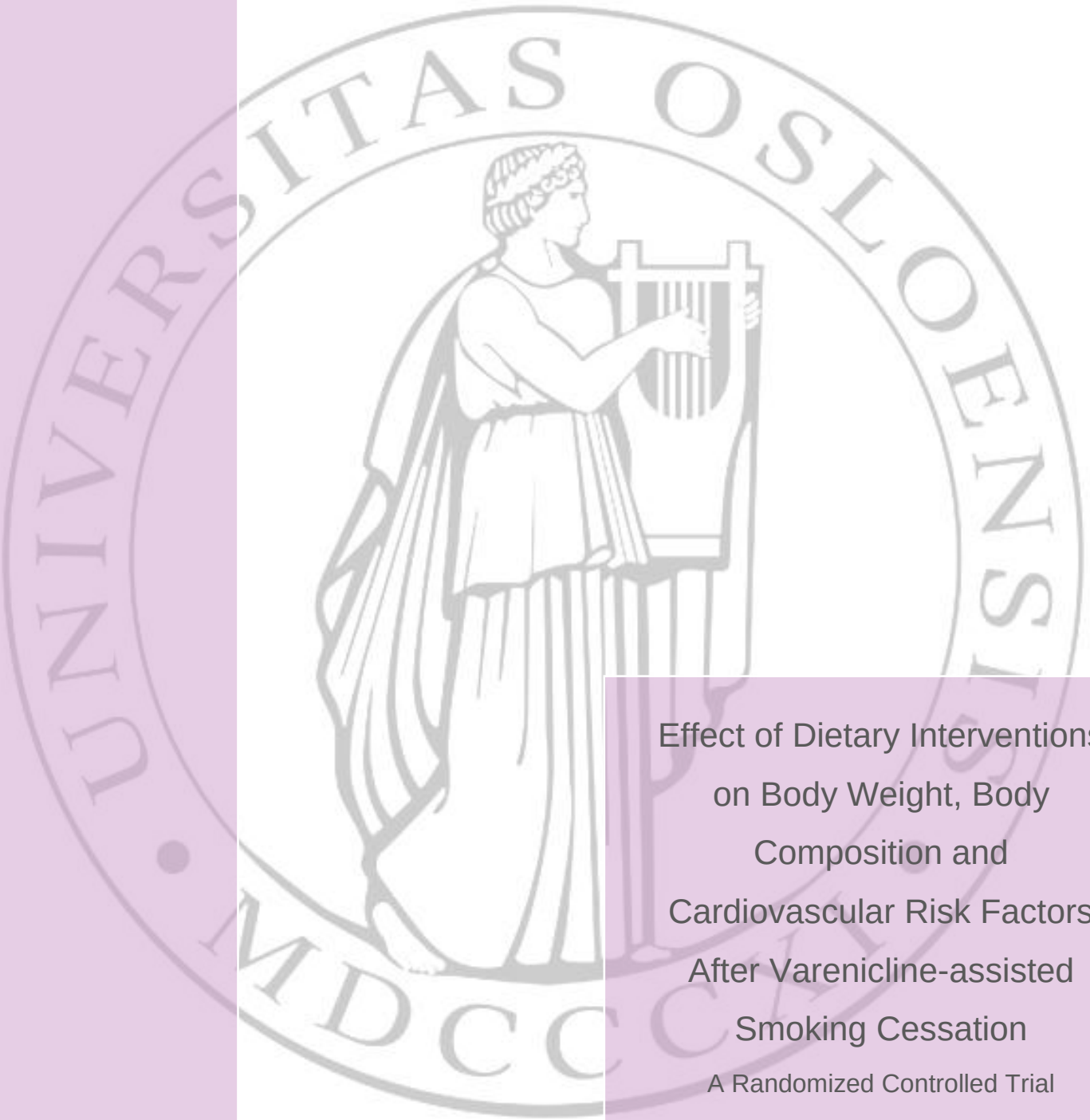

Effect of Dietary Interventions on Body Weight, Body Composition and Cardiovascular Risk Factors After Varenicline-assisted Smoking Cessation

A Randomized Controlled Trial

Master Thesis by
Thea Amalie Bergvatn

Department of Nutrition
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I wish you all the best!

Love, Thea

Summary

Introduction: Cigarette smoking is a major risk factor for the development of many lifestyle diseases, including cardiovascular disease. Overweight and obesity have also been shown to be associated with an increased risk for several lifestyle diseases, and co-occurrence of overweight and smoking has substantial consequences for health. Smoking cessation and weight reduction are associated with both immediate and long-term benefits including reduced risk of cardiovascular disease and increased life expectancy. Varenicline is an approved smoking cessation product shown to increase the chances of a successful attempt to quit smoking. However, smoking cessation is associated with weight gain, and it is suggested that this weight gain may offset some of the advantages of giving up smoking. Concern regarding post cessation weight gain seems to be a powerful motivator for continued smoking, and post cessation weight gain is also often the reason for relapsing after cessation. It is therefore necessary to find some interventions that may prevent, or at least reduce, the weight gain associated with smoking cessation so that a larger proportion of weight concerned smokers may successfully quit smoking.

Aims: The first aim of this thesis was to compare the efficacy of a low fat diet high in complex carbohydrates (LFHCC; ≤30 energy % fat, ≤20 energy % protein and ≥50 energy % carbohydrate) and a high protein diet moderately reduced in carbohydrates (HPMRC; ≥25 energy % protein, ≤55 energy % fat and ≤20 energy % carbohydrates) in preventing short-term weight gain four and 12 weeks after smoking cessation. The second and third aims were to compare the effects of the two diets on body composition and cardiovascular risk factors, respectively, 12 weeks after smoking cessation. The last aim was to compare dietary changes and examine correlations between the dietary changes and changes in body weight four weeks after smoking cessation.

Subjects and methods: A total of 80 healthy overweight or obese men and women who were smoking ≥ 10 cigarettes daily and willing to take varenicline were randomized. Mean age was 50 (SD 9) years and mean BMI was 31 (SD 4) kg/m^2. Both groups received individual counseling for diet and smoking cessation with a total of 12 visits, the first visit at the date of screening and the last visit 12 weeks after smoking cessation. Continuous abstinence rates were estimated based on self-reported smoking status, confirmed by CO-measurements at every visit. Body weight was measured every week. Body composition (waist circumference,

hip circumference, waist-to-hip ratio, body fat % and muscle mass in kg) and cardiovascular risk factors (blood pressure, fasting blood glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) were measured at randomization and 12 weeks after smoking cessation. For measuring of compliance with the intervention diets, 7-days weighed records were conducted at randomization and four weeks after smoking cessation. Statistical analyses were performed twice; once for the participants who were abstinent from smoking all 12 weeks after smoking cessation, and once for all completers regardless of their smoking status.

Results: A total of 70 participants met at the last visit, with no difference in completion-rates between the intervention groups. Of the participants randomized, 37.5% managed to be abstinent from cigarette smoking all twelve weeks after smoking cessation, with no significant difference between the dietary intervention groups. Four weeks after smoking cessation the change in body weight was not different between the groups ($p>.05$), but the HPMRC group had a significant ($p<.01$) mean weight reduction of -1.7 kg (95% CI -2.6, -.7). Post cessation weight gain 12 weeks after smoking cessation was prevented in both groups, with no significant difference ($p=.40$) in weight change between the groups. Mean difference in body fat was 1.4 (95% CI .0, 2.7) in favor of the HPMRC group ($p=.04$). No between-group differences in changes in waist and hip circumference, waist-to-hip ratio, muscle mass, blood pressure, glucose, total cholesterol, HDL, LDL or triglycerides were seen 12 weeks post cessation (all $p>.05$). However, both groups showed an increase in HDL ($p<.05$).

Among all completers, we found mean between-group differences in waist circumference reduction (2.3 cm [95% CI .2, 4.4], $p=.03$), fat mass (1.6 kg [95% CI .3, 2.9], $p=.02$) and triglycerides (.32 mmol/L [95% CI .03, .62], $p=.03$), all in favor of the HPMRC group. Both groups made several significant changes to their dietary composition, but no significant between-group difference in reduction of energy intake. The LFHCC group significantly reduced their intake of fat to $\leq$ 30 E% while the HPMRC group significantly increased their protein intake to $\geq$ 25 E%, but neither of the intervention groups met the target level for intake of carbohydrates. Despite this, we found a significant correlation between the change in intake of carbohydrate and change in body weight ($r=.51$, $p=.02$) in the HPMRC group among the nonsmokers. When we included the reduced smokers we found a significant correlation between changes in intake of protein and fat and changes in body weight ($r=.39$, $p=.01$ and $r=.36$, $p=.02$, respectively) in the HPMRC group.

Conclusion: Both a moderately energy-reduced diet with decreased intake of fat and increased intake of complex carbohydrate and a moderately energy-reduced diet with increased intake of protein and reduced intake of carbohydrates prevented short-term post cessation weight gain. However, it seems

like a diet with increased intake of protein and reduced intake of carbohydrate may result in more beneficial effects, such as decreased body fat, abdominal fat (waist circumference) and triglyceride levels compared to a diet with decreased intake of fat and increased intake of carbohydrate.

Contents

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Abbreviations

Added sugar	simple sugars that are not found naturally in the food
BMI	body mass index
CAR	Continuous Abstinence Rate; refers to those participants who quit smoking and maintain abstinence throughout the following period
CHD	coronary heart disease
CO	(expired-air) carbon monoxide
Complex carbohydrates	oligosaccharides, polysaccharides
CRF	case record form
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
DR	dietary record
e.g.	*exempli gratia*, meaning “for example” or “such as”
etc.	*et cetera*, meaning “and other things” or “and so forth”
E%	energy %, percentage of energy
FTND	Fagerström Test for Nicotine Dependence
GABA	gamma aminobutyric acid
HDL	high-density lipoprotein (cholesterol)
HPMRC	High Protein diet Moderately Reduced in Carbohydrates
i.e.	*id est*, meaning “that is” or “in other words”
Ischemic heart disease	collective term for myocardial infarction, angina pectoris and coronary atherosclerosis
LDL	low-density lipoprotein (cholesterol)
LFHCC	Low Fat diet High in Complex Carbohydrates
MI	myocardial infarction

MJ	megajoule (= 1000 kJ or 239 kcal)
N	number of subjects
nAChR	nicotinic acetylcholine receptor
NO	nitric oxide
NYHA	New York Heart Association
Overnight fast	minimum 8 hours fasting
PAL	physical activity level
pp	point prevalence abstinence; refers to smoking (yes vs. no) at a particular follow-up time point
ppm	parts per million
REE	resting energy expenditure
RMR	resting metabolic rate
SBP	systolic blood pressure
SC	smoking cessation
SD	standard deviation
TG	triglycerides
TIA	transient ischemic attack
WHO	World Health Organization
WHR	waist-to-hip ratio
24-EE	24-hours energy expenditure
95% CI	95% confidence interval
%COHb	percentage of carboxyhaemoglobin

1 Introduction

1.1 Smoking

1.1.1 Prevalence of smoking

Worldwide, more than 1 billion adults are regular tobacco smokers, and smoking rates are even higher among adolescents[1]. During the last 15 years the proportion of daily smokers in Norway has been almost halved. Yet, in 2011, 17% of the Norwegian population aged 16-74 years reported to be smoking daily[2]. This equals about 700 000 daily smokers in Norway. In addition, 11% reported to be smoking occasionally. Totally there have been comparable smoking habits in men and women the last 15 years, but there are some differences in different age groups. Among the youngest and among people aged 35-54 years, there are a larger proportion of female daily smokers than males. 9% of the men and 13% of the women aged 16-24 years reported to be smoking daily in 2011[2]. There is also a larger proportion of cigarette smokers in lower compared to higher socioeconomic classes[3].

1.1.2 Nicotine addiction

Although most of the toxicity of smoking is related to other components of the cigarette, it is the pharmacologic effects of nicotine that produce the addiction to tobacco and maintains smoking behavior. Nicotine meets all of the Surgeon General's primary criteria for drug addiction, which state that the drug must (1) promote highly controlled or compulsive use, (2) have psychoactive effects, and (3) reinforce its own use[4]. Nicotine is associated with many well-known pleasurable psychoactive effects, such as arousal, relaxation and improved mood[4].

When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and carried in the smoke particles into the lungs, where it is absorbed rapidly into the pulmonary venous circulation. It then enters the arterial circulation and moves quickly to the brain. Nicotine diffuses readily into brain tissue, where it binds to nicotinic acetylcholine receptors (nAChRs)[4]. The nAChR complex is composed of 5 subunits arranged in a ring around a central channel that opens to admit ions when the receptor is activated[5]. The mix of subunits in each nAChR gives the receptor its distinct pharmacological properties, including its

response to nicotine stimulation. There are several types of α- and β-subunits in the mammalian brain, but the predominant receptor subtype in the human brain is $\alpha_4\beta_2$. This is believed to be the main receptor mediating nicotine dependence. Nicotine interacts with nAChRs on different neurons, including dopaminergic neurons, in the brain's mesolimbic reward system. The interaction between nicotine and nAChRs on dopaminergic neurons results in release of the neurotransmitter dopamine. Increases in dopamine levels within the mesolimbic system give rise to rewarding effects[6], like stimulation and pleasure, and reduced stress and anxiety. In addition, smoking may improve concentration, reaction time and performance of certain tasks. Nicotine also stimulates dopamine release indirectly by binding to nAChRs located on excitatory glutamatergic neurons. This interaction results in glutamate release, which in turn stimulates dopaminergic neurons. In contrast will binding of nicotine to nAChRs located on inhibitory gamma aminobutyric acid (GABAergic) neurons lead to the release of gamma aminobutyric acid (GABA), which in turn will inhibit dopaminergic neurons. Both glutamate and GABA neurotransmission play important roles in the development of nicotine dependence[7].

Persistent nicotine use leads to tolerance that is mediated by neuroadaptations occurring in response to chronic nicotine exposure. Concurrent with this neuroadaptation is an increase of nAChRs in the brain. This increase is believed to represent upregulation in response to nicotine-mediated desensitization[4]. This desensitization may play a role in nicotine tolerance and dependence. When a person stops smoking, nicotine withdrawal symptoms will usually emerge. These include irritability, depressed mood, restlessness, anxiety, difficulty concentrating, increased hunger and eating, insomnia and craving for tobacco[4].

Measurement of nicotine addiction

The most widely used nicotine dependence measure is the Fagerström tolerance questionnaire, or the modified version, the Fagerström Test for Nicotine Dependence (FTND)[8]. The latter is a 6-item questionnaire concerning the replier's smoking behavior. The questionnaire generates test scores ranging from 0 to 10; the higher the score, the more nicotine dependent the smoker. The six questions are as follows: (1) How soon after you wake do you smoke your first cigarette? (2) Do you find it difficult to refrain from smoking in places where it is forbidden, for example church, library, cinema etc.? (3) Which cigarette would you hate most to give up? (4) How many cigarettes/day do you smoke? (5) Do you

smoke more frequently during the first hours after waking than during the rest of the day? and (6) Do you smoke if you are so ill that you are in bed most of the day?

The more nicotine dependent a smoker is the less is the probability of successful smoking cessation. It is reported that an increase of one unit in baseline FTND score decreases the odds of abstinence at week 24 after smoking cessation by 11%[9].

1.1.3 The health consequences of smoking

Cigarette smoking harms nearly every organ in the body, and is widely accepted as a major risk factor for the development of many lifestyle diseases, including cardiovascular disease, different kinds of cancer and respiratory diseases[10,11]. Tobacco smoking is the single greatest cause of avoidable morbidity and mortality in both the United States[10] and in Europe[12] and is one of the most hazardous health threats globally[13]. Approximately half of all long-term smokers die prematurely as a result of smoking, and the life span of the continuing smoker will be reduced by 10 years on average[1]. Globally, tobacco smoking accounts for over 5 million deaths annually[8,13], and the mortality burden is estimated to increase to over 10 million deaths per year in 2025 if present trends continue[8]. During 2000-2004, cigarette smoking and exposure to tobacco smoke resulted in at least 443 000 premature deaths and approximately 5.1 million years of potential life lost annually in the United States. Among adults aged $\geq$ 35 years, 41.0% of smoking-attributable deaths were caused by cancer, 32.7% by cardiovascular diseases, and 26.3% by respiratory diseases[14]. It is also shown that insulin resistance may be dose-dependently related to cigarette smoking[15], and that the risk of type 2 diabetes is greater in smokers than in nonsmokers[16,17]. In addition to the health consequences of smoking, cigarette smoking contributes to economic losses to society and a substantial burden on the health-care system, resulting in 96.8 billion US dollars in productivity losses annually in the United States during 2000-2004[14].

1.1.4 Smoking and cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of mortality in both men and women, and in the United States CVD accounts for an average of 1 death every 39 seconds[18]. In Norway there has been a decrease in the number of deaths from cardiovascular diseases from 1986 to 2010, but in 2010 still 2 out of 5 deaths are due to cardiovascular disease. A total of 6 out of 10 deaths were due to cardiovascular disease or cancer. Among the cardiovascular diseases,

ischemic heart disease was the most common cause of death. Among people younger than 65 years, more men than women die of ischemic heart disease[19]. The risk of coronary heart disease (CHD) increases with the number of cigarettes smoked and cigarette smoking has been reported to increase the incidence of myocardial infarction (MI) and fatal coronary artery disease in both men and women compared to nonsmokers of both sexes[20,21]. Even passive smoking (environmental tobacco exposure) is associated with approximately a 30% increase in risk of coronary artery disease, compared with an 80% increase in active smokers[21]. It is also shown that women who smoke may be at greater cardiovascular risk than men who smoke[22].

The pathophysiologic mechanisms underlying the health consequences of smoking are complex. The estimated number of compounds in cigarette smoke exceeds 4000, including many that are pharmacologically active, toxic, mutagenic and carcinogenic[11]. Increased oxidative stress due to free radicals arising from cigarette smoke[23] may play a central role in cigarette smoke-mediated diseases. It is hypothesized that cigarette smoking can cause release of excessive vasoactive prostanoids to the circulation[24]. Nitric oxide (NO) is a free radical primarily responsible for the vasodilatory function of the endothelium[25] and it's likely that cigarette smoking is associated with decreased NO availability[26]. This might be a part of the explanation of why cigarette smoking is associated with a decrease in vasodilatory function with impaired endothelium-dependent vasodilation[27,28] in both macrovascular beds such as coronary arteries and in microvascular beds[29,30]. In addition, NO also has other important biological functions, including inhibition of platelet adhesion and aggregation[31]. It is possible that smoking tobacco has direct effects on activation of platelets by decreasing the availability of platelet-derived NO and decreasing platelet sensitivity to exogenous NO, leading to increased activation and adhesion[32,33].

Vasomotor dysfunction, inflammation and modifications of lipids are integral components for the initiation and progression of atherosclerosis. Howard et al.[34] found that both active smoking and the duration of smoking plays a major role in the progression of atherosclerosis, and that smoking especially increased atherosclerosis progression rates among participants with diabetes and hypertension. Dyslipidemia is a risk factor for CVD[18], and smokers have increased total cholesterol, low-density lipoprotein cholesterol (LDL) and triglycerides (TG), together with decreased high-density lipoprotein cholesterol (HDL) compared to non-smokers[35-37]. The risk of CHD is inversely related to serum HDL, and a decrease in HDL of

0.40 mmol/L is associated with an approximately 70% increased risk of CHD in smokers, compared to 30% in non-smokers[38]. It is, however, shown that chronic cigarette smoking can enhance the progression of atherosclerotic lesions in carotid bifurcations even without hyperlipidemia[24]. Cigarette smoking also increases oxidative modification of LDL[39,40]. Oxidized LDL is more atherogenic than native LDL as it is recognized by the scavenger receptors and can therefor give rise to foam cell formation[41] and the initiation, or at least acceleration, of the atherosclerotic process. Adiponectin is an adipose-specific gene product shown to have an anti-inflammatory effect on endothelial cells, it inhibits the proliferation of vascular smooth muscle cells and suppresses the conversion of macrophages to foam cells[42]. It has been reported that cigarette smokers have significantly lower plasma concentrations of adiponectin compared to nonsmokers[42]. It is shown that smoking a single cigarette or receiving intravenous nicotine increases blood pressure, but smokers have equal or lower blood pressures than nonsmokers, probably due to development of tolerance and lower body weights among smokers[43].

1.2 Body weight and body composition

The prevalence of overweight and obesity is increasing in all age groups[44,45]. The worldwide prevalence of obesity almost doubled between 1980 and 2008. Overweight and obesity have been shown to be associated with an increased risk of heart disease, diabetes, arthritis and cancer[45,46], and there is a strong association between body mass index (BMI) and mortality in nonsmokers[47]. In addition to total body fat, there are some evidence that fat distribution may be an important determinant of morbidity and mortality. High amounts of abdominal fat have been shown to be associated with metabolic disease risk[48] and increased mortality[49], independent of overall adiposity and BMI[50,51].

1.2.1 Body weight and body composition in smokers

Smoking is associated with a lower body weight, and smokers have a lower BMI than non-smokers[35,52,53]. Smoking's effect on body weight could lead to weight loss by decreasing metabolic efficiency or decreasing caloric absorption through a reduction in appetite, since both are associated with tobacco use[53]. The metabolic effect of smoking could also explain the lower body weight found in smokers, since there is evidence that cigarette smoking increases 24-hour energy expenditure by approximately 10%[54]. However, even though there

is evidence that smokers have lower body weight than never smokers and former smokers, it is also showed in some previous studies that among smokers, increased amount of smoking tends to be positively associated with BMI, particularly among men[55-57]. This suggests that the factors associated with smoking counter and overtake the metabolic effect of smoking. One explanation could be that heavy smokers are more likely to adopt behaviors favoring weight gain, and it is shown that smokers eat less fruit and vegetables, adopt unhealthy patterns of nutrient intake, drink more alcohol and engage in less physical activity than nonsmokers do[53]. However, it is suggested that the lower BMI of smokers compared to nonsmokers reflects personality characteristics of those who choose to smoke[56], and it is shown that smoking initiation, especially in women, is associated with weight concern or dieting and overweight[58]. This may be a contributing reason for the associations seen between heavy smoking and obesity. The co-occurrence of overweight and smoking has substantial consequences for health, and in the Framingham Heart Study[59], the life expectancy of obese smokers was found to be 13 years less than that of normal-weight nonsmokers.

Even though smokers have a lower BMI than nonsmokers, smoking is not necessarily associated with a smaller waist circumference[53,60,61], and some evidence actually suggests that smoking is related to visceral fat accumulation[62]. In fact, several studies indicate that waist-to-hip ratio (WHR) is higher in smokers than in nonsmokers[60,61,63,64], and that there is a dose-response relation between WHR and the number of cigarettes smoked[56,61]. Actually, smokers tend to have both a larger waist circumference and a smaller hip circumference than do nonsmokers[37,64], which indicates less muscle mass at hip level in addition to greater abdominal fat deposition. This paradox of the combination of a high WHR with a low BMI is more frequent in smokers than in nonsmokers[65]. Less muscle mass at hip level in smokers may be due to impaired protein muscle synthesis and increased expression of genes associated with inhibition of muscle growth and catabolism caused by smoking cigarettes[66].

1.3 Cardiovascular risk factors

Cardiometabolic risk is the overall risk of cardiovascular disease resulting from the presence of traditional risk factors such as lipids (LDL and HDL), blood pressure, glucose, age, male gender, smoking and other risk factors (including genetic and inflammatory factors), and the metabolic syndrome[67]. Metabolic syndrome refers to a cluster of risk factors for CVD and type 2 diabetes mellitus (DM)[18].

1.3.1 Cigarette smoking

Cigarette smoking is a major cause of premature CHD[68], and is highly correlated with an increased incidence of CVD mortality[69]. Smoking actually more than doubles the risk of all types of CVD – CHD, ischemic stroke, peripheral arterial disease and abdominal aortic aneurism, and smoking is the strongest independent risk factor for abdominal aortic aneurism[70]. The risk of CHD associated with smoking has been shown to be proportionally higher in women than in men[70]. As mentioned above, smoking leads to an accumulation of central fat and insulin resistance, and this may represent a major link between cigarette smoking and the risk of cardiovascular disease[71].

1.3.2 Overweight and obesity

One of the most important parameters used to assess body weight is the BMI, which is calculated as the body weight in kg divided by the square of the height in meters. BMI is used to set cut-off limits for normal-weight and body weight that can increase the risk of diseases. The World Health Organization's (WHO) classification of BMI[72] is given in table 1.

Table 1: The WHO classification of BMI

BMI classification	
Underweight	< 18.5
Normal range	18.5 – 24.9
Overweight	≥ 25.0
Preobese	25.0 – 29.9
Obese	≥ 30.0
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese class III	≥ 40.0

WHO: World Health Organization, BMI: Body Mass Index, kg/m^2

Obesity is one of the most important health issues globally, with about 315 million of the world population having a BMI ≥ 30 kg/m^2 [73]. Today, as many as 1 out of 5 Norwegians are obese. This is twice as many as twenty years ago. The prevalence of obesity has increased both in developed and developing countries. Globally, women are obese more often than men, but among high-income nations, the prevalence of obesity is equivalent among women and men[69]. Obesity is associated with elevated blood pressure, dyslipidemia, physical inactivity and increased insulin resistance, all adding to an increased risk of CVD[69], including myocardial infarction and stroke[74]. As much as 23% of ischemic heart disease is attributable

to overweight and obesity[72]. Obesity increases not only the risk of cardiovascular diseases, but also the risk of several types of cancer, type 2 diabetes, gout, and infertility[74]. In fact, overweight and obesity are the reasons for 44% of diabetes and 7-41% of certain cancers globally[72]. Excess weight is an important contributing factor to the development of coronary heart disease in younger compared to older patients[68]. Having increased waist circumference is part of the metabolic syndrome, which is an independent predictor of major coronary events in patients with CHD[68]. Mortality from cardiovascular disease is increased in obese individuals with a BMI > 25 kg/m^2 [75].

Waist circumference or WHR is an indicator of the amount of visceral adipose tissue, and a greater amount of visceral adipose tissue is related to the metabolic syndrome, diabetes and cardiovascular diseases[76]. Results from the INTERHEART study indicated that abdominal obesity had higher correlation with risk of myocardial infarction compared with BMI[77]. De Koning et al.[78] found that both waist circumference and WHR are significantly associated with the risk of incident CVD events, and suggested that these simple measures of abdominal obesity should be incorporated into CVD risk assessments. Increased waist circumference (≥88 cm in women and ≥102 cm in men) is associated with 3-4 times increased prevalence of risk factors for CVD[74]. An elevated risk is also associated with a WHR >.90 in women and >1.0 in men[75].

1.3.3 Dyslipidemia

Dyslipidemia has the highest population-adjusted risk among women, and a continuous increase in CVD risk with worsening dyslipidemia has been noted[69]. It is estimated that the prevalence of total cholesterol levels ≥6 mmol/L among adults ≥20 years of age is 16.2%[18]. LDL-cholesterol levels of ≥3.3 mmol/L are considered borderline high, levels of ≥4.1 mmol/L are classified as high, and levels of ≥4.9 mmol/L are considered very high[18]. For HDL-cholesterol levels, <1.0 mmol/L in adult males and <1.3 mmol/L in adult females is considered low and is a risk factor for heart disease and stroke. A fasting TG level >1.7 mmol/L in adults is considered elevated and is also a risk factor for heart disease and stroke[18,79].

1.3.4 Hypertension

High blood pressure is defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or taking antihypertensive medications[18]. As many as one in 3 US adults has high blood pressure[18]. Hypertension is associated with increased risk of CVD[69,79], and approximately 69% of people who have a first heart attack and 77% of those who have a first stroke have blood pressure >140/90 mmHg[18]. Hypertension is also associated with shorter overall life expectancy, shorter life expectancy free of CVD, and more years lived with CVD[18].

1.3.5 Diabetes mellitus

An estimated 18.3 million Americans ≥20 years of age have physician-diagnosed DM. An additional 7.1 million adults have undiagnosed DM, and the prevalence of prediabetes (i.e. fasting blood glucose of 5.6 to <7.0 mmol/L) in the US population is nearly 37%[18]. Globally, there are more women diagnosed with DM than men. In addition, a higher correlation between CVD mortality and diabetes exists among women than men[69]. DM increases the risk of stroke, with the relative risk ranging from 1.8 to almost 10.0. DM increases ischemic stroke incidence at all ages, but this risk is most prominent before 55 years of age in blacks and before 65 years of age in whites[18]. All-cause and CVD mortality rates among men and women with and without DM decreased from 1950 to 2005, but all-cause and CVD mortality rates among individuals with DM remain approximately 2-fold higher than for individuals without DM[18,80].

1.3.6 Age

Advancing age is a major risk factor for CVD. The average annual rates of first cardiovascular events rise from 3 per 1000 men at 35 to 44 years of age to 74 per 1000 men at 85 to 94 years of age. For women, comparable rates occur 10 years later in life[18]. In 2008, the leading causes of death in both men and women ≥65 years of age were diseases of the heart[18]. Ischemic heart disease was the main cause of death among people aged 65 years or older in Norway in 2010[19].

1.3.7 Physical inactivity

Physical inactivity is responsible for 12.2% of the global burden of MI after accounting for other CVD risk factors, including cigarette smoking, DM, hypertension, abdominal obesity, and lipid profile[18]. The relative risk of CHD associated with physical inactivity ranges from 1.5 to 2.4. Subjects participating in ≥150 min of moderate physical activity weekly reduce their chance of ischemic heart disease by 30%[69].

1.3.8 Diet

Worldwide epidemiology studies and transmigration studies indicate a strong role for dietary composition with foods rich in saturated fat, cholesterol, and sugar being related to increased CHD mortality[81]. Conversely, an increased intake of fruits, grains, vegetables, and vegetable oils, as well as moderate alcohol intake, is associated with reduction in CVD risk factors and protection[81,82].

1.4 Smoking cessation

In the USA, although more than 79% of smokers want to quit every year and 45% make an attempt to quit, less than 5% in the general population are successful[8]. In Europe the percentage of smokers without intention to quit is even higher than in the USA[42]. Fear of weight gain after quitting smoking is often reported to act as a barrier to smoking cessation, especially among women[12,42]. Post cessation weight gain is also often the reason for relapsing after cessation[42,83]. The long-term abstinence rate for a given quit attempt among untreated smokers appears to be 3-5 %, and it may take as much as 10-14 quit attempts before a smoker is successful in achieving abstinence[84].

Most of those who quit cigarette smoking do this on their own, but for many people it would be easier to stop smoking if they got a little help. It is therefore previously recommended that all smokers should be provided with treatment for smoking cessation. In 2010, WHO pointed out that the tobacco cessation offer in Norway is too poor. Based on this, in 2012 Helsedirektoratet came up with a plan for a systematic and evidence based offer for smoking- and snus-cessation, addressing different treatments for tobacco cessation and organization of the work with tobacco in Norway[3].

1.4.1 Health effects

Quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general[10]. Smoking cessation quickly reduces the risk of developing diseases, and persons who quit smoking before 40 years of age do not have increased risk of premature mortality[3], but studies show that the substantial risks of smoking also can be reduced by successfully quitting at any age[10]. Smoking cessation reduces the risk of stroke with a marked risk reduction within 2-5 years after quitting, and that the risk approaches, but perhaps never quite reaches, the risk of never-smokers after 10-15 years[70]. Furthermore, it has been reported that for mortality from any cause and from the cause specific diseases (CVD, ischemic heart disease, stroke and smoking-related cancers), sustained ex-smokers have adjusted relative risks that not differs significantly from those of the never smokers[85]. The exception was the risk of dying from lung cancer in men, but this risk was significantly lower than the risk in male smokers. Cessation of smoking significantly reduces the increased risk of acute MI associated with cigarette smoking over a one- to three-year period, with an exponential decline approaching the risk in ex-smokers within five years of cessation[21]. In addition, smoking cessation improves insulin sensitivity and is associated with an increase in HDL cholesterol, also in spite of post cessation weight gain[42]. Some previous trials have suggested that the risk of diabetes in former smokers decreases progressively as the length of time since smoking cessation increases[17,86] and may return to normal after a few years[86].

1.4.2 Unintended health consequences of smoking cessation

Smoking cessation is associated with increased body weight, mostly due to increased body fat[66,87]. In the USA it is estimated that 80% of people who quit smoking gain weight, and studies have found that on average women gain more weight than men[88]. How much weight gain that is reported to follow smoking cessation is not consistent. O'Hara et al.[89] found that women gained 5.2 kg and men gained a mean of 4.9 kg the first year after smoking cessation, and Kleppinger et al.[66] reported a mean weight gain of 6.5 kg after 16 months. Moreover, it is also reported that most people will gain less than 4.5 kg after smoking cessation, but that as many as 13% may gain as much as at least 11 kg[42] The mechanisms for post cessation weight gain are not completely identified, but smoking cessation has been associated with a decrease in resting metabolic rate (RMR). In some trials the increased body weight was attributable to

a decrease in RMR and/or an increase in caloric intake[42,87]. However, other trials have not found any changes in RMR after smoking cessation[90]. It is also hypothesized that at least some of the weight gain associated with smoking cessation may be due to reduced fat oxidation, since fat oxidation increases with increasing nicotine uptake in smokers[37].

The weight gain following smoking cessation may produce undesirable health problems. Several previous studies have showed that smoking cessation also is associated with a substantial increase in waist circumference[91,92]. In men with a recent (within one year) premature major coronary event, current cigarette smoking and smoking cessation has been found to be associated with a greater prevalence of the metabolic syndrome[68]. A high waist circumference, as an indicator of increased abdominal fat, and dyslipidemia were the components of the metabolic syndrome that were more prevalent in exsmokers than in nonsmokers. Another study also found that smoking cessation may increase the risk of developing metabolic syndrome in women, mainly due to increased waist circumference[93]. In addition, a large study found that the onset of hypertension was higher in those who quit smoking (35%) than in those who continued to smoke (27%)[94]. This study found that the weight gain following cessation was largely responsible for the increased incidence of hypertension in quitters. However, another trial found that insulin sensitivity improved 8 weeks after smoking cessation in nonobese men, despite an increase in body weight[95]. It is suggested that the weight gain associated with smoking cessation may offset some of the advantages of giving up smoking[68], and it is in fact showed an increased risk for type 2 diabetes in people recently quitting smoking compared to both never-smokers and current smokers[96].

Despite these negative consequences, others indicate that the health problems following post cessation weight gain probably are modest given the large health benefits of quitting smoking[97]. It is in fact estimated that quitting smoking at age 35 will increase life expectancy with approximately 6-8 years, and even among smokers who quit at age 65 life expectancy may increase with almost 4 years[98]. However, concern regarding post cessation weight gain seems to be a powerful motivator for continued smoking, and it appears that concerns or beliefs regarding post cessation weight gain are more important than actual weight gain, and may be associated with continued maintenance of smoking[97]. In accordance with this, it is previously shown that weight-concerned smokers have poorer smoking treatment outcomes compared with smokers with lower levels of weight concerns[99]. It is therefore necessary to

find some interventions that may prevent, or at least reduce, the weight gain associated with smoking cessation, so that a larger proportion of weight concerned smokers may successfully quit smoking.

1.4.3 Smoking cessation treatment

Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments exist that can significantly increase rates of long-term abstinence. Counseling and medication are effective when used by themselves for treating tobacco dependence. It is, however, shown that the combination of counseling and medication is more effective than either alone[100]. Treatments are targeted towards dealing with the physical addiction to nicotine, the psychological reliance on the effects of nicotine, and the behavioral aspects of tobacco use[8]. Assistance for cessation includes both counseling (ideally, four or more sessions) and pharmacotherapies. Counseling involves motivating tobacco users to quit by examination of the results from smoking. It includes educating tobacco users about the beneficial health effects from stopping smoking, problem solving, and skills training, such as discussing methods and coping skills to deal with high-risk situations for tobacco use, and providing social support as part of treatment[8]. Pharmacotherapies for nicotine dependence can enhance quit rates by about two-three-fold. Both the UK and US Public Health Service guidelines therefore recommend that all smokers should be considered for pharmacotherapies[8]. However, special consideration or exception should be given to smokes with specific medical conditions, to those who smoke less than ten cigarettes daily, to pregnant or breastfeeding women, and to adolescents. Seven smoking cessation pharmacotherapies are currently approved by the US Food and Drug administration[101]. Five of these are nicotine replacement products (nicotine patch, -gum, -lozenge, -nasal spray and oral inhaler). Each delivers nicotine in a way that allows an individual to reduce nicotine withdrawal symptoms and cravings for cigarettes when quitting smoking, and it has been shown that nicotine replacement medications facilitate smoking cessation[102]. These products are obtained without prescription. The other smoking cessation products approved by the Food and Drug administration are bupropion (trade name Zyban®), which is hypothesized to aid smoking cessation by inhibiting dopamine reuptake in the mesolimbic dopamine system[103], and varenicline (trade name Chantix® in the USA and Champix® in Canada, Europe and other countries). Bupropion have previously been shown to increase smoking cessation rates compared to both placebo and nicotine replacement medications[104,105].

Varenicline was added to the limited list of first-line pharmacotherapies for smoking cessation by the 2008 update on smoking cessation issued by the Public Health Service[100]. Varenicline binds to the $\alpha_4\beta_2$ receptor subunit of nicotinic acetylcholine receptors and exerts effects both as a partial agonist that displays approximately 30-60% of the in vivo efficacy of nicotine by stimulating dopamine release, and as an antagonist by blocking the binding of nicotine to this site[106]. Varenicline is typically administered for 1 week prior to quitting and is believed to offer the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving through its agonist action, and at the same time blocking the reinforcing effects of continued nicotine use through the antagonist action. In theory, varenicline will therefore promote the extinction of smoking behavior. In fact, two identically designed, large randomized controlled trials conducted at two different centers both found that varenicline significantly reduced the urge to smoke, smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations and craving relief compared to placebo, with an effect size larger than that of bupropion[107,108]. In line with this, varenicline had higher continuous abstinence rates (CAR) and 7-days point prevalence abstinence rates (pp) than placebo at weeks 12 (44.0% vs. 17.7% CAR in one and 43.9% vs, 17.6% in the other), 24 (29.5% vs. 10.5% CAR in one and 29.7% vs. 13.2% in the other) and 52 (21.9% vs 8.4% CAR in one and 23% vs. 10.3% in the other). Both bupropion and varenicline can only be obtained with prescription from a physician. Compared to no treatment can nicotine replacement therapy, bupropion and varenicline be considered cost-effective in Norway, with varenicline being the most cost-effective drug alternative[3]. With structured counseling in addition to pharmacotherapy up to 40% can succeed with their smoking cessation attempt. It is shown that the chances to succeed with a smoking cessation attempt is about doubled if the person attend a smoking cessation group compared to quitting all by him/herself[3].

Assessment of smoking status

An accepted method to confirm self-reported smoking status is measuring of expired-air carbon monoxide (CO). This is performed with a monitor which analyzes the amount of carbon monoxide in a single exhaled breath and use this reading to automatically calculate the percentage of carboxyhaemoglobin (%COHb) in the blood[109]. Another accepted method is measuring of cotinine, the major metabolite of nicotine, in saliva, blood or urine[110].

Most trials comparing smokers and nonsmokers, or estimating smoking cessation-rates, use continuous abstinence rates (CAR) or point prevalence (pp). Continuous abstinence refers to those participants who quit smoking and maintain abstinence throughout the following period. In contrast, point prevalence abstinence refers to smoking (yes vs. no) at a particular follow-up time point, with no correction for previous or subsequent relapses to smoking[42].

1.5 Changes in body weight

1.5.1 Health effects of changes in body weight

The risk of cardiovascular disease increases with weight gain and decreases with weight loss[75]. Increased body weight is associated with increased blood pressure and increased risk of type 2 DM[79,111]. BMI is strongly related to overall mortality, with increased risk of mortality in subjects with BMI $\geq$27.5 kg/m^2 [112].

Weight reduction and regular physical activity decrease the risk of type 2 DM. A moderate weight reduction in the range of 5-10% of the body weight provide significant benefits in terms of blood pressure, insulin resistance, blood lipids and light sleeping problems. A greater weight reduction of 15-20% of the body weight can reverse the increased mortality risk in overweight subjects with type 2 diabetes[74].

1.5.2 Nordic and Norwegian recommendations for nutrition

The physical activity level and the diet composition have direct effects on important risk factors such as blood lipids and blood pressure, on the risk of developing chronic diseases and the risk of premature death. Physical activity level and diet composition also affects the risk of cardiovascular diseases, type 2 diabetes and several types of cancers[74]. The Nordic and Norwegian recommendations for nutrition and physical activity are based on scientific documentation and aims to provide a basis for planning of a diet and physical activity level to help prevent lifestyle diseases, such as obesity, type 2 DM, CVD and cancer[113]. In brief, the recommended macronutrient composition should be 25-35 energy% from fat, 50-60 energy% from carbohydrate, and 10-20 energy% from protein. The intake of saturated fat, monounsaturated fat and polyunsaturated fat should be $\leq$10, 10-15, and 5-10 energy%, respectively. The intake of added sugar should not contribute to more than 10% of energy

intake. The intake of dietary fiber should be 25-35 g/day, equivalent to 3 g/MJ. In terms of physical activity it is recommended that adults exert physical activity at moderate or vigorous intensity for at least 30 minutes every day. To prevent weight gain it is probably necessary with 60 minutes of physical activity daily. In 2011, Helsedirektoratet published national dietary advices to prevent lifestyle diseases[114]. These advices are based on food groups rather than the macronutrient composition, but a diet in accordance with these advices will also meet the macronutrient composition recommended in the Norwegian recommendations for nutrition and physical activity published in 2004.

1.5.3 Dietary interventions for weight reduction

Though obesity is caused by an imbalance between the amount of energy consumed and energy expenditure, the exact mechanisms and their relative importance in explaining this energy imbalance is not clear[115]. Clinical intervention programs have studied different nutritional treatments in order to improve both weight loss and weight maintenance, and the majority has focused on different macronutrient compositions[116]. So far, it seems like several diets with different macronutrient composition can successfully reduce body weight as long as they are energy-reduced[117,118].

The introduction of low-fat, high-complex carbohydrate diets for the prevention and treatment of obesity was based on the link between dietary fat and body fatness; weight loss is correlated positively to the reduction in dietary fat content. A reduction of 10% fat energy produces an average weight loss in obese persons of 5 kg[119]. Fat is less satiating than carbohydrate and protein. It is shown that persons who had high hunger levels overate when receiving high-fat foods but not when receiving high-carbohydrate foods. Furthermore, it has been suggested that periodic exposure to high-fat meals, particularly when hunger is high, may be sufficient to lead to an over-consumption of energy from fat that is not compensated by a later reduction in energy intake[119]. In addition, the Finnish Diabetes Prevention Project randomized over 500 middle-aged overweight and obese subjects with impaired glucose tolerance to usual-care or an intensive lifestyle-intervention group[120]. The intervention goals were to reduce dietary total (<30 E%) and saturated (<10 E%), and increase physical activity and dietary fiber, and this intervention was highly successful in preventing diabetes. However, a previous meta-analysis concluded that low carbohydrate diets were as effective as low-fat diets in reducing body weight for up to one year[121]. Several dietary intervention trials

have reported greater short-term (≤ 6 months) weight loss in subjects following a high-protein, low-carbohydrate diet versus a low-fat, high-carbohydrate diet, but with no significant weight loss differences after one year[122-125]. In addition, the high-protein, low-carbohydrate diet was associated with greater decrease in TG and greater increase in HDL-cholesterol. It is hypothesized that the beneficial effects of high-protein diets on adiposity may be due to increased thermogenesis and satiety[126,127]. It is, however, suggested that high-protein, low-carbohydrate diets (ketogenic diets) do not offer much advantage over high-protein, moderate-carbohydrate diets in terms of appetite control or metabolic advantage[128].

Calculation of estimated energy requirements

Dietary interventions for weight reduction usually include energy-reduction in addition specific macronutrient compositions, and an accurate method of assessing overall energy requirements is important in weight management of both normal-weight and obese individuals. The assessment of 24-hours energy expenditure (24-EE, in kcal/day) is a requirement for establishing caloric prescriptions for patients. The best predictor of 24-EE is the resting energy expenditure (REE), or RMR, as determined by indirect calorimetric measurement[75]. However, measuring of REE or RMR with indirect calorimetry is not always available. For these situations the Mifflin-equations for REE[75] can be used:

For females: REE = 10 x weight (kg) + 6.25 x height (cm) – 5 x age (years) – 161

For males: REE = 10 x weight (kg) + 6.25 x height (cm) – 5 x age (years) + 5

These equations are based on a sample of both normal-weight and obese subjects. Usually an individual's REE is multiplied by an activity factor to arrive at the 24-EE. The WHO values of physical activity level (PAL) are 1.53 for a sedentary or light activity lifestyle, 1.76 for an active or moderately active lifestyle, and 2.25 for a vigorously active lifestyle[129].

Dietary interventions to prevent post cessation weight gain

There is some evidence that weight management education with personalized support giving feedback on personal goals and a personal energy prescription can limit post cessation weight gain. However, some evidence also suggests that interventions that limit dietary intake may potentially reduce smoking cessation success, because hunger can undermine quit efforts and increases urges to smoke in current smokers[88]. Furthermore, others have suggested that

dietary interventions might serve to encourage reluctant quitters to try to stop smoking if they can be reassured that weight gain might be limited. It is therefore necessary to find some dietary interventions that prevents, or at least reduces, post cessation weight gain without decreasing abstinence rates, but to our knowledge, no studies comparing the effects of diets with different macronutrient compositions on weight gain after smoking cessation have been performed.

2 Aims and efficacy outcomes

2.1 Main aim

The main aim of this master thesis was to compare two dietary interventions in efficacy of preventing undesired weight gain after smoking cessation. The master thesis is based on an ongoing study at Oslo Universitetssykehus, Ullevål, and is analyzing the results after 4 and 12 weeks after smoking cessation for the first eighty participants included in the study.

2.2 Efficacy outcomes

2.2.1 Primary efficacy outcomes

The primary objective was to compare the effect of a low fat diet high in complex carbohydrates (≤30 energy % fat, ≤20 energy % protein and ≥50 energy % carbohydrate) or a high protein diet moderately reduced in carbohydrates (≥25 energy % protein, ≤55 energy % fat and ≤20 energy % carbohydrates) on body weight 4 and 12 weeks after smoking cessation.

2.2.2 Secondary efficacy outcomes

The secondary objective was to compare the effect of a low fat diet high in complex carbohydrates (≤30 energy % fat, ≤20 energy % protein and ≥50 energy % carbohydrate) or a high protein diet moderately reduced in carbohydrates (≥25 energy % protein, ≤55 energy % fat and ≤20 energy % carbohydrates) on body composition (body fat, lean body mass, waist circumference, hip circumference, waist-to-hip ratio) 12 weeks after smoking cessation.

2.2.3 Third efficacy outcomes

The third objective was to compare the effect of a low fat diet high in complex carbohydrates (≤30 energy % fat, ≤20 energy % protein and ≥50 energy % carbohydrate) or a high protein diet moderately reduced in carbohydrates (≥25 energy % protein, ≤55 energy % fat and ≤20 energy % carbohydrates) on cardiovascular risk factors (glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and blood pressure) 12 weeks after smoking cessation.

2.2.4 Fourth efficacy outcomes

Compare dietary changes within the two intervention groups and examine correlations between the dietary changes and changes in body weight four weeks after smoking cessation.

3 Subjects and methods

3.1 Subjects

Participants were recruited by advertisement in newspapers (appendix 1) or referral to the Department of Preventive Cardiology at Oslo University Hospital, Ullevål.

3.1.1 Inclusion criteria

- Men and women aged 20 to 65 years.
- Smoking ≥ 10 cigarettes per day.
- BMI 25-40 kg/m^2.
- No attempt to quit smoking in the previous 3 months.
- Change in weight of 4 kg or less during the previous 3 months.
- No major change in physical activity level in the previous 3 months.
- Willing to use varenicline.

3.1.2 Exclusion criteria

- Smoking < 10 cigarettes per day or using snus or other forms of tobacco than cigarettes daily.
- BMI > 40 kg/m^2 or < 25 kg/m^2.
- CVD within last 2 months (i.e. myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous transluminal intervention, stroke or transient ischemic attack (TIA)).
- Chronic heart failure classified as symptomatic; New York Heart Association (NYHA) class III-IV[130].
- Diabetes type I or type II taking insulin for diabetes.

- History of serious psychiatric disorder (e.g. panic disorder, psychosis, bipolar disorder, suicidal attempt).
- Ongoing major depressive illness or major depressive illness during the last year.
- Ongoing anti-depressive treatment.
- History of alcohol/drug abuse.
- Clinical disorders including gastrointestinal disease impairing compliance with dietary recommendations.
- Participation of a drug trial during the previous 30 days before the baseline visit.
- Use of drugs (Xenecal, Reductil), nutritional supplements or herbs for weight loss within the 4 weeks prior to the baseline visit or participation in an active weight loss program.
- Pregnancy or lactation or planned pregnancy during the study.
- History of obesity surgery.
- Exclusively vegan or vegetarian diet.
- Not willing to be randomized to either diet.
- Individual judged by the clinical investigator to be unable to follow instructions and procedures of the study.

3.1.3 Number of subjects

To be able to detect a difference in weight gain of 3 kg between the groups, the main study will need 58 participants in each group. With this number the trial will meet a 90% power to detect a 3 kg difference with 5% significance assuming that the standard deviation (SD) of the change in weight will be 5 kg.

The number of subjects (N) in each group was calculated according to the equation:

$$N > \frac{(u + v)^2(\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_0)^2} = \frac{(1.28 + 1.96)^2 (5^2 + 5^2)}{3^2} \approx 58$$

Where:

$\mu_1 - \mu_0$:	difference between the means, 3 kg
σ_1, σ_2:	standard deviations, 5 kg
u:	estimated from the test power (1-β) $P(Z \geq u) = 100\%-(1-\beta)$ $u = 1.28$ ($P(Z \geq 1.28) = 0.10$)
v:	estimated from the significance level (α) $P(Z \geq v) = \alpha/2$ $P(Z \geq v) = 0.025$, $v = 1.96$
1-β:	90%
α:	5%

Allowing dropouts the main study will therefore require 60 subjects in the two intervention groups, respectively. Since the main study is ongoing and will include the last participants during the fall 2012, only the first 80 subjects randomized in the trial was included in the master thesis. The first 64 subjects participated in the trial in the period January 2010 to September 2011, while the remaining 16 subjects were included in September and October 2011.

3.2 Study design

This was a randomized, controlled, parallel group study. Subjects responding to the advertisement in the newspaper consulted a physician at the first visit. Eligible subjects (i.e. subjects who met all inclusion criteria and had no exclusion criteria present) provided written informed consent. At the next visit all included subjects were randomized to one of the two intervention groups. Randomization was done in blocks. When a new subject was ready for randomization a pre-numbered and sealed envelope was opened and the intervention allocation was entered into the subjects clinical report form. See appendix 2 for flow chart of the study. All consultations with subjects and data collection took place at the Department of Preventive Cardiology at Oslo University Hospital, Ullevål. If a subject did not show up for a planned visit, the subject was contacted by one of the investigators by either telephone or e-mail. Follow-up visits were encouraged regardless of smoking status and dietary adherence.

3.2.1 Smoking cessation

Trained counselors provided motivational support and tips regarding behavioral therapy for smoking cessation. Counseling focused on problem solving and skills training for coping with high-risk situations[8]. Prior to the stop smoking day and for 4 weeks after the target-quit date counseling was given at weekly visits. The next 8 weeks counseling was given in biweekly visits. The target date for smoking cessation was decided at the first counseling session (at the date of screening). To improve smoking cessation rate, the subjects were offered the drug varenicline (trade name Champix®) free of charge. Table 2 shows the administration of varenicline.

Table 2: Treatment with varenicline 1-2 weeks before smoking cessation

Days before quitting	Dose	Frequency
Day 1-3	0.5 mg	Once a day
Day 4-7	0.5 mg	Twice a day
Day 8	1 mg	Twice a day

The dose of 1 mg varenicline twice a day was used for up to 12 weeks depending on the choice of the subject. Smoking status was assessed by expired-air carbon monoxide (CO) measurement at every visit. CO values ≤ 5 parts per million (ppm) was assessed as no smoking status[131].

3.2.2 Dietary intervention

The subjects were randomized to follow one of two intervention diets; a low fat diet high in complex carbohydrates (from now on referred to as LFHCC) or a high protein diet moderately reduced in carbohydrates (from now on referred to as HPMRC). The intention with the LFHCC was to reach a macronutrient composition of ≤30 energy % fat, ≤20 energy % protein and ≥50 energy % carbohydrate. To achieve recommended level of fat, the dietary intake of fat had to be limited to 67 g at a daily energy level of 2000 kcal. Dietary carbohydrates should be the most abundant macronutrient. At an energy level of 2000 kcal per day, almost 250 g per day of mainly complex carbohydrates (i.e. oligosaccharides and polysaccharides) from whole meal bread, oat based-cereals, brown rice, whole meal pasta, legumes, fruits and vegetables should be included in the diet. The subjects in this intervention group were also advised to restrict the intake of fatty snack products and products high in simple

carbohydrates, such as fatty cakes, chocolate, potato chips and sugar containing drinks, as much as possible. A restricted amount of unsaturated fat such as soft margarine, vegetable oil, nuts and fish was recommended to ensure the intake of essential fatty acids.

In the HPMRC group the intention was to reach a macronutrient composition of ≥25 energy % protein, ≤20 energy % carbohydrate and ≤55 energy % fat. In this diet the emphasis was on increasing dietary intake of protein and reducing dietary intake of carbohydrate. To achieve the recommended level of protein, the intake of protein had to be almost 125 g per day at a daily energy level of 2000 kcal. This diet included increased amounts of low fat meat, chicken, fish, shellfish and cheese. The energy % from carbohydrate was planned to be about 20 %, and the amount of carbohydrate should be reduced to 100-120 g per day. This is a moderate carbohydrate reduction allowing for a restricted amount of bread, fruit and vegetables. This diet allowed a higher intake of fat than the low fat diet, but the subjects were recommended to choose unsaturated fat from fish, vegetable oils, soft margarine, avocado and nuts etc. instead of saturated fat from meat and full-fat dairy products. The high protein diet group was advised to choose rye bread and protein rich bread spread for breakfast, increase portions of meat, fish or shellfish for lunch and dinner, and to reduce the intake of potatoes, rice, pasta and fruits. The subjects in this intervention group were also advised to restrict the intake of sugar containing food items such as cakes, ice-cream, deserts and drinks as much as possible.

Approximately 5 energy % from alcohol (equals about 1 alcohol equivalent i.e. 350 mL beer, 135 mL wine and 40 mL 40% spirit at an energy level of 2000 kcal) was allowed in both diets.

Trained nutritionists gave cognitive behavioral therapy for the dietary intervention. Prior to the stop smoking day and for four weeks after smoking cessation counseling was given at weekly visits. The next eight weeks counseling was given in biweekly visits. At the screening visit, participants received a food diary (appendix 3), and were guided in how to implement a 7-days weighed dietary record (DR). All participants were offered to borrow a digital kitchen scale, and were encouraged to weigh all food and beverages to be consumed for the next seven days as far as possible. If they for some reason not were able to weigh the food, they were encouraged to write down what they ate, and use household measures or size and numbers of the food eaten. This was not optimal, but may have led to that a greater proportion of the participants recorded more days, due to a smaller workload. At the second visit,

participants were randomized to either of the two intervention diets. The participants received written information and advices tailored to the intervention diet they were randomized to (appendix 4 and 5). They also received some recipes for lunch- and dinner meals (appendix 6 and 7), and a written list over alternative proposals for a diet plan (appendix 8 and 9). Individualized specific advices, in line with the general advices given in the two intervention groups, were given orally based on their weighed dietary records. These specific advices gave the participants a better opportunity to adapt the intervention diet to their original diet and food preferences. Estimated RMR measured at the beginning of the visit, in addition to reported physical activity, was used to give individualized recommendations for energy intake, approximately 500 kcal less than assumed total energy expenditure (measured RMR multiplied with assumed PAL). Since measured levels of physical activity not were used in this calculation, recommendations for estimated energy intake were not as accurate as they in theory could have been.

In theory, written information made it easier for the participants to estimate and calculate the amount of calories, carbohydrate, fat and protein in different foods and meals. It is, however, always a possibility that written information not will be considered any further by some of the participants. For these participants, the oral information and dietary advices given at each visit were probably of more importance.

The high protein diet moderately reduced in carbohydrate was a little more expensive than the low fat diet high in complex carbohydrate due to the high proportions of pure meat and fish, which is more expensive than carbohydrate rich foods like potatoes and whole meal bread, rice and pasta. It was, however, emphasized that the participants anyway would save more money by quitting smoking than they would spend extra on the changes they had to make to their diet, and financial expenses should therefore not be an obstacle for any of the dietary interventions.

At the visit three weeks after their smoking cessation date, participants received a second food diary, and the instructions on how to implement the weighed DR was repeated. They were then asked to record all their consumed foods and beverages for the next consecutive week. The DRs were collected at the visit four weeks after smoking cessation. No dietary records were implemented and collected at the visit twelve weeks after smoking cessation, and it is therefore impossible to say anything about the participants' adherence to the diet interventions at this time point of the study.

One main meal (lunch) and one snack meal was provided for the first four days after smoking cessation and for the first three days of the second week after smoking cessation. This was primarily done to increase the compliance during the most acute effects of nicotine withdrawal[132], but these meals also served as practical examples to give the participants an impression of the amounts of foods rich in carbohydrate, fat and protein. Three different lunch meals were offered in both intervention groups and the subjects were free to choose the ones they preferred. Appendix 10 and 11 shows the lunch meals and the macronutrient composition of the meals that were offered in both groups. The lunches had energy contents in the range of 345 kcal to 410 kcal. In the LFHCC group the content of fat was in the range of 9 g to 13 g and was about half the amount served in the HPMRC group diet. The content of protein in the lunch meals in the HPMRC group was in the range 40 g to 43 g and this amount was almost twice as much as the amount served in the LFHCC group. Likewise the carbohydrate content was in the range of 41 g to 51 g in the LFHCC group and in the range of only 3 g to 5 g in the HPMRC group.

Emphasize was also given to the snack meals, given that nicotine deprivation has been associated with increased reward value of appealing snack foods[133]. Both intervention groups were offered 4 snack meals the first week after smoking cessation and 3 snack meals the second week after smoking cessation. The LFHCC group was offered pre-packed yoghurt with muesli. Other recommendations for snack meals in the low fat group included fruits, vegetables, oat porridge with milk and hard bread with smooth brown cheese (prim). The HPMRC group was offered high protein yoghurt (SKYR). Other dietary recommendations for the snack meals in the high protein group included natural yoghurt with almonds, egg, cheese, chicken wings, shellfish and fish.

Subjects in both intervention groups were advised to reduce daily coffee drinking to 2 cups for women and 3 cups for men due to increased effects of caffeine during nicotine withdrawal[134].

3.3 Study measurements and variables

Characteristic variables included sex, age, weight, height, body composition, resting metabolic rate, BMI in kg/m^2, waist circumference, hip circumference, waist-to-hip ratio, systolic and diastolic blood pressure, serum lipids and serum glucose and number of cigarettes

smoked daily. The resting metabolic rate was included in the master thesis in order to estimate the individual energy level for energy restriction in the dietary intervention and to estimate misreporting of energy intake reported in the dietary records.

3.3.1 Assessment of smoking status

Participants were encouraged to write a smoking diary (appendix 12), and were asked at each visit how many cigarettes they had smoked since the last visit. Measurement of expired-air CO was performed at every visit using a breath carbon monoxide monitor (piCO+^{TM} Smokerlyzer®, Bedfont Scientific Ltd., Kent, United Kingdom). Abstinence at each visit was defined as a self-report of no smoking of any kind, not even a puff, since the previous visit, confirmed by an expired carbon monoxide level of ≤ 5 ppm in exhaled air. CAR for all 12 weeks of treatment after smoking cessation has been used, and the group of all participants that were continuous abstinent for all twelve weeks is from this point forward defined as nonsmokers, unless otherwise stated. In addition, CAR for the first four weeks (weeks 1-4) was calculated, and nonsmokers during these four weeks have been in the correlation analyses performed in accordance with the fourth efficacy outcome. CAR for the last four weeks (weeks 9-12) were also calculated to compare CAR in the current study with CARs from previous trials, since this measurement of smoking cessation rates has been used in several smoking cessation trials[107,108,135,136]. Another often used measurement of smoking cessation rates is point prevalence. In most studies using point prevalence, participants self-report their smoking status in the previous 7 days[107,137-139]. This was not done in this trial, but 14-days point prevalence for week 12 was calculated to be able to compare smoking cessation rates in the current study with point prevalence rates in other trials. The 14-days point prevalence in the current thesis was defined as a self-report of no smoking in the previous 14 days (since the last visit), confirmed with an expired carbon monoxide level of ≤ 5 ppm. Any participant claiming to be abstinent from smoking, but having a level of CO > 5 ppm, was considered smoking. Participants who have been abstinent for the first 10-11 weeks, but then have failed to meet for counseling, were also considered smoking again unless otherwise stated.

Assessment of nicotine dependence

Technically, nicotine dependence was measured with Fagerström Test for Nicotine Dependence[140] for every person at the time of the screening visit. This is a recommended tool for assessment of nicotine dependence[8]. In this study a Norwegian version of FTND (appendix 13), translated and published by Helsedirektoratet, was used[141].

In accordance to the FTND, nicotine dependence was divided into three categories, low, medium and high nicotine dependence, in this master thesis. Low nicotine dependence is defined as a total score of 0-3 points, medium nicotine dependence as a total score of 4-6 points, and high nicotine dependence as a total score of 7-10 points[141].

3.3.2 Clinical measurements

Anthropometrics

Body weight was measured at every visit by a digital scale. Body weight was measured in light indoor clothing without shoes. Height was measured once at the screening visit using a standard scale, without shoes. BMI was calculated as the ratio of weight in kilograms divided by the square of the height in meters. Waist circumference was measured midway between lower costa and crista while the subject was unclothed and standing[74]. Hip circumference was measured at the level of the greater trochanter. BMI, waist and hip were measured at randomization and four and 12 weeks after smoking cessation. Body composition was measured after an overnight fast (minimum eight hours) by impedance (InBody720®, Biospace Co Ltd., Seoul, Korea) at randomization and four and 12 weeks after smoking cessation. Measurements were performed in light indoor clothing without shoes and socks. The participants were standing on the electrodes embedded in the scale platform of the analyzer. After their body weight was measured they were instructed to stand upright and to grasp the handles of the analyzer, thereby providing contact with a total of eight electrodes (two for each foot and hand). The participants' screening number, height, age, and sex were entered into the analyzer, and the participants were instructed to slightly abduct their arms and remain still during the assessment[142].

Blood pressure

Blood pressure was measured at the screening visit, at randomization and four and 12 weeks after smoking cessation. Measurements were conducted after at least five minutes of rest using an electronic blood pressure monitor (Omron 5 Series^{TM}, Omron Healthcare, Kyoto, Japan) with an appropriately sized cuff with the patient sitting in the upright position. Three measurements were recorded, and the average of the three measurements was used in the analyses.

Resting metabolic rate

RMR was measured indirectly with a standard portable ventilated hood system (Vmax Spectra 229, Sensormedics®, Sensormedics Corporation, Yorba Linda, California) at randomization and four weeks post-cessation. The measurements and calculations were done after standardized procedures[143]. The last five minutes in steady state was used for the calculations of RMR. Participants who not were fasting when they met at the date of randomization, four weeks after smoking cessation and/or 12 weeks after smoking cessation, were asked to come back for fasting impedance measurement, indirect calorimetry and blood samples the following day.

3.3.3 Laboratory measurements

Eligibility laboratory measurements (hemoglobin, white blood cells, ASAT/ALAT, creatinine and TSH) were done at the screening visit. Blood samples obtained after an overnight fast (minimum eight hours) were collected for analysis of blood lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol and TG) and glucose at the date of randomization and four weeks and 12 weeks post-cessation. The blood measurements were analyzed by conventional laboratory methods at Department of Clinical Chemistry, Oslo University Hospital Ullevål.

3.3.4 Assessment of diet

In this study, weighed DR was used to assess compliance with the dietary interventions for 7 consecutive days. The DR was performed twice; the first week after the screening visit, and during the fourth week after smoking cessation. Participants received a blank food diary and were provided with food scales. They were instructed to weigh each individual food item using the digital scaled weight and provide notes on ingredients of composite dishes with

approximate quantities. When weighing was not appropriate, portion sizes were estimated with the use of household measures and an photographic atlas with photographs of food items[144]. Days that were very poorly recorded were excluded. These were days where food items not were specified (e.g. "tapas") and/or portion sizes or numbers not were recorded at all, and the atlas not had been used. The term "sugar" in the chapters of results and discussion, refers to added sugar (i.e. simple sugars that are not found naturally in the food). Mono- and disaccharides naturally occurring in the food items, like in milk and fruits, are included in the term "carbohydrate". In studies done here there is a chance of misreporting. To estimate errors like over- or under-reporting, the Goldberg equation[145] (ratio of estimated intake to measured RMR) was used.

3.3.5 Measurements conducted but not included in the master thesis

Several other measurements were conducted in the main study, including $HbA1_c$, insulin, urine creatinine, albumin, CRP, ASAT/ALAT, inflammatory markers (TNFα, IL-6, MCP-1, PAI-1), adipokines (ghrelin, adiponectin, leptin, resistin, visfatin), eating behavior (dietary restraint, disinhibition, binge eating, hunger), food cravings and assessment of total withdrawal discomfort or craving after smoking cessation (Minnesota nicotine withdrawal symptoms questionnaire). Physical activity was measured for 7 consecutive days by an accelerometric device (ActiGraph GT3X+, ActiGraph™, Pensacola, Florida) the first week after the screening visit and the fourth week after smoking cessation.

These measurements were not included in the master thesis to prevent the workload being too comprehensive, and because some of the measurements not will be analyzed before the main study has completed acquisition of data.

3.4 Safety and adverse events

An adverse event was:

- Any unintended unfavorable laboratory or clinical sign or symptom.
- Any new illness or disease or deterioration of existing illness or disease.
- Any clinical relevant deterioration in a laboratory variable or other clinical test whether or not considered intervention related.

Planned hospital admission and surgical procedures for illness or disease that existed before the start of the trial were not considered to be adverse events. Date of onset, duration and intensity was recorded on the adverse event form in the case record form (CRF). All adverse events not resolved were followed up.

3.5 Data management, statistical procedures and calculation of dietary intake

3.5.1 Data management

Data were collected and recorded in case record forms, and entered, coded and edited into a protected database system (Epi Info^{TM}) of Oslo University Hospital, Ullevål to provide data protection.

3.5.2 Statistical procedures

All statistical analyses were performed using IBM SPSS Statistics 19 for Windows. Descriptive statistics were performed for anthropometric characteristics and efficacy variables. The primary efficacy outcome was differences in body weight change between the dietary intervention groups from the date of randomization to four weeks after smoking cessation and 12 weeks after smoking cessation. Other outcomes were between-group differences in the change in body composition (waist circumference, hip circumference, WHR, body fat, lean body mass) and cardiovascular risk factors (glucose, lipids, blood pressure) from randomization to 12 weeks after smoking cessation. Estimates for the main efficacy variables are mean ± standard deviation (SD), between-group differences are mean

(95% confidence interval). However, median (1^{th} and 3^{rd} quartile) are given in addition for triglycerides due to a non-normal distribution. Changes (from randomization to (four) 12 weeks after smoking cessation) in all of these variables were tested for differences between the dietary intervention groups by independent-samples t-test. Mean differences between the groups are the mean change in the HPMRC group subtracted from the mean change in the LFHCC group. The difference in TG from randomization to 12 weeks after smoking cessation was normally distributed in both groups, and independent-samples t-test was used to test the difference between the groups. Changes from randomization to 12 weeks after smoking cessation within groups were tested by paired-samples t-test in each of the two intervention groups. Dietary changes within and between the intervention groups from the date of randomization to four weeks after smoking cessation have been tested with paired-samples t-test and independent-samples t-test, respectively. For all t-tests listwise excluding of missing values have been performed. This means that if a subject has missed one of the visits included in the analyses, this subject has been excluded from the analyses. Chi-square test was used in comparisons of categorical variables. Pearson correlation analyses were performed to test for correlations between the changes in intake of macronutrients (fat, protein and carbohydrate) and changes in body weight from randomization to four weeks after smoking cessation. Other regression analyses have not been performed. All tests were two-tailed and a p-value of $<.05$ was regarded as the level for statistical significance.

All statistical analyses were performed twice for the participants who met at both the fasting visits at randomization and 12 weeks after smoking cessation. Once regardless of their smoking status (referred to as "nonsmokers + reduced smokers"), and once for the proportion of participants who succeeded to be abstinent from smoking all continuous twelve weeks following their smoking cessation dates (referred to as "nonsmokers"). Statistical analyses on changes in body weight were performed for participants who met at all three fasting visits (randomization, and four and 12 weeks after smoking cessation). Analyses on body weight were also done on an intention-to-treat basis, with a last-measurement-moved-forward approach for non-completers. Intention-to-treat analyses for other efficacy outcomes have not been performed in this master thesis. In addition to these analyses, tables showing mean values for all participants met at any of the three time points for measurements (randomization and four and 12 weeks after smoking cessation) have been made. Due to rounding, all estimates may not match.

3.5.3 Calculation of dietary intake

The dietary records were coded manually for the calculation of energy intake, energy yielding nutrients and food items using a software program (Mat på data 5.0, Mattilsynet, Oslo, Norway, 2007) based on the Norwegian food composition table[146]. For food products where several different types exists, like soft margarine and bread, one type has been used for all dietary records failing to specify which type the participant has been eating. Food items recorded, but not included in the Norwegian food composition table, were searched for in the Swedish food composition table[147] or the USDA National Nutrient Database for Standard Reference[148]. The food items and their nutrient contents were then added to the Mat på data software program through the Reorg-function. For composite dishes recipes were applied for on the internet and then added to Mat på Data. For some composite dishes ordered in restaurants or fast food outlets, the chef weighed the ingredients or the amounts have been obtained from the restaurant's recipe. For kebab especially, the meat producer has been contacted to find out what the meat mixture used in kebabs usually consist of, and then all the ingredients in a regular kebab, purchased from the largest kebab outlet (Bislett Kebab House) in Oslo, have been weighed separately. This was done because Bislett Kebab House refused to give any information concerning their products. Recipes were also added for mixed drinks, such as Caffè Latte, Caffè Mocca and Irish Coffee, after getting information about the proportions of the various ingredients used in different coffee shops in Oslo.

For Norwegian food items not included in Mat på data, the producers of the food items have been contacted to get a more detailed nutritional content than enlightened on the products. All obtained information about the nutritional content in different products has been added to the software program. If the producers didn't have more information about the nutritional content of the product, a similar product was used instead. For food items with a different composition of macronutrients than other similar products, such as Vita hjertego'-products, the food items have been added with a limited nutritional content.

For minced meat and some types of pure meat, only the nutrition contents in the raw meat were available in Mat på Data 5.0. Since the participants always ate these food products prepared, minced meat and some types of pure meat have been prepared several times and the food has been weighed at every step of the preparation to be able to calculate the nutrition content in 100 grams of prepared meat. For meat dishes, e.g. meat sauce and taco meat, the meat dishes have been prepared several times, and in each step of preparation the food has

been weighed. It has then been calculated how much of the water content in the food that has evaporated, and how much of the finished dish that is meat and how much that are other ingredients, such as spices or vegetables. The nutritional content of raw ingredients has then been used to calculate the total nutritional content of the finished dish, and this has been added to the software program. For other types of meat, like grilled chicken, chicken wings and chops with bone, the food item has been weighed in one piece and the meat, bone and skin or fat rim have been weighed separately, and the % of the total weight has been calculated for each part. This has been used to calculate the amount eaten when only the total weight or number has been recorded.

In the dietary records fruits and vegetables were often not weighed, rather only indicated by number and sometimes an estimated size, e.g. "two clementines" or "one large apple". In these occasions average weights, obtained by weighing several examples of a fruit or a vegetable, have been used. This was not exactly correct, but it was better than using randomly chosen weights for every dietary record not completed correctly. The fruits and vegetables used to get estimated averages have been acquired from different grocery stores in and nearby Oslo during a time period of three months (October 2011 to January 2012). See appendix 14 for averages used in the coding of the dietary records. For other types of food products and dishes, a picture book has been used to estimate the portion sizes.

All these efforts were made to be able to calculate the nutrient contents recorded in the best possible way. Despite this, some food products are missing values for the content of several of the micronutrients, and a good estimate of the intake of micronutrients can never be calculated using this software program. In addition many of the participants failed to record beverages, especially water, and the intake of fluids can therefore not be calculated accurately.

3.6 Declaration of Helsinki and ethical review

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. At the screening visit the subjects were given full and adequate verbal and written information (appendix 15) about the nature, purpose, possible risks and benefit of the study. The subjects had the opportunity to ask questions, and were given time for consideration. All subjects provided written informed consent before enrollment (appendix 15).

3.7 The student's tasks

In this study, the master student had the following tasks:

- Dietary counseling and measuring of body weight for the last 16 participants randomized in the main study (the participants screened in September and October 2011).
- Coding of dietary records and calculation of reported energy intake and intake of energy yielding nutrients for all participants randomized in the main study during 2011 (a total of 49 participants).
- Contacting restaurants and producers of different food items, in addition to preparing and weighing several food products to obtain as accurate information about the nutritional content as possible.
- Entering and coding of the case record forms into the EpiInfo software program for all participants randomized in the main study during 2011.
- Performing statistical analyses.

Coding of dietary records and case record forms for the first 31 participants randomized in the main study were performed by two former master students, Åshild Margrethe Lode and Edith Berntzen, in 2010.

4 Results

In this chapter there is first a brief description of the subject characteristics, screening failures and smoking cessation rates before the description of the outcomes on body weight, body composition and cardiovascular risk factors. Results from the dietary interventions and correlation analyses are described in the last part. All statistical analyses are performed with listwise exclusion of missing values unless otherwise stated.

4.1 Subject characteristics

4.1.1 Characteristics at the date of screening

The characteristics of the subjects in the study, at the date of screening, are given in table 3. A female predominance was seen, 58 women (72.5 %) and 22 men (27.5 %). On average, both men and women were 50 (SD 9) years of age, obese with a mean BMI of 31 (SD 4) kg/m^2, reported smoking 18 cigarettes per day, and were moderately nicotine-dependent (mean score of FTND was 4.8). However, compared with men, women had a lower mean height (mean difference -12.9 cm [95% CI -15.9, -9.9]), weight (mean difference -13.8 kg [95% CI -20.4, -7.1]) and waist circumference (mean difference -9.4 cm [95% CI -14.4, -4.3]). There were no other statistically significant differences for the rest of the characteristics at the date of screening.

Table 3: Characteristics and smoking status at the date of screening.

	Females	Males
N (%)	58 (72.5)	22 (27.5)
Age, years	50 ± 9	51 ± 9
Height, cm	167.7 ± 5.5	180.6 ± 7.2***
Weight, kg	87.8 ± 13.0	101.6 ± 14.1***
BMI, kg/m^2	31.1 ± 3.8	31.1 ± 3.2
Waist, cm [a]	98.7 ± 9.8	108.1 ± 10.8***
Hip, cm [b]	112.9 ± 9.0	110.8 ± 6.8
Systolic blood pressure, mmHg	126 ± 18	132 ± 15
Diastolic blood pressure, mmHg	80 ± 9	84 ± 10
Smoking status		
Cigarettes/day [c]	18 ± 6	20 ± 7
Nicotine dependence [d]	4.9 ± 1.9	4.5 ± 1.5

Values are means ± SD (standard deviation) or numbers (%) where specified. Statistically significant differences between males and females are indicated.
*** p<.001, Independent Samples T-Test
[a] Missing values for 1 female
[b] Missing values for 1 female and 1 male
[c] Missing values for 5 females and 1 male
[d] Estimated with Fagerström Test for Nicotine Dependence (FTND). Scores range from 1 to 10, with higher scores indicating greater nicotine dependence.

4.1.2 Characteristics at the date of randomization

Eighty participants were randomly assigned to the two intervention groups (see figure 1 for participant flow). After randomization, the gender distribution between the intervention groups was comparable with 12 (34.3%) males in the LFHCC group and 10 (22.2%) males in the HPMRC group (p=.23). There were no significant differences between the two intervention groups in any of the variables measured at randomization. A total of 71 (88.8%) participants were contacted and reached at the visit 12 weeks after their smoking cessation date. One of the participants was, unable to attend the visit, hence, measurements are missing for this person. However, since this person was reached by telephone and confirmed that she still wanted to participate in the study, she was not considered a drop out. There was no apparent difference in the relative number of participation (in percent) between the LFHCC and HPMRC groups (31 (88.6%) in the LFHCC group vs 40 (88.9%) in the HPMRC group, p=.67).

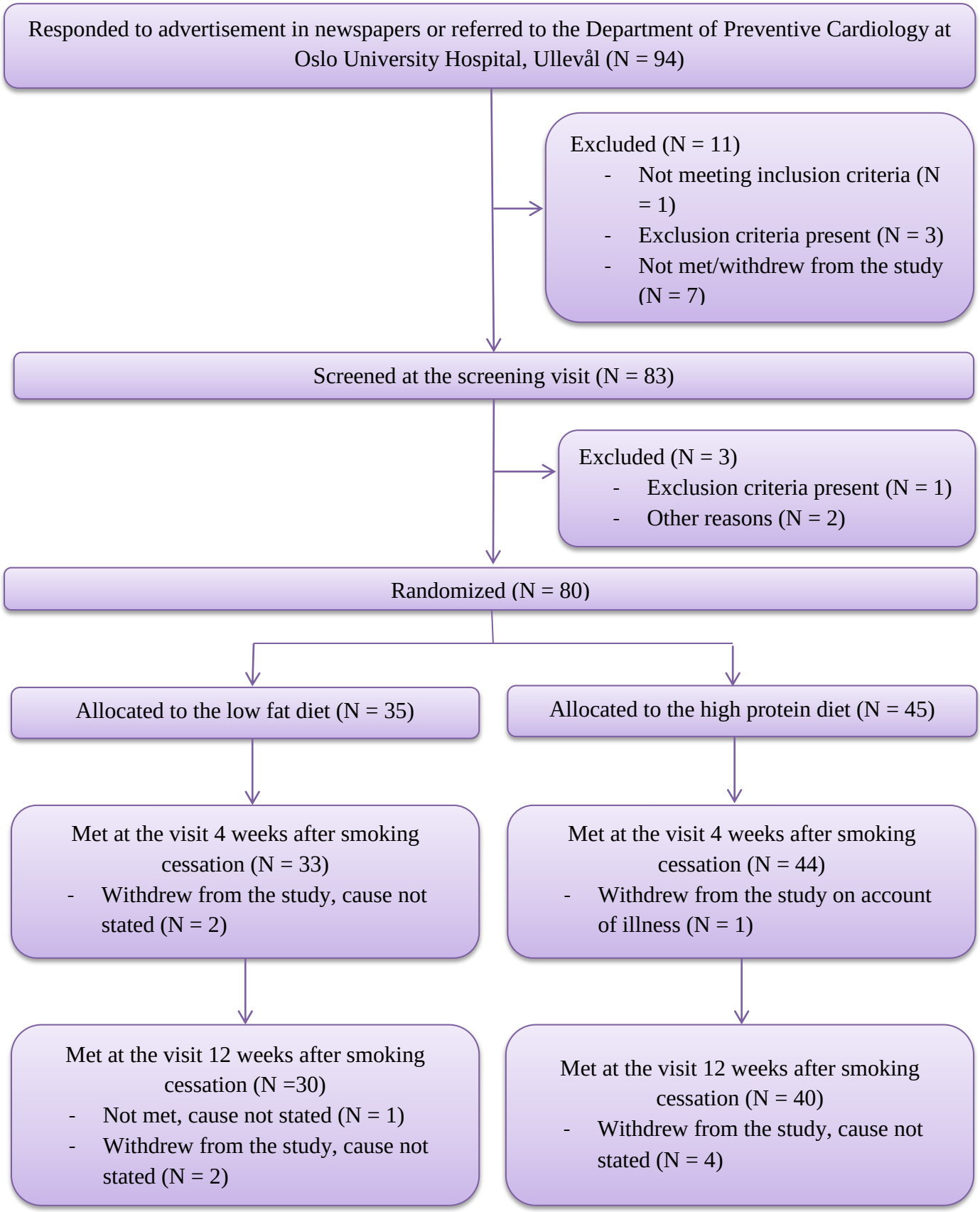


Figure 1: Flow diagram of the progress throughout the different phases of the trial.

4.1.3 Screening failures

One of the subjects included in the study had a BMI>40 (41.6 kg/m^2). Two of the included subjects were more than 65 years of age (66 and 68 years) at the time of the screening visit. One of the participants was not willing to take varenicline. Two of these 4 subjects were randomized to the LFHCC group, and the other two to the HPMRC group. Even though these 4 subjects did not meet all the inclusion criteria, they were still included in the analyses to not influence the randomization or restrict the sample size any further. The participant who did not wish to take varenicline informed that she did not smoke during the 12 weeks after smoking cessation, and this was supported by low CO-measurements at every visit post cessation.

4.1.4 Determination of smoking status

Mean score with Fagerström Test for Nicotine Dependence was 4.7 (SD 1.9) and 4.8 (SD 1.7) in the LFHCC group and the HPMRC group, respectively (p=.89). As a part of the inclusion criteria, at the screening visit all participants reported that they smoked at least 10 cigarettes per day. Furthermore, there was a significant decrease in mean cigarettes smoked daily from the date of screening to the date of randomization (mean difference -1 cigarette/day [95% CI -2, -0], p<.05). See table 4 for changes in number of daily cigarettes and measured CO from screening to randomization. In addition, at randomization the mean CO-measurements in the LFHCC group and the HPMRC group were comparable 16 ppm (SD 10) and 16 ppm (SD 8), respectively (p=.78). Moreover, at the randomization visit a total of 7 participants reported that they were smoking less than 10 cigarettes per day. Furthermore, at the date of randomization the mean number of cigarettes smoked daily were reported to be 18 (SD 8) in the LFHCC group, and 17 (SD 5) in the HPMRC group (p=.55).

Table 4: Smoking status for all participants at the date of screening and randomization

	Screening	Randomization	Difference from screening to randomization	
	Mean ± SD		Mean (95% CI)	p
CO, ppm (N = 45)	16 ± 8	16 ± 10	-.3 (-3.0, 2.4)	.82
Cigarettes, number (N = 74)	18 ± 6	17 ± 6	-1 (-2, -0)	**<.05**

Mean (95% confidence interval) differences from the date of screening to the date of randomization in CO-measurements and number of daily cigarettes. Analyses are performed with paired-samples t-test.
For 35 of the participants CO-measurements were not performed at the screening visit. For 6 of the participants information about number of daily cigarettes is missing at the date of screening.
Missing values are excluded listwise.
SD: standard deviation

4.2 Smoking cessation

4.2.1 Continuous abstinence rate and point prevalence

Drop-out participants were assumed smoking in all analyses. The one participant not able to physically meet at the 12 weeks visit reported to have been continuous abstinent from her smoking from the date of cessation, and was considered a non-smoker in all analyses. Of the 80 participants included in the study, 30 (37.5%) managed to be continuous abstinent all 12 weeks. There was no significant (p=.60) difference in the proportion of participants who were abstinent continuously for 12 weeks between the intervention groups, with 12 (34.3%) participants in the LFHCC group and 18 (40%) participants in the HPMRC group (figure 2).

Irrespective of intervention groups CAR for the first 4 weeks (weeks 1-4) was 47.5 % (38 participants), while 48 participants (60 %) were continuous abstinent the last 4 weeks (weeks 9-12). The 14-days point prevalence measured twelve weeks after smoking cessation was almost 69% (55 participants). The continuous abstinence rates at weeks 1-4, weeks 9-12 or weeks 1-12 were not significantly different between the intervention groups (figure 2). We found a significant higher proportion non-smokers among the participants with low nicotine-dependence (FTND score <4) than among the medium (FTND score 4-7) and high nicotine-dependent participants (FTND score ≥7) (12 weeks CAR 66.7%, 25.5% and 40.0%, respectively, p<.01).

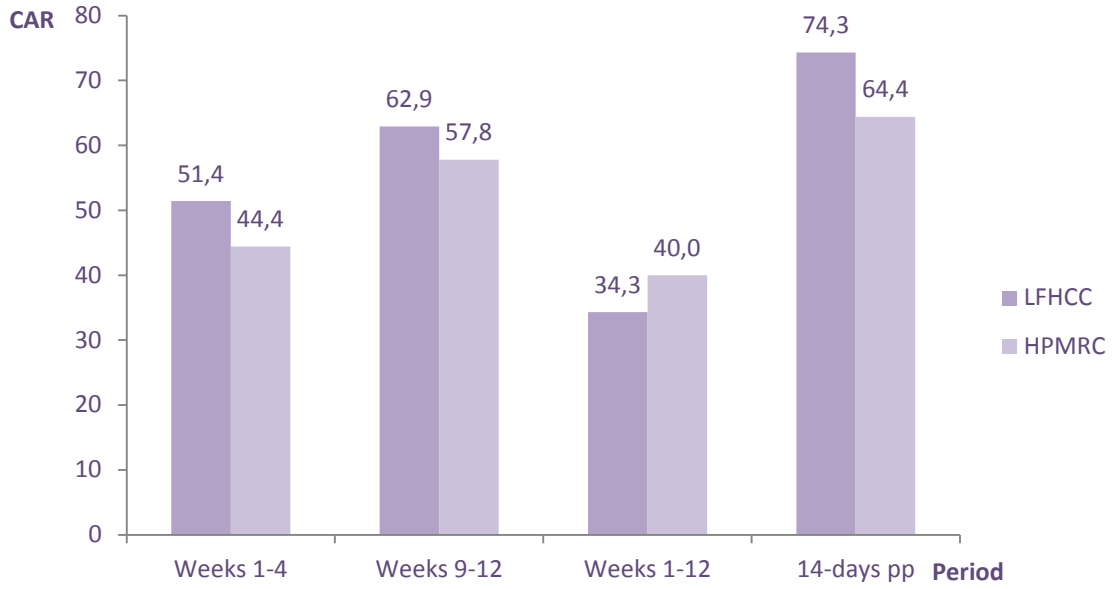


Figure 2: Abstinence rates in the two intervention groups.
Continuous abstinence rates (CAR) of the two dietary intervention groups, LFHCC (dark purple) and HPMRC (light purple) for the first four weeks (Weeks 1-4), for the last four weeks (Weeks 9-12) and for all twelve weeks (Weeks 1-12) after smoking cessation, and the 14-days point prevalence (14-days pp) of abstinence measured twelve weeks after smoking cessation. All values are percent nonsmokers in the different periods.
LFHCC: Low Fat diet High in Complex Carbohydrates
HPMRC: High Protein diet Moderately Reduced in Carbohydrates

4.2.2 CO measurements and reported number of cigarettes

Nonsmokers

Among the participants that reported not smoking at all during the last 12 weeks from their smoking cessation date, mean CO measurements at randomization were 15 (SD 8) ppm and 16 (SD 9) ppm in the LFHCC and the HPMRC groups, respectively. Twelve weeks after smoking cessation, the mean CO measurements were 2 (SD 1) ppm in the LFHCC group and 3 (SD 1) ppm in the HPMRC group.

Nonsmokers + reduced smokers

Regardless if the participants were abstinent or not, mean CO measurements in both the LFHCC group and the HPMRC group were 4 (SD 3) ppm at the 12 weeks visit. Mean number of cigarettes smoked during the last 14 days was less than 1 in the LFHCC group, and slightly higher than 4 in the HPMRC group (p=.09).

4.3 Outcome variables

4.3.1 Changes in body weight

Nonsmokers

As can be seen from table 5, the HPMRC group had a significant ($p<.01$) mean weight reduction of -1.7 kg (95% CI -2.6, -.7) four weeks after smoking cessation, but there was no significant between-group difference. There was no significant difference in change in body weight between the food intervention groups from randomization to 12 weeks after smoking cessation among the nonsmokers, or from four to twelve weeks after smoking cessation. A last measurement moved forward analysis was performed to include the participant in the LFHCC group as the participant was unable to meet at the last visit. There was no significant difference ($p=.48$) between the dietary intervention groups in change in body weight12 weeks post cessation after imputing missing values. An overview over the changes in body weight from the date of screening to twelve weeks after smoking cessation is given in figure 3. Among the nonsmokers there were no significant within-group changes in body weight in either of the two dietary intervention groups.

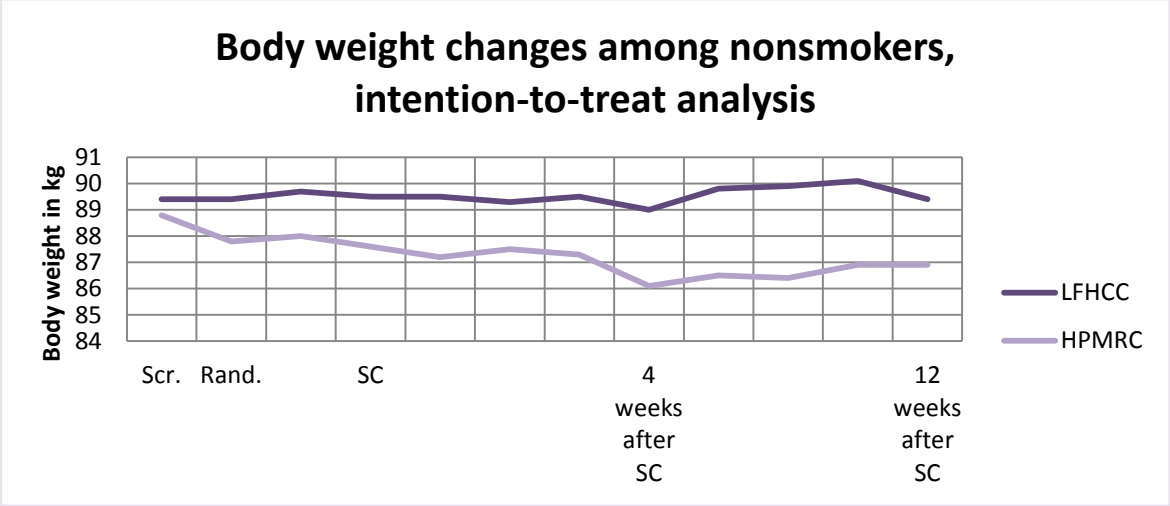


Figure 3: Body weight changes from the date of screening to twelve weeks after smoking cessation among the nonsmokers.
Mean body weight at every visit among the nonsmokers in the two dietary intervention groups, LFHCC (dark purple, N = 12) and HPMRC (light purple, N = 18), from the date of screening to twelve weeks after smoking cessation. Imputation of missing values with a last measurement moved forward method has been performed.
LFHCC: Low Fat diet High in Complex Carbohydrates
HPMRC: High Protein diet Moderately Reduced in Carbohydrates
Scr.: date of screening, Rand.: date of randomization, SC: date of smoking cessation

Table 5: Weight changes from the date of randomization to twelve weeks after smoking cessation, both among the completers and among all randomized subjects.

		LFHCC				HPMRC			Between-group differences					
		Randomization	4 weeks	12 weeks		Randomization	4 weeks	12 weeks	Randomization to 4 weeks		4 weeks to 12 weeks		Randomization to 12 weeks	
Nonsmokers	N	Mean ± SD			N	Mean ± SD			Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Body weight, completers	11	88.5 ± 10.6	88.2 ± 10.5	88.7 ± 9.3	18	87.8 ± 10.1	86.1 ± 9.3**	86.9 ± 9.3	1.2 (-.2, 2.6)	.08	-.3 (-1.9, 1.2)	.67	1.1 (-1.5, 3.6)	.40
Body weight, Intention-to-treat	12	89.4 ± 10.6	89.0 ± 10.4	89.4 ± 9.2	18	87.8 ± 10.1	86.1 ± 9.3**	86.9 ± 9.3	1.2 (-.2, 2.6)	.08	-.4 (-1.8, 1.1)	.61	.9 (-1.6, 3.3)	.48
Nonsmokers + reduced smokers														
Body weight, completers	30	91.7 ± 17.4	91.3 ± 17.8	92.3 ± 17.6	40	89.5 ± 12.1	88.1 ± 11.8***	88.7 ± 11.8	1.1 (.1, 2.1)	**.03**	.4 (-.5, 1.3)	.39	1.4 (-.1, 2.9)	.07
Body weight, Intention-to-treat	35	92.2 ± 16.8	92.0 ± 17.2	92.9 ± 17.0	45	89.5 ± 12.5	88.1 ± 12.3***	88.7 ± 12.6	1.1 (.1, 2.1)	**.03**	.3 (-.6, 1.1)	.54	1.4 (.0, 2.7)	.05

Mean between-group differences in body weight change from randomization to 4 weeks after smoking cessation, from 4 weeks to 12 weeks after smoking cessation and from randomization to 12 weeks after smoking cessation, all with p-values, are given. Independent-samples t-test is used on the within-group differences to test differences between groups.

The upper line for both nonsmokers and nonsmokers + reduced smokers shows the changes in body weight among the completers (those met at both the randomization visit and at the visit 12 weeks after smoking cessation), while the lower line, for both nonsmokers and nonsmokers + reduced smokers, shows an intention-to-treat analysis of changes in body weight, using a last measurement moved forward-approach for the non-completers.

** Significant within-group change from randomization, p<.01 (paired-samples t-test)

*** Significant within-group change from randomization, p<.001 (paired-samples t-test)

LFHCC: Low Fat diet High in Complex Carbohydrates

HPMRC: High Protein diet Moderately Reduced in Carbohydrates

SD: standard deviation

CI: confidence interval

Nonsmokers + reduced smokers

Among both nonsmokers and reduced smokers the HPMRC group had a significant (p=.03) greater reduction in body weight from the date of randomization to four weeks after smoking cessation (mean difference 1.1 [95% CI .1, 2.1]). Only the HPMRC group had a significant (p<.001) reduction in body weight from randomization to four weeks after smoking cessation (mean change -1.3 kg [95% CI -2.0, -.6]). No significant differences in body weight change were seen from randomization to 12 weeks, or from four to 12 weeks after smoking cessation. A last measurement moved forward-analysis was performed to include participants who had missed one or more of the visits. As can be observed from table 5, this analysis had a borderline p-value of .05 for the difference in body weight change between the groups (mean difference 1.4 kg [95% CI -.0, 2.7]) from the date of randomization to twelve weeks after smoking cessation. There was a significant (p=.03) difference in body weight change between the two groups from the date of randomization to four weeks after smoking cessation, but no significant difference from four to twelve weeks after smoking cessation. An overview over the changes in body weight from the date of screening to twelve weeks after smoking cessation is given in figure 4. Neither of the two intervention groups showed a significant within-group change in body weight from randomization to 12 weeks after smoking cessation. In the LFHCC group, mean difference in body weight from randomization to 12 weeks after smoking cessation was .6 kg (95% CI -.5, 1.7), p=.29. In the HPMRC group, the corresponding mean difference in body weight was -.8 kg (95% CI -1.8, .2), p=.13.

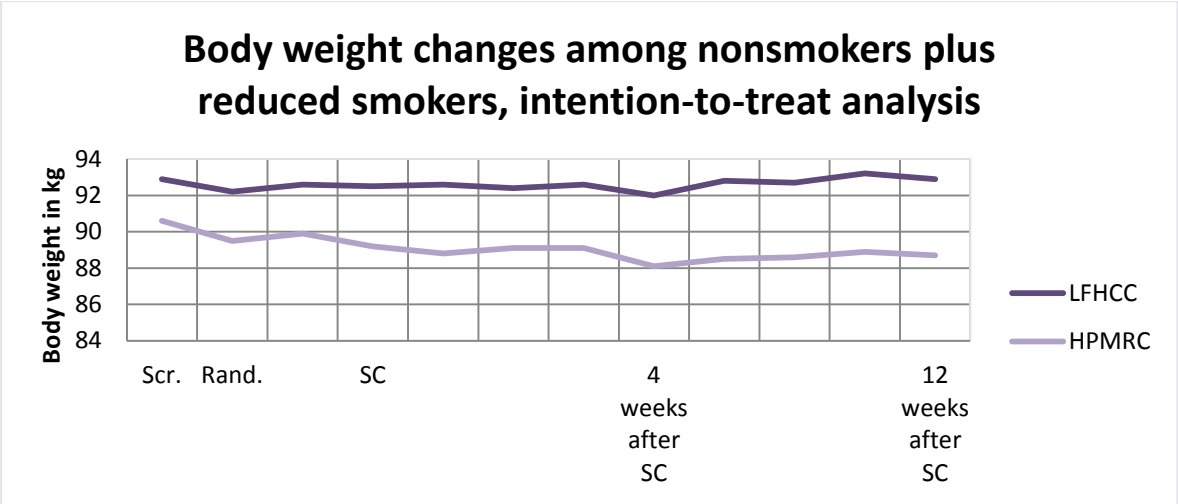


Figure 4: Body weight changes from the date of randomization to twelve weeks after smoking cessation among nonsmokers + reduced smokers.
Mean body weight at every visit among all participants in the two dietary intervention groups, LFHCC (dark purple, N = 35) and HPMRC (light purple, N = 45), from the date of screening to twelve weeks after smoking cessation. Imputation of missing values with a last measurement moved forward method has been performed.
LFHCC: Low Fat diet High in Complex Carbohydrates
HPMRC: High Protein diet Moderately Reduced in Carbohydrates
Scr.: date of screening, Rand.: date of randomization, SC: date of smoking cessation

4.3.2 Changes in body composition

Nonsmokers

As seen from table 6, the body fat % increased in the LFHCC group compared to the HPMRC group (mean difference 1.4 [95% CI .0, 2.7], p=.04). There were no other significant differences in changes in body composition between the LFHCC group and the HPMRC group from the date of randomization to 12 weeks post cessation. Within the HPMRC group there was a mean decrease in waist circumference of -4.2 cm (95% CI -6.0, -2.4), p<.001, from randomization to 12 weeks after smoking cessation. In addition, this group had a mean decrease in waist/hip-ratio of -.04 (95% CI -.06, -.02), p<.01. There were no significant changes in the LFHCC group.

Table 6: Mean values and changes from randomization to 12 weeks after smoking cessation for the participants with 12 weeks continuous abstinence

	LFHCC (N = 11)		HPMRC (N = 18)		Between-group difference	
	Randomization	**12 weeks**	**Randomization**	**12 weeks**		
	Mean (95% CI)		Mean (95% CI)		Mean (95% CI)	p
BMI, kg/m^2	29.9 (27.9, 31.9)	29.9 (28.3, 31.5)	30.4 (28.9, 31.9)	30.1 (28.7, 31.6)	.3 (-.5, 1.2)	.42
Waist, cm [a]	100.8 (94.2, 107.4)	97.9 (91.7, 104.1)	101.4 (97.9, 104.9)	97.2 (93.6, 100.8)***	1.3 (-2.4, 5.1)	.48
Hip, cm [a]	110.5 (104.5, 116.4)	109.4 (104.8, 113.9)	107.5 (104.0, 111.0)	107.1 (104.6, 109.7)	-.7 (-4.2, 2.9)	.70
Waist/hip-ratio [a]	.92 (.85, .98)	.90 (.84, .95)	.94 (.91, .98)	.91 (.87, 94)**	.02 (-.01, .05)	.24
Body Fat, %	34.6 (30.1, 39.0)	35.3 (31.4, 39.2)	36.9 (32.8, 41.1)	36.3 (32.0, 40.6)	1.4 (.0, 2.7)	**.04**
Muscle Mass, kg	32.2 (28.9, 35.4)	31.9 (28.8, 35.0)	31.0 (27.8, 34.1)	31.4 (28.3, 34.5)	-.7 (-2.5, 1.1)	.42
Systolic blood pressure, mmHg	109 (100, 117)	109 (99, 118)	116 (110, 121)	116 (109, 123)	-0 (-7, 6)	.91
Diastolic blood pressure, mmHg	74 (68, 79)	72 (67, 76)	77 (73, 82)	76 (71, 82)	-1 (-5, 4)	.52
Biochemical measures						
Glucose, mmol/L	5.3 (4.8. 5.7)	5.3 (5.1, 5.6)	5.5 (5.2, 5.7)	5.7 (5.4, 5.9)	-.1 (-.5, .2)	.53
Total cholesterol, mmol/L	4.7 (4.0, 5.4)	4.8 (4.3, 5.3)	5.8 (5.3, 6.3)	5.6 (5.1, 6.1)	.4 (-.3, 1.0)	.29
HDL, mmol/L	1.27 (.96, 1.57)	1.41 (1.04, 1.77)*	1.49 (1.26, 1.72)	1.68 (1.42, 1.94)**	-.05 (-.22, .11)	.52
LDL, mmol/L [a]	2.80 (2.11, 3.49)	2.65 (2.17, 3.13)	3.54 (3.08, 4.00)	3.14 (2.79, 3.49)	.25 (-.39, .90)	.43
Triglycerides, mmol/L	1.38 (.90, 1.86)	1.64 (.85, 2.43)	1.97 (.75, 3.18)	1.76 (.74, 2.77)	.47 (-.10, 1.03)	.10
Median (Q_1, Q_3)	1.24 (.52, 2.13)	1.12 (.73, 2.69)	1.13 (.92, 2.31)	1.24 (.82, 1.69)		

Estimates are mean (95% confidence interval) unless otherwise stated.

Mean between-group differences in change from randomization to 12 weeks after smoking cessation (LFHCC group – HPMRC group) with p-values are given. Independent-samples t-test is used on the within-group differences to test differences between groups.

LFHCC: Low Fat diet High in Complex Carbohydrates

HPMRC: High Protein diet Moderately Reduced in Carbohydrates

* Significant change from randomization to 12 weeks after smoking cessation. p<.05, paired-samples t-test

** Significant change from randomization to 12 weeks after smoking cessation. p<.01, paired-samples t-test

*** Significant change from randomization to 12 weeks after smoking cessation. p<.001, paired-samples t-test

[a] N = 17 in the high protein group. Missing values are excluded listwise.

Nonsmokers + reduced smokers

Table 7 shows that when smoking status is not taken into account, waist circumference was more reduced in the HPMRC group compared to the LFHCC group (mean between-group difference 2.3 cm [95% CI .2, 4.4], p=.03) from randomization to 12 weeks after smoking cessation. In addition, there was a significant difference (p=.04) in the change in body fat % (mean difference .9 [95% CI .0, 1.9]) between the groups. Within the HPMRC group there was a mean decrease in waist circumference of -3.6 cm (95% CI -4.9, -2.2), p<.001, from the date of randomization to 12 weeks after smoking cessation.

4.3.3 Changes in cardiovascular risk factors

Nonsmokers

Table 6 also shows that there were no significant differences between the two groups of nonsmokers in the change in cardiovascular risk factors. Both groups had a significant within-group increase in mean HDL cholesterol, from 1.27 mmol/L (95% CI .96, 1.57) to 1.41 (95% CI 1.04, 1.77), p<.05 for the LFHCC group, and from 1.49 (95% CI 1.26, 1.72) to 1.68 (1.42, 1.94), p<.01 for the HPMRC group. There were no significant within-group changes in the other cardiovascular risk factors.

Nonsmokers + reduced smokers

When including all participants, regardless if they were abstinent from smoking or not, there was a significant (p=.03) difference between the groups in change in TG with a mean difference of .32 mmol/L (95% CI .03, .62) from the date of randomization to 12 weeks after smoking cessation. There were no other between-group differences in cardiovascular risk factors.

Table 7: Mean values and changes from randomization to 12 weeks after smoking cessation in nonsmokers plus reduced smokers.

	LFHCC (N = 30)		HPMRC (N = 40)		Between-group difference	
	Randomization	12 weeks	Randomization	12 weeks		
	Mean (95% CI)		Mean (95% CI)		Mean (95% CI)	p
BMI, kg/m^2 [a]	30.7 (29.4, 32.1)	30.9 (29.6, 32.3)	30.6 (29.5, 31.7)	30.3 (29.2, 31.3)	.5 (-.1, 1.0)	.08
Waist, cm [b]	104.4 (99.5, 109.3)	103.1 (98.1, 108.2)	101.1 (97.9, 104.2)	97.5 (94.6, 100.4)***	2.3 (.2, 4.4)	**.03**
Hip, cm [b]	110.6 (107.2, 114.0)	109.6 (106.6, 112.7)	109.7 (107.1, 112.4)	108.2 (105.5, 111.0)	.5 (-1.8, 2.9)	.65
Waist/hip-ratio [b]	.95 (.91, .98)	.94 (.90, .98)	.92 (.90, .95)	.90 (.88, .93)*	.02 (-.01, .04)	.17
Body Fat, % [c]	35.5 (33.2, 37.8)	36.1 (33.9, 38.3)	36.3 (33.4, 39.1)	35.9 (33.1, 38.7)	.9 (.0, 1.9)	**.04**
Muscle Mass, kg [c]	33.0 (30.3, 35.8)	32.8 (30.1, 35.6)	32.0 (29.8, 34.2)	32.1 (29.9, 34.3)	-.3 (-1.1, .5)	.43
Systolic blood pressure, mmHg	115 (109, 121)	114 (108, 120)	117 (112, 122)	116 (112, 120)	0 (-5, 5)	.96
Diastolic blood pressure, mmHg	79 (76, 83)	78 (74, 82)	79 (76, 82)	78 (75, 81)	0 (-3, 3)	.98
Biochemical measures						
Glucose, mmol/L [d]	6.0 (5.4, 6.7)	6.1 (5.5, 6.7)	5.4 (5.3, 5.6)	5.6 (5.4, 5.7)*	-.2 (-.5, .2)	.41
Total cholesterol, mmol/L	5.3 (4.9, 5.8)	5.5 (5.1, 6.0)	5.5 (5.1, 5.9)	5.4 (5.1, 5.8)	.3 (-.1, .6)	.20
HDL, mmol/L	1.24 (1.10, 1.38)	1.37 (1.22, 1.52)***	1.42 (1.28, 1.56)	1.58 (1.43, 1.73)***	-.03 (-.12, .06)	.49
LDL, mmol/L [e]	3.38 (2.95, 3.81)	3.35 (2.93, 3.77)	3.38 (3.03, 3.73)	3.20 (2.90, 3.51)	.14 (-.21, .49)	.42
Triglycerides, mmol/L	1.58 (1.24, 1.91)	1.75 (1.34, 2.16)	1.63 (1.09, 2.17)	1.49 (1.02, 1.96)	.32 (.03, .62)	**.03**
Median (Q_1, Q_3)	1.37 (.99, 1.90)	1.27 (1.01, 2.55)	1.19 (.92, 1.76)	1.16 (.82, 1.60)		

Estimates are mean (95% confidence interval) unless otherwise stated. Missing values are excluded listwise.

Mean between-group differences in change from randomization to 12 weeks after smoking cessation (LFHCC group – HPMRC group) with p-values are given. Independent-samples t-test is used on the within-group differences to test differences between groups.

LFHCC: Low Fat diet High in Complex Carbohydrates

HPMRC: High Protein diet Moderately Reduced in Carbohydrates

* Significant change from randomization to 12 weeks after smoking cessation. p<.05, paired-samples t-test

*** Significant change from randomization to 12 weeks after smoking cessation. p<.001, paired-samples t-test

[a] Missing values for 1 participant in the high protein group (N = 39)

[b] Missing values for 2 participants in the high protein group (N = 38)

[c] Missing values for 3 participants in the high protein group (N = 37)

[d] Missing values for 1 participant in the low fat group (N = 29)

[e] Missing values for 1 participant in the low fat group (N = 29) and 1 participant in the high protein group (N = 39)

4.4 Dietary intervention

A total of 9 participants were not included in the dietary intervention analysis. This was due to at least one missing dietary record for these participants; one participant did not deliver any of the two records, one participant did not deliver the first record, three participants withdrew from the study before the second recording, and four records were missing from the journals.

4.4.1 Dietary changes

Nonsmokers

Among the 30 participants who were 12 weeks continuous abstinent from smoking, 28 turned in dietary records both at randomization and 4 weeks after their date of smoking cessation.

The HPMRC group had a greater reduction in carbohydrate intake than the LFHCC group (mean difference 52 g [95% CI 6, 98], p=.03). There were no significant differences between the within-group changes in daily intake of protein (mean difference -9 g [95% CI -30, 13], p=.42) or fat (mean difference -9 g [95% CI -29, 12], p=.39). As seen from table 8, there were several significant between-group differences in the changes in energy %.

The dietary records conducted before randomization and four weeks after smoking cessation in the LFHCC group, showed that this group had several significant within-group changes in their diet (see table 8). This intervention group had a significant mean reduction in daily intake of fat, with a mean difference of -24 g (95% CI -37, -11), p<.01. The mean differences in daily intake of carbohydrate and protein were -7 g (95% CI -43, 28), p=.66, and 5 g (95% CI -21, 30), p=.70, respectively. The LFHCC group had a significant increase in fiber from randomization to four weeks after smoking cessation, and the mean intake of fiber was equivalent to an increase from 2.3 g/MJ (SD .8) to 3.4 g/MJ (SD 1.3).

Table 8 also shows that the HPMRC group had several significant within-group changes in their reported diet, including a significant reduction in reported energy intake from 1814 kcal to 1475 kcal. This group had a mean increase in daily protein intake of 13 g (95% CI 3, 23), p<.05. Mean difference in daily intake of carbohydrates was -60 g (95% CI -89, -30), p<.01. Mean reduction in intake of fat was -15 g (95% CI -29, -2), p<.05. The intake of fiber did not

change significant in this intervention group from the date of randomization to 4 weeks after smoking cessation (2.4 g/MJ [SD .7] and 2.4 g/MJ [SD .6], respectively, p=.91).

Table 8: Results from dietary records and indirect calorimetry for the participants with 12 weeks continuous abstinence

	LFHCC (N = 10)		HPMRC (N = 18)		Difference between groups	
	Randomization	4 weeks	Randomization	4 weeks		
	Mean ± SD		Mean ± SD		Mean (95% CI)	p
Days	6.0 ± 1.7	6.4 ± .8	6.3 ± 1.7	6.3 ± 1.1	.5 (-1.3, 2.2)	.60
Kcal	1860 ± 389	1671 ± 685	1814 ± 697	1475 ± 377*	149 (-310, 608)	.51
Energy %						
Protein	17.1 ± 1.9	20.2 ± 3.3*	19.2 ± 3.7	26.7 ± 4.2***	-4.5 (-7.9, -1.1)	**.01**
Fat	37.5 ± 4.9	27.4 ± 5.6**	38.2 ± 5.0	38.4 ± 4.9	-10.2 (-15.6, -4.8)	**<.01**
Saturated fat	16.2 ± 3.0	10.2 ± 2.9***	15.0 ± 2.0	13.4 ± 2.2*	-4.5 (-6.9, -2.1)	**<.01**
Monounsaturated fat	12.9 ± 2.1	9.5 ± 2.3***	13.3 ± 2.5	13.7 ± 2.3	-3.8 (-6.1, -1.6)	**<.01**
Polyunsaturated fat	5.6 ± 1.3	5.2 ± 1.2	6.8 ± 2.1	7.5 ± 2.8	-1.2 (-3.5, 1.2)	.31
Carbohydrate	41.0 ± 6.3	45.8 ± 7.3	36.4 ± 4.8	28.3 ± 6.2***	12.9 (8.1, 17.6)	**<.001**
Fiber	1.9 ± .6	2.7 ± 1.0*	1.9 ± .6	1.9 ± .5	.9 (.3, 1.4)	**.01**
Added sugar	7.8 ± 5.1	5.6 ± 3.7	5.7 ± 3.7	3.0 ± 1.9**	.6 (-2.7, 3.8)	.73
Alcohol	2.5 ± 3.9	4.4 ± 5.6	4.3 ± 3.0	4.7 ± 4.9	1.5 (-2.9, 5.8)	.50
Resting metabolic rate (RMR) and under reporting						
RMR	1683 ± 240	1672 ± 253	1983 ± 521	1699 ± 280*	272 (31, 513)	**.03**
Kcal/RMR	1.14 ± .25	1.02 ± .34	.92 ± .30	.88 ± .24	-.09 (-.33, .16)	.48

Estimates are mean ± SD (standard deviation). Differences are mean (95% confidence interval).

Difference between groups in change from randomization to 4 weeks after smoking cessation (LFHCC group – HPMRC group). Independent-samples t-test is used on the within-group differences to test differences between groups.

LFHCC: Low Fat diet High in Complex Carbohydrates

HPMRC: High Protein diet Moderately Reduced in Carbohydrates

RMR: Resting metabolic rate

* Significant change from randomization to 4 weeks after smoking cessation. p<.05, paired-samples t-test

** Significant change from randomization to 4 weeks after smoking cessation. p<.01, paired-samples t-test

*** Significant change from randomization to 4 weeks after smoking cessation. p<.001, paired-samples t-test

Nonsmokers + reduced smokers

Dietary intake data and RMR for all participants, regardless of their smoking status, are shown in table 9. A significant difference between the LFHCC group and the HPMRC group in the mean within-group change in intake of carbohydrate (mean difference 73 g [95% CI 46, 100], p<.001) was seen. The LFHCC group had a significant smaller increase in mean daily protein intake than the HPMRC group, with a mean difference of -12 g (95% CI -24, -1), p=.03. The reduction in daily fat intake in the LFHCC group was not significantly larger than the reduction in the HPMRC group (mean difference -8 g [95% CI -20, 4], p=.20).

The dietary records conducted before randomization and four weeks after smoking cessation in the LFHCC group, showed that this group significantly (p<.001) reduced the mean intake of fat, with a mean difference of -26 g (95% CI -35, -17). The LFHCC group had no significant within-group changes in mean daily intakes of carbohydrate (mean difference 3 g [95% CI -17, 24], p=.75), or protein (mean difference 4 g [95% CI -5, 14], p=.36). The increased mean daily intake of fiber was equivalent to an increase from 2.4 g/MJ (SD .9) to 3.4 g/MJ (SD 1.3), p<.001 .

The dietary records conducted in the HPMRC group showed that this group had a significant (p<.001) mean increase in daily intake of protein, with a mean difference of 17 g (95% CI 10, 24). There was a mean reduction in the daily intake of fat of -18 g (95% CI -27, -10), p<.001. This was also the case for daily intake of carbohydrates, with a mean difference of -70 g (95% CI -88, -51), p<.001. Mean daily intake of fiber in g/MJ changed from 2.4 (SD .6) to 2.7 (SD .9) in the HPMRC group, p<.05.

The reported and intended intake of macronutrients among nonsmokers plus reduced smokers in both dietary intervention groups are shown in table 10.

Table 9: Results from dietary records and indirect calorimetry for the participants who completed at both measurement times (randomization and 4 weeks after smoking cessation).

	LFHCC (N = 29)		HPMRC (N = 42)		Difference between groups	
	Randomization	4 weeks	Randomization	4 weeks		
	Mean ± SD		Mean ± SD		Mean (95% CI)	p
Days	5.7 ± 2.0	6.1 ± 1.1	6.1 ± 1.4	5.9 ± 1.5	.5 (-.5, 1.5)	.32
Kcal	1838 ± 511	1644 ± 561*	1851 ± 639	1481 ± 536***	175 (-53, 404)	.13
Energy %						
Protein	17.7 ± 2.6	20.8 ± 3.2***	18.6 ± 3.9	27.9 ± 5.2***	-6.2 (-8.3, -4.1)	**<.001**
Fat	38.3 ± 5.6	28.1 ± 6.3***	37.9 ± 6.0	36.6 ± 6.2	-8.8 (-12.8, -4.8)	**<.001**
Saturated fat	15.6 ± 3.3	10.4 ± 3.3***	15.2 ± 3.1	12.7 ± 3.2***	-2.7 (-4.6, -.8)	**.01**
Monounsaturated fat	13.4 ± 3.2	9.5 ± 2.5***	13.3 ± 3.3	13.3 ± 3.0	-3.9 (-5.9, -2.0)	**<.001**
Polyunsaturated fat	6.0 ± 1.5	5.5 ± 1.7	6.4 ± 1.7	7.1 ± 2.4	-1.2 (-2.4, -.04)	**.04**
Carbohydrate	38.4 ± 7.5	44.7 ± 6.5***	38.6 ± 6.8	29.1 ± 7.4***	15.7 (11.8, 19.6)	**<.001**
Fiber	1.9 ± .7	2.8 ± 1.0***	1.9 ± .5	2.2 ± .7*	.6 (.2, .9)	**<.01**
Added sugar	6.8 ± 5.2	5.7 ± 4.1	6.8 ± 5.2	2.9 ± 2.0***	2.8 (.4, 5.2)	**.02**
Alcohol	3.7 ± 4.9	3.9 ± 4.9	2.9 ± 3.2	4.4 ± 5.3*	-1.3 (-3.6, .9)	.24
Resting metabolic rate (RMR) and under reporting						
RMR [a]	1889 ± 560	1815 ± 423	1891 ± 401	1752 ± 287*	65 (-98, 228)	.43
Kcal/RMR	1.03 ± .33	.93 ± .27	.99 ± .33	.84 ± .27**	.04 (-.10, .19)	.54

Estimates are mean ± SD (standard deviation). Differences between groups are mean (95% confidence interval).

Difference between groups in change from randomization to 4 weeks after smoking cessation (LFHCC group – HPMRC group). Independent-samples t-test is used on the within-group differences to test differences between groups.

LFHCC: Low Fat diet High in Complex Carbohydrates

HPMRC: High Protein diet Moderately Reduced in Carbohydrates

RMR: Resting metabolic rate

* Significant change from randomization to 4 weeks after smoking cessation. p<.05, paired-samples t-test

** Significant change from randomization to 4 weeks after smoking cessation. p<.01, paired-samples t-test

*** Significant change from randomization to 4 weeks after smoking cessation. p<.001, paired-samples t-test

[a] N = 31 in the LFHCC group, and N = 43 in the HPMRC group

Table 10: Intended and reported intake of macronutrients in the two intervention groups four weeks after smoking cessation (nonsmokers + reduced smokers).

	LFHCC		HPMRC	
	Intended	Reported	Intended	Reported
	g (E%)		g (E%)	
Fat	≤55 (≤30)	54 (28)	≤ 91(≤55)	62 (37)
Protein	≤82 (≤20)	83 (21)	≥93 (≥25)	99 (28)
Carbohydrate	≥206 (≥50)	179 (45)	≤74 (≤20)	106 (29)

Intended and reported intake of macronutrients in grams and energy % among nonsmokers plus reduced smokers. Intended intake has been calculated from reported energy intake and planned composition of macronutrients in energy %.
LFHCC: Low Fat diet High in Complex Carbohydrates
HHPMRC: High Protein diet Moderately Reduced in Carbohydrates.
g: gram, E%: energy %

4.4.2 Misreporting

Nonsmokers

Among the nonsmokers there was no significant difference between the two intervention groups in misreporting at the date of randomization (data not shown). Table 8 shows that the change in misreporting of energy intake from the date of randomization to four weeks after smoking cessation not was significant different between the LFHCC and the HPMRC groups. However, the HPMRC group had a significant (p=.03) greater reduction in RMR from the date of randomization to four weeks after smoking cessation than the LFHCC group (mean difference 272 kcal [95% CI 31, 513]).

In the LFHCC group there were no significant changes in either misreporting or RMR. There was no significant change in misreporting in the HPMRC group, but this group had a significant (p<.05) decrease in measured RMR (from 1983 kcal to 1699 kcal).

Nonsmokers + reduced smokers

There was no significant difference in misreporting between the LFHCC and the HPMRC group at randomization (data not shown). Table 9 shows that there were no significant differences between the two intervention groups in mean change from randomization to 4 weeks after smoking cessation, neither in misreporting nor in measured RMR.

Furthermore, within the LFHCC group there were no significant changes in misreporting or measured RMR from randomization to 4 weeks after smoking cessation. In the HPMRC

group there was a significant (p<.01) change in misreporting, with a change in estimated intake/measured RMR-rate from .99 (95% CI .89, 1.10) at the date of randomization to .84 (95% CI .76, .93) four weeks after smoking cessation. The HPMRC group also had a significant (p<.05) decrease in measured RMR from before to after smoking cessation (from 1891 kcal to 1752 kcal).

4.4.3 Correlations between changes in body weight and dietary changes

Nonsmokers (weeks 1-4)

Among the participants who managed to be abstinent from their smoking the first four weeks after smoking cessation (weeks 1-4), there was a positive correlation between change in body weight and the reported change in daily intake of carbohydrate (r = .51, p=.02) in the HPMRC group four weeks after smoking cessation. There were no significant correlations between the change in body weight and the reported changes in dietary intake in the LFHCC group (see table 11). There were no correlations between changes in energy % and change in body weight in any of the dietary intervention groups (data not shown).

Nonsmokers + reduced smokers

Among all participants, regardless of their smoking status, there was a positive correlation between the change in body weight from randomization to four weeks after smoking cessation and the reported change in daily intake of protein (r = .36, p=.02) in the HPMRC group. In this intervention group there was also a positive correlation between the change in body weight and the reported change in daily intake of fat (r = .39, p=.01) four weeks after smoking cessation. There were no correlations between the change in body weight and the reported changes in dietary intake in the LFHCC group four weeks after smoking cessation (see table 11). There were no correlations between changes in energy % and change in body weight in any of the dietary intervention groups (data not shown).

Table 11: Correlations between changes in mean daily intake of macronutrients and change in body weight from randomization to four weeks after smoking cessation.

	LFHCC		HPMRC	
	r	p	r	p
Nonsmokers	N = 17		N = 20	
Carbohydrate, g	.01	.98	.51	**.02**
Fat, g	.19	.46	.42	.07
Protein, g	-.09	.74	.18	.44
Nonsmokers + reduced smokers	N = 29		N = 42	
Carbohydrate, g	.11	.59	.29	.06
Fat, g	.15	.44	.39	**.01**
Protein, g	-.11	.56	.36	**.02**

r: Pearson correlation

p: p-value

LFHCC: Low Fat diet High in Complex Carbohydrates

HPMRC: High Protein diet Moderately Reduced in Carbohydrates

5 Discussion

In this chapter the discussion of subjects and methods will precede the discussion of the results.

5.1 Discussion of subjects and methods

5.1.1 Subjects

Gender

In this study there was a female predominance (72.5 % women). One reason for this may be that women are more concerned than men about gaining weight after quitting smoking[149,150], and that they were therefore more willing to participate in a smoking cessation trial with intention to prevent undesired weight gain. All subjects in the current study were randomized to the intervention groups. Proper randomization reduces selection bias at trial entry and is the crucial component of high quality randomized controlled trials[151]. Randomization has therefore minimized the chances that any significant differences at the date of screening have affected any of the outcomes.

Screening failures

Despite that four of the eighty subjects randomized did not meet all the inclusion criteria and of these, only three completed the trial and one managed to be continuous abstinent, they were all included in the analyses. This was done since any analysis which omits patients is open to bias because it no longer compares the groups as randomized[152]. The one participant who did not wish to take varenicline was moderately nicotine dependent with a FTND score of 4, and at the screening visit she reported to be smoking 13 cigarettes daily. Twelve weeks after smoking cessation, her body weight was increased by 3.9 kg since the date of randomization. She managed to be continuous abstinent from her smoking all twelve weeks without taking varenicline. This may be due to a high motivation to quit cigarette smoking, and it is also possible that she was prepared for and accepted some weight gain during the first post cessation period, and therefore did not relapse despite an increase in body weight. One of the two participants over the age of 65 years at the screening visit was randomized to

the LFHCC group, while the other was randomized to the HPMRC group. Neither of them managed to stop smoking, and both were included as smokers in all analyses of abstinence rates. The fact that these participants not managed to be abstinent is not likely to be due to their age, since it has previously been shown that abstinence rates for people ≥ 60 years are not different from abstinence rates for people < 60 years[153]. It is also shown that sarcopenia, defined as the gradual reduction in skeletal muscle mass and strength observed with advancing age, increases with age and current smoking[154]. In addition, it is known that blood pressure and the prevalence of hypertension tends to increase with advancing age[155]. However, the two participants older than 65 years in the current study did not have any outlier values for muscle mass or blood pressure, and it is therefore not likely that the higher age of the two participants have influenced the data. There was also a female participant with BMI > 40 kg/m^2 included in the current study. She was not continuous abstinent all 12 weeks, only the last four weeks (weeks 9-12). Despite this, 12 weeks after smoking cessation she had lost 4.3 kg since the date of randomization. It is previously reported that blood pressure, fasting blood glucose and lipids, in addition to underreporting of energy intake, increases with increasing BMI[156,157]. The participant with the highest BMI in the current study had normal blood pressure (<120/80 mmHG), glucose and lipids, and underreported less than the mean level of underreporting in the current study. We therefore concluded that including this participant would have affected outcomes only marginally.

Study completion and drop-outs

Eight women and two men did not meet at the visit 12 weeks after smoking cessation. One of the women met at the 6 months visit (this visit was not included in the current master thesis), and hence she was not considered a drop-out. In addition to these well-defined factors that could influence the results, other and to us unknown factors may also exist that may have influenced the results.

Almost 90% of the participants completed the study for 12 weeks, with no difference in completion-rate between the intervention groups. Previous smoking cessation trials have study-completion rates ranging from approximately 50 to 90 percent in trials with study duration of three months up to one year[107,108,135,137,138]. These trials included a significant higher number of subjects than the current study, ranging from almost 400 to over 1200 randomized participants.

Study-completion rates in previous dietary intervention trials range from 58 to almost 100 percent in trials with study duration of three months up to one year[115,117,118,158,159]. The number of participants in these trials ranged from 65 to over 800. The trials with shortest duration (3 months) included approximately 200 and 800 participants, and had a study-completion of 94% and almost 100%, respectively[115,159]. Compared to these trials, the current study had a lower completion rate. A possible reason for this is that the current study combined a dietary intervention with a smoking cessation intervention, which contributed to a greater burden on the participants. It must also be considered that random outliers will have greater impact on the results in studies with small size, as we have here.

5.1.2 Study design and measurements

Assessment of smoking status

The main purpose of this study was to assess the effect of two different dietary interventions on preventing undesired weight gain 12 weeks after smoking cessation. Since it is shown that the combination of counseling and medication is more effective than either alone[100], conditions in the current study were therefore set for increasing the participants' opportunities to be able to stop smoking.

Smoking diaries concern normally self-reported smoking status, and it is previously shown that accurate estimates of the prevalence of cigarette smoking can be derived from self-reported data on smoking status[160]. Different variants of smoking diaries have been used in previous trials assessing smoking status[161,162]. To assess smoking status, we calculated CAR and point prevalence based on smoking diaries and CO-measurements. CAR, defined as no smoking at all based on self-reported cigarettes per day and CO-measurements, has been calculated for all twelve consecutive weeks. All participants who reported to be abstinent the first 12 weeks after their smoking cessation dates, confirmed by CO-measurements, have been included in the analyses as nonsmokers. Using a combination of self-report and an objective biochemical measurement to assess smoking status has minimized the chances of misclassification of participants as nonsmokers.

Another method often used to confirm smoking status is cotinine. Cotinine is the major metabolite of nicotine and have a higher sensitivity and specificity than CO, and can be measured in plasma, urine or saliva. It also has a longer half-life than CO, and can be detected

up to 3-4 days after exposure[163]. Measurement of cotinine has been used in several previous trials to assess smoking status[164-166], and may have been a more accurate method to determine smoking status and should probably be applied in future studies as conducted here. In addition, cotinine can be measured in saliva, and would certainly not have constituted a greater burden on the participants than the measurements of CO in exhaled air.

With regard to the CO-measurement, a level of ≤ 5 ppm was assumed as a no smoking status. In other smoking cessation trials, this level has been set at 8-10 ppm[107,108,135,167,168]. These studies are multicenter trials, and the CO-level may have been set as high as ≤ 10 ppm due to a higher level of air pollution, which may influence the expired CO-level in nonsmokers. It is, however, demonstrated that the optimal cut-off level of exhaled carbon monoxide to discriminate between nonsmokers and smokers should be 5.5 ppm[131]. Taking this into account, we decided a CO-level of ≤ 5 ppm to be a reasonable number to confirm reported abstinence from smoking. This was decided since measurements of carbon monoxide in exhaled air is an accepted method for detection of smoking status[169], and since this is a method that measure short-time abstinence. It should however be noted that this method of measuring CO has a low specificity and sensitivity[163], as there are several environmental sources of CO in addition to cigarette smoke that may influence the results, such as CO from combustion of coal, petrol and inhaling air in rooms where other people are smoking. In addition, the participants may have failed to report single events of smoking, such as a puff. If such events did not occurred immediately before measuring CO-levels, they may not have influenced the measurements despite that these events could have influenced the participants' physiology and hence weight etc. To what extent this has influenced the measurements here is unknown.

As some participants missed one or more visits, self-reported smoking status is the only available documentation of smoking status. Participants were tested for CO-levels at the visits before and after a missing visit. If low levels of CO were confirmed, the participants were considered nonsmokers. Participants who, in contrast, reported to be smokers at other visits or dropped out, were considered smokers at missing visits. Similar assumptions are supported as they have been made in other trials[108,168]. Failure to classify smokers from nonsmokers may have influenced CARs. The use of CAR instead of point prevalence to define the participants as nonsmokers have strengthen the analyses of changes in post cessation weight gain, since using the point prevalence abstinence to define abstainers is likely to underestimate actual

weight gain because of smoking cessation[170]. Misclassification may also have influenced other parameters such as changes in HDL and body weight. The latter is expected as continued smokers are expected not to gain weight during a relatively short period of time. To this end smoking cessation has also been shown to influence HDL levels as quitting smoking is associated with an increase in HDL-levels[90,94]. Furthermore, it should also be considered that misclassification of nonsmokers as smokers may also lead to fewer nonsmokers, which may certainly influence the test power. Finally, as the participants were randomized, different degree of nicotine dependence may not have influenced the results reported here. Proper randomization is considered the best and most reliable method to ensure comparable distribution between the two intervention groups[151].

Smoking cessation

In this thesis 37.5% of the participants who were randomized to follow either of the two intervention diets managed to be continuous abstinent all twelve weeks starting at their planned smoking cessation date. Few, if any, other smoking cessation trials have reported continuous abstinence rates for the continuous first twelve weeks. It is therefore difficult to say whether this was a high or low CAR compared to other trials. Klesges et al.[170] did, however, measure CAR at one month and at six months after smoking cessation, and found CARs of 30% and 26%, respectively. CARs for the first four weeks (weeks 1-4) and for the last four weeks (weeks 9-12) in the current study were 47.5% and 60%, respectively. For comparison, previous smoking cessation trials using varenicline had a CAR (weeks 9-12) ranging from 35% to 54%[107,108,135,136]. One of these trials, Hawk et al.[136], compared an extended pre-quit varenicline treatment period of four weeks with a standard pre-quit varenicline treatment period of one week. They found that CAR during the final four weeks (weeks 9-12) of treatment was higher in the extended group than in the standard group (67% vs 35%, respectively). Except from Hawk et al., these trials included about 600-1000 subjects, which are markedly larger trials than the current study. However, in the Hawk et al. study, only 60 subjects were included and had the lowest CAR (in the standard group) of all these trials. This suggests that low numbers of subjects not necessarily results in high abstinence rates. Seven-days point prevalence abstinence at week 12 has been approximately 40-50% in other trials looking at varenicline-assisted smoking cessation rates[107,137,138]. In the current study 7-days point prevalence was not measured, but abstinence rate for the last 14 days, confirmed with CO-measurements at week 12, was almost 69%. Compared to previous trials,

the current study has a high rate of continuous abstinence among the participants. Considering our efforts to minimize the risk of misclassification of smokers, we assume that the CAR found here was not overestimated. Participants claiming to be abstinent, but were measured with CO-level above 5 ppm, were considered smoking. This was done despite that CO-levels of 6 ppm may be caused by passive smoking or passing traffic dense areas before the visit. Based on this it may be that the limit of CO ≤ 5 ppm can actually have led to a lower CAR than what really is the case. All participants apart from one received varenicline. Several trials have shown that the use of varenicline increases smoking cessation rates[107,108,135,137,168]. However, varenicline adherence has not been analyzed in this master thesis. It is therefore difficult to say if the high CAR was due to good compliance with the medication, the dietary intervention focusing on prevention of post cessation weight gain, or both. Indeed, a previous pilot study showed that offering a weight management program to overweight and obese weight-concerned smokers increased the probability of the participants to be 6 months abstinent[171]. In contrast, there is some evidence suggesting that combining diet and smoke cessation, in attempt to prevent weight gain, may undermine the attempt to quit smoking[42,172]. Temporary smoking cessation rates in the current study do not support this, since we reached a CAR comparable with CARs in large trials assessing efficacy of varenicline for smoking cessation[107,108,138].

It is possible that the subjects participating in this study were highly motivated as they were recruited through an advertisement in the newspaper and had to make their own initiative to sign on. Another aspect is the fact that all visits were at daytime, meaning that many of the participants had to take time off from work. All participants reported to smoke at least 10 cigarettes daily when they met at the screening visit, but seven of them reported to be smoking less than 10 cigarettes/day when they met at the next visit (the randomization visit). This may indicate that some of the participants started to reduce the number of daily cigarettes already after the first visit, probably to prepare themselves for smoking cessation, which may suggest a high motivation. Another possibility is that these participants did not smoke an average of as much as 10 cigarettes daily at the beginning, and hence were over-reporting in order to be included in the study. If this is the case, these participants did not meet all the inclusion criteria, and the subjects included in the analyses were not be representative for the population meant to be included.

Clinical and biochemical measurements

Any measurement found to be clearly incorrect, e.g. a blank print from the impedance measurement, was repeated if discovered immediately, or excluded if it first was detected after the participant had finished the visit. Any excluded measurement would appear as a missing value in the statistical analyses. Several missing values in statistical tests would have weakened the power of the tests to detect any differences between the intervention groups. To ensure comparable measurements, participants who were not fasting when they met at visit 2, 8 or 12 (randomization and 4 and 12 weeks post-cessation, respectively), were asked to come back for fasting impedance measurement, indirect calorimetry (at visit 2 and 8), and blood samples the following day.

Body weight was measured with impedance at randomization and four and 12 weeks after smoking cessation and with a digital scale at the remaining visits. This has most likely not influenced the measurement of body weight since all scales used in the current study are tared once every year. We have also sought to minimize measurement errors due to slightly different method executions by limiting the number of study personnel doing the tests. Two nutritionists were responsible for measuring waist and hip circumference. Hence, any measurement errors due to different performance of the nutritionists are most likely equally distributed between the intervention groups and over time, and may therefore not have affected the outcome results markedly. Measurements were, however, not performed blinded and, in theory, this may have influenced the measurements. Despite this, to further minimize biased measurements in favor of either of the two diet groups, we suggest that such measurements should be performed blinded in future studies.

The blood measurements were taken after one overnight fast (at least 8 hours fasting), and were analyzed by conventional laboratory methods at Department of Clinical Chemistry, Oslo University Hospital Ullevål. If the amount of TG was higher than 4.5 mmol/L, LDL could not be analyzed, and LDL values are therefore missing for two participants, one in each group, with high TG both at randomization and 12 weeks after smoking cessation. However, as LDL values are only missing for one participant in each group, we assume that this has minor effect on the results for LDL levels.

Statistics

Since all statistical tests performed have been done on only 70 participants, which is a considerably lower number of subjects than originally estimated to be required, the power of the tests are less than optimal. According to Altman's nomogram for calculating sample size or power[173] these analyses only had, approximately, a 70% power to detect a 3 kg difference with 5% significance assuming that the SD of the change in weight was 5 kg. Analyses performed on the group of participants who were 12 weeks continuous abstinent had significantly lower power than this and cannot be used to draw any absolute conclusions. This because a low test power increases the risk of type II errors (not detecting an existing difference between the groups).

Paired-samples t-test was performed to assess within-group changes, while between-group differences were analyzed with independent-samples t-test for continuous variables, and chi-squared test for categorical variables. These tests have been used for similar assessments in other trials with normally distributed variables[117,174,175]. However, a one-way analysis of variance (ANOVA) is another often used method to test for differences between two or more independent groups, and could have been a good alternative to the independent-samples t-test[117,176]. The chi-squared test is an accepted method of analyzing categorical variables, such as differences in proportion of drop-outs[158,175]. In the current thesis, Pearson correlation was used to assess correlations between changes in body weight and changes in dietary intake of macronutrients. Pearson correlation has been used in previous trials[37,117]. However, due to the small sample size, multiple linear regression analyses were not performed. This makes it difficult to identify any other possible relationships between the outcomes and dietary changes, or if there are any interactions or confounders present (e.g. age, gender, education level etc). This can be considered a weakness in the current thesis.

Intention-to-treat is a strategy for the analysis of randomized controlled trials that compares participants in the groups to which they were originally randomly assigned, i.e. includes all participants regardless of whether they actually satisfied the entry criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol[152,177]. The intention-to-treat approach has two main purposes. Firstly, the approach maintains treatment groups that are similar apart from random variation. This is the reason for randomization, and the feature may be lost if analysis is not performed on the groups produced by the randomization process. Secondly, intention-to-treat analysis allows for non-compliance and

deviations from policy by clinicians[177]. However, no consensus exists about how missing responses should be handled in intention-to-treat analyses, and different approaches are used. In the current thesis a last-measurement-moved-forward analysis was performed for body weight, since this was the only effect variable measured at every visit. This intention-to-treat approach to implement missing values has been used in some previous trials[176,178]. However, even though intention-to-treat analyses are necessary to keep the randomization intact, there is some controversy about using intention-to-treat approaches in analyses of body weight in smoking cessation trials. As mentioned above, cigarette smokers have lower body weight than nonsmokers[52,53], and quitting is associated with weight gain[170,179]. Moreover, those who return to smoking tend not attend clinics for follow-up[88]. Including those who were not abstinent can reduce the mean weight gain, since it is likely that the body weight will depend on time since relapse. People who try to become abstinent but fail after a few days do not gain weight, while those who relapse to smoking seem to lose the weight they gained previously[88]. A last-measurement-moved-forward analysis may therefore be slightly misleading. In accordance with this and in order to evaluate the effect of smoking status on body weight, the analysis both with and without missing values were performed to detect potential changes, both among nonsmokers and among all participants randomized to the intervention diets. The last-measurement-moved-forward analysis on body weight among the nonsmokers in the current study did not differ from the analysis performed only on the completers (those met at both randomization and twelve weeks post-cessation). This strengthens the results we found for changes in body weight. For analyses in most randomized controlled trials intention-to-treat is a recommended approach, and almost half the reports of randomized controlled trials includes an analysis described as intention-to-treat[177]. For the other efficacy outcomes in the current thesis an intention-to-treat approach would probably have been closer to the effects likely to be encountered in subsequent clinical use[152], since it is rather rare that all patients will be able to follow a diet exactly as prescribed all the time, and since most cigarette smokers need several attempts before, if at all, they manage to quit smoking[84]. The fact that intention-to-treat analyses not have been performed for the other efficacy outcomes in this master thesis may therefore be considered a weakness.

Dietary intervention and assessment of diet

In this study a total of seven intervention meals were handed out at two time points, four and three meals, respectively. In some previous trials of compared different intervention diets all meals for the whole intervention period were provided at the same time[158,175]. In the present study, providing all meals would probably have resulted in a better adherence to the intervention diets. It is, however, not likely that this ever will be done in future practice, and we assume that not providing all meals most likely resulted in a more realistic effect of the intervention.

Both over- and underreporting of food intake are documented, although underreporting is the most regular event[180-183]. Furthermore, it is previously shown in postmenopausal women that a 7-day dietary record captures changes in dietary intake after smoking cessation[184]. Nelson et al.[185] have suggested that in order to be able to estimate daily energy intake, considering between- and within-subject variation, a total of 4 and 6 days of recording is necessary for men and women, respectively. In the present study weighed DRs were used to measure compliance to the intervention diets. However, due to some customization of number of days between the visits, it was impossible for some of the participants to conduct more than 5-6 days. Despite that this might have weakened the chance of detecting the daily variation in dietary intake, it was well in line with previous studies where food records were conducted for 3-5 days[117,118,174-176,186,187] or only as 24-hour recalls[188-190] or food frequency questionnaires[189,191]. Measurements of food intake are often prone to misreporting, especially when it comes to self-administered tools. To this end, validation of different methods of dietary assessment has shown that weighed records, compared to 24 hours recall and food-frequency questionnaires, is the most accurate method of dietary assessment, despite problems of underreporting[192]. To use the method of weighed DR to measure compliance in the current study may therefore not have resulted in poorer estimation of dietary intake than other used methods. Furthermore, here the Golderg equation which is commonly used to identify misreporters[145] was used. Moreover, Tooze et al.[193] compared the classification of underreporters using the Goldberg method with underreporters classified using doubly labeled water, and concluded that the Goldberg method is a reasonable approach to characterize underreporting. Goldberg et al. made cut-off limits to recognize underreporting at the group level[180], and unless a person has a very inactive lifestyle, a physical activity level (PAL) <1.35 is not very likely. A PAL value of 1.55 is the WHO value for a sedentary lifestyle[129]. In our study we report that the LFHCC and the HPMRC groups had a mean PAL <1.35, both before

and after smoking cessation. This may indicate underreporting in both groups. In the current study all participants were overweight or obese, and it is shown that people with high BMI often underreport more than lean people[157,192,194]. Moreover, there is some evidence that women and smokers may underreport more than males and nonsmokers, respectively[157,194]. Since the participants in the current study were smokers, and predominantly women in addition to all being overweight or obese, this may support that underreporting was present. Also eating behaviors like eating restraint and eating disinhibition are associated with misreporting, and this may be contributing factors to underreporting here. It has been suggested that eating disinhibition may affect a person's ability or motivation to accurately report energy intake, while eating restraint directly reduces "normal" intake, thereby contributing to underreporting[195].

The possible underreporting of energy intake in both groups provides a great uncertainty about the participants' actual diet, since it is impossible to know what kind of food items they underreported. It has previously been reported that energy and energy-yielding nutrients like fat and sucrose[119], in addition to cakes, were underreported, while vegetables, potatoes and meat, amongst others, were not underreported[192]. If this is the case in the current study, the macronutrient composition of the diets consumed in the two intervention groups would have been somewhat different than reported. In addition, it has previously been suggested that the number of days of diet records required to estimate the intake of protein, fat and carbohydrate are up to 8, 7 and 6 days, respectively[185]. This indicates that the number of days recorded in the current study, may not have been enough to estimate the true daily intake of macronutrients in the first place. However, more days of dietary recording would have been a greater burden on the participants, and would probably have led to less motivation among the subjects and poorer recording.

The software program Mat på data 5.0 was used to calculate the reported intake of calories, carbohydrate, fat and protein. Since this program not has been updated for several years, it is incomplete when it comes to the number of food items. The Mat på Data 5.0 software program do not have options for getting results of intake of different food items, only different food groups, which makes it difficult to evaluate if any decrease or increase in a nutrient might be due to a reduced or increased intake of a specific type of food. One previous trial comparing a low glycemic load diet high in protein and a low-fat diet, found that the group following the diet high in protein significantly reduced their intake of bread, potatoes

and rice, in addition to increase their total intake of meat[115]. It is possible that the HPMRC group in the current study have made similar changes to their diet. The Mat på Data 5.0 software program is well suited to estimate energy intake and energy percent from the different macronutrients recorded in the dietary records. Even though we are not able to differentiate between different food groups, the use of this program has most likely given a good estimate of the reported macronutrient composition in the current study.

5.1.3 Can the results be generalized?

This thesis is based on a relatively small sample size. In addition, a relative smaller number of men compared to women were included in the study group. This makes it difficult to generalize the results to the Norwegian cigarette smoking population, considering the low power of statistical tests and the fact that there are at least as many male smokers as female smokers in Norway[2]. Furthermore, due to the inclusion and exclusion criteria, results cannot be generalized to normal-weighed smokers or smokers with obesity class III, smokers taking insulin for diabetes or smokers who have history of serious psychiatric disorder or depressive illness. Finally, the current study only shows results after a few months duration, and any long-term effects of the interventions are thus far unknown.

5.2 Discussion of results

5.2.1 Outcome variables

Body weight

Twelve weeks post cessation both dietary interventions seem to be equally successful in preventing undesired weight gain. Previous smoking cessation trials without dietary interventions have found a significant increase in body weight following smoking cessation, although most of these trials have looked at weight gain during the first year or longer after smoking cessation[88]. Klesges et al.[170], however, found an average increase in body weight of 3 kg after one month and 5.5 kg after 6 months among continuous abstinent participants, and it is shown that the weight gain is greatest the first 1-2 months following smoking cessation[55,170]. Compared to these findings, the lack of any within- or between-group

difference in body weight 12 weeks after smoking cessation in this thesis suggests that both dietary interventions successfully prevented short-term post cessation weight gain.

However, since changes in physical activity were not considered here, we do not know whether the relatively stable body weight in the current study was due to an increase in physical activity among the participants or other factors. There are some evidence that exercise interventions may reduce body weight after smoking cessation, but the results from different trials are inconsistent, and increased physical activity seems to be most effective in the long term and if it is of vigorous intensity[196-200]. Since participants in the current study only were encouraged to increase physical activity and no exercise interventions were performed, and, in addition, body weight was measured after only four and 12 weeks after smoking cessation, it is not likely that a change in physical activity is the whole explanation. In addition, previous studies have either shown no change in physical activity[201,202] or a decrease in physical activity[53] after smoking cessation. It is previously shown that post cessation weight gain is inversely associated with socioeconomic status[42,203], but this has not been included in the statistical analyses in this master thesis, and whether a high economic status among the participants can explain some of the reason for the absence of weight gain or not is not known.

There is evidence for varenicline reducing post cessation weight gain at the end of the treatment period[88], and the use of varenicline might therefore be some of the reason for the stable body weight seen in the current study. How much of the effect varenicline is responsible for is not known since analyses of varenicline adherence and regression analyses not have been performed. It is also possible that the close follow-up with regular recording of body weight and counseling has made the participants more aware of their dietary habits, like snacking between meals. Snacking is a common displacement activity after smoking cessation[204], and the delivery of recommended snack foods and the nutritional counseling may have prevented post cessation weight gain. The prevented weight gain in the current study may have contributed to the relatively high smoking cessation rates, since weight gain after smoking cessation is associated with relapse[83,97].

In the current study, we failed to show any difference between a low fat diet high in complex carbohydrates and a high protein diet moderately reduced in carbohydrates in preventing post cessation weight gain. This is in accordance with previous findings supporting that both low fat diets and diets high in protein and low in carbohydrate can reduce body weight[115,117,205].

However, when including the reduced smokers, we did find a greater weight reduction in the group following the diet with highest protein content six weeks after initiation of the diet. Twelve weeks post cessation we did no longer find a significant difference between the intervention groups. However, the difference in weight between groups was greater when reduced smokers were included than among nonsmokers only. This may indicate a true difference between diets in favor of the diet with highest protein content. Some previous trials have shown that higher protein diets may increase total weight loss[122,158]. Furthermore, there is evidence that modestly increasing the proportion of protein in the diet, while controlling energy intake, may improve body weight maintenance after weight loss[206]. The greater effect on weight loss of high protein diets compared to lower-protein diets is probably due to a lower spontaneous energy intake brought about by enhanced satiety[207] and a greater thermogenic effect[208].

Body composition

In this study a decrease in body fat % was seen in the HPMRC group compared to the LFHCC group. Even though the 95% confidence interval contained 0, and a possibility for a random finding exists, this finding together with the changes in waist circumference within the HPMRC group is in line with previous trials that have found decreased total body fat and waist circumference with a high protein diet[186,209]. Wycherley et al.[209] found, however, greatest effect for body weight, fat mass and waist circumference in the high protein group following a progressive resistance exercise training program. Exercise is associated with improved body composition[210], and it is demonstrated that a diet with higher protein and reduced carbohydrates combined with exercise additively improves body composition during weight loss[187]. Since the current study not included any kind of exercise interventions, it is not likely that one of the intervention groups would have increased their physical activity significant more than the other and the significant difference between the groups in mean change in waist circumference and body fat may indicate a beneficial effect of the high protein diet. There is some evidence that diets high in protein and low in carbohydrate favorably affect body mass and composition independently of energy intake[211]. Several studies have suggested that higher protein diets not only may increase total weight loss, but also may increase the percentage of fat loss[158,175,205]. A previous study found that a high-protein diet (E% 25) experienced a 10% greater reduction in intra-abdominal adipose tissue than a medium-protein diet (E% 12)[175]. This is in accordance with the reduction in waist

circumference observed in the group with highest protein intake in the current study. Parker et al.[208] found that women on a high protein diet (E% 28) lost significantly more total and abdominal fat compared with women on a low protein diet (E% 16), but that there was no difference in men. Since women and men not have been analyzed separately in this master thesis, it is not known whether this also is the case in the current study. However, since the gender distribution in the two intervention groups in the current study was comparable, this should not have any influence on the outcomes. Even though we found a significant reduction in waist circumference only in the diet with the highest content of protein, both interventions prevented the increase in waist circumference previously associated with smoking cessation[91,96,212]. It has also previously been found that a higher intake of protein is associated with maintenance or accretion of fat-free mass[174,205,213], although there was no significant difference in the change in muscle mass between the LFHCC and the HPMRC groups in the current study. This may in part be due to the relative short follow-up period, or the lack of exercise intervention since Josse et al.[214] found lean mass gain during diet- and exercise-induce weight-loss.

Cardiovascular risk factors

Among the nonsmokers, there were no significant differences between the LFHCC group and the HPMRC group when it comes to changes in cardiovascular risk factors 12 weeks post cessation, but both groups had a significant increase in HDL cholesterol. The effects of diets low in carbohydrate on HDL reported in previous trials are inconsistent[205,215], while low fat diets have been shown to decrease HDL[119,216]. We found increases in HDL in both groups in the current study, which suggests that the effect on HDL was due to quitting cigarette smoking rather than the dietary interventions as it has previously been shown that smoking cessation is associated with an increase in HDL[94,217,218]. If not considering smoking status, there was a significant between-group difference in the change in TG when analyzing all participants. We did not find any significant within-group alterations in TG from randomization to 12 weeks after smoking cessation. Low-fat diets have previously been shown to increase TG, at least under weight-maintenance conditions[219]. In contrast did one previous trial found that a diet low in carbohydrate gave a greater decrease in triglyceride levels compared with a low-fat diet in severely obese subjects[122]. Evidence from other trials also shows that high-protein diets decrease fasting plasma TG[158,187,205]. Most of these trials had study duration of four to six months, and the short duration of only three months in the

current study may explain some of the reason for why we failed to observe a significant reduction in TG. However, Layman et al.[205] found a significant decrease in TG after only 10 weeks on a high protein diet. Although there was no significant decrease in TG in the current study, mechanisms for the changes in TG exists and may relate to a lower daily blood glucose concentration and lower daily insulin which primary functions as a hormone are to promote storage of blood glucose in skeletal muscle and adipose tissue and to inhibit lipolysis and promote triglyceride synthesis and storage rather than release[220]. The significant increase in fasting blood glucose from the date of randomization to 12 weeks post cessation seen in the HPMRC group is, however, not in accordance with this theory. Previous trials studying the effects of a high-protein diet usually have found no effect[117,118,175] or a decrease in blood glucose[208,221]. Moreover, some previous studies have found an increase in blood glucose after decreasing cigarette smoking[96,166,212]. Increased glucose may be a contributor to the increased risk for type 2 diabetes the first years after smoking cessation, since post cessation weight gain only partially explains this increased risk[96]. However, we did only find increased blood glucose when we included the reduced smokers, and we suggest that this result was mainly caused by the reduced smokers who were least compliant to the intervention diet (i.e. those who gained most body weight). This may indicate that successful prevention of post cessation weight gain and following increased blood glucose may prevent the increased risk for type 2 diabetes associated with smoking cessation.

In the current study, we did not find any changes in systolic or diastolic blood pressure. A recent meta-analysis showed a greater mean decrease in both systolic and diastolic blood pressure after 3 months with higher- compared to lower-protein diets[222]. Furthermore, there is some evidence suggesting that the dietary content of fat not has a large impact on blood pressure[223,224], while others have found that a diet rich in fruits, vegetables and low-fat dairy products and with reduced saturated and total fat (the DASH-diet) can lower blood pressure[225]. Moreover, epidemiologic data support a positive association between body weight and blood pressure, and randomized controlled trials have demonstrated that a reduction in weight is associated with a reduction in blood pressure[226]. Our participants were normotensive at randomization in addition to maintaining a stable body weight during the follow-up period, and a decrease in blood pressure would therefore not be expected. However, smoking cessation has been associated with increased blood pressure and incidence of hypertension, mainly due to post cessation weight gain[94,227]. Our findings suggests that by preventing weight gain after smoking cessation, an increase in blood pressure will also be prevented.

Among weight-reduction diets, low-fat diets have been reported to decrease total cholesterol and LDL more than high-protein, low-carbohydrate diets[117,118,219]. We did not find any changes in LDL or total cholesterol, which may be due to the stable body weight.

5.2.2 Dietary interventions

Compliance with the dietary interventions

To achieve the planned macronutrient compositions at a daily energy level of 2000 kcal, the study protocol estimated limits for intake of fat and carbohydrate in the LFHCC group and for intake of protein and carbohydrate in the HPMRC group. In this dietary intervention study the reported dietary intake showed that the intended intake in the intervention groups was not achieved with regard to carbohydrates. The reported intake of carbohydrates was too low in the LFHCC group and too high in the HPMRC group. Previous trials have also shown too low compliance with the dietary interventions[115,117], with the greatest discrepancy from target level for carbohydrates[118]. Other trials have reported a good correspondence between reported intake and planned intake of macronutrients, but in these trials all food for the intervention groups were provided[158,175,228]. This suggests that it may be difficult for free-living subjects to comply with the macronutrient composition of specific diets. This was probably even harder for the participants included in the current study considering simultaneously smoking cessation.

Some of the participants in the LFHCC group reported that they thought it was difficult to choose sweet toppings like prim and jam when they were supposed to reduce their intake of added/refined sugars. Together with their attempt to reduce their intake of fat, this may have resulted in a greater use of ham and low-fat cheese than intended in this intervention group. This may be a reason for the low carbohydrate intake and high protein intake reported four weeks after smoking cessation in the LFHCC group. The HPMRC group managed to reach a reported intake of protein greater than 25 energy %, but they did not report a large enough reduction in carbohydrates. In accordance with this, they did not report an increased intake of fat, but rather a decrease in the intake of fat in grams, especially of saturated fat. This indicate that this group reduced the intake of sources to saturated fat, like whole fat dairy products and minced meat, in addition to increase the intake of unsaturated fat, like vegetable oils, fish and nuts. The fact that the HPMRC group reduced the reported intake of carbohydrate, but not the intake of fiber, suggests that these participants altered their food choices to more whole grain

products in addition to decreasing the total intake of food products rich in carbohydrate. They did, however, not reduce the intake of carbohydrate as much as intended, which may be due to increased cravings for sweet foods associated with smoking cessation[202]. It seems therefore that the dietary composition has improved, and is more in accordance with the Norwegian recommendations, especially regarding to the distribution of fatty acids[113].

Since neither the LFHCC group nor the HPMRC group managed to implement all the intended dietary changes, we have no data on the effects of the planned intervention diets. Hence there is a possibility that both the planned intervention diets would have given greater effects on body weight, body composition or cardiovascular risk factors, or that there would have been a greater difference between the intervention diets when it comes to changes in one or several of the efficacy outcome measures. It does, however, seem like the two groups have eaten diets with significant different macronutrient composition, and that these intervention diets are different enough to compare the effects. One previous trial found a significant difference on body weight between two groups with 15 and 18 energy % from protein, respectively[213], and in the current study there was a greater difference in reported energy % from protein between the dietary intervention groups than this. Since all data based on dietary records only are modestly reliable in assessing the true dietary intake over time, for instance due to underreporting and undereating, it must be considered that the clinical results in this master thesis may be consequences of exposing the participants to different dietary advices, and not as a direct consequence of the estimated macronutrient consumption in the two dietary intervention groups.

Correlations between changes in body weight and dietary changes

Both intervention groups tended to have a weight loss during the first six weeks of the dietary intervention, and then started to gain some weight again. This is in accordance with previous findings, which have suggested that the greatest effect of dietary interventions often can be seen during the first period of time, most likely partly due to a decrease of dietary adherence with time[117]. However, since no dietary records were conducted 12 weeks after smoking cessation here, it is not possible to say whether the dietary compliance decreased or not during the last eight weeks of treatment and follow-up.

Among the nonsmokers, there was a positive correlation between the change in intake of carbohydrate and the change in body weight four weeks after smoking cessation in the

HPMRC group. This suggests that those who followed the intervention diet best (i.e. reduced the carbohydrate intake the most) were those who had the best effect on changes in body weight (had the greatest reduction). This is in accordance with findings in a previous trial, where it was suggested that increased adherence was associated with greater weight loss, even though overall dietary adherence rates were low[117]. Considering that no other correlations between the dietary changes and the change in body weight were observed in any of the two intervention groups, it is possible that the positive correlation between changes in intake of carbohydrate and changes in body weight in the HPMRC group was due to a larger variation in the changes in carbohydrate intake than in intake of protein or fat.

When including the reduced smokers there were positive correlations between the changes in body weight and the changes in intake of fat and protein in the HPMRC group. If the participants who had the greatest increase in intake of fat and protein not reduced the carbohydrate enough, this would lead to an increase in body weight. This might be the reason for the positive correlations seen in the HPMRC group. The absence of any other correlations may be due to a small sample size, especially among the nonsmokers.

It must also be considered that weight loss predominantly results from reduced energy intake, not the macronutrient composition, as previously suggested[124]. This is also supported by the POUNDS LOST trial, which found no differences in weight loss between four energy-reduced diets with different macronutrient compositions[229].

6 Conclusion

Our results show that intervention of combined smoking cessation and restricted diet can successfully prevent short-term post cessation weight gain. However, close follow-up with personal counseling and medication may be necessary to obtain good results. The prevention of post cessation weight gain may prevent unintended health consequences of smoking cessation such as increased blood pressure and increased blood glucose. This may be of great clinical significance. Even though we did not find any significant difference between diets containing high carbohydrate or high protein in efficacy of prevention weight gain after smoking cessation, a diet high in protein and reduced in carbohydrates may have a better effect on body composition and some cardiovascular risk factors, especially waist circumference and triglycerides, compared to a low fat diet high in carbohydrates. It should however be stressed that the analysis reported here should be interpreted with caution due to the low statistical power, and the fact that neither the high carbohydrate group nor the high protein group reached the intended macronutrient composition of their reported diets. In addition, any long-term effects of the two dietary interventions cannot be estimated.

7 Future perspectives

This master thesis only included 12 weeks of treatment and follow-up after smoking cessation, and it is therefore not possible to say anything about the long-term effect on body weight of the two intervention diets used in the current study. It is first of all necessary to look at the effects after 6 months, which will be accomplished in a later and larger study, before it is possible to recommend any of the two dietary interventions for prevention of long-term weight gain after smoking cessation. Results after 6 months may indicate more beneficial effects of one of the diets over the other, and if so, effects after one year or longer should be included in future research. It is also necessary to adjust for all possible interacting or confounding factors, such as age, socioeconomic status and physical activity.

References

1. Escobar-Chavez JJ, Dominguez-Delgado CL, Rodriguez-Cruz IM. Targeting nicotine addiction: the possibility of a therapeutic vaccine. *Drug design, development and therapy.* 2011;5:211-224.
2. ssb. http://www.ssb.no/emner/03/01/royk/index.html. Accessed 30.05.2012.
3. Helsedirektoratet. http://helsedirektoratet.no/folkehelse/tobakk/snus-og-roykeslutt/Documents/Helsedirektoratets-plan-systematisk-kunnskapsbasert-tilbud-royke-og-snusavvenning.pdf. Accessed 04.07.2012.
4. Benowitz NL. Neurobiology of nicotine addiction: implications for smoking cessation treatment. *The American journal of medicine.* Apr 2008;121(4 Suppl 1):S3-10.
5. Changeux JP, Taly A. Nicotinic receptors, allosteric proteins and medicine. *Trends in molecular medicine.* Mar 2008;14(3):93-102.
6. D'Souza MS, Markou A. Neuronal mechanisms underlying development of nicotine dependence: implications for novel smoking-cessation treatments. *Addiction science & clinical practice.* Jul 2011;6(1):4-16.
7. Markou A. Review. Neurobiology of nicotine dependence. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences.* Oct 12 2008;363(1507):3159-3168.
8. Hatsukami DK, Stead LF, Gupta PC. Tobacco addiction. *Lancet.* Jun 14 2008;371(9629):2027-2038.
9. Fagerstrom K, Russ C, Yu CR, Yunis C, Foulds J. The Fagerstrom Test for Nicotine Dependence as a Predictor of Smoking Abstinence: A Pooled Analysis of Varenicline Clinical Trial Data. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Mar 30 2012.
10. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta GA2004.
11. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta GA2010.
12. Davies N. The effect of body image and mood on smoking cessation in women. *Nursing standard (Royal College of Nursing (Great Britain) : 1987).* Feb 22-28 2012;26(25):35-38.
13. Wipfli H, Samet JM. Global economic and health benefits of tobacco control: part 1. *Clinical pharmacology and therapeutics.* Sep 2009;86(3):263-271.
14. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000-2004. *MMWR. Morbidity and mortality weekly report.* Nov 14 2008;57(45):1226-1228.
15. Eliasson B, Attvall S, Taskinen MR, Smith U. The insulin resistance syndrome in smokers is related to smoking habits. *Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association.* Dec 1994;14(12):1946-1950.
16. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association.* Dec 12 2007;298(22):2654-2664.
17. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *The American journal of medicine.* Nov 2000;109(7):538-542.
18. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation.* Jan 3 2012;125(1):e2-e220.

19. ssb. http://www.ssb.no/dodsarsak/. Accessed 10.07.2012.
20. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ (Clinical research ed.).* Apr 4 1998;316(7137):1043-1047.
21. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *Journal of the American College of Cardiology.* May 19 2004;43(10):1731-1737.
22. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet.* Oct 8 2011;378(9799):1297-1305.
23. Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. *Annals of the New York Academy of Sciences.* May 28 1993;686:12-27; discussion 27-18.
24. Lassila R, Seyberth HW, Haapanen A, Schweer H, Koskenvuo M, Laustiola KE. Vasoactive and atherogenic effects of cigarette smoking: a study of monozygotic twins discordant for smoking. *BMJ (Clinical research ed.).* Oct 15 1988;297(6654):955-957.
25. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature.* Jun 11-17 1987;327(6122):524-526.
26. Ota Y, Kugiyama K, Sugiyama S, et al. Impairment of endothelium-dependent relaxation of rabbit aortas by cigarette smoke extract--role of free radicals and attenuation by captopril. *Atherosclerosis.* Jun 1997;131(2):195-202.
27. Barua RS, Ambrose JA, Eales-Reynolds LJ, DeVoe MC, Zervas JG, Saha DC. Dysfunctional endothelial nitric oxide biosynthesis in healthy smokers with impaired endothelium-dependent vasodilatation. *Circulation.* Oct 16 2001;104(16):1905-1910.
28. Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation.* Nov 1993;88(5 Pt 1):2149-2155.
29. Kugiyama K, Yasue H, Ohgushi M, et al. Deficiency in nitric oxide bioactivity in epicardial coronary arteries of cigarette smokers. *Journal of the American College of Cardiology.* Nov 1 1996;28(5):1161-1167.
30. Ijzerman RG, Serne EH, van Weissenbruch MM, de Jongh RT, Stehouwer CD. Cigarette smoking is associated with an acute impairment of microvascular function in humans. *Clinical science (London, England : 1979).* Mar 2003;104(3):247-252.
31. Radomski MW, Palmer RM, Moncada S. The anti-aggregating properties of vascular endothelium: interactions between prostacyclin and nitric oxide. *British journal of pharmacology.* Nov 1987;92(3):639-646.
32. Ichiki K, Ikeda H, Haramaki N, Ueno T, Imaizumi T. Long-term smoking impairs platelet-derived nitric oxide release. *Circulation.* Dec 15 1996;94(12):3109-3114.
33. Sawada M, Kishi Y, Numano F, Isobe M. Smokers lack morning increase in platelet sensitivity to nitric oxide. *Journal of cardiovascular pharmacology.* Oct 2002;40(4):571-576.
34. Howard G, Wagenknecht LE, Burke GL, et al. Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA : the journal of the American Medical Association.* Jan 14 1998;279(2):119-124.
35. Cullen P, Schulte H, Assmann G. Smoking, lipoproteins and coronary heart disease risk. Data from the Munster Heart Study (PROCAM). *European heart journal.* Nov 1998;19(11):1632-1641.

36. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *BMJ (Clinical research ed.).* Mar 25 1989;298(6676):784-788.
37. Jensen EX, Fusch C, Jaeger P, Peheim E, Horber FF. Impact of chronic cigarette smoking on body composition and fuel metabolism. *The Journal of clinical endocrinology and metabolism.* Jul 1995;80(7):2181-2185.
38. Nakamura K, Barzi F, Huxley R, et al. Does cigarette smoking exacerbate the effect of total cholesterol and high-density lipoprotein cholesterol on the risk of cardiovascular diseases? *Heart (British Cardiac Society).* Jun 2009;95(11):909-916.
39. Frei B, Forte TM, Ames BN, Cross CE. Gas phase oxidants of cigarette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma. Protective effects of ascorbic acid. *The Biochemical journal.* Jul 1 1991;277 (Pt 1):133-138.
40. Pech-Amsellem MA, Myara I, Storogenko M, Demuth K, Proust A, Moatti N. Enhanced modifications of low-density lipoproteins (LDL) by endothelial cells from smokers: a possible mechanism of smoking-related atherosclerosis. *Cardiovascular research.* Jun 1996;31(6):975-983.
41. Henriksen T, Mahoney EM, Steinberg D. Enhanced macrophage degradation of biologically modified low density lipoprotein. *Arteriosclerosis (Dallas, Tex.).* Mar-Apr 1983;3(2):149-159.
42. Filozof C, Fernandez Pinilla MC, Fernandez-Cruz A. Smoking cessation and weight gain. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* May 2004;5(2):95-103.
43. Krupski WC. The peripheral vascular consequences of smoking. *Annals of vascular surgery.* May 1991;5(3):291-304.
44. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA : the journal of the American Medical Association.* Jun 16 2004;291(23):2847-2850.
45. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA : the journal of the American Medical Association.* Jan 1 2003;289(1):76-79.
46. ssb. http://www.ssb.no/magasinet/slik_lever_vi/art-2004-01-22-01.html. Accessed 09.08.2012.
47. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *The New England journal of medicine.* Aug 24 2006;355(8):763-778.
48. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes care.* Apr 2000;23(4):465-471.
49. Bigaard J, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, Sorensen TI. Waist circumference, BMI, smoking, and mortality in middle-aged men and women. *Obesity research.* Jul 2003;11(7):895-903.
50. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *The American journal of clinical nutrition.* Mar 2004;79(3):379-384.
51. Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *The American journal of clinical nutrition.* Oct 2002;76(4):743-749.

52. Bjelke E. Variation in height and weight in the Norwegian population. *British journal of preventive & social medicine.* Nov 1971;25(4):192-202.
53. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat distribution, and insulin resistance. *The American journal of clinical nutrition.* Apr 2008;87(4):801-809.
54. Hofstetter A, Schutz Y, Jequier E, Wahren J. Increased 24-hour energy expenditure in cigarette smokers. *The New England journal of medicine.* Jan 9 1986;314(2):79-82.
55. Gordon T, Kannel WB, Dawber TR, McGee D. Changes associated with quitting cigarette smoking: the Framingham Study. *American heart journal.* Sep 1975;90(3):322-328.
56. Bamia C, Trichopoulou A, Lenas D, Trichopoulos D. Tobacco smoking in relation to body fat mass and distribution in a general population sample. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* Aug 2004;28(8):1091-1096.
57. Chiolero A, Jacot-Sadowski I, Faeh D, Paccaud F, Cornuz J. Association of cigarettes smoked daily with obesity in a general adult population. *Obesity (Silver Spring, Md.).* May 2007;15(5):1311-1318.
58. French SA, Perry CL, Leon GR, Fulkerson JA. Weight concerns, dieting behavior, and smoking initiation among adolescents: a prospective study. *American journal of public health.* Nov 1994;84(11):1818-1820.
59. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of internal medicine.* Jan 7 2003;138(1):24-32.
60. Barrett-Connor E, Khaw KT. Cigarette smoking and increased central adiposity. *Annals of internal medicine.* Nov 15 1989;111(10):783-787.
61. Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat. III. Effects of cigarette smoking. *JAMA : the journal of the American Medical Association.* Feb 24 1989;261(8):1169-1173.
62. Komiya H, Mori Y, Yokose T, Tajima N. Smoking as a risk factor for visceral fat accumulation in Japanese men. *The Tohoku journal of experimental medicine.* Feb 2006;208(2):123-132.
63. Rosmond R, Bjorntorp P. Psychosocial and socio-economic factors in women and their relationship to obesity and regional body fat distribution. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* Feb 1999;23(2):138-145.
64. Canoy D, Wareham N, Luben R, et al. Cigarette smoking and fat distribution in 21,828 British men and women: a population-based study. *Obesity research.* Aug 2005;13(8):1466-1475.
65. Jee SH, Lee SY, Nam CM, Kim SY, Kim MT. Effect of smoking on the paradox of high waist-to-hip ratio and low body mass index. *Obesity research.* Sep 2002;10(9):891-895.
66. Kleppinger A, Litt MD, Kenny AM, Oncken CA. Effects of smoking cessation on body composition in postmenopausal women. *Journal of women's health (2002).* Sep 2010;19(9):1651-1657.
67. Despres JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arteriosclerosis, thrombosis, and vascular biology.* Jun 2008;28(6):1039-1049.
68. Tonstad S, Svendsen M. Premature coronary heart disease, cigarette smoking, and the metabolic syndrome. *The American journal of cardiology.* Dec 15 2005;96(12):1681-1685.

69. Gupta D, Wenger NK. Guidelines for the prevention of cardiovascular disease in women: international challenges and opportunities. *Expert review of cardiovascular therapy.* Mar 2012;10(3):379-385.
70. Godtfredsen NS, Prescott E. Benefits of smoking cessation with focus on cardiovascular and respiratory comorbidities. *The clinical respiratory journal.* Oct 2011;5(4):187-194.
71. Reaven G, Tsao PS. Insulin resistance and compensatory hyperinsulinemia: the key player between cigarette smoking and cardiovascular disease? *Journal of the American College of Cardiology.* Mar 19 2003;41(6):1044-1047.
72. WHO. www.who.int/features/factfiles/obesity/facts/en/index.html. Accessed 25.07.2012.
73. James PT. Obesity: the worldwide epidemic. *Clinics in dermatology.* Jul-Aug 2004;22(4):276-280.
74. Helsedirektoratet. http://helsedirektoratet.no/publikasjoner/nasjonal-faglig-retningslinje-for-forebygging-utredning-og-behandling-av-overvekt-og-fedme-hos-voksne/Publikasjoner/nasjonal-faglig-retningslinje-for-forebygging-utredning-og-behandling-av-overvekt-og-fedme-hos-voksne.pdf. Accessed 02.07.2012.
75. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *The American journal of clinical nutrition.* Feb 1990;51(2):241-247.
76. Han TS, Sattar N, Lean M. ABC of obesity. Assessment of obesity and its clinical implications. *BMJ (Clinical research ed.).* Sep 30 2006;333(7570):695-698.
77. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet.* Nov 5 2005;366(9497):1640-1649.
78. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *European heart journal.* Apr 2007;28(7):850-856.
79. Haslam DW, James WP. Obesity. *Lancet.* Oct 1 2005;366(9492):1197-1209.
80. Dale AC, Vatten LJ, Nilsen TI, Midthjell K, Wiseth R. Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. *BMJ (Clinical research ed.).* 2008;337:a236.
81. Schaefer EJ, Gleason JA, Dansinger ML. The effects of low-fat, high-carbohydrate diets on plasma lipoproteins, weight loss, and heart disease risk reduction. *Current atherosclerosis reports.* Nov 2005;7(6):421-427.
82. Svendsen M, Blomhoff R, Holme I, Tonstad S. The effect of an increased intake of vegetables and fruit on weight loss, blood pressure and antioxidant defense in subjects with sleep related breathing disorders. *European journal of clinical nutrition.* Nov 2007;61(11):1301-1311.
83. Dobmeyer AC, Peterson AL, Runyan CR, Hunter CM, Blackman LR. Body image and tobacco cessation: relationships with weight concerns and intention to resume tobacco use. *Body image.* Jun 2005;2(2):187-192.
84. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction (Abingdon, England).* Jan 2004;99(1):29-38.
85. Bjartveit K, Tverdal A. Health consequences of sustained smoking cessation. *Tobacco control.* Jun 2009;18(3):197-205.
86. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *International journal of epidemiology.* Jun 2001;30(3):540-546.

87. Moffatt RJ, Owens SG. Cessation from cigarette smoking: changes in body weight, body composition, resting metabolism, and energy consumption. *Metabolism: clinical and experimental.* May 1991;40(5):465-470.
88. Farley AC, Hajek P, Lycett D, Aveyard P. Interventions for preventing weight gain after smoking cessation. *Cochrane database of systematic reviews (Online).* 2012;1:CD006219.
89. O'Hara P, Connett JE, Lee WW, Nides M, Murray R, Wise R. Early and late weight gain following smoking cessation in the Lung Health Study. *American journal of epidemiology.* Nov 1 1998;148(9):821-830.
90. Stamford BA, Matter S, Fell RD, Papanek P. Effects of smoking cessation on weight gain, metabolic rate, caloric consumption, and blood lipids. *The American journal of clinical nutrition.* Apr 1986;43(4):486-494.
91. Pisinger C, Jorgensen T. Waist circumference and weight following smoking cessation in a general population: the Inter99 study. *Preventive medicine.* Apr 2007;44(4):290-295.
92. Kahn HS, Tatham LM, Rodriguez C, Calle EE, Thun MJ, Heath CW, Jr. Stable behaviors associated with adults' 10-year change in body mass index and likelihood of gain at the waist. *American journal of public health.* May 1997;87(5):747-754.
93. Saxena AR, Seely EW. Smoking cessation and associated risk of metabolic syndrome in women. *Women's health (London, England).* Jul 2012;8(4):367-369.
94. Gerace TA, Hollis J, Ockene JK, Svendsen K. Smoking cessation and change in diastolic blood pressure, body weight, and plasma lipids. MRFIT Research Group. *Preventive medicine.* Sep 1991;20(5):602-620.
95. Eliasson B, Attvall S, Taskinen MR, Smith U. Smoking cessation improves insulin sensitivity in healthy middle-aged men. *European journal of clinical investigation.* May 1997;27(5):450-456.
96. Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Annals of internal medicine.* Jan 5 2010;152(1):10-17.
97. Klesges RC, Shumaker SA. Understanding the relations between smoking and body weight and their importance to smoking cessation and relapse. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 1992;11 Suppl:1-3.
98. Taylor DH, Jr., Hasselblad V, Henley SJ, Thun MJ, Sloan FA. Benefits of smoking cessation for longevity. *American journal of public health.* Jun 2002;92(6):990-996.
99. Perkins KA, Marcus MD, Levine MD, et al. Cognitive-behavioral therapy to reduce weight concerns improves smoking cessation outcome in weight-concerned women. *Journal of consulting and clinical psychology.* Aug 2001;69(4):604-613.
100. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. *Respiratory care.* Sep 2008;53(9):1217-1222.
101. fda. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm198176.htm. Accessed 29.05.2012.
102. Henningfield JE. Nicotine medications for smoking cessation. *The New England journal of medicine.* Nov 2 1995;333(18):1196-1203.
103. Warner C, Shoaib M. How does bupropion work as a smoking cessation aid? *Addiction biology.* Sep 2005;10(3):219-231.
104. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *The New England journal of medicine.* Oct 23 1997;337(17):1195-1202.

105. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *The New England journal of medicine.* Mar 4 1999;340(9):685-691.
106. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *Journal of medicinal chemistry.* May 19 2005;48(10):3474-3477.
107. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* Jul 5 2006;296(1):47-55.
108. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* Jul 5 2006;296(1):56-63.
109. http://www.bedfont.com/smokerlyzer/pico. Accessed 24.05.2012.
110. Benowitz NL. Cotinine as a biomarker of environmental tobacco smoke exposure. *Epidemiologic reviews.* 1996;18(2):188-204.
111. Andrade FC, Vazquez-Vidal I, Flood T, et al. One-year follow-up changes in weight are associated with changes in blood pressure in young Mexican adults. *Public health.* Jun 2012;126(6):535-540.
112. Park SY, Wilkens LR, Murphy SP, Monroe KR, Henderson BE, Kolonel LN. Body mass index and mortality in an ethnically diverse population: the Multiethnic Cohort Study. *European journal of epidemiology.* Jul 2012;27(7):489-497.
113. Helsedirektoratet. http://www.helsedirektoratet.no/publikasjoner/norske-anbefalinger-for-ernering-og-fysisk-aktivitet/Publikasjoner/norske-anbefalinger-for-ernering-og-fysisk-aktivitet.pdf. Accessed 09.08.2012.
114. Helsedirektoratet. Kostråd for å fremme folkehelsen og forebygge kroniske sykdommer: http://helsedirektoratet.no/publikasjoner/kostrad-for-a-fremme-folkehelsen-og-forebygge-kroniske-sykdommer/Publikasjoner/kostrad-for-a-fremme-folkehelsen-2011.pdf. Accessed 13.08.2012.
115. Klemsdal TO, Holme I, Nerland H, Pedersen TR, Tonstad S. Effects of a low glycemic load diet versus a low-fat diet in subjects with and without the metabolic syndrome. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* Mar 2010;20(3):195-201.
116. Abete I, Astrup A, Martinez JA, Thorsdottir I, Zulet MA. Obesity and the metabolic syndrome: role of different dietary macronutrient distribution patterns and specific nutritional components on weight loss and maintenance. *Nutrition reviews.* Apr 2010;68(4):214-231.
117. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA : the journal of the American Medical Association.* Jan 5 2005;293(1):43-53.
118. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *The New England journal of medicine.* Feb 26 2009;360(9):859-873.
119. Astrup A, Toubro S, Raben A, Skov AR. The role of low-fat diets and fat substitutes in body weight management: what have we learned from clinical studies? *Journal of the American Dietetic Association.* Jul 1997;97(7 Suppl):S82-87.

120. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *The New England journal of medicine.* May 3 2001;344(18):1343-1350.
121. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Archives of internal medicine.* Feb 13 2006;166(3):285-293.
122. Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. *The New England journal of medicine.* May 22 2003;348(21):2074-2081.
123. Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Annals of internal medicine.* May 18 2004;140(10):778-785.
124. Yancy WS, Jr., Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Annals of internal medicine.* May 18 2004;140(10):769-777.
125. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *The New England journal of medicine.* May 22 2003;348(21):2082-2090.
126. Halton TL, Hu FB. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. *Journal of the American College of Nutrition.* Oct 2004;23(5):373-385.
127. Clifton PM, Keogh J. Metabolic effects of high-protein diets. *Current atherosclerosis reports.* Dec 2007;9(6):472-478.
128. Johnstone AM. Safety and efficacy of high-protein diets for weight loss. *The Proceedings of the Nutrition Society.* May 2012;71(2):339-349.
129. Human energy requirements: report of a joint FAO/ WHO/UNU Expert Consultation. *Food and nutrition bulletin.* Mar 2005;26(1):166.
130. Hurst JW, Morris DC, Alexander RW. The use of the New York Heart Association's classification of cardiovascular disease as part of the patient's complete Problem List. *Clinical cardiology.* Jun 1999;22(6):385-390.
131. Kapusta ND, Pietschnig J, Plener PL, Bluml V, Lesch OM, Walter H. Does breath carbon monoxide measure nicotine dependence? *Journal of addictive diseases.* Oct 2010;29(4):493-499.
132. Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction (Abingdon, England).* Nov 1994;89(11):1461-1470.
133. Spring B, Pagoto S, McChargue D, Hedeker D, Werth J. Altered reward value of carbohydrate snacks for female smokers withdrawn from nicotine. *Pharmacology, biochemistry, and behavior.* Sep 2003;76(2):351-360.
134. Benowitz NL, Hall SM, Modin G. Persistent increase in caffeine concentrations in people who stop smoking. *BMJ (Clinical research ed.).* Apr 22 1989;298(6680):1075-1076.
135. Bolliger CT, Issa JS, Posadas-Valay R, et al. Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. *Clinical therapeutics.* Apr 2011;33(4):465-477.
136. Hawk LW, Jr., Ashare RL, Lohnes SF, et al. The effects of extended pre-quit varenicline treatment on smoking behavior and short-term abstinence: a randomized clinical trial. *Clinical pharmacology and therapeutics.* Feb 2012;91(2):172-180.
137. Williams KE, Reeves KR, Billing CB, Jr., Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. *Current medical research and opinion.* Apr 2007;23(4):793-801.

138. Swan GE, McClure JB, Jack LM, et al. Behavioral counseling and varenicline treatment for smoking cessation. *American journal of preventive medicine.* May 2010;38(5):482-490.
139. Catz SL, Jack LM, McClure JB, et al. Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* May 2011;13(5):361-368.
140. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British journal of addiction.* Sep 1991;86(9):1119-1127.
141. Helsedirektoratet. http://www.helsedirektoratet.no/publikasjoner/faktaark-fagerstroms-test-av-nikotinavhengighet/Publikasjoner/faktaark-fagerstroms-test-av-nikotinavhengighet.pdf. Accessed 24.06.2012.
142. http://www.bodyanalyse.no/InBody-720/Detaljert-forklaring/. Accessed 25.05.2012.
143. SensorMedics. Vmax Operator's Manual2002. http://www.viasyshealthcare.com/vmax_forum/Manuals/Operators/VmaxSpectraOp.pdf. Accessed 25.05.2012.
144. Svendsen M, Tonstad S. Orlistat after initial dietary/behavioural treatment: changes in body weight and dietary maintenance in subjects with sleep related breathing disorders. *Nutrition journal.* 2011;10:21.
145. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* Sep 2000;24(9):1119-1130.
146. Mattilsynet H, UiO. The Norwegian food composition table. Matvaretabellen 2006. www.matvaretabellen.no. Accessed 04.05.2012.
147. Livsmedelsverket. Livsmedelsdatabasen. www.slv.se/sv/grupp1/mat-och-naring/vad-innehaller-maten/livsmedelsdatabasen-/. Accessed 04.05.2012.
148. United States Department of Agriculture. USDA National Nutrient Database for Standard Reference. http://ndb.nal.usda.gov/. Accessed 04.05.2012.
149. Clark MM, Hurt RD, Croghan IT, et al. The prevalence of weight concerns in a smoking abstinence clinical trial. *Addictive behaviors.* Jul 2006;31(7):1144-1152.
150. Meyers AW, Klesges RC, Winders SE, Ward KD, Peterson BA, Eck LH. Are weight concerns predictive of smoking cessation? A prospective analysis. *Journal of consulting and clinical psychology.* Jun 1997;65(3):448-452.
151. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International journal of surgery (London, England).* 2012;10(1):28-55.
152. Lewis JA, Machin D. Intention to treat--who should use ITT? *British journal of cancer.* Oct 1993;68(4):647-650.
153. Jeremias E, Chatkin JM, Chatkin G, Seibert J, Martins M, Wagner M. Smoking cessation in older adults. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* Feb 2012;16(2):273-278.
154. Castillo EM, Goodman-Gruen D, Kritz-Silverstein D, Morton DJ, Wingard DL, Barrett-Connor E. Sarcopenia in elderly men and women: the Rancho Bernardo study. *American journal of preventive medicine.* Oct 2003;25(3):226-231.
155. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* Dec 2003;42(6):1206-1252.

156. Qian Y, Lin Y, Zhang T, et al. The characteristics of impaired fasting glucose associated with obesity and dyslipidaemia in a Chinese population. *BMC public health.* 2010;10:139.
157. Johansson G, Wikman A, Ahren AM, Hallmans G, Johansson I. Underreporting of energy intake in repeated 24-hour recalls related to gender, age, weight status, day of interview, educational level, reported food intake, smoking habits and area of living. *Public health nutrition.* Aug 2001;4(4):919-927.
158. Skov AR, Toubro S, Ronn B, Holm L, Astrup A. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* May 1999;23(5):528-536.
159. Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Annals of internal medicine.* Jul 4 2006;145(1):1-11.
160. Wong SL, Shields M, Leatherdale S, Malaison E, Hammond D. Assessment of validity of self-reported smoking status. *Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la sante / Statistique Canada, Centre canadien d'information sur la sante.* Mar 2012;23(1):47-53.
161. Windham GC, Mitchell P, Anderson M, Lasley BL. Cigarette smoking and effects on hormone function in premenopausal women. *Environmental health perspectives.* Oct 2005;113(10):1285-1290.
162. Burton S, Clark L, Jackson K. The association between seeing retail displays of tobacco and tobacco smoking and purchase: findings from a diary-style survey. *Addiction (Abingdon, England).* Jan 2012;107(1):169-175.
163. Benowitz NL. Biomarkers of environmental tobacco smoke exposure. *Environmental health perspectives.* May 1999;107 Suppl 2:349-355.
164. Kunzel B, Cabalza J, Faurot M, et al. Prospective pilot study of smoking cessation in patients undergoing urologic surgery. *Urology.* Jul 2012;80(1):104-109.
165. Dhavan P, Bassi S, Stigler MH, et al. Using salivary cotinine to validate self-reports of tobacco use by Indian youth living in low-income neighborhoods. *Asian Pacific journal of cancer prevention : APJCP.* 2011;12(10):2551-2554.
166. Lee SS, Seo JS, Kim SR, et al. The changes of blood glucose control and lipid profiles after short-term smoking cessation in healthy males. *Psychiatry investigation.* Jun 2011;8(2):149-154.
167. Fagerstrom K, Rutqvist LE, Hughes JR. Snus as a smoking cessation aid: a randomized placebo-controlled trial. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Mar 2012;14(3):306-312.
168. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* Jul 5 2006;296(1):64-71.
169. Stookey GK, Katz BP, Olson BL, Drook CA, Cohen SJ. Evaluation of biochemical validation measures in determination of smoking status. *Journal of dental research.* Oct 1987;66(10):1597-1601.
170. Klesges RC, Winders SE, Meyers AW, et al. How much weight gain occurs following smoking cessation? A comparison of weight gain using both continuous and point prevalence abstinence. *Journal of consulting and clinical psychology.* Apr 1997;65(2):286-291.
171. Love SJ, Sheffer CE, Bursac Z, Prewitt TE, Krukowski RA, West DS. Offer of a weight management program to overweight and obese weight-concerned smokers

improves tobacco dependence treatment outcomes. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* Jan-Feb 2011;20(1):1-8.

172. Hall SM, Tunstall CD, Vila KL, Duffy J. Weight gain prevention and smoking cessation: cautionary findings. *American journal of public health.* Jun 1992;82(6):799-803.

173. Altman DG. Statistics and ethics in medical research: III How large a sample? *British medical journal.* Nov 15 1980;281(6251):1336-1338.

174. Mojtahedi MC, Thorpe MP, Karampinos DC, et al. The effects of a higher protein intake during energy restriction on changes in body composition and physical function in older women. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Nov 2011;66(11):1218-1225.

175. Due A, Toubro S, Skov AR, Astrup A. Effect of normal-fat diets, either medium or high in protein, on body weight in overweight subjects: a randomised 1-year trial. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* Oct 2004;28(10):1283-1290.

176. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. *Diabetologia.* Apr 2011;54(4):731-740.

177. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ (Clinical research ed.).* Sep 11 1999;319(7211):670-674.

178. Friedmann N, Klutzaritz V, Webster L. Long-term safety of Remoxy(R) (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain. *Pain medicine (Malden, Mass.).* May 2011;12(5):755-760.

179. Kasteridis P, Yen ST. Smoking cessation and body weight: evidence from the behavioral risk factor surveillance survey. *Health services research.* Aug 2012;47(4):1580-1602.

180. Goris AH, Westerterp KR. Underreporting of habitual food intake is explained by undereating in highly motivated lean women. *The Journal of nutrition.* Apr 1999;129(4):878-882.

181. Vaz JS, Bittencourt M, Almeida JC, Gross JL, De Azevedo MJ, Zelmanovitz T. Protein intake estimated by weighed diet records in patients with type 2 diabetes: misreporting and intra-individual variability using 24-hour nitrogen output as criterion standard. *Journal of the American Dietetic Association.* May 2008;108(5):867-872.

182. Hill RJ, Davies PS. The validity of self-reported energy intake as determined using the doubly labelled water technique. *The British journal of nutrition.* Apr 2001;85(4):415-430.

183. Bandini LG, Schoeller DA, Cyr HN, Dietz WH. Validity of reported energy intake in obese and nonobese adolescents. *The American journal of clinical nutrition.* Sep 1990;52(3):421-425.

184. Allen SS, Hatsukami D, Brintnell DM, Bade T. Effect of nicotine replacement therapy on post-cessation weight gain and nutrient intake: a randomized controlled trial of postmenopausal female smokers. *Addictive behaviors.* Aug 2005;30(7):1273-1280.

185. Nelson M, Black AE, Morris JA, Cole TJ. Between- and within-subject variation in nutrient intake from infancy to old age: estimating the number of days required to rank dietary intakes with desired precision. *The American journal of clinical nutrition.* Jul 1989;50(1):155-167.

186. Brooking LA, Williams SM, Mann JI. Effects of macronutrient composition of the diet on body fat in indigenous people at high risk of type 2 diabetes. *Diabetes research and clinical practice.* Apr 2012;96(1):40-46.
187. Layman DK, Evans E, Baum JI, Seyler J, Erickson DJ, Boileau RA. Dietary protein and exercise have additive effects on body composition during weight loss in adult women. *The Journal of nutrition.* Aug 2005;135(8):1903-1910.
188. Feart C, Alles B, Merle B, Samieri C, Barberger-Gateau P. Adherence to a Mediterranean diet and energy, macro-, and micronutrient intakes in older persons. *Journal of physiology and biochemistry.* Jul 4 2012.
189. Temme E, Huybrechts I, Vandevijvere S, et al. Energy and macronutrient intakes in Belgium: results from the first National Food Consumption Survey. *The British journal of nutrition.* Jun 2010;103(12):1823-1829.
190. Vilar L, Oliveira CP, Faintuch J, et al. High-fat diet: a trigger of non-alcoholic steatohepatitis? Preliminary findings in obese subjects. *Nutrition (Burbank, Los Angeles County, Calif.).* Nov-Dec 2008;24(11-12):1097-1102.
191. Shahar DR, Yu B, Houston DK, et al. Misreporting of energy intake in the elderly using doubly labeled water to measure total energy expenditure and weight change. *Journal of the American College of Nutrition.* Feb 2010;29(1):14-24.
192. Bingham SA, Cassidy A, Cole TJ, et al. Validation of weighed records and other methods of dietary assessment using the 24 h urine nitrogen technique and other biological markers. *The British journal of nutrition.* Apr 1995;73(4):531-550.
193. Tooze JA, Krebs-Smith SM, Troiano RP, Subar AF. The accuracy of the Goldberg method for classifying misreporters of energy intake on a food frequency questionnaire and 24-h recalls: comparison with doubly labeled water. *European journal of clinical nutrition.* May 2012;66(5):569-576.
194. Briefel RR, Sempos CT, McDowell MA, Chien S, Alaimo K. Dietary methods research in the third National Health and Nutrition Examination Survey: underreporting of energy intake. *The American journal of clinical nutrition.* Apr 1997;65(4 Suppl):1203S-1209S.
195. Maurer J, Taren DL, Teixeira PJ, et al. The psychosocial and behavioral characteristics related to energy misreporting. *Nutrition reviews.* Feb 2006;64(2 Pt 1):53-66.
196. Marcus BH, Albrecht AE, King TK, et al. The efficacy of exercise as an aid for smoking cessation in women: a randomized controlled trial. *Archives of internal medicine.* Jun 14 1999;159(11):1229-1234.
197. Marcus BH, Lewis BA, Hogan J, et al. The efficacy of moderate-intensity exercise as an aid for smoking cessation in women: a randomized controlled trial. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Dec 2005;7(6):871-880.
198. Bize R, Willi C, Chiolero A, et al. Participation in a population-based physical activity programme as an aid for smoking cessation: a randomised trial. *Tobacco control.* Dec 2010;19(6):488-494.
199. Ussher M, West R, McEwen A, Taylor A, Steptoe A. Efficacy of exercise counselling as an aid for smoking cessation: a randomized controlled trial. *Addiction (Abingdon, England).* Apr 2003;98(4):523-532.
200. Ussher M, West R, McEwen A, Taylor A, Steptoe A. Randomized controlled trial of physical activity counseling as an aid to smoking cessation: 12 month follow-up. *Addictive behaviors.* Dec 2007;32(12):3060-3064.

201. Chiolero A, Wietlisbach V, Ruffieux C, Paccaud F, Cornuz J. Clustering of risk behaviors with cigarette consumption: A population-based survey. *Preventive medicine.* May 2006;42(5):348-353.
202. Rodin J. Weight change following smoking cessation: the role of food intake and exercise. *Addictive behaviors.* 1987;12(4):303-317.
203. Swan GE, Carmelli D. Characteristics associated with excessive weight gain after smoking cessation in men. *American journal of public health.* Jan 1995;85(1):73-77.
204. Leslie WS, Koshy PR, Mackenzie M, et al. Changes in body weight and food choice in those attempting smoking cessation: a cluster randomised controlled trial. *BMC public health.* May 29 2012;12(1):389.
205. Layman DK, Boileau RA, Erickson DJ, et al. A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. *The Journal of nutrition.* Feb 2003;133(2):411-417.
206. Westerterp-Plantenga MS, Lejeune MP, Nijs I, van Ooijen M, Kovacs EM. High protein intake sustains weight maintenance after body weight loss in humans. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* Jan 2004;28(1):57-64.
207. Weigle DS, Breen PA, Matthys CC, et al. A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. *The American journal of clinical nutrition.* Jul 2005;82(1):41-48.
208. Parker B, Noakes M, Luscombe N, Clifton P. Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. *Diabetes care.* Mar 2002;25(3):425-430.
209. Wycherley TP, Noakes M, Clifton PM, Cleanthous X, Keogh JB, Brinkworth GD. A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. *Diabetes care.* May 2010;33(5):969-976.
210. Slentz CA, Duscha BD, Johnson JL, et al. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE--a randomized controlled study. *Archives of internal medicine.* Jan 12 2004;164(1):31-39.
211. Krieger JW, Sitren HS, Daniels MJ, Langkamp-Henken B. Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression 1. *The American journal of clinical nutrition.* Feb 2006;83(2):260-274.
212. Balkau B, Vierron E, Vernay M, et al. The impact of 3-year changes in lifestyle habits on metabolic syndrome parameters: the D.E.S.I.R study. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology.* Jun 2006;13(3):334-340.
213. Lejeune MP, Kovacs EM, Westerterp-Plantenga MS. Additional protein intake limits weight regain after weight loss in humans. *The British journal of nutrition.* Feb 2005;93(2):281-289.
214. Josse AR, Atkinson SA, Tarnopolsky MA, Phillips SM. Increased consumption of dairy foods and protein during diet- and exercise-induced weight loss promotes fat mass loss and lean mass gain in overweight and obese premenopausal women. *The Journal of nutrition.* Sep 2011;141(9):1626-1634.
215. Thompson HJ, Sedlacek SM, Paul D, et al. Effect of dietary patterns differing in carbohydrate and fat content on blood lipid and glucose profiles based on weight-loss

success of breast-cancer survivors. *Breast cancer research : BCR.* Jan 6 2012;14(1):R1.

216. Rock CL, Flatt SW, Thomson CA, et al. Plasma triacylglycerol and HDL cholesterol concentrations confirm self-reported changes in carbohydrate and fat intakes in women in a diet intervention trial. *The Journal of nutrition.* Feb 2004;134(2):342-347.

217. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical trial. *American heart journal.* Jan 2011;161(1):145-151.

218. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. *Preventive medicine.* Oct 2003;37(4):283-290.

219. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, et al. Body weight and low-density lipoprotein cholesterol changes after consumption of a low-fat ad libitum diet. *JAMA : the journal of the American Medical Association.* Nov 8 1995;274(18):1450-1455.

220. Phillips SM, Van Loon LJ. Dietary protein for athletes: from requirements to optimum adaptation. *Journal of sports sciences.* 2011;29 Suppl 1:S29-38.

221. Volek JS, Phinney SD, Forsythe CE, et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. *Lipids.* Apr 2009;44(4):297-309.

222. Santesso N, Akl EA, Bianchi M, et al. Effects of higher- versus lower-protein diets on health outcomes: a systematic review and meta-analysis. *European journal of clinical nutrition.* Jul 2012;66(7):780-788.

223. Gulseth HL, Gjelstad IM, Tierney AC, et al. Dietary fat modifications and blood pressure in subjects with the metabolic syndrome in the LIPGENE dietary intervention study. *The British journal of nutrition.* Jul 2010;104(2):160-163.

224. Nowson CA, Worsley A, Margerison C, Jorna MK, Godfrey SJ, Booth A. Blood pressure change with weight loss is affected by diet type in men. *The American journal of clinical nutrition.* May 2005;81(5):983-989.

225. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *The New England journal of medicine.* Apr 17 1997;336(16):1117-1124.

226. Leiter LA, Abbott D, Campbell NR, Mendelson R, Ogilvie RI, Chockalingam A. Lifestyle modifications to prevent and control hypertension. 2. Recommendations on obesity and weight loss. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* May 4 1999;160(9 Suppl):S7-12.

227. Lee DH, Ha MH, Kim JR, Jacobs DR, Jr. Effects of smoking cessation on changes in blood pressure and incidence of hypertension: a 4-year follow-up study. *Hypertension.* Feb 2001;37(2):194-198.

228. Mikkelsen PB, Toubro S, Astrup A. Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrate. *The American journal of clinical nutrition.* Nov 2000;72(5):1135-1141.

229. de Souza RJ, Bray GA, Carey VJ, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. *The American journal of clinical nutrition.* Mar 2012;95(3):614-625.

Appendices

Appendix 1: Advertisement

Appendix 2: Flow chart of the study

Appendix 3: Food diary

Appendix 4: Written information to the participants randomized to the low fat diet high in complex carbohydrates.

Appendix 5: Written information to the participants randomized to the high protein diet moderately reduced in carbohydrates.

Appendix 6: Recipes for the low fat diet high in complex carbohydrates.

Appendix 7: Recipes for the high protein diet moderately reduced in carbohydrates.

Appendix 8: Alternative proposals for a diet plan for the low fat diet high in complex carbohydrates.

Appendix 9: Alternative proposals for a diet plan for the high protein diet moderately reduced in carbohydrates.

Appendix 10: The lunches and snack meals offered in both intervention groups.

Appendix 11: Macronutrient composition of the three lunches and snack meals.

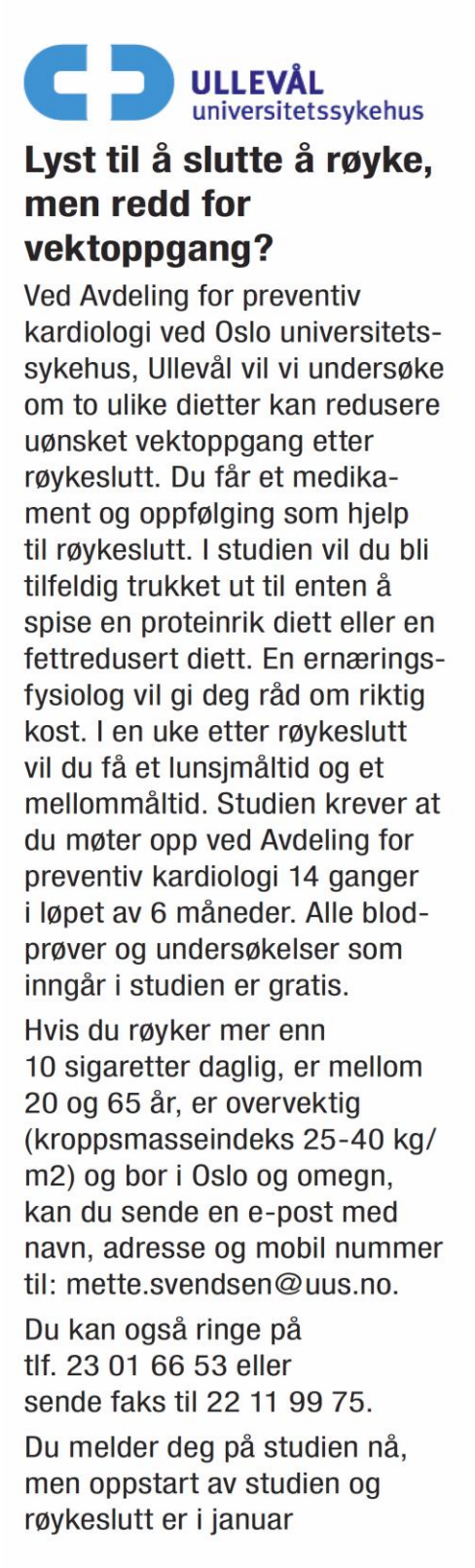
Appendix 12: Smoking diary

Appendix 13: Fagerström Test for Nicotine Dependence (Norwegian version).

Appendix 14: Averages used in the coding of the dietary records.

Appendix 15: Written information and informed consent.

Appendix 1: Advertisement



ULLEVÅL universitetssykehus

Lyst til å slutte å røyke, men redd for vektoppgang?

Ved Avdeling for preventiv kardiologi ved Oslo universitetssykehus, Ullevål vil vi undersøke om to ulike dietter kan redusere uønsket vektoppgang etter røykeslutt. Du får et medikament og oppfølging som hjelp til røykeslutt. I studien vil du bli tilfeldig trukket ut til enten å spise en proteinrik diett eller en fettredusert diett. En ernæringsfysiolog vil gi deg råd om riktig kost. I en uke etter røykeslutt vil du få et lunsjmåltid og et mellommåltid. Studien krever at du møter opp ved Avdeling for preventiv kardiologi 14 ganger i løpet av 6 måneder. Alle blodprøver og undersøkelser som inngår i studien er gratis.

Hvis du røyker mer enn 10 sigaretter daglig, er mellom 20 og 65 år, er overvektig (kroppsmasseindeks 25-40 kg/m2) og bor i Oslo og omegn, kan du sende en e-post med navn, adresse og mobil nummer til: mette.svendsen@uus.no.

Du kan også ringe på tlf. 23 01 66 53 eller sende faks til 22 11 99 75.

Du melder deg på studien nå, men oppstart av studien og røykeslutt er i januar

Appendix 2: Flow chart of the study

Weeks	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	24
	I----------			I----------				I----------								II----------	I
	S*	R*		SC*													Study end
Physical examination	X																
Body weight	X	X	X	X	X	X	X	X		X		X		X		X	X
Body composition		X						X								X	
Waist/hip-ratio		X						X								X	X
Blood pressure	X	X						X								X	
Laboratory measurements	X	X						X								X	
Urine test		X														X	
Resting metabolic rate		X						X									
Physical activity registration		X						X									
CO measurement	X	X	X	X	X	X	X	X		X		X		X		X	X
Counseling for SC*	X	X	X	X	X	X	X	X		X		X		X		X	X
Determination of SC*	X																
Varenicline treatment			X								(X)				X		
Smoking diary	X	X	X	X	X	X	X	X									
FTND*	X																
MNWS*				X	X	X	X	X		X		X		X		X	
EBQ*		X						X								X	
Dietary records (start)	X						X										
Dietary counseling	X	X	X	X	X	X	X	X		X		X		X		X	X

* S: Screening, R: Randomization, SC: Smoking cessation, FTND: Fagerström Test for Nicotine Dependence, MNWS: Minnesota Nicotine Withdrawal Questionnaire, EBQ: Eating behavior questionnaire. Everything marked with blue is not included in the master thesis.

Appendix 3: Food diary (2 pages)

Dag/dato:_____ Screeningnr:_____

Informasjon

Som deltager i denne studien ved Avdeling for preventiv kardiologi ved Oslo universitetssykehus Ullevål skal du nå skrive ned alt det du spiser og drikker i 7 dager.

Det er viktig at du **spiser og drikker det du vanligvis pleier og ikke endrer på inntaket ditt** fordi du skal veie eller anslå det du spiser. Det å registrere matinntaket over mange dager er slitsom, men det kan være en god hjelp for deg fordi du blir bevisst på dine matvaner. Dette er spesielt viktig nå som du skal slutte å røyke.

- Start med å skrive ned det første du drikker/putter i munnen den dagen registreringen starter. Skriv på ny linje for hver matvare. Spesifiser så nøyaktig du kan (f.eks: Gulost, lettere)
- Husk å føre opp om du bruker smør på brødskiven, olje til steking, dressing, saus etc.
- **Mengde:** Du vil få utdelt en vekt for best og mest mulig nøyaktig kunne registrere det du spiser/drikker. Vei en og en ting av gangen, og husk å nulle ut mellom hver matvare. Hvis du veier med kopp eller tallerken husk å nulle ut vekten før du legger på mat/drikke.

Tips:

- Når du har veid noe en gang, kan denne vekten kan du brukes hvis du spiser det samme ved en annen anledning (for eksempel ved lik frokost hver dag).
- Dersom det du skal spise har emballasje hvor det står oppført vekt på maten/drikken fører du opp dette i skjemaet.
- Dersom det av ulike grunner er vanskelig å få veid, skriver du ca størrelse; 1 glass, stk, 1 skive, osv. Husk uansett å skrive så detaljert som mulig.
- Ha med deg skjema der du er slik at du fortløpende kan føre opp;- lett å glemme underveis i løpet av dagen. Husk å føre opp drikke.

NB: Bein, skall osv, veies for seg etterpå og trekkes fra vekten på den totale matvaren. Dersom dette blir vanskelig- husk å notere at vekten på matvaren inkluderer bein osv.

Dag/dato:__________ Screeningnr:___________

Tidspunkt	Spist/drukket	Mengde

Appendix 4: Information about the low fat diet high in complex carbohydrates (3 pages).

Til deg på lav-fett kost

Bakgrunn for lav-fettkosten

De offentlige anbefalingene sier mindre enn 30 prosent av energien vi får fra maten vi spiser skal komme fra fett. Siden fett inneholder mer enn dobbelt så mye energi per gram sammenlignet med karbohydrater og proteiner vil man ved å redusere på mengden fett i kosten lettere kunne redusere det totale inntaket av energi (kilokalorier). Videre er det anbefalt at rundt 50-60 prosent av den energien vi spiser skal komme fra karbohydrat, og da fortrinnsvis fra grove kornprodukter, frukt og grønnsaker. Dette er matvarer som bidrar til å øke mettheten, samtidig som de bidrar til et kosthold som inneholder mindre energi.

Hva innebærer denne lavfett kosten?

I denne kosten vil det fokuseres på å redusere inntaket av fett.

Først og fremst vil du redusere:

- Mettet fettet fra fete meieriprodukter (for eksempel ost, fløte, rømme)
- Opplaget kjøttmat (f.eks kjøttdeig, pølser og salami). Kjøttet som velges bør være magert, og kan være feks **kylling uten skinn, rent svinekjøtt, kalkun, biff** etc. Skal du lage retter som inneholder kjøttdeig, velg enten karbonadedeig eller kjøttdeig av svinekjøtt eller kylling istedet. Alle inneholder mindre fett en vanlig kjøttdeig.
- Smør på brødet (erstatt med lettere varianter)
- Sjokolade, kaker og snacks, samt fra friterte matvarer (for eksempel potetchips, pommes frites og panert fisk)

Det umettede fettet fra olje, myk margarin, majones, avocado, oliven og nøtter, trenger vi i kosten. Hvis du bruker mer enn 1 ss av disse matvarene i måltidene vil du bli bedt om å redusere mengden til ca 1 ts per måltid. Fet fisk inneholder også fett som kroppen trenger å få tilført gjennom maten vi spiser. I denne kosten anbefaler vi at du spiser fet fisk som pålegg og til middag, men hvis du spiser doble porsjoner må du redusere litt på porsjonsstørrelsen.

En annen god måte å redusere inntaket av fett på er ved å sørge for at det er mye grønnsaker og frukt i kosten. Da spiser du deg mett på matvarer som inneholder veldig lite fett. Sørg derfor for at det er rikelig med **grønnsaker** både til middag og andre måltider, både som tillegg i måltidet, som snacks og som pålegg.

Bruk grønnsaker og frukt som mellommåltider og snacks. **Sukkererter, babygulrøtter, cherrytomater, eplebiter, gulrøtter, smoothie (med bær og banan). Druer** kan også fryses og spises frosne. Den første uken vil det bli utdelt yoghurt med musli (Go' morgen) som mellommåltid. Andre alternativer til mellommåltider kan være **frukt, grønnsaker, havregrøt med melk, lettyoghurt og knekkebrød med prim**.

Matvarer som inneholder mye fiber gir metthetsfølelse. Derfor anbefaler vi grove kornprodukter. Vi anbefaler deg at du velger det groveste brødet slik som merket under viser.

Til middag er det fint å velge **fullkornspasta, grov naturris eller andre gryn som bulgur**. Kok gjerne opp store porsjoner av dette, og bruk i salater til lunsj.



Du deltar nå i en studie der vi skal undersøke forskjellen mellom to ulike dietter. Diettene må være så ulike som mulig. Siden den andre kosten inneholder mye protein, er det viktig at du begrenser proteininntaket så mye som mulig i denne perioden du er med i studien. Proteiner finnes i de fleste matvarer, men i ulik grad. Matvarer som kjøtt, kylling, fisk, skalldyr og egg, og pålegg av kjøtt og fisk inneholder mye proteiner. Siden denne kosten skal ha et moderat innhold av proteiner er det et tips å spare store proteinkilder til middagsmåltidet.

Middagsmåltidet bør bestå av godt med grønnsaker. Ta utgangspunkt i at **halve tallerkenen din skal være dekket med grønnsaker**, og bruk **gjerne flere forskjellige typer** samtidig. Lag gjerne store porsjoner med middag, slik at du kan bruke som lunsj eller middag dagen etter. For forslag til middags- og lunsjretter se de vedlagte oppskriftene.

Gode påleggsalternativer kan være **lettsyltetøy, mager smøreost med ekstra grønnsaker på toppen, lettere brunost, mager prim, banan**. Siden kosten ikke skal inneholde for mye proteiner er det viktig at du ikke spiser for mye proteinrike pålegg hvis du ønsker kjøtt eller fisk til middagen. Pålegg som kokt skinke, reker, cottage cheese, mager leverpostei og gulost er rike på proteiner og bør derfor ikke spises på mer enn 1-2 skiver per dag.

Sukker er en type karbohydrat som inneholder energi, men ellers ingen næringsstoffer. Mange matvarer som inneholder mye sukker inneholder også mye fett, og er svært energirike. Matvarer som sjokolade, kaker, wienerbrød, muffins, kjeks, is og brus vil måtte begrenses så mye som mulig. Dette gjelder også salte og fete snacksprodukter som potetchips og peanøtter. Det kan være lurt å velge seg en fast dag i uka der du kan spise ditt valgte lørdagsgodteri.

Kaffe
Etter røykeslutt vil kroppen tåle kaffe dårligere enn den gjorde mens du røkte. Det betyr at du kan oppleve symptomer som rastløshet, søvnløshet og konsentrasjonsvansker.

Du kan også få problemer som diaré og kvalme om du drikker for mye kaffe. Det vil derfor være en fordel for deg om du reduserer inntaket av kaffe, og maksimalt drikker 2-3 kopper per dag.

Tips:

- Lag måltidsrutiner og vær forberedt. Planlegg dagen med tanke på hva du skal spise, når du skal spise og om du trenger å ha med mat/matpakke.
- Planlegg gjerne flere dager frem i tid, og sett opp handleliste når du skal i butikken
- Bruk grønnsaker til alle måltider, som pålegg og snacks og ved siden av matpakke.
- Du vil få oppskrift på lunsjmåltidene som deles ut i uken etter røykeslutt. Bruk gjerne disse som lunsj også etter den første uken.
- Les varedeklarasjoner, og pass på innhold av fett. Vi anbefaler kjøttprodukter med mindre enn 10% fett og ost med mindre enn 20% fett.

Personer som slutter å røyke opplever ofte situasjoner hvor de opplever suget etter røyk ekstra sterkt. Dette kan være situasjoner eller tidspunkter hvor man tidligere pleide å røyke. Det er viktig for deg å forsøke å unngå disse situasjonene. For mange vil det også være lett å erstatte røyken med noe annet å putte i munnen. Gjør derfor ting som avleder oppmerksomheten din, som å gå deg en tur, snakke i telefonen eller noe annet. Dersom du skal spise noe, velg først og fremst frukt eller grønnsaker som ekstra snacks.

Appendix 5: Information about the high protein diet moderately reduced in carbohydrates (3 pages).

Til deg på høyprotein kost

Bakgrunn for høyprotein kosten
Proteiner er en viktig bestanddel i maten vi spiser, sammen med karbohydrater og fett. Bakgrunn for denne kosten er studier som har vist at økt inntak av protein kan være gunstig i forhold til vektregulering, knyttet til en rekke fysiologiske mekanismer.

Hva innebærer en høyprotein kost?
Høyprotein kost innebærer at du øker inntaket av fisk, skalldyr, rent kjøtt, kylling, egg og magre meieriprodukter til alle måltider. **Ved å:**

- Spise større porsjon med rent kjøtt (for eksempel filé av kylling, kalkun og svin, samt biffkjøtt) til middag og lunsj.
- Velge proteinrike pålegg som skalldyr, skinke, roastbiff, egg og fisk (tunfisk, makrell i tomat, fiskepudding, lakse postei).
- Velge lettere gulost, lettere smøreoster og cottage cheese.
- Velge proteinrik yoghurt som Skyr og Yoplait yoghurt, 0,1%.

Når du spiser mer av en matvaregruppe, vil du måtte spise mindre av en annen når du samtidig ønsker å gå ned i vekt. I denne studien skal du **spise mindre av karbohydratrike matvarer som inneholder mye sukker, samt brød, kornprodukter, ris, pasta og poteter.**

- Redusere tidligere mengde ris/potet til middag.
- Redusere antall brødskiver, spise mer pålegg.
- Forsøke å unngå sukkerrike matvarer som is, kaker, boller, muffins, kjeks, sjokolade og godteri.
- Velg vann, farris eller kunstig søtet drikke i stedet for å drikke sukkerholdig brus og saft, nektar og juice.

Når det gjelder fett, anbefaler vi at du først og fremst spiser matvarer som inneholder det fettet kroppen trenger å få tilført gjennom maten du spiser. Derfor kan du ha opptil 1 ss fett fra olje, majones, nøtter og oliven i hvert måltid.

Øk inntak	Reduser inntak	Unngå
Magre proteinrike pålegg/hovedingrediens i salater: o *Lettere gulost* o *Kokt skinke, kalkunpålegg. roastbeef* o *Egg* o *Reker, krabbe,* *Fisk og mager kjøtt* til middag: o *Kylling/svinefilet, kalkun* o *Torsk, sei* o *Makrell, laks, ørret*	Brød* Pasta, ris, poteter og couscous* Kornblanding Frukt* Kaffe	Søte drikker: *brus, saft nektar og juice* Is, kaker, boller, muffins, kjeks Sjokolade og godteri Pålegg med mye sukker (syltetøy, honning, sjokoladepålegg, brunost, prim) Potetchips og pommes frites

*Se karbohydratkvote under.

Når det gjelder grønnsaker kan disse spises i den mengden du orker etter at du har spist anbefalt mengde proteinrike matvarer.

Kaffe
Etter røykeslutt vil kroppen tåle kaffe dårligere enn den gjorde mens du røykte. Det betyr at du kan oppleve symptomer som rastløshet, søvnløshet og konsentrasjonsvansker. Du kan også få problemer som diaré og kvalme om du drikker for mye kaffe. Det vil derfor være en fordel for deg om du reduserer inntaket av kaffe, og maksimalt drikker 2-3 kopper per dag.

Karbohydratkvote
I uken med matutdeling vil lunsj og snacks måltidet gjennomsnittlig innholde litt over 10 g karbohydrat. Total må du **redusere karbohydratinntaket ditt til rundt 110 g karbohydrat per dag** for å få spist nok protein uten å samtidig gå opp i vekt. Listen under viser brød og pasta/ris alternativer som naturlig innholder mindre karbohydrater og som er gode valg på høyprotein kost. Mengden karbohydrat må likevel begrenses; **Finn ut når du har mest behov for slike matvarer, og ha kontroll på hvor mye du kan spise i løpet av en dag**

Matvare	**Mengde**	**Karbohydrat (g)**
Brødskive/ knekkebrød*	1 brødskive/2 knekkebrød	15-20g
Tørr pasta/ris	50g	35g
Grønnsaker	150g	5-15 g
Frukt	150g	15-25
Sjokolade	*100g*	*50-60*
Potetgull	*100g*	*25-30*

***Brød**: Havrebrød, 100% sammalt, pumpernikkelbrød. Se etter brødskalamerking
***Knekkebrød:** Fiber pluss, husmann, rugsprø

Matvarer som inneholder mye fiber gir metthetsfølelse. Derfor anbefaler vi grove kornprodukter. Vi anbefaler deg at du velger det groveste brødet slik som merket under viser.

Tips

- Ha gjerne dobbelt lag med proteinrikt pålegg og skjær tynne brødskiver
- Middagsmåltidet er det måltidet det er enklest å spise størst mengde protein; bruk lunsj og middagsoppskrifter utdelt som utgangspunkt.
- Ha som en regel at halvparten av tallerken skal være dekket av kjøtt/fisk. Spis deretter grønnsaker til du er forsynt. Bruk middagsrester av kjøtt og fisk til lunsj dagen etter.
- Stek kjøtt/fisk i folie i ovnen så beholder det saftigheten og blir lettere å spise
- Bruk krydder, urter og sauser (se oppskrifter) slik at kjøttet og fisken blir mer smakfult
- Lag måltidsrutiner og gjør forberedelser. Planlegg dagen med tanke hva du skal spise, når du skal spise og om du trenger å ta med deg mat/matpakke
- Sett opp handleliste før du går i butikken

Generelle tiltak ved røykesug
Ved røykeslutt er det viktig å ha alternative ting å gjøre når suget melder seg:

- Ring en telefon; snakk
- Gjør noe: Les, gå en tur
- Gjør avspenningsøvelser
- Dersom du må putte noe i munnen, sørg for å ha gode alternativer tilgjengelig:

Forslag til snacks

Snacks når du er hjemme:	**Snacks på farten**
2 fiberpluss med lett-gulost/egnet pålegg 2 husmann med egnet pålegg Knekkebrød med lett-gulost og skinke Rugsprø med egnet pålegg (se over) Rett i koppen med kokt egg Roastbeef, kokt skinke Reker (med avocado og majones)	Skyr, yoghurt Kyllingvinger Snacksposer med friske grønnsaker: *-cherrytomater* *-babygulrøtter* *-sukkererter*

Appendix 6: Recipes for the low fat diet high in complex carbohydrates (6 pages).

Forslag til oppskrifter, lavfettkost

Lunchoppskrifter:

Pastasalat med skinke:

Isbergsalat, agurk, vårløk og mais 150g
Fullkornspasta 150 g
Kokt skinke 50 g
Grønn pesto 15g/1ss

Skjær skinken i strimler
Bland med salat og rør pestoen inn i den kokte og avkjølte pastaen.

Kylling i rataouille:

Fullkornspasta 100 g
Kyllingfilet 50g

Ratatouille av:
Hakkede tomater 50g
Løk 25g
Kikerter 50 g
Paprika 25g
Squash 50g

Stek kyllingen i strimler og la surre sammen med grønnsakene i noen minutter. Tilsett krydder etter smak.

Roastbeef med wraps

Fullkornswrap 80 g
Bønner 50 g
Roastbeef 50 g
Sukkererter
Salat
Tomater 75g
Dressing, fettredusert, 15 g/ 1ss

Skjær tomatene og sukkerertene i biter, og salaten i strimler. Varm opp wraps og legg på kjøtt, bønner og grønnsaker sammen med dressing.

Bulgursalat

Bulgur 140 g
Fetaost 30g
Salat 100g
Tomat 50 g
Oliven 20g
Olje og sitrondressing 1ss.

Kok opp bulgur eller spelt helkorn og la dette avkjøles. Skjær fetaosten i terninger og kutt opp salaten. Bland med oliven og bulgur og hell over dressingen.

Curry med svin

Mager svinefilet 50 g
Bønner 50 g
Brun ris 100 g
Løk 50 g
Erter 50g
Rosiner 10 g
Ananas 50 g
Olivenolje 5 g
Krydder

Kutt kjøttet i strimler og stek i oljen. Skjær løken i biter og la surre sammen med kjøttet. Ha i erter, rosiner, bønner og ananas mot slutten.

- Bruk middagsrester fra dagen før
- Kok gjerne opp store porsjoner med pasta, bulgur, helkorn etc og bruk dette til lunsj dagen etter
- Bruk gjerne lunsjalternativene som middag

Middagsoppskrifter

Kyllingfilet på grønnsakseng
(2 porsjoner)

2 kyllingfileter
1/2 rødløk
100 g purre
1 rød chili
2 tomater
1/2 grønn squash
1/2 aubergine
1 ss olivenolje
1 ss frisk hakket rosmarin

I stekeovn ved 180 °C

Del grønnsakene i passe biter og legg dem i en ildfast form sammen med kyllingfiletene. Hell over olje og dryss på krydder, salt og pepper. Stek retten 15-20 minutter.
Hell over litt ekstra vann m/buljong, og bruk dette som saus.

Serveres sammen med grov ris eller bulgur, og kokt brokkoli.

Ovnsbakt kyllingfilet m/sennep og tomat
(2 porsjoner)

2 kyllingfileter
1 ss dijonsennep
4 tomater
salt og kvernet pepper
1 ss griljermel/vanlig mel
1/2 ss mandelflak

Tørk kyllingfiletene godt og klem dem med hånden, slik at de blir litt flate. Bre et lag dijonsennep på hver. Skjær tomatene i tynne skiver og legg dem på kyllingfiletene. Bland sammen griljermel og mandelflak og dryss over. Legg bakepapir i bunnen av en liten ildfast for form og legg kyllingfiletene i formen. Stek filetene ved 180 °C i ca. 25 minutter.

Serveres med grov ris, fullkornspasta, spelt helkorn eller bulgur.

Kylling- og grønnsakwok
(2 porsjoner)

2 kyllingfileter, strimlet
1 ss olje
400 g blandede grønnsaker (paprika, vårløk, brokkoli, gulrot)
1/2 rød chili, finhakket
1 hvitløkbåter, finhakket
1/2 tommelstor bit ingefær, finhakket
1 ss soyasaus
Frisk koriander eller vårløk, hakket

Varm litt av oljen i en wokpanne eller en dyp stekepanne og stek kyllingbitene på høy temperatur til de er nesten gjennomstekt.
Ta dem ut av pannen og hold dem varme. Varm opp pannen igjen med resten av oljen og fres grønnsakene raskt sammen med chili, hvitløk, ingefær og cashewnøtter. Tilsett kjøtt og soyasaus, og stek det hele til det er gjennomvarmt. Dryss over hakkede urter.

Kyllingfilet med hvitvin
(1 porsjon)

1 kyllingfilet
2-3 champignoner
½ løk
litt hvitvin

Legg kyllingfilet sammen med sopp og løk i aluminiumsfolie. Dryss over salt og pepper, og hell over litt hvitvin. Stekes på 230 grader i cirka 30 minutter.
Serveres med enten grov ris/bulgur eller ovnsbakte båtpoteter. Skjær 2 små poteter i båter, og legg dem med skallet ned i en ildfastform. Dryss over salt og timian, og stek samtidig med kyllingfileten, samme temperatur og tid.

Steinbitfilet med hvitvin
(1 porsjon)

1 steinbitfilet, ca 130 g
2-3 champignoner
2 små soltørkede tomater
½ løk
litt hvitvin

Samme oppskriften som for kyllingfilet :)

Snitt opp de tørre tomatene og legg i bunnen. Legg fisken sammen med sopp og løk i aluminiumsfolien oppå tomatene. Dryss over salt og pepper, og hell over litt hvitvin.
Stekes på 230 grader i cirka 30 minutter.
Serveres med enten grov ris/bulgur eller ovnsbakte båtpoteter. Skjær 2 små poteter i båter, og legg dem med skallet ned i en ildfastform. Dryss over salt og timian, og stek samtidig med fisk og grønnsaker, samme temperatur og tid.

Smaker godt sammen med kokt brokkoli, grov ris eller bulgur.

Ovnsbakt fisk

Legg laks, ørret eller steinbitfilet i folie.
Smør over pesto eller olje med krydder.

Pakk sammen og stek i ovnen. Fileter ca 20 min på 200 grader. Prøv deg frem.

Ha gjerne også tomater, løk, sopp, paprika etc i folien, og kok opp gulrøtter og brokkoli ved siden av. Serveres sammen med kokte poteter eller grov ris.

Appendix 7: Recipes for the high protein diet moderately reduced in carbohydrates (4 pages).

Forslag til oppskrifter, høyproteinkost

Lunchoppskrifter:

Ost og skinkesalat:

Kokt skinke, 125g. Lettgulost, 50g. Isbergsalat 100g. Grønn pesto, 30g

-Skjær skinken i strimler og riv osten. Bland med salat og bruk pesto som dressing

Kylling i rataouille:

Kyllingfilet, 175g. Hakkede tomater, 50g. Løk, 25g. Paprika, 25g. Squash, 50g. Olivenolje, 1 ss.

-Stek kyllingen i strimler med oljen og la surre sammen med grønnsakene i noen minutter. Tilsett krydder etter smak.

Roasbeef og grønnsaker

Roastbeef, 175g. Sukkererter, Salat, Tomater. Olivenolje, 1 ss.

-Skjær tomatene i biter og skjær salaten i strimler. Bland med kjøttet og vend inn oljen.

Tunfisksalat

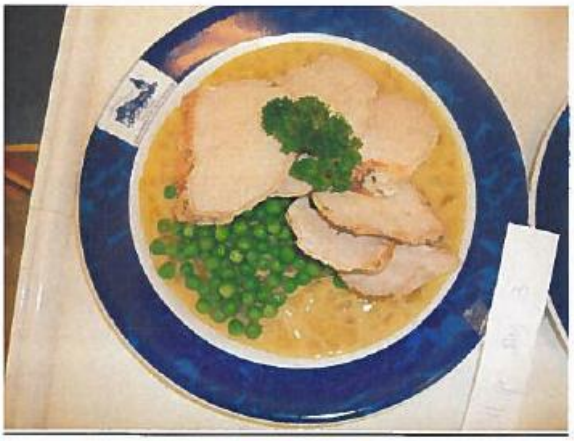
Tunfisk, 135g. Fetaost, 50g. Salat, 100g. Oliven, 20g. Olje og sitrondressing, 30g.

-Skjær opp feta i terninger og kutt opp salaten. Bland med oliven og tunfisk og hell over dressingen.

Curry med svin

Mager svinfilet, 175 g. Løk, 50g.
Erter, 50g. Melk, 50g.
Olje, 1ss.

-Kutt kjøttet i strimler og stek i oljen. Skjær løken i biter og la surre sammen med kjøttet og melken. Ha i erter mot slutten.



Middagsoppskrifter (til 2 pers):

Kyllingfilet på grønnsaksseng

400g kyllingfilet (4 små kyllingfileter)
1 rødløk
1 rød chili
3 tomater
1 grønn squash
1/2 aubergine
4 ss olivenolje
1 ss frisk hakket rosmarin

Del grønnsakene i passe biter og legg dem i en ildfast form sammen med kyllingfiletene. Hell over olje og dryss på krydder, salt og pepper. Stek retten 15-20 minutter, 180 °C

Ovnsbakte kyllingfileter med sennep og tomat

400g kyllingfilet
2 ss dijonsennep
2 tomater
salt og kvernet pepper
1 ss griljermel/vanlig mel
1 ss mandelflak

Tørk kyllingfiletene godt og klem dem med hånden, slik at de blir litt flate. Bre et lag dijonsennep på hver. Skjær tomatene i tynne skiver og legg dem på kyllingfiletene. Bland sammen griljermel og mandelflak og dryss over. Legg bakepapir i bunnen av en liten ildfast for form og legg kyllingfiletene i formen. Stek filetene ved 180 °C i ca. 25 minutter.

Kylling- og grønnsakwok

400g kyllingfileter, strimlet (eller 1 pakke strimlet kyllingkjøtt)
2 ss solsikkeolje
200 g blandede grønnsaker (paprika, vårløk, brokkoli, gulrot,
1 rød chili, finhakket
2 hvitløkbåter, finhakket
1 tommelstor bit ingefær, finhakket
50 g cashewnøtter
1 ss soyaasaus
1 ½ dl ferdig wok-saus
Frisk koriander eller vårløk, hakket

Varm 1 ss av oljen i en wokpanne eller en dyp stekepanne og stek kyllingbitene på høy temperatur til de er nesten gjennomstekt. Ta dem ut av pannen og hold dem varme. Varm opp pannen igjen med resten av oljen og fres grønnsakene raskt sammen med chili, hvitløk, ingefær og cashewnøtter. Tilsett kjøttet, sojasaus og wok-sausen, og stek det hele til det er gjennomvarmt. Dryss over hakkede urter.

Laks i folie

Legg laks, ørret eller steinbitfilet i folie.
Smør over pesto eller olje med krydder/ha i sopp, grønnsaker, urter osv.

Pakk sammen og stek i ovnen. Fileter ca 20 min på 200 grader. Prøv deg frem.

Omelett med ost og skinke

4 egg
4ss vann
litt salt
litt smør til steking

Visp sammen egg, vann og salt og hell røren i en stekepanne. Pannen må være så varm at en smørklatt freser når den slippes i. Trekk røren inn mot midten. Omeletten vil være ferdig på noen minutter. Hakk oppp skinke og gulost og legg på den ene halvdelen,- den andre halvdelen brettes over

Appendix 8: Alternative proposals for a diet plan for the low fat diet high in complex carbohydrates (2 pages).

Alternative forslag til kostplan fettredusert diett

Frokost-alternativer (300-400 kcal)

1. Grovbrød, 2 skiver (ca 120 g), med en banan og lettsyltetøy (2 ss)
2. Grovbrød, 2 skiver (ca 120 g), en skive med lettsyltetøy (2 ss) og en skive med lettere brunost (2 høvelskiver)
3. Grovt knekkebrød (3 stk, grovt, type Husman), tynt lag med lettmargarin. Et knekkebrød med magerost (bacon, skinke etc), et med lettsyltetøy (1 ss), et med kokt skinke (1 skive). Pynt med tomat og agurk
4. Kornblanding (feks 4korn, 1,5 dl) med 2 dl lettyoghurt

Lunsj-alternativer (250-500 kcal)

- Grovbrød, 2 skiver (ca 120 g), en med makrell-i-tomat (25 g) og agurk, og en med lettere brunost (2 skiver)
- Grovt rundstykke (ca 80 g), med lettmargarin og kokt skinke (2 skiver). Salat ved siden av, med isbergsalat, tomat, agurk og mais, og litt dressing.
- Rett-i-koppen-suppe med en skive grovbrød med lettmargarin og kokt skinke
- Alternativer fra oppskriftsheftet

Middags-alternativer

- Kyllingfilet (150 g) stekt i olje (10 g), med kokt ris (150 g) og grønnsaker
- Laksefilet (125 g) stekt i olje (10 g), med kokt potet(150 g) og grønnsaker
- Pasta (150 g kokt), med tomatsaus: karbonadedeig (100 g) stekt i olje (10 g), hermetiske tomater (2 dl), løk og sopp
- Fiskeburger (ca 150 g), stekt i olivenolje (10 g) med løk og sopp, med grønnsaker og kokt potet (150 g)

Mellommåltider under 100 kcal

- 200 g frukt
- en stor pose knaskerøtter (300 g)
- 1 beger sukkererter (150 g)
- Rett-i-koppen suppe (tomat, kylling etc)
- Salat med pasta (40 g), uten dressing
- 1 knekkebrød med pålegg (feks 1 ss lettsyltetøy, ½ banan, magerost, lettere prim)

Mellommåltider under 200 kcal

- Lettere Go' morgen/YT
- 2 grove knekkebrød med lettere brunost (2 skiver) og kokt skinke (2 skiver)
- 1 knekkebrød med banan og lettsyltetøy
- 1 eple i biter med 1,5 dl lettere vaniljeyoghurt over

Drikke, ca 100 kcal

- Skummetmelk (2 dl)
- Appelsinjuice (2 dl)
- Sukkerholdig brus (2 dl)
- 1 glass vin (1,5 dl)
- 1 flaske pils (3,3 dl)
- Brennevin, 4 cl

Energitette måltider (250-500 kcal)

- 1 liten hamburger
- 1 pølse med pølsebrød
- 1 stor hvetebolle
- 1 skolebrød
- 1 wienerbrød
- 1 muffins
- 1 vaffelplate med syltetøy
- 1 iskrem i kjeks
- 1 liten sjokolade
- 4 salte kjeks med ost
- 1 pakke nudler
- ½ liter sjokolademelk
- 1 flaske vin
- 1 liter brus

Energitette måltider (1000-1500 kcal)

- 1 pizza (580 g)
- 1 stor hamburger med pommes frites
- 1 pose boller
- 1 pakke kjeks
- 1 stor plate (200 g) sjokolade
- 1 pose (180 g) peanøtter
- 1 pakke (250 g) saltstenger
- 1 pose (300 g) smågodt
- 1 six-pack pils

Energitette måltider (ca 2000 kcal)

- 2 liter is
- 1 stor pose potetchips
- 1 eske konfekt

Appendix 9: Alternative proposals for a diet plan for the high protein diet moderately reduced in carbohydrates (2 pages).

Alternative forslag til kostplan
Proteinrik diett

Frokost alternativ (300-400 kcal)

- To knekkebrød med myk lettmargarin; ett med to skiver med lettere gulost (40g), ett med to skiver med kalkunpålegg, pluss salatgrønnsaker ved behov.
- En skive grovt brød til stekt egg, røkt skinke, tomater og oliven (15g).
- To knekkebrød med myk lettmargarin; ett med med smøreost, og ett med roastbiff og majones (lettere),- pluss salatgrønnsaker.

Lunsjalternativer (300-400 kcal)

- Et grovt rundstykke med myk lettmargarin. Salat med 100g kyllingfilet/tunfisk/roastbiff. Dressing, 1ss.
- 3 knekkebrød med myk lettmargarin; ett med makrell i tomat (30g), ett med lettere gulost (3 skiver), ett med kokt skinke (2 skiver) pluss paprika/agurk/salat
- En skive grovt brød med lettere margarin og ett kokt egg. Ett knekkebrød med roasbiff (50g) og majones (lettere)
- Ett grovt rundstykke med lettere margarin. Salat med reker (100g) og avocado (50g) og 1 ss lettere majones.
- Omelett (150g) med 2 skiver lettere gulost, 2 skiver kokt skinke og salat ved siden av.
- Alternativer fra oppskrifthefte.

Middagsalternativer (400-500 kcal)

- Kyllingfilet (200g = 2 store fileter) stekt i olje (maks 1ss) og wokkede grønnsaker (løk, paprika,sukkererter)
- Laks 150g/ hvitfisk (200g) stekt i olje (maks 1ss) og kokte grønnsaker (blomkål, brokkoli, gulrøtter)
- Karbonadedeig (200g) i tomatsaus + salat.
- Indrefilet/rent kjøtt stekt i smør (1ss) med tyttebær (1ss) og 1 ss kesam og og egnede grønnsaker

Mellommåltider < 200 kcal

- 1 knekkebrød med roastbeef 50g og majones 10g
- 2 knekkebrød med ost og skinke; lettere gulost (1 skive) og kokt skinke (1skive)
- ½ avocado med 100g reker og 10 g lettere majones
- Knekkebrød med røkelaks (30g) lettere majones og grov sennep (20g)

Mellommåltider <100 kcal

- Skyr yoghurt
- Yoghurt Yoplait, 0,1%
- Knekkebrød med cottage cheese, 20g og lettsyltetøy 10g
- 1 pose knaskegulrøtter
- Sukkererter (200g)

Drikke ca 100 kcal

- 1 glass (2 dl) skummet melk
- 1 glass (2 dl) appelsinjuice
- 1 glass (2 dl) sukkerholdig brus
- 1 flaske (3.3) pils
- 1 glass (1.5 dl) vin
- 4 cl brennevin

Energitette måltider 250-500 kcal

- 1 liten hamburger
- 1 pølse med pølsebrød
- 1 stor hvetebolle
- 1 skolebrød
- 1 wienerbrød
- 1 muffins
- 1 vaffelplate med syltetøy
- 1 iskrem i kjeks
- 1 liten sjokolade
- 4 salte kjeks med ost
- 1 pakke nudler
- 0.5 liter sjokolademelk
- 1 flaske vin
- 1 liter brus

Energitette måltider 1000-1500 kcal

- 1 pizza (580g)
- 1 stor hamburger med pommes frites
- 1 pose boller
- 1 pakke kjeks
- 1 stor plate (200g) sjokolade
- 1 pose (180g) peanøtter
- 1 pakke (250g) saltstenger
- 1 pose smågodt (300g)
- 1 "6-pack" pils

Energitette måltider ca 2000 kcal

- 2 liter is
- 1 stor pose potetchips
- 1 eske konfekt

Appendix 10: The lunches and snack meals offered in both dietary intervention groups.

	Low fat diet high in complex carbohydrates	**High protein diet moderately reduced in carbohydrates.**
Lunch 1	Iceberg salad, cucumber spring onion and maize (150 g) with pasta (150 g) and ham (50 g). Salad dressing (15 g).	Ham (125 g) and low fat cheese (50 g) with iceberg salad (100 g). Salad dressing (30 g).
Lunch 2	Whole meal pasta (100 g), and ratatouille (tomato sauce 50 g, garbanzo beans 50 g, onions 50, squash 50, peppers 50 g and chicken (50 g).	Chicken (175 g) and ratatouille (tomato sauce 50 g, onion 25 g, peppers (25 g) squash (50 g). Olive oil (15g)
Lunch 3	Whole meal wrap (80 g) with beans (50 g) and beef (50 g) with sugar snaps (75 g) and tomatoes (75 g). Low fat dressing (15 g).	Beef (175 g) with sugar snaps (50 g) and tomatoes (50 g). Olive oil (15 g).
Snack meal 1	YT yoghurt including müsli (25 g)	SKYR yoghurt and sun flower seeds (20 g)
Snack meal 2	Go´morgen yoghurt including müsli (25 g)	SKYR yoghurt and sun flower seeds (30 g)

Appendix 11: Macronutrient composition of the three lunches and snack meals.

	Low fat diet high in complex carbohydrates				**High protein diet moderately reduced in carbohydrate**			
	Energy, kcal	Protein, g	Fat, g	Carbohydrate, g	Energy, kcal	Protein, g	Fat, g	Carbohydrate, g
Lunch 1	405	18	13	51	410	40	26	4
Lunch 2	350	22	9	41	350	43	17	5
Lunch 3	375	23	9	45	345	42	18	3
Snack meal 1*	204	11	4	29	212	22	10	8
Snack meal 2*	260	9	6	43	270	24	15	9

Appendix 12: Smoking diary

Røykedagbok **Randnr. _____** **Screeningnr. _____**

Dag 1 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 2 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 3 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 4 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 5 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 6 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 7 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 8 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 9 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 10 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 11 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 12 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 13 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Dag 14 Dato _____

Hvor mange sigaretter har du røkt de siste 24 timene ? _____

Appendix 13: Fagerström test for nicotine dependence

1. Hvor lang tid etter at du våkner røyker du din første sigarett?

Innen 5 min	3
6–30 min	2
31–60 min	1
Etter 60 min	0

2. Er det vanskelig for deg å ikke røyke på steder hvor det er forbudt, for eksempel på kino eller fly?

Ja	1
Nei	0

3. Hvilken sigarett har du minst lyst til å gi opp?

Morgenens første	1
En av de andre	0

4. Hvor mange sigaretter røyker du per dag?

10 eller mindre	0
11–20	1
21–30	2
30 eller mer	3

5. Røyker du oftere de første timene etter at du våkner enn resten av dagen?

Ja	1
Nei	0

Røyker du selv om du er så syk at du er sengeliggende mesteparten av dagen?

Ja	1
Nei	0

Appendix 14: Averages used in the coding of the dietary records (2 pages).

Vegetable/fruit				
	Small	**Medium**	**Large**	**Edible percentage**
Edible part (whole fruit/vegetable)				
Apple		**174g (190g)**		92
Avocado	104g (146g)	**127g (191g)**		69
Baby corn		**8g**		100
Banana	83g (134g)	**131g (213g)**	177g (291g)	61
Bell pepper	92g (99g)	**168g (188g)**	203g (233g)	90
Broccoli (without stem)		**298g**		100
Carrot	42g (56g)	**85g (110g)**	122g (153g)	77
Cauliflower		**595g**		100
Celery, one stalk		**50g**		100
Champignon		**46g**	68g	100
Clementine	52g (64g)	**80g (105g)**	98g (120g)	80
Corn cob		**181g (279g)**		65
Cucumber		**382g**		100
Grapefruit		**323g (456g)**		71
Grapes, seedless		**5g**		100
Iceberg lettuce		**463g (489g)**		95
Kiwi	58g (75g)	**83g (114g)**		75
Nectarine		**146g (157g)**		93
Onion, red		**158g (165g)**		96
Onion, yellow		**177g (185g)**		96
Orange	165g (242g)	**190g (311g)**	234g (365g)	64
Pear		**195g (203g)**		96
Plum		**79g (81g)**		98
Radish		**26g**		100
Raspberries		**5g**		100
Squash		**375g (393g)**		95
Spring onion		**18g (19g)**		95
Sugar snaps		**4g**		100
Tomato,	95g	**112g**	166g	100
Tomato, beef		**203g**		100
Tomato, cherry	11g	**16g**		100
Tomato, taste-		**40g**		100

Meat				
	Grilled chicken	Chicken (leg)	Chicken (wing)	Pork chop
Total (1 piece)	695 g	173 g	17 g	158 g
Bone/cartilage	164 g	40 g	5 g	41.5 g
Skin/fat rim	39 g	27 g	4 g	54 g
Meat	492 g (~71%)	106 g (~61%)	8 g (~47%)	62.5 g (~40%)
Total edible portion	531 g (~76%)	133 g (~77%)	12 g (~71%)	116.5 g (~74%)

Weight losses during preparation of meat:

- Pure meat/filet: ~31% weight loss during preparation/cooking in a frying pan.
  - One piece chicken filet (prepared) weigh approximately 112 g.
- Ground beef: ~26% weight loss during preparation/cooking in a frying pan.
  - Ground beef w/Dolmio: ~47% is cooked ground beef.
  - Ground beef for taco: ~89% is cooked ground beef.
    ~7.5% is spices
    ~3.5% is added water

Appendix 15: Written information and informed consent (8 pages).

ULLEVÅL universitetssykehus

Forespørsel om deltakelse i forskningsprosjektet: "Effekten av proteinrik versus fettredusert diett i forhold til vekt, kroppssammensetning, energiforbruk, metabolske risikofaktorer og spiseadferd etter røykeslutt"

Bakgrunn og hensikt
Dette er en forespørsel til deg om å delta i en studie som skal undersøke effekten av to ulike dietter for å forebygge vektoppgang etter røykeslutt. Ved Avdeling for preventiv kardiologi ønsker vi å undersøke effekten av proteinrik diett sammenliknet med fettredusert diett. Vi vil undersøke kroppsvekt og kroppssammensetning, forbruk av kalorier, risikofaktorer for hjerte- og karsykdom (blodtrykk, kolesterol, blodsukker) og svar på et spørreskjema angående forhold til mat. Friske personer som røyker minst 10 sigaretter daglig og er mellom 20 og 65 år og som ikke har hatt alvorlig psykisk sykdom og ikke får behandling for depresjon kan delta i studien. I alt vil 120 personer delta i studien som varer i 6 måneder. Du er blitt spurt om å delta i studien fordi du er overvektig og er villig til å slutte å røyke, og følge en av de to diettene (tilfeldig valgt ved trekning). Oslo universitetssykehus, Ullevål er ansvarlig for studien.

Hva innebærer studien?
Dersom du er villig til det, vil du først få en legeundersøkelse for å sjekke om du kan være med i studien. Legeundersøkelsen innebærer blant annet sykehistorie, blodprøver, måling av blodtrykk og vekt før studiestart. Hvis du ikke blir med i studien, blir dine medisinske opplysninger kun registrert i din journal ved Avdeling for preventiv kardiologi, Oslo universitetssykehus Ullevål.

Deltagelse i studien innebærer at

1. du vil gjøre et forsøk på å slutte å røyke og
2. du spiser den dietten som du blir trukket ut til å spise i 6 måneder etter røykeslutt.

Dato for røykeslutt bestemmer du selv 3 uker etter første oppmøte i studien. Røykeslutt avhjelpes med medikamentet Champix (varenicline) som du starter med cirka 10 dager før røykesluttdagen og fortsetter med i 8-12 uker. Dette medikamentet er anbefalt som et ledd i røykesluttbehandlingen fordi det reduserer abstinenssymptomene i forbindelse med røykeslutt. I studien vil du få oppfølging av erfarne veiledere for røykeslutt. Før du slutter å røyke registrerer du matinntaket ditt og måler din fysiske aktivitet i 7 dager. Disse registreringene vil være utgangspunkt for de kostrådene du får for å følge den dietten du blir trukket ut til å spise. I syv dager etter røykeslutt, vil du få utlevert gratis ett lunsjmåltid og ett mellommåltid ved Avdeling for preventiv kardiologi. Disse måltidene skal gjøre det lettere for deg å følge kosten den første uken etter røykeslutt. Å delta i studien innebærer at du spiser den maten du får utlevert. Mat som ikke blir spist skal registreres. Etter de første 7 dagene skal du følge kostrådene, men kjøpe og lage all mat som du skal spise selv. I løpet av de første 7 dagene vil du også få tilbud om å være med på en gruppesamtale med fokus på adferdsendring i forbindelse med røykeslutt.

Totalt 2 ganger i løpet av studien skal du registrere ditt matinntak ved å veie og skrive ned alt det du spiser i 7 dager. Samtidig som du registrerer matinntaket ditt, skal du registrere fysisk aktivitet ved å gå med en liten monitor i 7 dager. Denne monitoren er så liten at den kan festes i et kjede eller i et belte. Du vil også ta blodprøver, måle hvilestoffskifte og kroppssammensetning og svare på spørreskjema om ditt forhold til mat 3 ganger i løpet av den tiden du deltar i studien. Totalt vil studien kreve at du kommer til visitter ved Avdeling for preventiv kardiologi 14 ganger. I tillegg får du tilbud om et frivillig gruppemøte. Timeavtaler for alle visittene ved avdelingen vil bli gitt i starten av studien.

For å undersøke om du har sluttet å røyke, vil du bli bedt om å avgi en puste prøve ved hver visitt. Du skal også skrive en røykedagbok og svare på spørreskjema. Selv om du ikke klarer å slutte å røyke

under studien, vil du bli fulgt opp i forhold til studieprotokollen i den tiden studien varer. Dette innebærer at du møter opp til avtalte visitter og spiser den maten du har fått råd om.

Relevant informasjon fra din pasientjournal vil også bli samlet inn.

Mulige fordeler og ulemper
Det er ikke tidligere blitt gjort en undersøkelse der to ulike dietter sammenlignes ved røykeslutt. Vi kan derfor ikke si om den ene dietten vil være bedre enn den andre.

Alle prøver, undersøkelser og mat som blir utdelt er gratis. Blod- og urinprøver vil bli tatt både før og etter studien for å sjekke eventuelle bivirkninger.

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 gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Alle registrerte opplysninger vil bli avidentifisert og det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Prøver og opplysninger vil oppbevares til 2015 før de destrueres og slettes.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Hvis du ønsker å delta etter at du har fått all informasjon og etter at du har fått tid til å stille spørsmål og vurdere deltagelse, vil du bli bedt om å undertegne dette informerte samtykket. Du vil få med deg en kopi av dette informasjonsskrivet hjem.

Annen informasjon
Har du spørsmål til studien, ta kontakt med klinisk ernæringsfysiolog Mette Svendsen telefon 23016653 eller mobil 45212344. Du kan også sende en e-post til: mette.svendsen@uus.no eller: mettsven@online.no

Ved spørsmål som trenger svar fra lege, kan du kontakte:
Lege Eli Heggen telefon 22119982 eller Dr. med Tor Ole Klemsdal telefon 22119453

- **Ytterligere informasjon om studien finner du i kapittel A – Utdypende forklaring om hva studien innebærer**
- **Ytterligere informasjon om personvern, biobank, økonomi og forsikring finner du i kapittel B**
- **Samtykkeerklæring finner du etter kapittel B**

Kapittel A- utdypende forklaring om hva studien innebærer

Kriterier for å delta

For å kunne delta i studien må du røyke minst 10 sigaretter daglig, være villig til å slutte, være mellom 20 - 65 år og ha en kroppsmasseindeks mellom 25 – 40 kg/m^2. Du kan ikke bruke medikament for depresjon og du kan heller ikke ha hatt alvorlig psykisk sykdom eller insulinbehandlet diabetes. Tarmsykdom eller allergi mot matvarer slik at du ikke kan spise maten som blir delt ut i studien vil også hindre deg fra å kunne delta.

Bakgrunnsinformasjon om studien

For mange er redsel for vektoppgang i forbindelse med røykeslutt et hinder til å slutte å røyke. Røykeslutt gir mindre risiko for sykdom og død, men stor vektoppgang i forbindelse med røykeslutt kan redusere helseeffekten. Hva som er årsak til vektoppgangen i forbindelse med røykeslutt er ikke avklart, men studier har vist at økt energiinntak, redusert hvilestoffskifte og totalt energiforbruk, samt redusert fettforbrenning kan være medvirkende årsaker. En studie der man sammenligner effekten av to ulike dietter i forhold til vekt, kroppssammensetning, energiforbruk og spiseadferd er tidligere ikke blitt gjennomført.

De to diettene i studien

Begge diettene vil være moderat energireduserte og tilpasset deg ut i fra målinger av hvilestoffskifte og fysisk aktivitet.

Den ene dietten er proteinrik. Det vil si at om du kommer i den gruppen, øker du inntaket av proteinrike pålegg som lettere ost, magert kjøttpålegg, skalldyr og fisk. Du øker også mengden magert kjøtt, kylling, skalldyr eller fisk til middag og lunsj. Siden du øker porsjonen av protein, vil vi anbefale at du reduserer mengden karbohydrater fra brød, poteter, ris og pasta så mye du klarer. I tillegg anbefaler vi en begrensing på frukt og at du kutter ut alle søte varer som sjokolade, is, kaker, brus og juice/saft/nektar. Grønnsaker har ingen andre restriksjoner enn at du kan spise den mengden du ønsker når du har spist din anbefalte porsjon av de proteinrike matvarene. I den proteinrike dietten er det ikke strenge begrensninger på fett og vi anbefaler spesielt umettet fett fra olje, majones, nøtter og oliven.

Den andre dietten er fettredusert. Det vil si at når du velger magre meieri- og kjøttprodukter, kan du spise omtrent 1 ss med oljerike produkter per dag. I denne dietten vil du først og fremst øke porsjonen av frukt, grønnsaker og kornprodukter som grovt brød, fullkornspasta, brun ris, bulgur eller eventuelt grovt brød til middag og lunsj. For å få forskjell mellom diettene vil vi anbefale at du reduserer på porsjonen kjøtt og fisk til middag og velger mindre mengde proteinrike pålegg.

I de 7 dagene du får utlevert lunsj og mellommåltid, kan du velge mellom 3 lunsjer. Du får ett mellommåltid utlevert, men du kan i tillegg spise andre mellommåltider som du vil få råd om. Du møter opp ved avdelingen 2 ganger i løpet av uken for å hente mat. Du får utlevert mat for 1 ekstra dag i tilfelle visitten må utsettes. Det er viktig at det er bare du som spiser maten du får utlevert i studien og ikke deler den med andre. Den maten som du ikke har spist, tar du med deg til neste visitt slik at vi får en oversikt over hvor mye du har spist av utlevert mat i løpet av perioden. I forbindelse med utlevering av mat, vil du også få tilbud om å delta på et gruppemøte med fokus på adferdendringer ved røykeslutt.

Mulige ubehag, bivirkninger og risiko

Endring av kostsammensetning kan medføre ubehag fra mage og tarm. Ubehaget er som regel forbigående.

Medikamentet varenicline som reduserer abstinenssymptomene ved røykeslutt, kan ha bivirkninger som søvnløshet, uvanlige drømmer og hodepine. Det er rapportert få alvorlige bivirkninger, men det er rapportert en mulig økt forekomst av økt risiko for adferdsendring, nedstemthet, selvmordstanker og selvmord.

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 oppfølging for røykeslutt ved Avdeling for preventiv kardiolog.

Ubehag i forbindelse med studieprosedyrer

Når du skal måle hvilestoffskifte, krever dette at du kommer til Avdeling for preventiv kardiologi fastende om morgenen. Du vil bli bedt om å ligge rolig i ca 20 minutter før målingen utføres. Når målingen skjer, vil du ligge under en gjennomsiktig plastikk-kuppel med god ventilasjon. Vi måler ditt oksygen forbruk og din produksjon av karbondioksid. Erfarent personell vil være tilstede under målingen og den er ikke forbundet med risiko, men noen kan få en følelse av ubehag når de blir plassert under plastikk kuppelen.

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

Kroppssammensetning vil bli målt ved omkrets av liv og hofte og ved impedans vekt. Målingene er ikke forbundet med ubehag.

Studiedeltagerens ansvar

Legen ved Avdeling for preventiv kardiologi vil avgjøre om du fyller kravene for å delta. Visse medisiner og medisinske tilstander kan utelukke deg. Du må komme til avtalte visitter og undersøkelser, spise mat og medisin for røykeslutt som avtalt og levere den maten du ikke har spist. Du må også være villlig til å avgi pusteprøve for mengde karbonmonoksid og skrive røykedagbok. Dersom en annen lege vil gi deg nye medisiner mens du deltar i studien, må du informere om at du deltar i en forskningsstudie. Vennligst kontakt studiepersonalet før du starter på ny medisin hvis mulig.

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

Avbrutt studiedeltagelse

Legen eller studieansvarlig kan stoppe din deltagelse i studien hvis:

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

Informasjon til kvinner

Det er absolutt helsegevinst med røykestopp ved graviditet eller amming. Disse tilstandene vil imidlertid kunne påvirke de undersøkelsene vi gjør i studien og derfor må kvinner i fruktbar alder bruke prevensjon godkjent av studielegen under studien. Det vil bli tatt en graviditetstest av all kvinner i fruktbar alder ved randomisering og ved behandlingsslutt. Det er ikke sikkert testen avslører en tidlig graviditet, informer derfor studieansvarlig så snart som mulig hvis du tror du er gravid.

Oversikt over studiebesøkene

Uker	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	24
	I----------I----------I----------II----------I																
	B	R		Røykestopp													Studieslutt
Lege undersøkelse	x																
Kroppsvekt	x	x	x	x	x	x	x	x		x		x		x		x	x
Kroppssammensetning		x						x								x	
Liv/hofte omkrets	x	x						x								x	x
Hvilestoffskifte		x						x									
Aktivitetsregistrering		x						x									
CO måling		x	x	x	x	x	x	x	x	x	x		x		x	x	x
Veiledning for røykeslutt	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Bestemme dato for røykeslutt	x																
Start varenicline		x															
Stopp varenicline											(x)			x			
Røykedagbok	x	x	x	x	x	x	x	x									
Spørre skjema røyk	x			x		x		x		x		x					
Spørreskjema spiseadferd	x							x								x	
Registrering av mat	x							x									
Kostveiledning	x	x	x	x	x	x	x	x		x		x		x		x	
Opptelling av mat					x	x											
Blodtrykk		x						x								x	
Blodprøver	x	x						x								x	
Urinprøve		x														x	
Gruppemøte					(x)												

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

Personvern
All informasjon vil bli behandlet konfidensielt. Fastlegen din blir vanligvis informert om din deltagelse hvis du ikke har noe i mot det. Personlige opplysninger om deg som kan være sensitive (for eksempel sykehistorie og medisinbruk), vil bli samlet inn og behandlet, men kun til forskningsformål i forbindelse med studien. Du vil ikke bli referert til ved navn eller bli identifisert i noen publikasjon, så dataene kan ikke spores tilbake til deg.

Oslo universitetssykehus er databehandlingsansvarlig for studien.

Forskningsbiobank
Blod- og urinprøvene som blir tatt vil bli lagret i en forskningsbiobank. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet inngår i biobanken. Oslo Universitetssykehus, Ullevål ved biobankkoordinator Roger Bjugn er ansvarshavende for forskningsbiobanken. Biobanken planlegges å vare til 2015. Etter dette vil materiale bli ødelagt etter interne retningslinjer.

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 korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Finansiering
Denne studien er finansiert ved hjelp av opptjente forskningsmidler ved Avdeling for 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 ikke bevise at det var noen sin skyld. Dersom det viser seg at problemene oppstod som følge av studien, vil du få erstatning. Du er forsikret i henhold til Oslo Universitetssykehus Ullevål sine egne forsikringer.

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

Samtykke for deltagelse i studien

Jeg er villig til å delta i studien

(Signert og datert av deltager)

Deltagers navn med blokkbokstaver

Deltagers fødselsdato

Bekreftelse på at informasjon er gitt deltageren i studien

Jeg bekrefter å ha gitt skriftlig og muntlig informasjon om studien

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(Signert og datert av lege)

Legens navn med blokkbokstaver/stempel