study. The first sibling couple was randomised and allocated to the intervention group. The second pair of siblings was randomised to the control group. In the third pair, however, one sibling was randomised to the intervention group while the other sibling was randomised to the control group.

Only five out of six siblings completed the study. Both sibling couples that were randomised together into the same groups completed the trial. In the sibling couple where the siblings were split up in different groups, only the sibling allocated to the control group completed the trial. The other one decided to withdraw from the study before the second visit.
3.3.2 Consent and ethics

Study approval

The idea of the study design of the 1839-S was based on the previous lifestyle intervention study by Tonstad et al (110) at Preventive Cardiology. After the initial recruitment period for Tonstad’s study the medical staff continued to recruit subjects for the upcoming 1839-S. The two studies were different with respect to intensity of the dietary intervention, duration of the intervention and the exclusion of advice for and registration of physical activity.

Due to staff changes the new 1839-S and its accompanying changes were never registered with the Norwegian Regional Committee of Medical Ethics until December 2011 when communication was finally re-established between the committee and Preventive Cardiology. The committee replied on the date of 02.02.2012 that they had no ethical objections to the 1839-S (appendix 5).

De-identification

Data collected from the electronic- and paper medical records at Preventive Cardiology were kept in a secure file on a research server at the hospital. The data was de-identified using codes and a separate code list where each subject was given an unique identification number that connected them to the data file. The code list was locked away in an office.

3.3.3 Interventions

Intervention I: Smoking cessation aid

Controls were given routine smoking cessation advice consisting of brief information regarding the detrimental effects of smoking on cardiovascular health and an oral recommendation to quit smoking.

Intervention subjects who smoked \( \geq 1 \) cigarette per day were offered intense smoking cessation aid, which was administered by the study physician. The anti-smoking aid included thorough information on the dangers of smoking and information with regards to the positive health-benefits associated with smoking cessation. Furthermore, the physician informed about smoking abstinence and pharmacotherapy support (Champix, Bupropion or Nicotine
replacement therapy) to aid in the smoking cessation process. However, subjects who chose to use them had to buy and pay for them themselves.

Subjects were informed about available online sources to aid in their smoking cessation. In addition, they were offered additional motivational support, counseling and follow-up during the intervention weeks. The support included one to five follow-up telephone calls (given by the study physician or nurse) or visits at Preventive Cardiology as indicated.

If a subject was motivated to quit smoking during the intervention period the study physician recommended that the subject chose a date for smoking cessation. Nevertheless, irrespective of motivational level the subject was still reminded of the importance of quitting. In addition, the study physician offered the unmotivated subject a random call one month later to see if he/she had changed his/her mind about quitting smoking.

Subjects who smoked <1 cigarette/day were strongly advised to quit smoking and were sometimes also offered motivational support by telephone contact if desired. Users of snuff were informed about the health risks with snuffing, advised to quit snuffing and offered motivational support if they were motivated to quit snuffing. However, snuffing cessation was not an aim of the trial.

**Intervention II: Dietary advice**

On the basis of the FFQ, the dietary advice was individually specified and given by the RD of Preventive Cardiology. Only subjects in the intervention group received dietary advice at the initial visit whereas the control group had to wait until the follow-up visit. Common advice and food suggestions given are presented in [appendix 6](#).

The amount and type of detailed advice was somewhat dependent on the blood lipids that were elevated (elevated LDL-C or elevated TG) but on overall basic heart-friendly dietary advice. Although fabricated products containing plant sterols were not part of the routine dietary advice these were sometimes recommended to especially high risk subjects with very abnormal lipid profiles.

Each initial session began with a brief repetition about why the subject had been included in the study and how the RD could help. Although the foundation of the conversations was very individual the RD steered the dialogue towards nutritional advice regarding the lipid profile of
the subject. If the subject had had a recent weight-loss the RD asked how the weight loss had been achieved. Although weight loss was not targeted directly, attention was given to meal rhythm and total caloric intake in overweight subjects.

The RD took into consideration the subject’s personal food preferences. If a specific food item was important to the subject, but not considered heart-friendly, the RD recommended adjustment of the portion size or frequency of the food.

The RD advised the subject to choose lean meats with less than ten percent dietary fat. Dairy products were advised to be replaced by lower fat alternatives. To prevent the subject’s fat intake from becoming too low the RD advised inclusion of vegetable fats with each meal. Subjects were also advised to consume fatty fish on a weekly basis.

Fruits and vegetables were recommended and advised as two portions of fruit and three portions of vegetables daily. One portion being equal to one’s filled hand. Heart-friendly practical examples to spice up vegetables and salads were suggested using spices, Thousand Island dressing or pesto. All subjects were given the advice to fill half of their plate with vegetables. Subjects were told that part of the CHO content (rice and pasta) on their plate could be reduced to make space for more vegetables if desired. This was especially advised for subjects with elevated fasting TG if their current CHO intake was dominated by refined starch.

Subjects were recommended to choose the CHO alternatives with the highest content of whole grain. Examples of bread with a high content of whole grain were given using the Norwegian bread scale (114) where three or four filled quarters is equal to wholegrain bread. Moreover, subjects were advised to reduce their intake of sugar (i.e. sweets, desserts, cakes, chocolate and sodas) and to reduce alcohol consumption.
3.4 Creating a database

As part of this master thesis, the student was asked to create a database for current and future use at Preventive Cardiology. EpiInfo™ version 3.5.3 was used to create the database. The database itself and all of the following alterations mentioned in this section were created and completed by the master student alone.

Creating the database

The medical staff of Preventive Cardiology were consulted to ascertain that all key information was incorporated into the database. All data was obtained from non-electronic medical records, electronic medical records and the archives of Preventive Cardiology. In instances when information with regards to biochemical parameters was absent the master student personally called Fürst laboratories to track down missing information.

Modifications of the SPSS datafile

Subsequent to all information having been incorporated into the database its contents were converted into a SPSS file for statistical analysis. Modifications and adjustments in the SPSS file were made when necessary. The adjustments of importance for this thesis included

- calculation of days in between visit one and two
- calculation of the participants’ ages
- calculation of blood pressure
- calculation of WHR
- recording of personal perception of body weight

The calculation of days and ages

All dates including date of birth and date of the visits had been included in the EpiInfo™ database for each subject. However, due to differences in Epi Info and SPSS Statistical package, SPSS was unable to calculate the number of days in between visits and the age of
the subjects. Consequently, all dates had to be calculated manually by the master student. The calculations were conducted using the Norwegian online date to date calculator (115).

**Calculation of blood pressure**

If more than one measurement of SBP or DBP had been taken during the medical examination they were averaged in the database as one single value.

**Calculation of WHR**

The master student calculated the WHR manually in SPSS by dividing waist circumference with hip circumference.

**Body perception**

Body weight satisfaction was manually registered directly into SPSS using a basic coding system. The information was to be found in the FFQ where the subjects could express their body weight satisfaction by ticking off the one box corresponding to the answer that they considered most truthful.

The three possible answers in the FFQ were recorded into the SPSS file as;

1) Yes.
2) No, I want to lose weight.
3) No, I want to gain weight.

**Additional data**

The master student collected information from the non-electronical archives of Preventive Cardiology to determine the number of primary relatives of patients with premature CHD that had been available for screening for the 1839-S. The student searched the archives dated between 2002 and 2011 to exclude relatives recruited for the predecessor study (110). Primary relatives aged 18 to 39 years who had been available for contact were identified using family trees. Responders and non-responders were recognised by the presence or absence of blood analyses from Fürst laboratory. Eligibility and reason for non-participation was available in previous recordings from the study physician.
Definition of the metabolic syndrome in the database

The AHA definition of the metabolic syndrome was chosen for this thesis since it does not regard abdominal obesity as a mandatory criteria. The definition is described in Table 1 where an individual is characterised as having the syndrome if he/she presents with at least three out of five risk factors.

**TABLE 1.** Risk factors of the metabolic syndrome according to the criterion of the American Heart Association.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>≥88</td>
<td>≥102</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>≥1.7</td>
<td>≥1.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>≥130</td>
<td>≥130</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>≥85</td>
<td>≥85</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>≥5.6</td>
<td>≥5.6</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>&lt;1.29</td>
<td>&lt;1.03</td>
</tr>
</tbody>
</table>
3.5 **Statistics**

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Two-sided P-values were used. A P-value of less than 0.05 was considered statistically significant. All individuals were analysed as randomised regardless of deviation from inclusion criteria.

**Analytical method**

Listwise and pairwise exclusion are the two basic options for handling missing data in the SPSS statistical package. In pairwise analysis each mean and standard deviation are estimated on a somewhat different dataset and therefore listwise exclusion was chosen by the student as the method for data exclusion.

**Sample size**

Data from the predecessor study (110) was used to estimate the mean and standard deviation (SD) of LDL-C in the study population. A feasible reduction in LDL-C by dietary modification was based on Katcher’s (116) suggestion that an approximate reduction in LDL-C equivalent to 11-15% is achievable by restricting SFA and dietary cholesterol intakes.

**Calculation of sample size:**

Clinically relevant difference between the two groups: 0.1 x 4.29 mmol/l LDL-C.

\[ \delta = 0.429 \]

Standard deviation of LDL-C, approximately 0.75 mmol/l.

\[ s = 0.75 \]

The standardised difference is:

\[ \delta/s = 0.572 \]

According to Altman’s nomogram (117) for calculating sample size, a standardised difference of 0.572 required approximately a total sample size of 100 patients with 50 subjects in each group to detect a ten percent difference with a power of 0.8 (80%) at a significance level of 0.05.
**Categorical variables**

Categorical variables were analysed using 2x2 contingency tables and Fisher’s exact test when the assumption of independence was violated for the Chi Squared test. Within group associations were tested using Mc Nemar’s test. The variables were presented using exact numbers and corresponding percentage counts.

**Continuous variables**

Histograms and normality plots (Q-Q Plots) were used to assess the normality of the data. Since the inclusion criteria allowed for subjects with both hyperlipidemia and hypercholesterolemia the data consisted of several outliers. Outliners were identified using box plots and the genuineness of the outliers was checked prior to analysis.

The variability of the data was described using either mean and standard deviation (SD) or median and minimum (Min) and maximum (Max) value, depending on the distribution of the data.

Variables with a normal distribution were tested with independent-samples t-test and paired-samples t-test. Variables with a non-normal distribution were transformed to attain a more normal distribution.

Subanalyses assessing changes in weight and WHR within different BMI groups were tested using Wilcoxon signed rank test.
Transformation of data

In this thesis we transformed skewed TG variables to attain normal distributions. Two explanatory calculations are shown below to aid in the interpretation of the results in this thesis.

**Between group differences in change**

We wished to find a difference in change between the intervention group and the control group.

Change in the intervention group from baseline to follow-up is:

\[ C_1: \text{(follow-up)} - \text{(baseline)} \]

Change in the control group from baseline to follow-up is:

\[ C_2: \text{(follow-up)} - \text{(baseline)} \]

Logarithms cannot be based on negative numbers. Therefore we had to log transform the raw data before calculating the changes between baseline and follow-up. Original data was transformed by taking the logarithm:

\[ C_1: \log(\text{follow-up}) - \log(\text{baseline}) \]

\[ C_2: \log(\text{follow-up}) - \log(\text{baseline}) \]

Since division of two expressions corresponds to subtraction of their logs we have:

\[ C_1: \log \left( \frac{\text{follow-up}}{\text{baseline}} \right) \]

\[ C_2: \log \left( \frac{\text{follow-up}}{\text{baseline}} \right) \]

The histograms now revealed normal distributions and an independent-samples t-test could be conducted. The mean difference calculated by the t-test was equal to:

\[ \log \left( \frac{C_1}{C_2} \right) \]
The geometric mean of the data is calculated using the antilog.

\[
\text{Antilog of } \log \left( \frac{C_1}{C_2} \right)
\]

gives us the geometric mean:

\[
\frac{C_1}{C_2}
\]

The geometric mean of our data can be interpreted as:

\(<1: C_1 < C_2\>
\>
\(<1: C_1 > C_2\>

where a geometric mean of 1 is equal to no difference in the ratio of change between the intervention group and the control group.

**Within group changes**

We wished to find a within group change from baseline to follow-up. Original data was transformed by taking the logarithm.

TG values at baseline: \(\log(\text{baseline})\)

TG values at follow-up: \(\log(\text{follow-up})\)

The change from baseline to follow-up for paired-samples t-test is equal to:

\[
\log(\text{follow-up}) - \log(\text{baseline})
\]

Since division of two expressions corresponds to subtraction of their logs we have:

\[
\log \left[ \frac{\text{follow-up}}{\text{baseline}} \right]
\]
The geometric mean of the data is calculated using the antilog.

\[
\text{Antilog of } \log \frac{\text{follow-up}}{\text{baseline}}
\]

gives us the geometric mean:

\[
\frac{\text{follow-up}}{\text{baseline}}
\]

The geometric mean of our data can be interpreted as:

\(<1\): follow-up < baseline
\(>1\): follow-up > baseline

where a geometric mean of 1 is equal to no change in the ratio between baseline and follow-up.

**Confidence intervals**

In this thesis confidence intervals (CI) were used to show the degree of uncertainty related to our research data in addition to reporting the effect sizes and hence clinical importance (118) of our results.
4 Results

The first part of this section aims to describe the baseline characteristics of the subjects that were included in this thesis. Following that is the section that answers the main hypotheses of this thesis. Finally there are few additional exploratory analyses.

4.1 Dropouts, attended time between visits and baseline characteristics

4.1.1 Dropouts

A total of 149 subjects completed the trial. Five subjects in the intervention group and seven subjects in the control group withdrew on their own account before the follow-up visit. Their reasons for discontinuing participation in the study were given in Figure 2. There was little information given in the journals stating as to why a subject had dropped out from the study.

4.1.2 Attended time between visits

A majority of the subjects (93%) waited more than the unequivocal timeline of 112 days before they returned to Preventive Cardiology for their follow-up visit. The mean number of days between visit one and two in the intervention group was 153 (SD: 49) days. The minimum number of days was 100 and the maximum number of days 344. In the control group the mean number of days between visits was 151 (SD: 45) days with a minimum of 97 days and a maximum of 374 days. No difference in mean number of days between the groups was seen (P=0.81).
4.1.3 **Baseline characteristics**

Gender distribution of the first-degree relatives screened for eligibility (data not shown) was almost similar for both sexes although the majority of non-responders (68%) were male. In our randomised study sample, 46% of the male subjects and 50% of the female subjects had been recruited by a relative.

**Table 2** describes the characteristics based on the inclusion criteria of all the 161 participants at baseline prior to randomisation. Lp(a) was only measured once at baseline. A total of 82% of the subjects had a primary relative with premature CHD and 37% had above optimal blood pressure. Altogether 44 women and 117 men were randomised at the initial visit, of which 27 women and 57 men were randomised to the intervention group.

Eighteen subjects fitted the exclusion criteria. These subjects were aged above 39 years (n=3), were receiving current medicinal treatment for their hypertension (n=3), pregnant (n=1), suffering from grade II obesity (n=6), had a TC above 8.0 mmol/l (n=4) and suffered from grade II obesity in addition to having a TC above 8.0 mmol/l (n=1).

At baseline 36% of the subjects reported taking any form of medication. In the vast majority of cases (66%) the medicinal use consisted of allergy medicine and oral contraceptives. Not one reported taking any cholesterol-lowering drugs at baseline.
### TABLE 2. Baseline characteristics of all the randomised subjects (n = 161).

<table>
<thead>
<tr>
<th></th>
<th>Females (n=44)</th>
<th>Males (n=117)</th>
<th>Range (min to max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 (7)</td>
<td>32 (5)</td>
<td>(18-43)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 (17.1)</td>
<td>85.0 (12.8)</td>
<td>(51.5-130.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 (5.9)</td>
<td>26.2 (3.6)</td>
<td>(18.1-43.9)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>84.5 (13.2)</td>
<td>91.0 (9.2)</td>
<td>(66.0-124.0)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.80 (0.06)</td>
<td>0.88 (0.06)</td>
<td>(0.68-1.03)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116 (8)</td>
<td>124 (10)a</td>
<td>(100-150)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 (6)</td>
<td>78 (7)a</td>
<td>(55-102)</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>5.9 (1.0)</td>
<td>6.1 (1.0)</td>
<td>(3.6-8.5)</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.87 (1.02)</td>
<td>4.20 (0.96)b</td>
<td>(1.44-6.78)</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>4.6 (1.6)</td>
<td>5.5 (1.7)a</td>
<td>(1.9-11.3)</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.40 (0.4)</td>
<td>1.19 (0.34)c</td>
<td>(0.55-2.82)</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.47 (0.81)</td>
<td>1.86 (1.55)</td>
<td>(0.42-10.89)</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>1.05 (0.25)</td>
<td>1.14 (0.24)c</td>
<td>(0.10-1.70)</td>
</tr>
<tr>
<td>Lp(a) (g/l)</td>
<td>791 (730)d</td>
<td>424 (399)d</td>
<td>(&lt;60-2344)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.0 (0.5)e</td>
<td>5.1 (0.5)g</td>
<td>(3.5-6.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>10 (23)</td>
<td>28 (24)</td>
</tr>
<tr>
<td>Snuffer</td>
<td>2 (5)</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>7 (16)</td>
<td>23 (20)</td>
</tr>
</tbody>
</table>

Continuous variables are shown as mean (SD) for men and women
Minimum and maximum values of the variables are given for both sexes as a whole group
Categorical variables are shown as count and percentage (%)

a n=116
b n=111
c n=115
d n=15 for females, n=34 for males
e n=39 for females, n=90 for males

Abbreviations: WHR = waist to hip ratio, SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL-C = LDL-cholesterol; HDL-C = HDL-cholesterol; TG = triglycerides, ApoB = apolipoprotein B, Lp(a) = lipoprotein A, BMI = body mass index

Prevalence of the metabolic syndrome

According to the AHA definition there were 24 subjects with the MetS present in the study sample at baseline. Out of these, eleven had been randomised to the intervention group while the rest had been allocated to the control group.

At the follow-up visit, 36% of the subjects in the intervention group and 15% of the subjects in the control group could no longer clinically be defined as having the MetS. There was no statistical association between treatment allocation and reverse of the MetS (P=0.29) between the groups or within the intervention group (P=0.21).
4.2 The results of the trial

4.2.1 Changes in between treatment groups

The results of the intervention expressed in the cardiovascular risk factors TC, LDL-C, HDL-C, TG, weight, WHR, SBP and DBP are shown in Table 3. At baseline there were no differences between the intervention- and the control group except for lower HDL-cholesterol levels in the control group (P=0.02).

There were no significant differences in change between the intervention- and the control group in any of the risk factors at the end of the trial. The results did not change when the analysis excluded the subjects who fitted the exclusion criteria (data not shown). Additional analyses (data not shown) for waist circumference (P=0.13) and apoB (P=0.27) did not reveal a significant difference in change.

Stratifying the groups by gender (data not shown) to compare differences in change in HDL-C and WHR had no effect on the results (all P>0.08).

4.2.2 Differences within respective groups

Changes in the risk factors from baseline to follow-up within both groups are seen in Table 3.

In the intervention group there was a reduction in systolic blood pressure by -3.7% (P<0.0005) and a reduction in diastolic blood pressure by -2.8% (P=0.008).

There was a reduction in systolic blood pressure by -2.1% (P=0.008) and an increase in HDL-cholesterol by +4.2% (P=0.007) in the control group.

Additional analyses of waist circumference and apoB (data not shown) did not reveal significant changes within either group (all P>0.19). There were no significant changes (all P>0.09) in WHR or in HDL-C in males or females within either group during the trial (data not shown).

The results did not change when the analysis excluded the subjects who fitted the exclusion criteria (data not shown).
TABLE 3. Changes in cardiovascular risk factors from baseline to follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (n = 73)</th>
<th>Control (n=62)</th>
<th>Between group difference in change (95% CI)</th>
<th>P-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-82.4 (14.4)</td>
<td>-83.7 (15.0)</td>
<td>-0.23 (-1.18; 0.72)</td>
<td>0.63</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-82.0 (14.1)</td>
<td>-83.5 (15.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-0.4 (-1.04; 0.21)</td>
<td>-0.2 (-0.88; 0.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-0.85 (0.08)</td>
<td>-0.86 (0.07)</td>
<td>-0.01 (-0.02; 0.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-0.85 (0.07)</td>
<td>-0.86 (0.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-0.00 (-0.01; 0.00)</td>
<td>-0.01 (-0.00; 0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-121.1 (8.6)</td>
<td>-121.6 (9.9)</td>
<td>-2.03 (-4.67; 0.60)</td>
<td>0.12</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-116.6 (10.7)</td>
<td>-119.1 (11.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-4.5 (-6.36; -2.63)</td>
<td>-2.5 (-4.38; -0.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-77.3 (7.32)</td>
<td>-78.0 (7)</td>
<td>-1.17 (-3.30; 0.96)</td>
<td>0.28</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-75.1 (8.08)</td>
<td>-77.0 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-2.2 (-3.88; -0.59)</td>
<td>-1.0 (-2.37; 0.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-6.2 (1.0)</td>
<td>-5.9 (1.0)</td>
<td>-0.16 (-0.40; 0.09)</td>
<td>0.20</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-6.1 (1.0)</td>
<td>-6.0 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-0.1 (-0.25; 0.10)</td>
<td>-0.1 (-0.08; 0.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-4.16 (1.04)</td>
<td>-4.07 (0.94)</td>
<td>-0.01 (-0.23; 0.22)</td>
<td>0.94</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-4.11 (0.93)</td>
<td>-4.03 (0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-0.05 (-0.22; 0.10)</td>
<td>-0.04 (-0.21; 0.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-1.33 (0.35)</td>
<td>-1.19 (0.35)</td>
<td>-0.03 (-0.09; 0.04)</td>
<td>0.39</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-1.35 (0.34)</td>
<td>-1.24 (0.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-0.02 (-0.03; 0.07)</td>
<td>-0.05 (0.01; 0.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-1.52 (0.77)</td>
<td>-1.48 (0.74)</td>
<td>-0.87 (0.76; 1.01)</td>
<td>0.13</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-1.42 (0.68)</td>
<td>-1.63 (0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (95% CI)</td>
<td>-0.95 (0.87; 1.05)</td>
<td>-1.10 (0.98; 1.23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Variables are expressed as mean (SD) and mean change (95% CI)
A negative sign before numbers is equal to a decrease while no sign is equal to an increase
¹ Mean difference in change between the intervention and the control group
² P-value for independent-samples t-test
³ Statistically significant change for paired-samples t-test (P<0.01)
⁴ Geometric mean ratio for within group change and antilog of 95% CI
⁵ Geometric mean ratio for difference in change between groups and antilog of 95% CI
Abbreviations: WHR = waist to hip ratio, SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL-C = LDL-cholesterol; HDL-C = HDL-cholesterol; TG = triglycerides
4.2.3 **Smoking cessation**

The direct effects of the smoking cessation aid as given by the study physician is seen in Table 4.

| TABLE 4. Smoking status at baseline and follow-up in subjects who completed the trial (n=149). |
|---|---|---|
| Variable | Intervention (n = 79) | Control (n = 70) | P-value |
| Smoker* at baseline | 13 | 21 | 0.88 |
| CO-level | 4 (1-14)b | 8 (1-21)b | |
| Non-smoker* at follow-up | 6 | 6 | 0.86 |
| CO-level | 1 (0-3)c | 1 (0-2)c | |

Data on smoker status is given in absolute numbers CO-level is expressed as median (Min-Max)

* Smoker is defined as smoking ≥1 cigarette/day
b Missing values for (n=2 in Intervention, n=3 missing in Control)
c Missing values for (n=1 in Intervention, n=2 in Control)

Chi-square test for independence is statistically significant when P<0.05

Abbreviations: CO = carbon monoxide

Smoking cessation rates were 46% in the intervention group and 29% in the control group.

There was no association between group allocation and smoking cessation (P=0.86).

**Smoking cessation and resumption**

Subjects who claimed to have quit smoking during the trial had their smoking cessation status verified by their measured CO-levels. Six subjects in the intervention group and six subjects in the control group had quit smoking altogether by the follow-up visit. Out of these twelve subjects, three in the control group and one in the intervention group had replaced their cigarettes with snuff during the trial.

A total of four non-smokers at baseline, two in each group, had taken up smoking by the follow-up visit. Two of these subjects, one subject in the intervention group and one in the control group, were former social smokers who had increased their total amount of cigarettes smoked on a weekly basis. The remaining two subjects were former smokers who had quit smoking shortly before being randomised and had resumed their smoking during the trial.
Smoking cessation and motivation

At baseline there had been four smokers in the intervention group and eight in the control group who had labeled themselves as being motivated to quit smoking. However, out of these twelve subjects there was only one in the intervention group and three in the control group that actually quit smoking. On the contrary, a total of five subjects in the intervention group and one subject in the control group who had labeled themselves as unmotivated to quit smoking at baseline reported having quit smoking altogether by the follow-up visit.
4.3 Additional analyses

Weight according to BMI categories and perceived body satisfaction

Weight classification and weight satisfaction may indicate if the subjects wanted to lose weight or not. The intervention group was split into two subgroups: subjects with a BMI below 25 kg/m² (BMI<25) and subjects with a BMI above 25 kg/m² (BMI>25). No weight reduction or increase was seen in subjects with BMI <25 (P=0.37) or BMI>25 (P=0.14).

The weight satisfaction at baseline in the intervention group is shown in Figure 3 and Figure 4. Few of the participants had omitted the question about weight satisfaction although the absence of response was greater in the BMI >25 group, suggesting that it may have been a sensitive question for some of the subjects.

<table>
<thead>
<tr>
<th>Figure 3. Baseline weight satisfaction in individuals in the intervention group with a BMI &lt;25 kg/m² (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfied, wish to gain weight</td>
</tr>
<tr>
<td>Unsatisfied, wish to lose weight</td>
</tr>
<tr>
<td>Satisfied</td>
</tr>
<tr>
<td>Missing response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Figure 4. Baseline weight satisfaction in individuals in the intervention group with a BMI ≥25 kg/m² (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfied, wish to gain weight</td>
</tr>
<tr>
<td>Unsatisfied, wish to lose weight</td>
</tr>
<tr>
<td>Satisfied</td>
</tr>
<tr>
<td>Missing response</td>
</tr>
</tbody>
</table>

No weight reduction was seen among the subjects reporting that they wanted to lose weight (P=0.78). Furthermore there was no change in WHR (P=0.67).

Similar analysis in the control group (data not shown) revealed no weight changes within the BMI<25 group or the BMI>25 group (P>0.20).
**Difference in lipids between screening and baseline**

**Table 5** display the changes in blood lipids that occurred between screening and baseline in subjects who had their blood analysed at Fürst laboratories prior to 07.09.2009.

<table>
<thead>
<tr>
<th></th>
<th>Screening (n=55)</th>
<th>Baseline (n=55)</th>
<th>Mean difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mmol/l)</td>
<td>6.2 (0.8)</td>
<td>6.0 (1.1)</td>
<td>-0.17 (-0.39; 0.04)</td>
<td>0.12</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>4.12 (0.86)</td>
<td>4.07 (1.01)</td>
<td>-0.05 (-0.25; -0.15)</td>
<td>0.62</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.28 (0.36)</td>
<td>1.24 (0.37)</td>
<td>-0.04 (-0.08; -0.00)</td>
<td>0.03</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.80 (0.80)</td>
<td>1.58 (0.80)</td>
<td>-0.87 (0.77; 0.98)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD).

A negative sign before numbers is equal to a decrease while no sign is equal to an increase.

a Screening defined as a point in time during which the subjects’ blood was analysed at Fürst laboratories

b P-value for paired-samples t-test

c Geometric mean ratio for change and antilog of 95% CI

Abbreviations: TC = total cholesterol; LDL-C = LDL-cholesterol; HDL-C = HDL-cholesterol; TG = triglycerides

Analyses revealed significant reductions in HDL-C and TG from screening to baseline.
5 Discussion

Our randomised trial has several strengths and limitations. In this section these are discussed followed by the principal results found in this thesis. Finally conclusions are drawn and future perspectives are discussed.

5.1 Discussion of subjects and method

5.1.1 Recruiting young adults in a hospital setting

In this trial we recruited subjects by three different methods. Since current guidelines offer no guiding principle for how to approach and identify young adults with an elevated risk of premature CHD in a population (7;49) we have with this study provided further insight to the question.

In our study we found that the response rate to a family based screening approach in a hospital setting was approximately 42% among young adults aged 18 to 39 years during a screening period of eight years. Previous response rates among young adults have been 56% when the method was initially implemented by Tonstad & Westheim over a three year period (14) and 93% over a one year period (110). Nevertheless, in the latter trial Tonstad failed to differentiate between the number of responders referred by primary relatives and by general practitioners as well as other medical staff. Combined, our results suggest that the response rate to a family based screening in a hospital setting in Norway may be moderate to low.

We found a response rate of 100% for recruitment by general practitioners. Although our numbers are limited this does suggest that this approach may be a more effective method of recruitment for young adults than a family based approach. However, the success of this method is heavily dependent on the primary relatives to visit their health care centers and on the general practitioners to screen and refer them. Although the response rate was also 100% for recruitment by medical staff our numbers are too small to suggest a difference in response rate.
Limitations

In our study 58% of the contacted primary relatives failed to respond to an invitation for a CHD risk assessment. Since cohort studies have reported that non-responders have a higher incidence of the outcome disease and a higher mortality rate (119;120), we thereby run the risk of excluding subjects who may need our preventive care and CHD risk screening the most. Especially considering that their potential clustering of cardiovascular risk factors may otherwise go unnoticed until a clinical manifestation occurs.

The majority of our non-responders (68%) were of male gender. This was also found to be the case in the study by Tonstad & Westheim (14) where 64% of young non-responders were male. Although being young and male in general are representative attributes of typical non-responders (62-68%) in Oslo (121), our non-responders may have a different risk profile than the general non-responders due to their additional familial risk. For instance, males with a family history of CHD may be more prone to future CHD events than females are (122), making them an especially important group with respect to preventive strategies.

Since our sample is likely to represent the typical responders in Oslo, we may have a sample of more self- or health conscious adults who are interested in and motivated to make lifestyle changes to reduce their personal CHD risk (123;124). Consequently our findings are therefore not attributable to our intended target population as a whole that consists of both responders and non-responders.

A final limitation of our recruitment method is that due to a low response rate and narrow inclusion criteria our final subjects only represent 17% of the original available sample population. This limits our external validity further since our subjects are unlikely to be a representative sample of our intended target population (125).
5.1.2 **Potential advantages and shortcomings of method and study design**

Although the design of our study was innovative there are some methodological limitations that have implications to the interpretation of our results.

**Strengths**

To the knowledge of this master student only one previous trial has been aimed at our target population consisting of young adults aged 18 to 39 years with an increased risk profile for future premature CHD (110). Therefore, an advantage in our design is that we have provided more insight with regards to the feasibility of interventions targeted at these young adults. In our study 93% of the subjects completed the trial, suggesting that a majority were willing to take time for primary preventive care. Our finding is similar to the predecessor study where only 13% of participants were lost to follow-up or withdrew their consent (110).

Since the 1839-S intends to recruit a total of 200 subjects the choice of simple randomisation was the most appropriate (126). The decision not to exclude any randomised subjects was based on the CONSORT statement that exclusion of randomised subjects may compromise the randomisation itself (111). Furthermore, the randomisation is our greatest strength in the study design since we consequently have accounted for an equal distribution of Regression to the mean (RTM) (127) between our groups.

Although our sample has clinical diversity, due to the eleven percent of our subjects who were included in spite of deviation from protocol, it may be a more representative sample of the patients that are actually referred to a clinic such as Preventive Cardiology. Furthermore, restriction of our analysis to subjects who only met the inclusion criteria did not change the primary or secondary results of our trial. This suggests that the results of our dietary intervention are still transmittable to a sample that fit our specified inclusion criteria.

**Limitations**

A limitation of the smoking intervention is the absence of information with regards to whom used pharmacotherapy in their aid to quit smoking during the trial. As a consequence, it remains unknown if our results are due to pharmacotherapy usage or due to the intense motivational support by the study physician. Furthermore, there was no definition set for the
classification of smoking cessation besides CO measurements. Accordingly, we do not know for how long the subjects had been abstinent from smoking prior to their follow-up visits.

Although modification of physical activity levels may confound changes in blood pressure and HDL-C, this was not taken into the consideration of the 1839-S design. We consequently have no information with regards to this potentially confounding factor.

A limitation of this master thesis is that we did not use the dietary data from the FFQ. This was due to our inability to recruit a supervisor from the Department of Nutrition at the University of Oslo who was willing to take responsibility to aid the master student in the scanning and evaluation of the FFQ. We nevertheless acknowledge that dietary habits are difficult to measure regardless of dietary assessment method (128).

Although the predecessor study assessed levels of endothelial markers of distress, we did not have this information available for our subjects and as a consequence cannot identify such a treatment effect.

**Accuracy of outcome measurements**

In this thesis all measurements have been routinely collected beforehand in a clinical setting. As a consequence the sampling and handling of data has not been strictly controlled per protocol. As is with any manually measured outcomes, both systematic and individual measuring errors may occur. Nevertheless, since all anthropometric measurements were measured by the same medical staff at Preventive Cardiology, all using the same equipment, these errors should be equally distributed within both our randomised groups.

If a subject presented with elevated blood pressure it was measured twice as described in the method’s section. This may reduce the risk of overestimating changes in blood pressure due to the “white coat effect” (129) in susceptible subjects. Still this does not eliminate its confounding effects since averaging two measurements into one value may also create the appearance of a reduction in blood pressure in between visits if the subject only has one measurement taken at the follow-up visit. An alternative approach could consequently have been to measure 24 hour ambulatory blood pressure as well in these particular subjects.

Although CO-measurements are commonly used to confirm the self-reported abstinence from smoking in studies, several of our self-reported smokers had CO-levels below the suggested
threshold at baseline. Although 2-3 ppm are valid cut-off levels in smokers (113), according to the manufacturers (130) the CO levels do tend to decline overnight and our subjects had their measurements taken in the morning. Since smokers are more likely to underreport than over report smoking status (131) it is unlikely that we have falsely classified non-smokers as smokers.

For our subanalysis of changes in lipids in between screening and baseline we only included individuals with blood analyses from Fürst laboratory to reduce the risk of analytical and biological variation attributing to any differences detected.

5.1.3 **Statistical choices and subsequent consequences**

In this thesis the threshold for statistical significance was set at $P<0.05$ in spite of our increased probability of finding a $P$-value below 0.05 due to our repeated statistical testing (118;132). To account for this we could have chosen to apply different methods such as the Bonferroni adjustment (117). Nonetheless, a more strict significance level than $P<0.05$ was not set in this master thesis. Instead, we decided that caution should be taken when interpreting our results since it is more important to differentiate between a significant result with no clinical relevance, that is due to a type I error, and a non-significant result with clinical relevance that may be due to a type II error (111).

Although several outliers were present in our dataset they were directly connected to subjects suspected of having a lipid disorder. Since Altman recommends that no observations should be excluded from analyses unless there are reasons to doubt their credibility (118) we included all of our outliers in our analyses.

By including all outliers in our dataset we increased the risk of making a type I statistical error since we chose to use the more sensitive parametric tests to analyse our data. Although the t-tests is robust in sample sizes over 30 (133), our TG distributions were markedly skewed and we consequently decided to transform our data to attain a more normal distribution.

Our choice to use listwise exclusion in our dataset resulted in a loss of nine percent of available subjects due to the absence of baseline or follow-up data. In the majority of cases the exclusion was due to missing LDL-C values. The missing LDL-C values were attributable to the limitations of the Friedewald formula (112) which give inaccurate estimations for LDL-
C when the TG level of a subject is above 4.50 mmol/l. Since our inclusion criteria did allow for patients with hypertriglyceridemia a loss of data was to be expected.

Although a loss of data introduces the risk of losing valuable statistical power we did not have more subjects with missing outcome data (16%) than what is otherwise seen in trials (0-20%) (134;135). Furthermore, missing data is only of concern if the frequency or cause for absence differ between groups (111), which it did not.

Since our subjects deviated from protocol an intention to treat (ITT) analysis would have been the appropriate statistical approach (111). In spite of considering several imputation models (Last Observation Carried Forward (LOCF) (136), mean imputation (137) and multiple imputation (MI)(138)) in order to try to replace our missing data it was decided not to perform an ITT analysis. MI is a very advanced method and both LOCF and mean imputation restrict the natural variability of the data (136) and bias results.

In this thesis we wanted to test for differences in change since it is a more statistically powerful method than comparing endpoint values. To control for any disparities in baseline values (139) we wished to use analysis of covariance (ANCOVA). However, we found that the prerequisites of a linearity assumption was violated.
5.2 **Discussion of results**

5.2.1 **Absence of change in blood lipids**

In this study we found no differences in change within or between groups for the blood lipid parameters. This was also confirmed by our subsequent analyses of apoB. Our finding is rather surprising considering that the mean total cholesterol level was 6.10 mmol/l in our sample and we would expect such high TC levels to fall even with modest dietary changes. Especially considering that general adherence is low when a diet is randomly assigned (140) and our subjects received personalised dietary advice which should have enabled them to better implement the suggested changes.

Since our subjects were given dietary advice to specifically reduce SFA intakes a reduction in LDL-C and TC was expected if they adhered to the advice since Tonstad et al (110) found a significant difference in LDL-C between the intervention and the control group after a reduction in SFA intake in our predecessor study. Our finding is nevertheless very similar to the -0.16 mmol/l difference in TC between two randomised groups found in a published study by Estruch et al (141). In their subsample (n=772) of the PREDIMED study, negligible differences in the intake of SFA could easily explain the indifferences in TC and LDL-C. Similar to our approach, Estruch’s low fat diet subjects were treated like a control group and the intervention subjects received substantially more intensive dietary counseling. However, unlike them our statistical power was too low (<20%) to be able to detect such a small difference as -0.16 mmol/l.

Another study that has assessed the effects of dietitians versus physicians in hypercholesterolemic subjects was the randomised study by Henkin et al (142). Henkin randomised hypercholesterolemic adults aged 30-65 to receive dietary advice either as given by a dietitian or a physician. After three, but not after six months, the reductions for TC and LDL-C were significantly different between the treatment groups favoring dietitians (-4% TC and -5% LDL-C). The difference in reductions within the dietitian group was -9% for TC and -12% for LDL-C. Although not significantly different from each other, their reductions in these lipids were still greater than ours even after six months in both treatment groups.

In Henkin’s study, subjects were excluded if they had been given dietary counseling in the past since this may have otherwise confounded the effects of the intervention. In our study,
we have not accounted for this and therefore cannot exclude the possibility that our subjects may have made dietary changes prior to baseline. This is not a foreign concept considering that our subjects had to wait between being told that they had an increased risk and visiting Preventive Cardiology. Since dietary information is readily available online, in magazines, in books and on television it is likely that our subjects may already have introduced positive dietary changes prior to baseline by using other health resources available to them (143).

Although we had restricted statistical power we did find an indication that there might have been modest reductions in all lipids prior to baseline in our subsample. Unfortunately since we do not have the dietary data we do not know if this may be due to a reduction in fat intake. These differences could also be attributed to RTM since our subjects were not randomised prior to baseline in addition to high initial observations commonly being followed by RTM (127). Furthermore, TC concentrations have been shown to fluctuate according to season and are lower during the summer months (144). Therefore, since our recruited subjects had to wait for an appointment at Preventive Cardiology, it is also plausible that the differences seen in TC could be due to seasonal variation.

If our subjects have in fact changed their diets prior to baseline their low physiological response to our dietary intervention could be explained by the findings by Henkin et al (142). Henkin showed that the reductions in TC and LDL-C concentrations were substantially lower during the first three months of a dietary intervention subsequently followed by a three months maintenance period and thereafter a regression. Accordingly, our minor reductions in lipids during the trial could have been due to our subjects being in a maintenance or regression phase. As a consequence this could have confounded the furthermore reduction in cholesterol that was achievable by our dietary intervention.

Our findings are similar to what Mosca et al found in the FIT-heart trial where primary relatives of patients with premature CHD participated (145). Mosca et al randomised relatives of premature CHD patients aged 20 to 79 years to receive intensive dietary counseling or a pamphlet with brief dietary and lifestyle advices. After one year, in spite of an intensive intervention with frequent motivational support by telephone, Mosca also found no differences in major cardiovascular risk factors between the randomised groups accompanied by an overall low adherence to the intervention.
It is important to acknowledge that our results illustrate the overall effect of individual changes among our subjects. In spite of no impressive overall change in risk factors, a couple of subjects in both groups achieved great reductions in their cardiac risk factors, although others’ maintained or worsened theirs. Consequently, even though the approach was insufficient to promote significant changes in the majority of our subjects, for some being included was just enough.

Our results however suggest that our approach may have been too simple to induce major dietary changes in most of our subjects and more frequent follow-up visits may have been needed. For instance in the study by Jenkins et al (135) routine dietary counseling including two visits to the dietitian reduced TC significantly by as much as 20% and LDL-C by 16% compared with control treatment after six months. However Jenkin’s trial implemented a diet approach that focused on the intake of plant sterols, which may in part help explain their impressive results.

5.2.2 **Weight maintenance and changes in blood pressure**

We found no differences in change in blood pressure between our randomised groups but nevertheless significant within group changes in SBP in both the intervention and in the control group. Although weight loss may be a confounding factor for reductions in blood pressure, we found no significant weight changes within either group. This was also confirmed in our subgroup analysis stratified by BMI and by intention of weight loss among the subjects. As a consequence, weight loss cannot account for the significant decreases seen in SBP within our intervention- and control groups although RTM and biological variation may.

As previously stated, a random design does cause RTM to be equally distributed among subjects in the intervention- and the control group. Therefore, according to Barnett (127) we can use the mean change in the control group to adjust our observed treatment effect for RTM. Since the reduction in SBP in the intervention group was -4.5 mmHg the true effect probably lies somewhere closer to -2.0 mmHg, which is the SBP reduction in the intervention group subtracted by the reduction in SBP (-2.5 mmHg) in the control group.

Since more than one third of the subjects had above optimal blood pressure at baseline the “white coat” effect is a plausible explanation for the reduction seen between baseline and
follow-up. Although it is possible that changes in diet and physical activity could have contributed to the reductions in blood pressure, we do not have the data required to explore this suggestion.

Although it could be hypothesised that the remaining difference in SBP, adjusted for RTM, is due to an increased intake of fruits and vegetables in the intervention group this notion is not supported by previous data. For instance, in the original DASH diet study by Appel et al (25) a diet rich in fruits and vegetables only induced decreases in SBP and in DBP by -0.8 mmHg and -0.3 mmHg respectively in non-hypertensive subjects. Furthermore it has been suggested that variability in BP can be ascribed measurement error or short-term fluctuations (129;146) which is a more plausible explanation for our findings.

Interpretation of our confidence intervals (CIs) indicate that the results of this thesis may be classified as a definite result of the 1839-S intervention, with regards to its effect size. Although the between group CI for SBP indicate a clinically important effect of -4.67 mmHg in the upper 5th percentile there is only a small chance that a population reduction would be equal to this or more (132). Consequently, the true difference is more likely to be closer to the middle of our 95% CI.

Our only result that comes close to significance is the between group difference in change for WHR. However this finding has no clinical importance and is most likely a result of our repeated statistical testing. Furthermore, WHR would have been better used as a subsequent analysis variable if we had in fact found a difference in weight change between or within our groups.

**Additional findings**

When comparing baseline characteristics of men and women it seemed like women had lower levels of LDL-C and SBP than did the men. The difference in TC/HDL-C was nevertheless not surprising considering that women naturally have higher HDL-C concentration than men. Although the number of females is limited in our study sample, the differences found indicate that the men in our study sample were unhealthier than the women. This finding is in accordance with the findings in the study by Tonstad et al where young men had slightly elevated LDL-C levels than did young women of similar ages (14).
As mentioned, both repeated statistical testing and RTM may cause one to find a statistical difference even when there is really none. In our trial, the intervention group had a small reduction in DBP while the control group reduced their SBP and increased their HDL-C significantly. Although all of our P-values were well above our pre-determined threshold for significance these findings could still be attributed to biological variation or RTM. It could nonetheless be hypothesised that the increase in HDL-C in the control group reflected an increased fat intake during the trial.

5.2.3 Smoking cessation in young adults

Since the collection of our data has been ongoing for over eight years, it is unfeasible to compare the prevalence of daily smokers in our sample with the general prevalence of young smokers living in Norway today (147). Nevertheless, in our study the overall prevalence of smokers at baseline was 24% which is considerably lower than the prevalence found in the predecessor study (37%) (110).

Although we did not find an association between smoking cessation and group allocation an important limitation of our result is the absence of information regarding usage of pharmacotherapy support. Hence, we do not know if smoking cessation in the control group was due to usage of pharmacotherapy or not. Considering this we cannot rule out that the smokers, motivated and unmotivated, quit due to pharmacotherapy usage and that our observed effect was unrelated to the intense smoking cessation aid in itself, as was suggested by our statistical testing.

In the CARDIA study (148), the likelihood of young adults to quit smoking was low even after an incidence of CHD in the family. Langner et al (149) made similar observations when they interviewed offspring of adults with premature CHD with regards to changes in lifestyle behaviors after an incident of premature CHD in the family. Also, Langner found that smokers were three times less likely than non-smokers to report having made efforts to introduce lifestyle behavioral changes. Although the knowledge of one’s own risk with regards to CHD may be insufficient for behavioral change in young adults, the 1839-S design rely on this argument to promote smoking cessation. Our method may therefore not have had the right approach when aimed at young adults, or may have been too short since our predecessor study achieved almost a 30% reduction in smokers within a mean duration of eight months (110). In addition our subjects might have been less inclined to try to give up
smoking since they did not receive the pharmacotherapy free of charge, as the subjects did in the predecessor study.

It may be that there is a need to establish novel methods to reduce smoking prevalence among young adults. This has been taken into account for in recent trials that have assessed the effectiveness of text messaging (150) and internet based programmes (151) as alternative approaches among mature teenagers and young adults. In these studies, text messaging resulted in a significant smoking cessation rate of 9% (n=2915) according to the ITT principle while an internet based programme resulted in a significant abstinence rate of 22.3% (n=396). Nevertheless, in the latter trial smoking cessation was self-reported without any other confirmatory measurement. In these trials smoking abstinence was defined as point in time or continuous which make them differ further from our design since we only confirmed abstinence at follow-up. Although our achieved smoking cessation rate is higher than what was achieved in these trials, we lack the necessary information to support a true treatment difference. Furthermore, our numbers are too small, making it unfeasible to weigh our results against larger trials.
5.3 Additional and ethical considerations

Although there is currently no available data on the mean blood cholesterol levels in young adults in Oslo (152), there is data to support that adults with a family history of CHD do have higher cholesterol levels compared with adults with no family history (15). As well as a data (14;15;153) to support that a clustering of cardiovascular risk factors is more common than rare among family members. Since our eligibility criteria only allowed for individuals with elevated cholesterol levels, in addition to us lacking relevant information of our non-responders, we cannot conclude that our target population has a higher prevalence of elevated blood cholesterol levels than the average Oslo population.

In our predecessor study (110), change in total cholesterol was associated with change in endothelial adhesion molecules. Likewise, in the PREDIMED study (141) a difference in markers of endothelial distress was found, indicating that the intervention induced an anti-inflammatory effect. A similarity between these two trials is that both produced important changes in endothelial markers of distress but non-significant differences in TC. Although it is tempting to suggest that the same could be true for our findings, it does not change the clinical implication of our results since classic cardiovascular risk factors still remain the foremost recommended markers for assessment of risk (40).

Although desirable, we cannot assess the potential change in future cardiovascular risk in our subjects since only NORRISK is a suitable algorithm for Norwegians (154) which does not estimate risk in a population younger than 40 years of age. Furthermore, even in subjects aged above 40 the risk would be less than one percent.

At baseline there were 16% of our subjects who could be defined as having the MetS. At follow-up 25% of these subjects had improved their metabolic risk factors enough to no longer fit the definition. Our numbers are unfortunately too small to detect a treatment difference if there is one.
Ethical considerations

Although the ethical committee approved the late protocol modifications of the 1839-S, most of our subjects waited longer than the estimated 16 weeks for their follow-up visit. Some waited more than one year. This finding has some ethical implications since some of our subjects are considered high risk and may warrant medicinal support.
6 Conclusion and future perspectives

In the present study we found:

a)  
- no statistical differences in change in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio, weight or blood pressure between the intervention and the control group

b)  
- no statistical changes in total cholesterol, LDL-cholesterol, triglycerides, waist-to-hip ratio or weight within the intervention group or the control group.

- a significant reduction in systolic blood pressure in both the intervention and in the control group.

- a significant reduction in diastolic blood pressure in the intervention group.

- a significant increase in HDL-cholesterol in the control group

c)  
- no significant association between group allocation and smoking cessation in subjects smoking ≥1 cigarette/day

In conclusion we failed to show a significant difference in treatment effect in our present study data. Although we found significant changes in some risk factors within both groups we cannot verify them since we currently lack the dietary data necessary. Our current results suggest that dietary counseling given once to young adults with an increased risk of premature CHD may be as ineffective as no dietary advice given, with regards to inducing short-term changes (mean duration 20 weeks) in classic cardiovascular risk factors.
6.1 **Future perspectives**

In our results we have raised some questions with regards to what is the most feasible method to recruit and treat young adults with elevated cardiovascular risk factors for CHD.

- There is a very limited number of trials assessing the effects of interventions aimed at reducing cardiovascular risk factors in young adults aged 18 to 39 years with elevated risk factors. More trials are needed to determine how to best treat and approach this particular group.

- It appears difficult to recruit young adults, especially males, in a population. Future trials should explore the feasibility of other recruitment methods than a hospital based setting.

- Since referral by general practitioners appears to be an effective method to recruit patients to special preventive care clinics, general practitioners should be encouraged to screen subjects with an increased future risk of premature CHD.

- Although we have not shown a beneficial treatment effect in our trial the dietary data retrieved from the 1839-S subjects should be explored to confirm our findings and to assess whether our results are due to low adherence to dietary counseling or due to preceding dietary changes.
Reference List


Ref Type: Report

Ref Type: Report


Ref Type: Online Source


43. Jensen MK, Rimm EB, Furdado JD, Sacks FM. Apolipoprotein C-III as a Potential Modulator of the Association Between HDL-Cholesterol and Incident Coronary Heart Disease (http://jaha.ahajournals.org/content/1/2/jah3-e000232.full). Journal of the American Heart Association 2012.


Ref Type: Report


Ref Type: Report


Ref Type: Report


Ref Type: Report


Ref Type: Report


Ref Type: Report

70. Rajaram S, Haddad EH, Mejia A, Sabate J. Walnuts and fatty fish influence different serum lipid fractions in normal to mildly hyperlipidemic individuals: a randomized controlled study. Am J Clin Nutr 2009;89:1657S-63S.


Ref Type: Report


Ref Type: Report


Ref Type: Report


Ref Type: Online Source

Ref Type: Journal (Full)


Ref Type: Report


125. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 2005;365:82-93.


Ref Type: Online Source


Ref Type: Report


Ref Type: Online Source


Ref Type: Online Source


Appendices

Appendix 1: Letter of invitation to primary relatives of patients with premature CHD

Appendix 2: A simple questionnaire for primary relatives of patients with premature CHD

Appendix 3: Information regarding participation in the “18 to 39” study

Appendix 4: Food frequency questionnaire

Appendix 5: Approval of the trial by the Regional Committee of Medical Ethics

Appendix 6: A summary of common dietary advice and food alternatives suggested during the dietary counseling
Informasjon til slektninger

Du får dette brevet gjennom din ..................... fordi han/hun har fått hjerte- og karsykdrom i ung alder.


Hvis du ikke ønsker å teste deg, vennligst send oss svarsliken i returkonvolutten. Har du spørsmål angående denne forespørselen, vennligst ta kontakt med lege Eli Heggen. Forespørselen er godkjent av Regional Etisk Komité for Helse Sør-Øst.

Vennlig hilsen

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**Jeg ønsker ikke å ta blodprøver:**

Navn: ____________________________
Dato: ____________________________

Oslo universitetssykehus består av de tidligere helseforetakene Aker universitetssykehus, Rikshospitalet og Ullevål universitetssykehus
Appendix 2

Kjære “slektning”

Du er blitt kontaktet fordi du har et familiemedlem som har fått hjerte- og karsykdom i ung alder (før 55 år). Dine svar på dette spørreskjema hjelper oss i vurderingen av dine blodprøver:

1. Har du tidligere tatt en blodprøve til bestemmelse av kolesterol?
   - [ ] Ja
   - [ ] Nei
   - [ ] Vet ikke

   Hvis ja, hva var kolesterolverdien da? _____

   Hvilket årstall ble verdien målt? _____

2. Har du eller har du hatt:

<table>
<thead>
<tr>
<th>Hjerteinfarkt</th>
<th>Utopsion på hovedpulsåren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>Smert i bena som gjør at du må stoppe når du går</td>
</tr>
<tr>
<td>Hjerteoperasjon (skiftet blodåre/bypass)</td>
<td>Høyt blodtrykk</td>
</tr>
<tr>
<td>Blokking av blodårene i hjertet (PTCA)</td>
<td>Diabetes (sukkersyke)</td>
</tr>
<tr>
<td>TIA (kortvarig stopp i blodforsyning til hjertet)</td>
<td>Hjerneslag</td>
</tr>
</tbody>
</table>

3. Bruker du noen medisiner?  [ ] Ja  [ ] Nei
   (Kvinner: Husk østrogen eller p- piller)

   Hvis ja, skriv ned navnet og doseen på medisin(er) du bruker
   a)   Dose: ______
   b)   Dose: ______
   c)   Dose: ______

4. Røyker du?  [ ] Ja  [ ] Nei

   Hvis ja, kryss av for type og angi antall per dag eller uke.
   _____ sigaretter; antall _____ per dag
   _____ rulletobakk; antall _____ pk/uke
   _____ cigarer/cigarillos; antall _____ per dag
   _____ pipe: mengde ______
   _____ snus; priser/bokser
Hvis du ikke røyker daglig, men røyker i blant, angi antall sigarettet per uke: ____
Dersom du nå ikke røyker sigarett daglig, men har gjort det tidligere, skriv ned
dato eller årstall da du sist sluttet: __________

5. Hvor høy er du? ________

6. Hvor mye veier du? ________

7. Hva synes du om å bli kontaktet av et familiemedlem for å ta blodprøver?

| meget positivt | positivt | verken positiv eller negativt | negativt | meget negativt |

Kommentar: ________________________________________________________________________________

8. Hvis det viser seg at du har høye blodverdier av kolesterol eller fettstoffer, ønsker du å få videre råd/behandling?

☐ Ja  ☐ Nei

Hvis ja, kryss av for hvor du ønsker videre råd/behandling:

_____ Ved Oslo Universitetssykehus, Ullevål, avdeling for preventiv kardiologi
_____ Hos min vanlige lege

Hvis du ønsker oppfølgjing hos din vanlige lege, vennligst skriv ned navn og adressen til legen din her:

__________________________________________________________________________________________

9. Hvis du ikke ønsker videre kontakt, vennligst angi hvorfor

| Har allerede fått råd/behandling |
| Føler ikke behov for råd/behandling |
| Ønsker ikke å ta medisin |
| Ønsker ikke å forandre levealenar |
| Ønsker ikke å forandre kosthold |

Annet: ________________________________________________________________________________
Appendix 3

Forspørsel om deltakelse i forskningsprosjektet:
"Effekten av å endre livsstil i forhold til risikofaktorer for hjerte- og karsykdom"

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie for å undersøke om det er mulig å endre matvaner, fysisk aktivitet og eventuelt slutte å røyke og med dette påvirke risikofaktorer for hjerte og karsykdom (kolesterol, blodsukker, blodtrykk, vekt, midje- og hofteomkrets, fysisk form). Du er valgt ut til å bli med i studien fordi du er i aldersgruppen 18-39 år og har økt risiko for hjerte- og karsykdom på grunn av arv og høyt nivå av fett eller sukker i blodet. I alt vil 200 personer delta i studien som varer i 4 måneder. Oslo Universitetssykehus er ansvarlig for studien.

Hva innebærer studien?
Hvis du blir med i studien, vil du få legeundersøkelse som innebærer blant annet sykdomshistorie, du tar blodprøver, måler blodtrykk, midjeomkrets og vekt før studiestart. Hvis du ikke blir med i studien, blir dine medisinske opplysninger registrert i din journal ved seksjon for preventiv kardiologi, Oslo universitetssykehus.

Deltagelse i studien innebærer at:
1. Du er villig til å gjøre endringer i matvaner, fysisk aktivitet og eventuelt prøve å slutte å røyke hvis det er aktuelt.
2. Du er villig til å møte opp ved Seksjon for preventiv kardiologi to ganger i løpet av ca 4 måneder.

I studien vil du fylle ut et spørreskjema om kosthold, ta blodprøver, måle blodtrykk, vekt, og midje- og hofteomkrets to ganger, samt en ultralydundersøkelse av halspulsårene og gjennomføre en sykkeltest for å avgjøre din fysiske form én gang.

Hvis du ikke ønsker å være med i studien vil du få tilbud om annen behandling ved Seksjon for preventiv kardiologi.

Mulige fordeler og ulemper
Fordelene ved å delta i studien er at du får mulighet til å gjennomgå undersøkelser som ikke er rutineundersøkelser (ultralydundersøkelse av halspulsåre og sykkeltest). Alle prøver og undersøkelser er gratis.

Ulempen ved studien er at du kan risikere å komme i kontrollgruppen og da får du råd om å endre vaner først etter 4 måneder.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer, eller andre direkte gjenkjennerende opplysninger. En kode knytter deg til dine opplysninger og prøver...

**Frivillig deltakelse**

**Annen informasjon**
Regional komité for medisinsk og helsefaglig forskningsetikk har godkjent prosjektet. Har du spørsmål til studien, ta kontakt med klinisk ernæringsfysiolog Mette Svendsen telefon 23016653 eller mobil 45212344.

Ved spørsmål som trenger svar fra lege, kan du kontakte: Overlege Eli Heggen telefon 22119982

**Ytterligere informasjon om studien finnes i Kapittel A – utdypende forklaring om hva studien innebærer.**

**Ytterligere informasjon om biobank, personvern og dine rettigheter finnes i Kapittel B – Personvern, Biobank, økonomi og forsinkring.**

**Samtykkeerklæring følger etter kapittel B.**
Kapittel A- utdypende forklaring om hva studien innebærer

Kriterier for å delta

For å kunne delta i studien må du være mellom 18-39 år og ha høyt nivå av fettsøffer eller sukker i blodet og ha en nær slektning som har hatt hjerte- og karsykdom i ung alder (menn yngre enn 55 år og kvinner yngre enn 65 år).

Du kan ikke delta i studien hvis du bruker et medikament for å redusere blodtrykket, fettsøffer eller sukker i blodet. Du kan heller ikke ha svært høyt nivå av fettsøffer i blodet (mer enn 8 mmol/l) eller ha sykelig overvekt (kroppsmasseindeks over 35 kg/m²).

Bakgrunnsinformasjon om studien

Resultater fra en rekke undersøkelser viser at hjerte- og karsykdom før 60 års alder i en stor grad er arvelig. Videre er det vist at fettsøffer i blodet kan avleire seg i blodårenggveugen allerede fra 20 års alder hos personer som er disponert. For å forebygge denne sykdomsprosessen kan endringer i kosthold, fysisk aktivitet og røykeslutt ha stor effekt. I denne studien ønsker vi å undersøke om det er mulig å gjennomføre slike endringer i løpet av 4 måneder, etter å ha fått individuelt tilpassede råd av lege og klinisk ernæringsfysiolog én gang.

Mulige ubehag, bivirkninger og risiko

Endring av kosthold kan medføre ubehag fra mage og tarm. Ubehaget er som regel forbigående. Økt fysisk aktivitet kan medføre at du blir støl, men dette er ikke farlig og går over i løpet av 3-4 dager. Røyeslutt kan medføre abstinens symptomer som irritabilitet, søvnvansker og økt matlust.

Du er fri til å trekke deg fra studien når du måtte ønske. Hvis du trekker deg fra studien vil du få tilbud om ordinær behandling ved Sektjon for preventiv kardiolog.

Ubehag i forbindelse med studieprosedyrer

Når du skal gjennomføre sykkeltesten vil du bli svett og andpusten, men du skal ikkje sykle til du blir utmattet.

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

Måling av fettaavleiringer i halspusåren skjer ved en ultralydundersøkelse der en ultralydsensor føres over huden på ytersiden av halsen. Testen innebærer ingen stråling og du får ikke noe ubehag.

Studiedeltagerens ansvar


Avbrutt studiedeltagelse
Legen eller studieansvarlig kan stoppe din deltagelse i studien hvis:
- Du ikke følger opp studieprotokollen som avtalt.
- Du får en alvorlig sykdom.
- Studielegen mener at deltagelse i studien ikke er til ditt beste.
- Du blir gravid eller planlegger å bli gravid.

Informasjon til kvinner
Graviditet vil kunne påvirke de undersøkelsene vi gjør i studien og derfor må kvinner i fruktbar alder bruke prevenjon godkjent av legen i studien. Hvis du har tatt en graviditetstest er det ikke sikkert testen avslører en tidlig graviditet. Hvis du tror du er gravid, informer derfor studieansvarlig så snart som mulig.
Kapittel B – Ytterligere informasjon om personvern, biobank, økonomi og forsikring

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

Forskningsbiobank

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

Finansiering
Denne studien er finansiert ved hjelp av opptjente forskningsmidler ved Sektjon preventiv kardiologi.

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

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

Jeg er villig til å delta i studien

(Signert og datert av deltager)

Deltagers navn med blokkbokstaver  Deltagers fødselsdato

Bekreftelse på at informasjon er gitt deltageren i studien

Jeg bekrerter å ha gitt skriftlig og muntlig informasjon om studien

(Signert og datert av lege)

Legens navn med blokkbokstaver/stempel
HVA SPISER DU?

I dette skjemaet spør vi om dine spisevaner slik de er nå. Vi er klar over at kostholdet varierer fra dag til dag. Prøv derfor så godt du kan å gi et "gjennomsnitt" av dine spisevaner. Der du er usikker, anslå svaret.

Skjemaet skal leses av en maskin, og det er derfor viktig at du setter et tydelig kryss i avmerket rute.

Riktig markering er slik: ❌

Bruk helst svart eller blå kulepenn (ikke rød). Bløt blyant kan også brukes, men marker da ekstra tydelig.

Av hensyn til den maskinelle lesingen pass på at arkene ikke blir brettet.

Alle svar vil bli behandlet strengt fortrolig.
EKSEMPEL PÅ UTFYLLING AV SPØRSMÅL 1.
Kari Nordmann spiser daglig 5 skiver brød og ett knekkebrød. Hun spiser vanligvis kneippbrød, men i helgene blir det en del loff. Hun fyller ut første spørsmål slik:

1. HVOR MYE BRØD PLEIER DU Å SPISE?
Legg sammen det du bruker til alle måltider i løpet av en dag.
(1/2 rundstykke = 1 skive, 1 baguett = 5 skiver, 1 ciabatta = 4 skiver)

<table>
<thead>
<tr>
<th>Antall skiver pr. dag</th>
<th>0</th>
<th>1/2</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fint brød</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>(loff, baguett, fine rundstykker o.l.)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mellomgrovt brød</td>
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<td></td>
</tr>
<tr>
<td>(lys helkorn, lys kneipp, lys hj. bakt o.l.)</td>
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<tr>
<td>Grovt brød</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(fiberkneipp, mørk kneipp, mørkt hj. bakt o.l.)</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Knekkebrød</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(kavring, grov skonrokk o.l.)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Sum skiver pr. dag = 6
Antall skiver pr. uke: $6 \times 7 = 42$. Tallet brukes i spørsmål 5.
1. HVOR MYE BRØD PLEIER DU Å SPISE?
Legg sammen det du bruker til alle måltider i løpet av en dag.
(1/2 rundstykke = 1 skive, 1 bagueett = 5 skiver, 1 ciabatta = 4 skiver)

<table>
<thead>
<tr>
<th>Antall skiver pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1/2 1 2 3 4 5 6 7 8 9 10 11 12+</td>
</tr>
</tbody>
</table>

- Fint brød
  (løff, bagueetter, fine rundstykker o.l.)
- Mellungrovt brød
  (lys helkorn, lys kneipp, lys hj. bakt o.l.)
- Grovt brød
  (fibervkneipp, mørk kneipp, mørkt hj. bakt o.l.)
- Knekkebrød
  (kavring, grov skonrok o.l.)

Sum skiver pr. dag = ___
Antall skiver pr. uke: ___ x 7 = ___. Tallet brukes i spørsmål 5.

2. HVA PLEIER DU Å SMØRE PÅ BRØDET?
Merk av både for hverdag og helg, selv om du bruker det samme.

<table>
<thead>
<tr>
<th>Hverdager</th>
<th>Lørdager, søndager</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Bruker ikke</td>
<td></td>
</tr>
<tr>
<td>□ Smør (meierismør)</td>
<td></td>
</tr>
<tr>
<td>□ Bremykt</td>
<td></td>
</tr>
<tr>
<td>□ Breielett</td>
<td></td>
</tr>
<tr>
<td>□ Soft-, soymargarin (pakke, bøger)</td>
<td></td>
</tr>
<tr>
<td>□ Solsikke</td>
<td></td>
</tr>
<tr>
<td>□ Oliven</td>
<td></td>
</tr>
<tr>
<td>□ Vita</td>
<td></td>
</tr>
<tr>
<td>□ Olivero</td>
<td></td>
</tr>
<tr>
<td>□ Omega</td>
<td></td>
</tr>
<tr>
<td>□ Soft light</td>
<td></td>
</tr>
<tr>
<td>□ Vita lett</td>
<td></td>
</tr>
<tr>
<td>□ Annen margarin</td>
<td></td>
</tr>
</tbody>
</table>

3. OM DU BRUKER FETT PÅ BRØD, HVOR MYE BRUKER DU?

<table>
<thead>
<tr>
<th>En porsjonspakning på 12 g rører til antall skiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 □</td>
</tr>
<tr>
<td>2 □</td>
</tr>
<tr>
<td>3 □</td>
</tr>
<tr>
<td>4 □</td>
</tr>
<tr>
<td>5 □</td>
</tr>
</tbody>
</table>

4. MELK SOM DRIKK
(1 glass = 1,5 dl)

<table>
<thead>
<tr>
<th>Drikker sjelden/ ikke</th>
<th>Drikker sjelden/ ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 1 2 3 4 5 6 7 8+</td>
<td></td>
</tr>
</tbody>
</table>

Helmelk, søt, sur  □  □  □  □  □  □  □  □  □
Lettmelk, søt, sur □  □  □  □  □  □  □  □  □
Lettmelk, ekstra lett □  □  □  □  □  □  □  □  □
Skummet melk, søt, sur □  □  □  □  □  □  □  □  □
### 5. PÅLEGGSSORTER

Bruk sum skiver pr. uke fra spørsmaål 1. Til antall skiver pr. uke

<table>
<thead>
<tr>
<th>Produkt</th>
<th>Mindre enn 1</th>
<th>2-3</th>
<th>4-5</th>
<th>6-7</th>
<th>8-14</th>
<th>15-21</th>
<th>22-28</th>
<th>29-35</th>
<th>36+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brun ost, prim</td>
<td>□</td>
<td>□</td>
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<td>□</td>
<td>□</td>
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</tr>
<tr>
<td>-ivit ost, helfet, 27% fett (Jarlsberg, Norvegia o.l., smøreost; eske, tube)</td>
<td>□</td>
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<tr>
<td>-ivit ost, halvfet, 16% fett (Jarlsberg, Norvegia o.l., smøreost; eske, tube)</td>
<td>□</td>
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<tr>
<td>Ost med mør enn 27% fett (kremost, Normanna, Ridderost)</td>
<td>□</td>
<td>□</td>
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<td>□</td>
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</tr>
<tr>
<td>Leverpostei, vanlig</td>
<td>□</td>
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<td>□</td>
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<tr>
<td>Leverpostei, mager</td>
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<td>□</td>
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<tr>
<td>Servalat, vanlig</td>
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</tr>
<tr>
<td>Lett servelat, kalverull, koft skinke, okserull o.l.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Salt pølse, spekepølse (fårepølse, salami o.l.)</td>
<td>□</td>
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<tr>
<td>Kaviar</td>
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<td>□</td>
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<tr>
<td>Makrell i tomat, røkt makrell</td>
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</tr>
<tr>
<td>Sardiner, sursild, ansjos o.l.</td>
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<tr>
<td>Laks, ørret</td>
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<tr>
<td>Reker, krabbe</td>
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<tr>
<td>Syltetøy, marmelade, frysetøy</td>
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</tr>
<tr>
<td>Honning, sirup, sjokolade-, nøttepålegg</td>
<td>□</td>
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</tr>
<tr>
<td>Grønnsaker som pålegg (agurk, tomat o.l.)</td>
<td>□</td>
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</tr>
<tr>
<td>Frukt som pålegg (banan, eple o.l.)</td>
<td>□</td>
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<tr>
<td>Salater med majones</td>
<td>□</td>
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<tr>
<td>Majones på smørbrød</td>
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</tbody>
</table>

### 6. EGG

(kokt, stekt, eggerøre, omelett)

<table>
<thead>
<tr>
<th>Antall pr. uke</th>
<th>Mindre enn 1</th>
<th>2-3</th>
<th>4-5</th>
<th>6-7</th>
<th>8+</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

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103
### 7. FROKOSTGRYN, GRØT OG YOGHURT

Svar enten pr. måned eller pr. uke. <1 betyr sjeldnere enn 1 gang.

<table>
<thead>
<tr>
<th></th>
<th>Gang pr. måned</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havregryn, kornblanding (4-korn, usøtet müsli o.l.)</td>
<td>0 &lt;1 1 2 3</td>
<td>1 2-3 4-5 6-7 8+</td>
<td>1 11/2 2 3+</td>
</tr>
<tr>
<td>Cornflakes, puffet ris, havrenøtter o.l.</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 (dl)</td>
<td>0 0 0 0 0 (dl)</td>
</tr>
<tr>
<td>Havregrøt</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 (dl)</td>
<td>0 1/2 1 1/2 2 3+</td>
</tr>
<tr>
<td>Sukker til frokostgryn, grøt</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 0 (ts)</td>
<td>0 1 2 3-4 5+</td>
</tr>
<tr>
<td>Yoghurt, naturell, frukt</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 (befer)</td>
<td>0 1/2 1 11/2 2+</td>
</tr>
<tr>
<td>Lettyoghurt</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 (befer)</td>
<td>0 1/2 1 11/2 2+</td>
</tr>
<tr>
<td>Go’morgen yoghurt, inkl. müsli</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 (befer)</td>
<td>0 1/2 1 11/2 2+</td>
</tr>
<tr>
<td>Melk søt, sur på gryn, grøt og dessert</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 (dl)</td>
<td>0 0 0 0 0 (dl)</td>
</tr>
</tbody>
</table>

### 8. KAFFE OG TE

(1 kopp kaffe = 1,2 dl 1 kopp te = 2 dl)

<table>
<thead>
<tr>
<th></th>
<th>Drikker ikke/ikke daglig</th>
<th>Antall koppar pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaffe, kokt</td>
<td>0 0 0 0 0 0 0 0</td>
<td>0 1/2 1 2 3-4 5-6 7-8 9-10 11+</td>
</tr>
<tr>
<td>Kaffe, traktet, filter</td>
<td>0 0 0 0 0 0 0 0</td>
<td>0 1/2 1 2 3-4 5-6 7-8 9-10 11+</td>
</tr>
<tr>
<td>Kaffe, pulver (instant)</td>
<td>0 0 0 0 0 0 0 0</td>
<td>0 1/2 1 2 3-4 5-6 7-8 9-10 11+</td>
</tr>
<tr>
<td>Kaffe, koffein fri</td>
<td>0 0 0 0 0 0 0 0</td>
<td>0 1/2 1 2 3-4 5-6 7-8 9-10 11+</td>
</tr>
<tr>
<td>Te</td>
<td>0 0 0 0 0 0 0 0</td>
<td>0 1/2 1 2 3-4 5-6 7-8 9-10 11+</td>
</tr>
<tr>
<td>Nypete, urtete</td>
<td>0 0 0 0 0 0 0 0</td>
<td>0 1/2 1 2 3-4 5-6 7-8 9-10 11+</td>
</tr>
</tbody>
</table>

Antall teksjer eller bitter pr. kopp

<table>
<thead>
<tr>
<th></th>
<th>0 1/2 1 2 3 4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sukker til kaffe</td>
<td>0 0 0 0 0 0</td>
</tr>
<tr>
<td>Sukker til te</td>
<td>0 0 0 0 0 0</td>
</tr>
<tr>
<td>Kunstig søtstoff til kaffe eller te</td>
<td>0 0 0 0 0 0</td>
</tr>
<tr>
<td>Fløte til kaffe</td>
<td>0 0 0 0 0 0</td>
</tr>
</tbody>
</table>
9. ANDRE DRIKKER
Svar enten pr. måned eller pr. uke. <1 betyr sjeldnere enn 1 gang. Merk at porsjonsenhetene er forskjellige. 1/3 liter tilsvarer en halvflaske øl og 2/3 liter tilsvarer en helflaske.

<table>
<thead>
<tr>
<th></th>
<th>Gang pr. måned</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vann</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appelsinjuice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen juice, most, nektar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saft, solbær sirup m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sukker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saft, kunstig søtet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brus, Cola, Solo o.l.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>med sukker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brus, Cola, Solo o.l.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kunstig søtet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farris, Selters, Soda o.l.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkoholfritt øl, vørterøl, lettøl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilsnerøl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brennevin, likør</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. MIDDAGSRETTER
Vi spør både om middagsmåltidene og det du spiser til andre måltider. Tell til slutt sammen antall retter du har merket av for å se om summen virker sannsynlig.
En "dl" tilsvarer omtrent mengden i en suppepose. Med "ss" menes en spiseske.
<table>
<thead>
<tr>
<th>Gang pr. måned</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizza (500-600 g)</td>
<td>0</td>
</tr>
<tr>
<td>Biff (alle typer kjøtt)</td>
<td>1/2</td>
</tr>
<tr>
<td>Koteletter (lam, okse, svin)</td>
<td>1/2</td>
</tr>
<tr>
<td>Stek (lam, okse, svin)</td>
<td>1/2</td>
</tr>
<tr>
<td>Stek (elg, hjort, reinsdyr o.l.)</td>
<td>1/2</td>
</tr>
<tr>
<td>Gryterrett med helt kjøtt, frikassè, färkål o.l.</td>
<td>1</td>
</tr>
<tr>
<td>Lapskaus, suppelapskaus, betasuppe</td>
<td>1/4</td>
</tr>
<tr>
<td>Bacon, stekt flesk</td>
<td>1/2</td>
</tr>
<tr>
<td>Kylling, høne</td>
<td>1/2</td>
</tr>
<tr>
<td>Leverretter</td>
<td>1/2</td>
</tr>
<tr>
<td>Fiskekaker, fiskepudding, fiskeboller</td>
<td>1</td>
</tr>
<tr>
<td>Fiskepinner</td>
<td>1/2</td>
</tr>
<tr>
<td>Torsk, sei, hyse (kokt)</td>
<td>1/2</td>
</tr>
<tr>
<td>Torsk, sei, hyse (stekt, panert)</td>
<td>1/2</td>
</tr>
<tr>
<td>Siild (fersk, speket, røkt)</td>
<td>1</td>
</tr>
<tr>
<td>Makrell (fersk, røkt)</td>
<td>1</td>
</tr>
<tr>
<td>Laks, ørret (sjø, oppdrett)</td>
<td>1</td>
</tr>
<tr>
<td>Fiskeegrøt, -grateng, suppe med fisk</td>
<td>1/2</td>
</tr>
<tr>
<td>Reker, krabbe</td>
<td>1/2</td>
</tr>
<tr>
<td>Risgrøt, annen melkegrøt</td>
<td>1/2</td>
</tr>
<tr>
<td>Pannekaker</td>
<td>1/2</td>
</tr>
<tr>
<td>Suppe (tomat, blomkål, ertesuppe o.l.)</td>
<td>1/2</td>
</tr>
<tr>
<td>Vegetarrett, vegetarpizza, grønnaksgrateng, -paj</td>
<td>1/2</td>
</tr>
<tr>
<td>Brun/hvit saus</td>
<td>1/2</td>
</tr>
<tr>
<td>Smeltet maroarin, smør til fisk</td>
<td>1/2</td>
</tr>
<tr>
<td>Bearnaisesaus o.l.</td>
<td>1/2</td>
</tr>
<tr>
<td>Majones, remulade</td>
<td>1/2</td>
</tr>
<tr>
<td>Ketchup</td>
<td>1/2</td>
</tr>
</tbody>
</table>
11. POTETER, RIS, SPAGHETTI, GRØNNSAKER

Svar enten pr. måned eller pr. uke. < 1 betyr sjeldenere enn 1 gang.
Disse spørsmålene dreier seg først og fremst om tilbehør til middagsretter, men spiser du for eksempel en rå gulrot eller salat til lunsj, skal det tas med her.

<table>
<thead>
<tr>
<th></th>
<th>Gang pr. måned</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  1  2  3  4-5 6-7 8+</td>
<td>1  2  3  4  5+</td>
<td></td>
</tr>
<tr>
<td><strong>Poteter, kokte</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pommes frites, stekte poteter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Potetmos, -stuing, gratinerte poteter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ris</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spaghetti, makaroni, pasta</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gulrot</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hodekåler</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kålrot</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blomkål</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Brokkoli</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rosenkål</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grønnkål</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Løk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spinat, andre bladgrønns.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sopp</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Avocado</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paprika</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tomat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tomatbønner, bønner/linser</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mais</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Erter, frosne grønnsakblanding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salatblandinger</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dressing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rømme</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange ganger om dagen spiser du vanligvis grønnsaker utenom grønnsakene du spiser til middag? [ ] 0  [ ] 1  [ ] 2  [ ] 3  [ ] 4  [ ] 5+
### 12. TYPE FETT TIL MÅLING

<table>
<thead>
<tr>
<th>Smør/margarin</th>
<th>Oljer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smør (melerismør)</td>
<td>Olivenolje</td>
</tr>
<tr>
<td>Bremykt</td>
<td>Soyaolje</td>
</tr>
<tr>
<td>Melange, Per</td>
<td>Maisolje</td>
</tr>
<tr>
<td>Soft-, soymargarin (pakke, beger)</td>
<td>Solsikkeolje</td>
</tr>
<tr>
<td>Solsikke</td>
<td>Valnettolje</td>
</tr>
<tr>
<td>Oliven</td>
<td>Andre oljer</td>
</tr>
<tr>
<td>Annen margarin</td>
<td></td>
</tr>
</tbody>
</table>

### 13. FRUKT

"Svar enten pr. måned eller pr. uke. < 1 betyr sjeldnere enn 1 gang.

<table>
<thead>
<tr>
<th></th>
<th>Gang pr. måned</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 &lt;1 1 2 3</td>
<td>1 2-3 4-5 6-7 8+ (stk)</td>
<td>1/2 1 2 3+</td>
</tr>
<tr>
<td>Appelsin, mandarin, grapefrukt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Druer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eksotisk frukt (kiwi, mango)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen frukt (fersken, pære m.v.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jordbær, bringebær (friske, frosne)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blåbær</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muiter</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange frukter spiser du vanligvis pr. dag? 0 1 2 3 4 5 6 7 8 9+
## 14. DESSERT, KAKER, GODTERI

Svar enten pr. måned eller pr. uke. < 1 betyr sjeldnere enn 1 gang.

<table>
<thead>
<tr>
<th></th>
<th>Gang pr. måned</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Hermetisk frukt, fruktgrøt</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Puddinger (sjokolade, karamell o.l.)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Is (1 dl=1 pinne=1 kremmerhus)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Boiler, julekake, kringle</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Skolebrød, skillingsbolle</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Wienerbrød, -kringle o.l.</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Smultring, formkake</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Vafler</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Sjokoladekake, bløtkake, annen fylt kake</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Søt kjeks, kakekjeks (Cookies, Bixit, Hob Nobs)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Sjokolade (60 g)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Drops, lakris, seigmenn o.l.</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Smågodt (1 hg = 100g)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Potetgull (1 pose 100g=7 dl)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Annen snacks (skruer, crisp, saltstenger, lettsnacks o.l.)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Peanøtter, andre nøtter (1 pose 100g = 4 never)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
### 15. KOSTTILSKUDD (bs = barneskje, ts = teskje)

<table>
<thead>
<tr>
<th></th>
<th>Hele året</th>
<th>Bare vinterhalvåret</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trankapsler</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fiskeoljekapsler</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Multipreparater</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Sanasol</strong></td>
<td></td>
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<tr>
<td><strong>Blo Vit</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Vitaplex</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Kostpluss</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitamineral</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>-Annet</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Hvis annet, hvilket?**

<table>
<thead>
<tr>
<th></th>
<th>Hele året</th>
<th>Bare vinterhalvåret</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jernpreparater</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ferro C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemofer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duroferon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duretter</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Annet</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Hvis annet, hvilket?**

<table>
<thead>
<tr>
<th></th>
<th>Hele året</th>
<th>Bare vinterhalvåret</th>
<th>Gang pr. uke</th>
<th>Mengde pr. gang</th>
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</thead>
<tbody>
<tr>
<td><strong>B-vitamin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>C-vitamin</strong></td>
<td></td>
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<tr>
<td><strong>D-vitamin</strong></td>
<td></td>
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<tr>
<td><strong>E-vitamin</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Folat (folsyre)</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Kalktabletter</strong></td>
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<tr>
<td><strong>Fluortabletter</strong></td>
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<td></td>
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</tr>
<tr>
<td><strong>Annet</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Hvis annet, hvilket?**
16. NÅR SPISER DU PÅ HVERDAGER?

HOVEDMÅLTIDER som frokost, formiddagsmat, middag, kvelds.
Omtrent klokken

<table>
<thead>
<tr>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
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<td>☐</td>
</tr>
</tbody>
</table>

MELLOM MÅLTIDER som kaffe, frukt, godteri, snacks m.v.
Omtrent klokken

<table>
<thead>
<tr>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
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</thead>
<tbody>
<tr>
<td>☐</td>
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</tr>
</tbody>
</table>

17. MENER DU SVARENE I SPØRRESKJEMAET GIR ET BRUKBART BILDE AV KOSTHOLDET

Ja ☐  Nei ☐

Er det matvarer/produkter du regelmessig bruker, og som ikke er nevnt i skjemaet?

18. ER DU FORNØYD MED KROPPEVEKTEN DIN SLIK DEN ER NÅ?

☐ Ja

☐ Nei, jeg ønsker å slanke meg

☐ Nei, jeg ønsker å legge på meg

19. KJØNN

Mann ☐  Kvinne ☐

Vennligst se etter at du har svart på alle spørsmål.

Takk for innsatsen!
Appendix 5

Mette Svendsen
Avdeling for forebyggende medisin
Preventiv kardiologi
Postboks 4956 Nydalen

2011/2641 Effekten av livsstilsintervensjoner på endotelfunksjon hos unge voksne med økt risiko for hjerte- og karsykdom


Disse endringene søkes nå godkjent av ny prosjektleder Mette Svendsen.

Endringene består i:
- Skifte av prosjektleder fra Ingvar Hjermann til Mette Svendsen.
- Skifte av ansvarstilværende for forskningsbibliotek fra Ingvar Hjermann til Wenche Reed.
- Utvidelse av studien med 200 nye deltagere. Av disse er 160 allerede inkludert, og det gjenstår 40 som skal inkluderes suksessivt.
- Endring i inklusjonskriterier: Øvre aldersgrense for inklusjon er økt til 39 år.
- Intervensjonen er gjort mindre intensiv og oppfølgingsstiden er kortet ned til 4 måneder.
- Prosjektmedarbeider har gått ut av prosjektet.

Vurdering
Komiteen vil påpeke at vesentlige prosjektendringer skal meldes til REK. Dette er prosjektleders ansvar. Nåværende prosjektleder kan imidlertid ikke lastes for at dette ikke har blitt gjort.

Komiteen har vurdert endringene og har ingen forskningsetiske innvendinger.

Informasjonsskriv

Vedtak
Komiteen godkjenner prosjektendringen. Revidert informasjonsskriv skal sendes komiteen til orientering.

---

Besøksadresse:
Gulhaug torg 4 A,
Nydalen, 0484 Oslo

Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: 

All post og e-post som ingår i saksbehandling, bes adressert til REK sør-øst og ikke til enkelte personer
Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff
Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileden for Personvern og informasjons sikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren.

Hvis forskningsbiobanken opphører, nedlegges eller overtas av andre, skal det søkes REK om tillatelse, jf. § 30.

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


Med vennlig hilsen,

Arvid Heiberg (sign.)
prof. dr.med
leder

Gjarill Bergva
rådgiver

Kopi til: Oslo universitetssykehus
Appendix 6

A summary of common dietary advice and food alternatives suggested during the dietary counseling.

<table>
<thead>
<tr>
<th>Dietary advice:</th>
<th>Food alternatives suggested:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replace red meat high in SF(^1) (&gt;10% of energy from fat) with reduced fat alternatives (&lt;10% of energy from fat)</td>
<td>Low fat ground beef made of swine, cow or chicken</td>
</tr>
<tr>
<td></td>
<td>Low fat alternatives to sausage such as ham, turkey or chicken</td>
</tr>
<tr>
<td>Replace high fat dairy products with lower fat alternatives</td>
<td>Low-fat alternatives to milk, yoghurt, cottage cheese and cheese</td>
</tr>
<tr>
<td>Use vegetable fats to replace spreads that are rich in SF (e.g. butter, high fat cheese) with spreads high in MUF and PUF</td>
<td>Vegetable based spreads, oils, nuts, avocado, olives. Mayonnaise based spreads. Canola- or olive oil when cooking or preparing foods.</td>
</tr>
<tr>
<td>Increase intake of fatty fish</td>
<td>Salmon, mackerel</td>
</tr>
<tr>
<td>Consume nuts daily</td>
<td>Any type of nuts</td>
</tr>
<tr>
<td>Increase intake of fiber (soluble)</td>
<td>Soluble: Oats, beans, barley, some vegetables and fruit</td>
</tr>
<tr>
<td>Reduce intake of added sugar</td>
<td>Regular and flavored carbonated water, artificially sweetened or low-sugar alternatives to soda or squash</td>
</tr>
<tr>
<td>Reduce alcohol consumption (if the subject had elevated triglycerides)</td>
<td>Non-alcoholic beverages</td>
</tr>
</tbody>
</table>

\(^1\) Saturated fat 
\(^2\) Monounsaturated fat 
\(^3\) Polyunsaturated fats 
\(^4\) HDL-cholesterol